Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 05-7006

54. **TÍTULO** Ciclobuten-1,2-dionas 3,4 di-sustituidas como ligandos del receptor de quimiocina CXC.

51. **CLASIFICACIÓN INTERNACIONAL** C07C 237/36

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

DOMICILIO _____

74. **APODERADO** Carlos B. Olarte

22. **BOGOTÁ, D. C.,** Enero 28, 2005

(FORMA P-10)

05/07

OLARTE RAISBECK

Industria y Comercio
SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
Radicacion : 05007006 00000000 Folios: 450
Fecha (AMD): 2005-01-28 10:12:17
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL 28-02-2005

(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 Folio 3...

(5) PCT (86)

Solicitud Internacional No. PCT/US03/023785 Fecha 30 de Julio de 2003
Publicación Internacional No. WO 2004/011418 Fecha 5 de Febrero de 2004

(6) Título (54) CICLOBUTEN-1,2-DIONAS 3,4-DI-SUSTITUIDAS COMO LIGANDOS DEL RECEPTOR DE QUIMIOCINA CXC.

(7) Clasificación Internacional (51) C07C 237/36,

(8) Prioridad SI [X] N [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Julio 30, 2002	10/208,412
US	Septiembre 11, 2002	10/241,326

(9) Comprobante de pago No. 4,060 Fecha ENER 19, 2005

2
2

(0) **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 inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(1) **FIGURA CARACTERÍSTICA:**

(2) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

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

Invent r(s):

TAVERAS, Arthur, G., citizen of the United States of America, residing at 3 Headley Court, Denville, New Jersey, 07834, U.S.A.

AKI, Cynthia, J., citizen of the United States of America, residing at 36 North Ashby Avenue, Livingston, New Jersey, 07039, U.S.A.

CHAO, Jianping, citizen of China, residing at 23 Brainerd Road, Summit, New Jersey, 07901, U.S.A.

DWYER, Michael, citizen of the United States of America, residing at 235 Katherine Street, Scotch Plains, New Jersey, 07076, U.S.A.

CHAO, Jianhua, citizen of China, residing at 2431 Crossing Way, Wayne, New Jersey, 07470, U.S.A.

YU,Younong, citizen of China, residing at 280 Bromley Place, East Brunswick, New Jersey, 08816, U.S.A.

MERRITT, J., Robert, citizen of the United States of America, residing at 14 Gloucester Lane, Ewing, New Jersey, 08618, U.S.A.

BIJU, Purakkattle, J., citizen of India, residing at 55 Country Club Lane, Scotch Plains, New Jersey, 07076, U.S.A

JAKWAY, James, citizen of the United States of America, residing at 67 Claire Drive, Bridgewater, New Jersey, 08807, U.S.A.

LAI, Gaifa, citizen of the United States of America, residing at 8-7B Koster Boulevard, Edison, New Jersey, 08837, U.S.A.

WU, Minglang, citizen of China, residing at 43 Kingsland Circle, Monmouth Junction, New Jersey, 08852, U.S.A.

HECKER, Evan, A., citizen of the United States of America, residing at 10926 Jollyville Road, Apt. 1501, Austin, Texas, 78759, U.S.A.

LUNDELL, Daniel, citizen of the United States of America, residing at 21 Sleepy Hollow Drive, Flemington, New Jersey, 08822, U.S.A.

FINE, Jay, S., citizen of the United States of America, residing at 11 Aldon Terrace, Bloomfield, New Jersey, 07003, U.S.A.

SUPERINDUSTRIA Y COMERCIO
Radicacion : 05007006 00000000 Folios: 450
Fecha (AMD): 2005-01-28 10:12:17
Tramite : 011 PCT-PATENT 379 FASE NACI 4/1 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176099-2

RECIBO OFICIAL DE CAJA : 05 - 4,060
FECHA : ENERO 19 DE 2005

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ALEX SANTOS	CONSIGNACION	BANCO POPULAR	050-00110-6	29810430	18/01/2005	7,223,000.00

***** 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 [illegible] poder de representación fechado el 4 noviembre de 2002.

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

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

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

6

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

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

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

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

CERTIFIED

5. AT TRENTON, NEW JERSEY

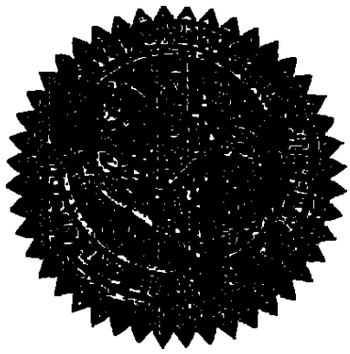
6. THE 29TH DAY OF AUGUST 2003

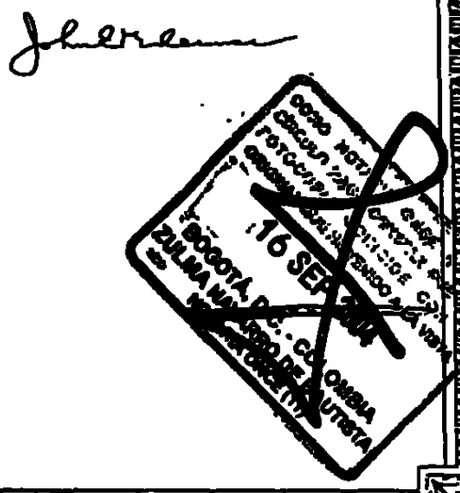
7. BY: John E McCormac, CPA, NEW JERSEY TREASURER

8. NO. A180345

9. SEAL/STAMP:

10. SIGNATURE





OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
CALLE 100 NO. 8A-55 PISO 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-8200
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 María Frieri** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's Patents, Utility Models and Industrial Designs in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, appeals, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

Poder

El suscrito,

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

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

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

Date/Fecha: August 7, 2003

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



OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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

www.olarteraisbeck.com

Notarial Certification

On this date, August 7, 2003

The undersigned Notary Public certifies:

1. That Edward H. Mazer

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

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

3. That SCHERING CORPORATION having its principal place of business located in 2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530, U.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

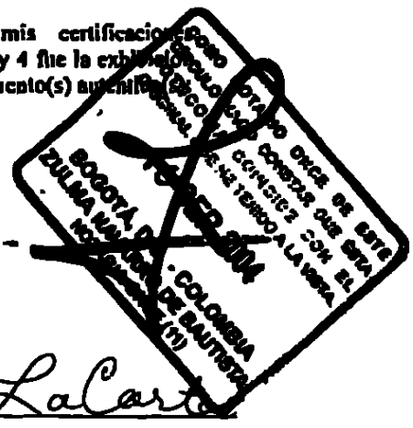
3. Que

con sede principal ubicada en

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

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

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





NOTARY PUBLIC (Signature):

Marguerite LaCorte

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

TRADUCCION OFICIAL No. 04-368

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

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

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

APOSTILLA

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

1. País: Estados Unidos de América

   El presente documento público

2. Fue firmado por: Melanie J. Rice

EL SUSCRITO NOTARIA ONCE (E) DE ESTE CIRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
0 2 NOV 2004
BOGOTA D.C. COLOMBIA
MONICA ZULMA 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
13 NOV 2004
BOGOTA, D.C. COLOMBIA
MONICA ZULMA BAUTISTA NAVARRO
NOTARIA ONCE (E)

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

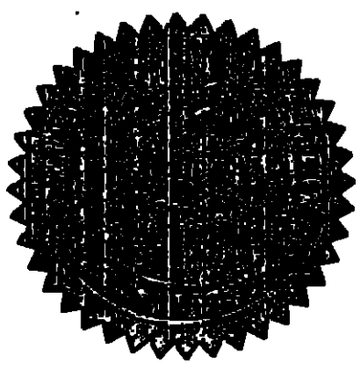
5. AT TRENTON, NEW JERSEY

6. THE 25TH DAY OF OCTOBER 2004

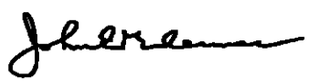
7. BY: John E McCormac, CPA, NEW JERSEY TREASURER

8. NO. A211395

9. SEAL/STAMP:



10. SIGNATURE



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

06 NOV 2004

BOGOTA, D.C. - COLOMBIA

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: +57-1 638-6200
FAX: +57-1 638-6201

www.olarteraisbeck.com

Power of Attorney

The undersigned, 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] New Jersey 08512-3516 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: [signature]
Brian M. Posner, Vice President of Finance

Date/Fecha: 1 October 2004

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

ESTE ES FIEL COPIA DE LA QUE SE ME PRESENTO QUE CONSTA DE ONCE (11) FOLIOS Y QUE HE COTEJADO CON EL ORIGINAL QUE ME FUE DEVUELTO A LA VISTA
07 OCT 2004
BOGOTA D.C. - COLOMBIA
MONICA PATRICIA 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: +57-1 638-6200
FAX: +57-1 638-6201

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

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 February 2004 (05.02.2004)

PCT

(10) International Publication Number
WO 2004/011418 A1

(51) International Patent Classification[7]: C07C 237/36, 237/44, 311/39, C07D 207/323, 217/24, 307/52, 307/68, 307/81, 307/82, 307/83, 317/46, 319/18, 333/20, 405/12, 409/12, 409/14, 413/12, 413/14, A61K 31/341, 31/36, 31/381, 31/40, 31/4025, 31/42, 31/472, 31/496, 31/506, 31/5377, A61P 29/00, 31/00, 35/00

(21) International Application Number:
PCT/US2003/023785

(22) International Filing Date: 30 July 2003 (30.07.2003)

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(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: TAVERAS, Arthur, G.; 3 Headley Court, Denville, NJ 07834 (US). AKI, Cynthia, J.; 36 North Ashby Avenue, Livingston, NJ 07039 (US). CHAO, Jianping; 23 Brainerd Road, Summit, NJ 07901 (US). DWYER, Michael; 235 Katherine Street, Scotch Plains, NJ 07076 (US). CHAO, Jianhua; 93 Lakeview Court, Pompton Lakes, NJ 07442 (US). YU, Younong; 60 Country Club Lane, Scotch Plains, NJ 07076 (US). MERRITT, J., Robert; 14 Gloucester Lane, Ewing, NJ 08618 (US). BIJU, Purakkattle; 55 Country Club Lane, Scotch Plains, NJ 07076 (US). JAKWAY, James; 67 Claire Drive, Bridgewater, NJ 08807 (US). LAI, Gaifa; 8-7B Koster Blvd., Edison, NJ 08837 (US). WU, Minglang; 524 Northumberland Way, Monmouth Junction, NJ 08852 (US). HECKER, Evan, A.; 123 Probasco Road, East Windsor, NJ 08520 (US). LUNDELL, Daniel; 21 Sleepy Hollow Drive, Flemington, NJ 08822 (US). FINE, Jay, S.; 11 Aldon Terrace, Bloomfield, NJ 07003 (US).

(74) Agent: JEANETTE, Henry, C.; Schering-Plough Corporation, Patent Department K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

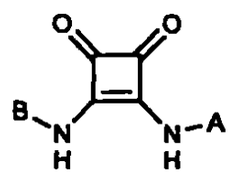
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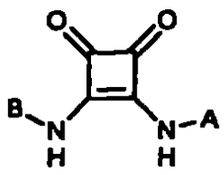
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(54) Title: 3,4-DI-SUBSTITUTED CYCLOBUTENE-1, 2-DIONES AS CXC-CHEMOKINE RECEPTOR LIGANDS



(I)



(II)

(57) Abstract: Disclosed are novel compounds of the formula (I) or a pharmaceutically acceptable salt or solvate thereof. Also disclosed is the treatment of chemokine-mediated diseases using compounds of the formula (II)

WO 2004/011418 A1

OC01406K7 RFD

3,4-DI-SUBSTITUTED CYCLOBUTENE-1,2-DIONES AS CXC-CHEMOKINE RECEPTOR LIGANDS

FIELD OF THE INVENTION

The present invention relates to novel substituted cyclobutenedione compounds, pharmaceutical compositions containing the compounds, and the use of the compounds and formulations in treating CXC chemokine-mediated diseases.

BACKGROUND OF THE INVENTION

Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T-cells, eosinophils, basophils, neutrophils and endothelial cells to sites of inflammation and tumor growth. There are two main classes of chemokines, the CXC-chemokines and the CC- chemokines. The class depends on whether the first two cysteines are separated by a single amino acid (CXC-chemokines) or are adjacent (CC-chemokines). The CXC-chemokines include interleukin-8 (IL-8), neutrophil-activating protein-1 (NAP-1), neutrophil-activating protein-2 (NAP-2), GROα, GROβ, GROγ, ENA-78, GCP-2, IP-10, MIG and PF4. CC chemokines include RANTES, MIP -1α, MIP-2β, monocyte chemotactic protein-1 (MCP-1), MCP-2, MCP-3 and eotaxin. Individual members of the chemokine families are known to be bound by at least one chemokine receptor, with CXC-chemokines generally bound by members of the CXCR class of receptors, and CC-chemokines by members of the CCR class of receptors. For example, IL-8 is bound by the CXCR-1 and CXCR-2 receptors.

Since CXC-chemokines promote the accumulation and activation of neutrophils, these chemokines have been implicated in a wide range of acute and chronic inflammatory disorders including psoriasis and rheumatoid arthritis. Baggiolini et al., FEBS Lett. 307, 97 (1992); Miller et al., Crit. Rev. Immunol. 12, 17 (1992); Oppenheim et al., Annu. Fev. Immunol. 9, 617 (1991); Seitz et al., J. Clin. Invest. 87, 463 (1991); Miller et al., Am. Rev. Respir. Dis. 146, 427 (1992); Donnely et al., Lancet 341, 643 (1993).

ELRCXC chemokines including IL-8, GROα, GROβ, GROγ, NAP-2, and ENA-78 (Strieter et al. 1995 JBC 270 p. 27348-57) have also been implicated in the induction of tumor angiogenesis (new blood vessel growth). All of these chemokines are believed to exert their actions by binding to the 7 transmembrane G-protein coupled receptor CXCR2 (also known as IL-8RB), while IL-8 also binds CXCR1 (also known as IL-8RA). Thus, their angiogenic activity is due to their binding to and activation of CXCR2, and possible CXCR1 for IL-8, expressed on the surface of vascular endothelial cells (ECs) in surrounding vessels.

Many different types of tumors have been shown to produce ELRCXC chemokines and their production has been correlated with a more aggressive phenotype (Inoue et al. 2000 Clin Cancer Res 6 p. 2104-2119) and poor prognosis (Yoneda et. al. 1998 J Nat Cancer Inst 90 p. 447-454). Chemokines are potent chemotactic factors and the ELRCXC chemokines have been shown to induce EC chemotaxis. Thus, these chemokines probably induce chemotaxis of endothelial cells toward their site of production in the tumor. This may be a critical step in the induction of angiogenesis by the tumor. Inhibitors of CXCR2 or dual inhibitors of CXCR2 and CXCR1 will inhibit the angiogenic activity of the ELRCXC chemokines and therefore block the growth of the tumor. This anti-tumor activity has been demonstrated for antibodies to IL-8 (Arenberg et al. 1996 J Clin Invest 97 p. 2792-2802), ENA-78 (Arenberg et al. 1998 J Clin Invest 102 p. 465-72), and GROα (Haghnegahdar et al. J. Leukoc Biology 2000 67 p. 53-62).

Many tumor cells have also been shown to express CXCR2 and thus tumor cells may also stimulate their own growth when they secrete ELRCXC chemokines. Thus, along with decreasing angiogenesis, inhibitors of CXCR2 may directly inhibit the growth of tumor cells.

Hence, the CXC-chemokine receptors represent promising targets for the development of novel anti-inflammatory and anti-tumor agents.

There remains a need for compounds that are capable of modulating activity at CXC-chemokine receptors. For example, conditions associated with an increase in IL-8 production (which is responsible for chemotaxis of neutrophil and T-cell subsets into the inflammatory site and growth of tumors) would benefit by compounds that are inhibitors of IL-8 receptor binding.

SUMMARY OF THE INVENTION

This invention provides a method of treating a chemokine mediated disease in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least one compound (e.g., 1-3, and usually one) of formula IA (or a pharmaceutically acceptable salt or solvate thereof), as described below, said chemokine mediated disease being selected from the group consisting of: chronic inflammation, acute inflammatory pain, chronic inflammatory pain, acute neuropathic pain, chronic neuropathic pain, acute respiratory distress syndrome, delayed type hypersensitivity reaction, atherosclerosis, cerebral and cardiac ischemia, osteoarthritis, multiple sclerosis, restinosis, angiogenesis, osteoporosis, gingivitis, respiratory viruses, herpes viruses, hepatitis viruses, HIV, Kaposi's sarcoma associated virus, meningitis, cystic fibrosis, pre-term labor, cough, pruritis, multi-organ dysfunction, trauma, strains, sprains, contusions, psoriatic arthritis, herpes, encephalitis, CNS vasculitis, traumatic brain injury, CNS tumors, subarachnoid hemorrhage, post surgical trauma, interstitial pneumonitis, hypersensitivity, crystal induced arthritis, acute and chronic pancreatitis, acute alcoholic hepatitis, necrotizing enterocolitis, chronic sinusitis, angiogenic ocular disease, ocular inflammation, retinopathy of prematurity, diabetic retinopathy, macular degeneration with the wet type preferred and corneal neovascularization, polymyositis, vasculitis, acne, gastric and duodenal ulcers, celiac disease, esophagitis, glossitis, airflow obstruction, airway hyperresponsiveness, bronchiectasis, bronchiolitis, bronchiolitis obliterans, chronic bronchitis, cor pulmonae, cough, dyspnea, emphysema, hypercapnea, hyperinflation, hypoxemia, hyperoxia-induced inflammations, hypoxia, surgical lung volume reduction, pulmonary fibrosis, pulmonary hypertension, right ventricular hypertrophy, peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD), granulocytic ehrlichiosis, sarcoidosis, small airway disease, ventilation-perfusion mismatching, wheeze, colds, gout, alcoholic liver disease, lupus, burn therapy, periodontitis, transplant reperfusion injury and early transplantation rejection, acute inflammation, and rheumatoid arthritis.

This invention provides a method of treating acute inflammatory pain, chronic inflammatory pain, acute neuropathic pain, or chronic neuropathic pain in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, and usually

one) compound of formula IA (or a pharmaceutically acceptable salt or solvate thereof), as described below.

This invention provides a method of treating a chemokine mediated disease in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, usually 1) compound selected from the group consisting of the compounds of formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088, or a pharmaceutically acceptable salt or solvate of said compounds

This invention provides a method of treating acute inflammatory pain, chronic inflammatory pain, acute neuropathic pain, or chronic neuropathic pain in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, and usually one) compound selected from the group consisting of the compounds of formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088, or a pharmaceutically acceptable salt or solvate of said compounds.

This invention also provides a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, usually 1) compound selected from the group consisting of the compounds of formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088, or a pharmaceutically acceptable salt or solvate of said compounds.

This invention also provides a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, usually 1) compound selected from the group consisting of the compounds of formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088, or a pharmaceutically acceptable salt or solvate of said compounds, concurrently or sequentially with: (a) a microtubule affecting agent, or (b) an antineoplastic agent, or (c) an anti-angiogenesis agent, or (d) a VEGF receptor kinase inhibitor, or (e) antibodies against the VEGF receptor, or (f) interferon, and/or g) radiation.

This invention also provides a method of inhibiting angiogenesis, in a patient in need of such treatment, comprising administering to said patient an effective amount of at least one (e.g., 1-3, usually 1) compound selected from the group consisting of the compounds of formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088, or a pharmaceutically acceptable salt or solvate of said compounds.

This invention also provides a method of treating angiogenic ocular disease (e.g., ocular inflammation, retinopathy of prematurity, diabetic retinopathy, macular degeneration with the wet type preferred and corneal neovascularization), in a patient in need of such treatment, comprising administering to said patient and effective amount of at least one (e.g., 1-3, usually 1) compound selected from the group consisting of the compounds of formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088, or a pharmaceutically acceptable salt or solvate of said compounds.

This invention also provides a method of treating a disease selected from the group consisting of: gingivitis, respiratory viruses, herpes viruses, hepatitis viruses, HIV, kaposi's sarcoma associated virus and atherosclerosis, in a patient in need of such treatment, comprising administering to said patient an effective amount of at least one (e.g., 1-3, usually 1) compound selected from the group consisting of the compounds of formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088, or a pharmaceutically acceptable salt or solvate of said compounds.

This invention also provides novel compounds selected from the group consisting of the compounds of formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088.

This invention also provides novel compounds selected from the group consisting of the pharmaceutically acceptable salts (e.g., sodium, or calcium salts), or solvates, of the compounds of formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088.

This invention also provides a pharmaceutical composition comprising at least one (e.g., 1-3, usually 1) compound selected from the compounds of formulas 1.0A,

3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088, or a pharmaceutically acceptable salt or solvate of said compounds, and a pharmaceutically acceptable carrier.

This invention also provides a method of treating a chemokine mediated disease in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, usually 1) compound of formula IB, as described below.

This invention also provides a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, usually 1) compound of formula IB, as described below.

This invention also provides a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, usually 1) compound of formula IB, as described below, concurrently or sequentially with: (a) a microtubule affecting agent, or (b) an antineoplastic agent, or (c) an anti-angiogenesis agent, or (d) a VEGF receptor kinase inhibitor, or (e) antibodies against the VEGF receptor, or (f) interferon, and/or g) radiation.

This invention also provides a method of inhibiting angiogenesis, in a patient in need of such treatment, comprising administering to said patient an effective amount of at least one (e.g., 1-3, usually 1) compound of formula IB, as described below.

This invention also provides a method of treating angiogenic ocular disease (e.g., ocular inflammation, retinopathy of prematurity, diabetic retinopathy, macular degeneration with the wet type preferred and corneal neovascularization), in a patient in need of such treatment, comprising administering to said patient and effective amount of at least one (e.g., 1-3, usually 1) compound of formula IB, as described below.

This invention also provides a method of treating a disease selected from the group consisting of: gingivitis, respiratory viruses, herpes viruses, hepatitis viruses, HIV, kaposi's sarcoma associated virus and atherosclerosis, in a patient in need of such treatment, comprising administering to said patient an effective amount of at least one (e.g., 1-3, usually 1) compound of formula IB, as described below.

This invention also provides novel compounds of formula IB, as described below.

This invention also provides novel compounds selected from the group consisting of the pharmaceutically acceptable salts (e.g., sodium, or calcium salts), or solvates, of the compounds of formula IB, as described below.

This invention also provides a pharmaceutical composition comprising at least one (e.g., 1-3, usually 1) compound of formula IB, as described below, and a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION OF THE INVENTION

When any variable occurs more than one time in any moiety, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

Unless indicated otherwise, the following definitions apply throughout the present specification and claims. These definitions apply regardless of whether a term is used by itself or in combination with other terms. For example, the definition of "alkyl" also applies to the "alkyl" portion of "alkoxy".

"Patient" includes both human and other mammals, preferably human.

"Mammal" includes a human being, and preferably means a human being.

"Alkyl" means a straight or branched saturated hydrocarbon chain having 1 to 20 carbon atoms, preferably 1 to 12 carbon atoms, more preferably 1 to 6 carbon atoms.

"Alkoxy" means an alkyl-O- group wherein alkyl is as defined above. Non-limiting examples of alkoxy groups include: methoxy, ethoxy, n-propoxy, iso-propoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen.

"Alkenyl" means a straight or branched aliphatic hydrocarbon group having at least one carbon-carbon double bond, and 2 to 20 carbon atoms, preferably 2 to 12 carbon atoms, and more preferably 2 to 6 carbon atoms. Non-limiting examples of alkenyl groups include: ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl.

"Alkynyl" means a straight or branched aliphatic hydrocarbon group having at least one carbon-carbon triple bond, and 2 to 15 carbon atoms, preferably 2 to 12 carbon atoms, and more preferably 2 to 4 carbon atoms. Non-limiting examples of

alkynyl groups include ethynyl, propynyl, 2-butynyl, 3-methylbutynyl, n-pentynyl, and decynyl.

"Aryl" means an aromatic monocyclic or multicyclic ring system, wherein at least one ring is aromatic, comprising about 6 to about 14 carbon atoms, and preferably about 6 to about 10 carbon atoms. Non-limiting examples of suitable aryl groups include: phenyl, naphthyl, indenyl, tetrahydronaphthyl, indanyl, anthracenyl, and fluorenyl.

"Arylalkyl" means an aryl group, as defined above, bound to an alkyl group, as defined above, wherein the alkyl group is bound to the parent moiety. Non-limiting examples of suitable arylalkyl groups include benzyl, phenethyl and naphthleneylmethyl.

"Cycloalkyl" means saturated carbocyclic rings having 3 to 10 (e.g., 3 to 7) carbon atoms, preferably 5 to 10 carbon atoms, and more preferably 5 to 7 carbon atoms, and having one to three rings. Non-limiting examples of cycloalkyl groups include: cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and adamantyl.

"Cycloalkylalkyl" means a cycloalkyl group bound to the parent moiety through an alkyl group. Non–limiting examples include: cyclopropylmethyl and cyclohexylmethyl.

"Cycloalkenyl" means a non-aromatic mono or multicyclic ring system comprising 3 to 10 carbon atoms, and preferably 5 to 10 carbon atoms, and having at least one carbon-carbon double bond. Preferred cycloalkenyl rings have 5 to 7 carbon atoms. Non-limiting examples of cycloalkyl groups include cyclopentenyl, cyclohexenyl, cycloheptenyl, and norbornenyl.

"Halo" means fluoro, chloro, bromo, or iodo groups. Preferred are fluoro, chloro or bromo, and more preferred are fluoro and chloro.

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

"Haloalkyl" means an alkyl group as defined above wherein one or more hydrogen atoms on the alkyl is replaced by a halo group defined above.

"Heterocyclyl" or "heterocyclic" or "heterocycloalkyl" means a non-aromatic saturated monocyclic or multicyclic ring system (i.e., a saturated carbocyclic ring or ring system) comprising 3 to 10 ring atoms (e.g., 3 to 7 ring atoms), preferably 5 to 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 have 5 to 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom, respectively, is present as a ring atom. The 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 monocyclic heterocyclyl rings include: piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, and tetrahydrothiopyranyl.

The term heterocyclic acidic functional group is intended to include groups such as, pyrrole, imidazole, triazole, tetrazole, and the like.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising 5 to 14 ring atoms, preferably 5 to 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 5 to 6 ring atoms. 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 heteroaryls include: pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, and benzothiazolyl.

"Heteroarylalkyl" means a heteroaryl group, as defined above, bound to an alkyl group, as defined above, where the bond to the parent moiety is through the alkyl group.

N-oxides can form on a tertiary nitrogen present in an R substituent, or on =N- in a heteroaryl ring substituent and are included in the compounds of formula I.

The term "prodrug," as used herein, represents compounds that are rapidly transformed *in vivo* to the parent compound of the above formula, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-

drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

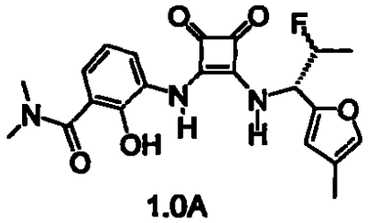
As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

As used in the methods of this invention,"an effective amount" means a therapeutically acceptable amount (i.e., that amount which provides the desired therapeutic effective).

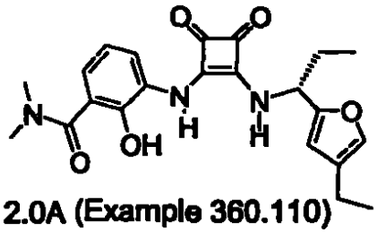
Also, as used herein, with reference to chemical structures or formulas, "Bn" represents benzyl, "Et" represents ethyl, "Me" represents methyl, and "Ph" represents phenyl.

Representative embodiments of this invention are described below. The embodiments have been numbered for purposes of reference thereto.

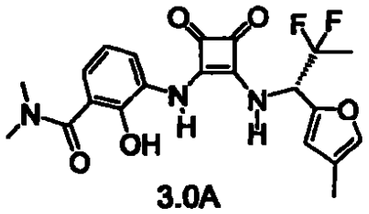
Compounds of formulas 1.0A, 2.0A, 3.0A, 4.0A, 5.0A and 6.0A are:



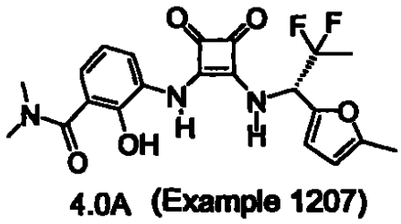
1.0A



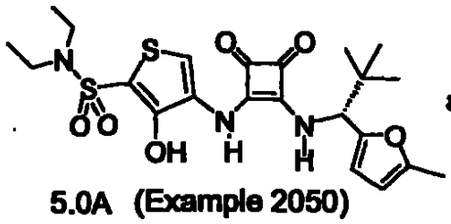
2.0A (Example 360.110)



3.0A

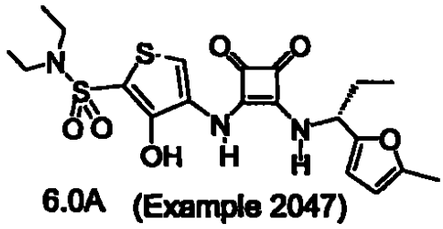


4.0A (Example 1207)



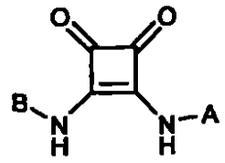
5.0A (Example 2050)

and



6.0A (Example 2047)

For the methods of treatment that use compounds of formula IA, as described above, said compounds of formula IA are:

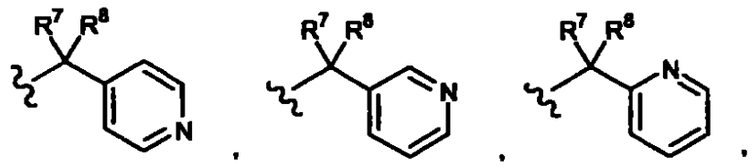


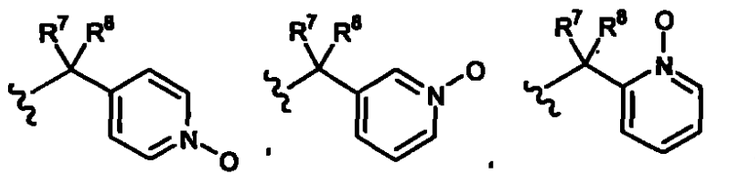
(IA)

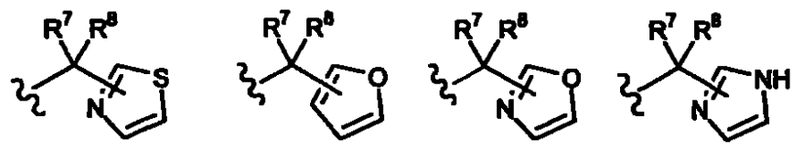
and the pharmaceutically acceptable salts (e.g., sodium or calcium salt) and solvates thereof, wherein:

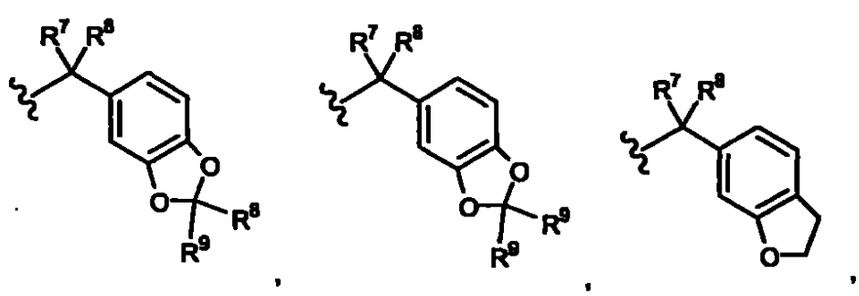
A is selected from the group consisting of:

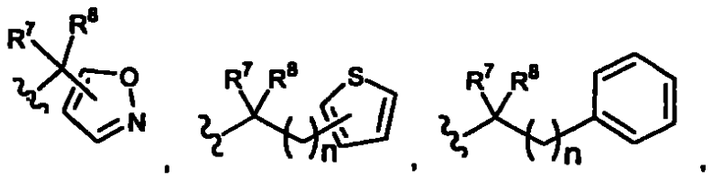
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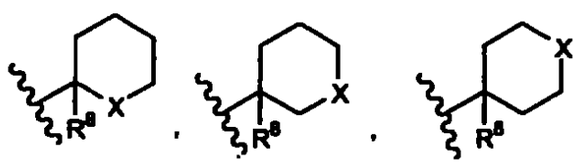


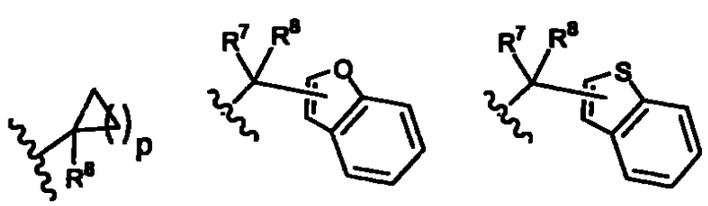


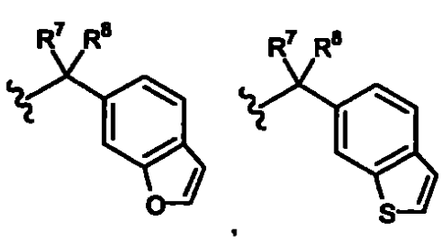


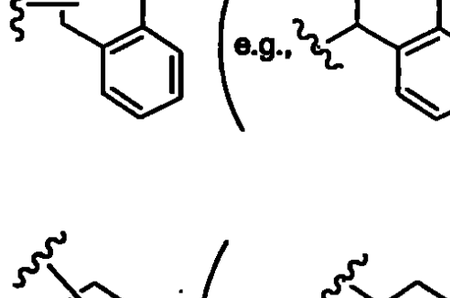




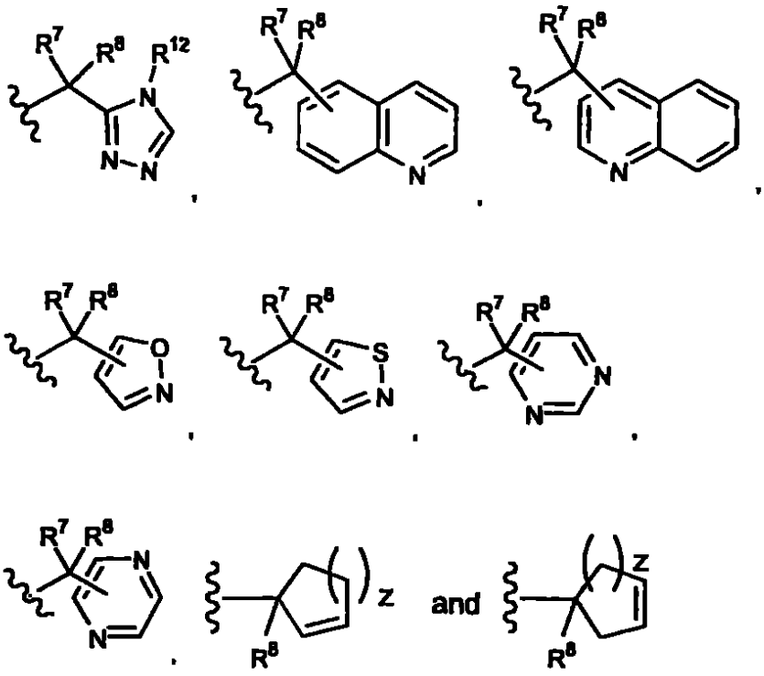






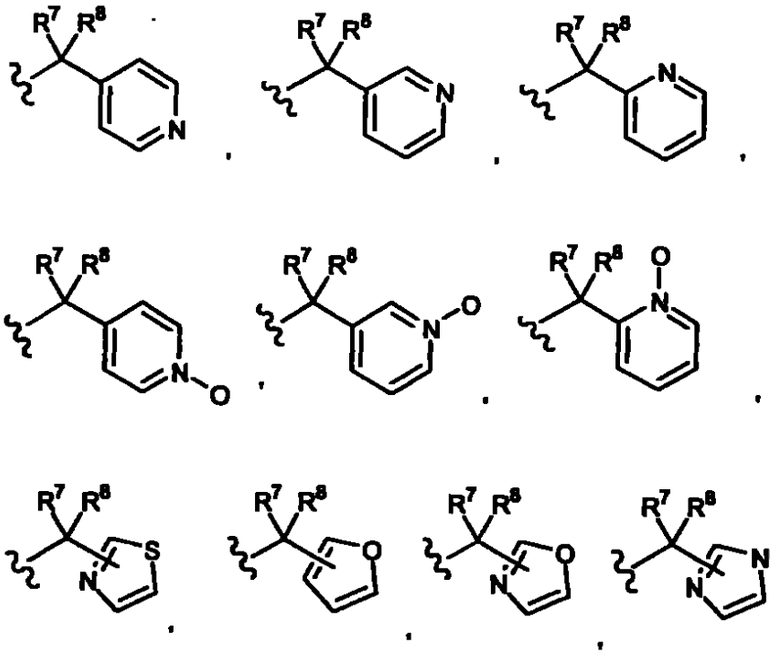


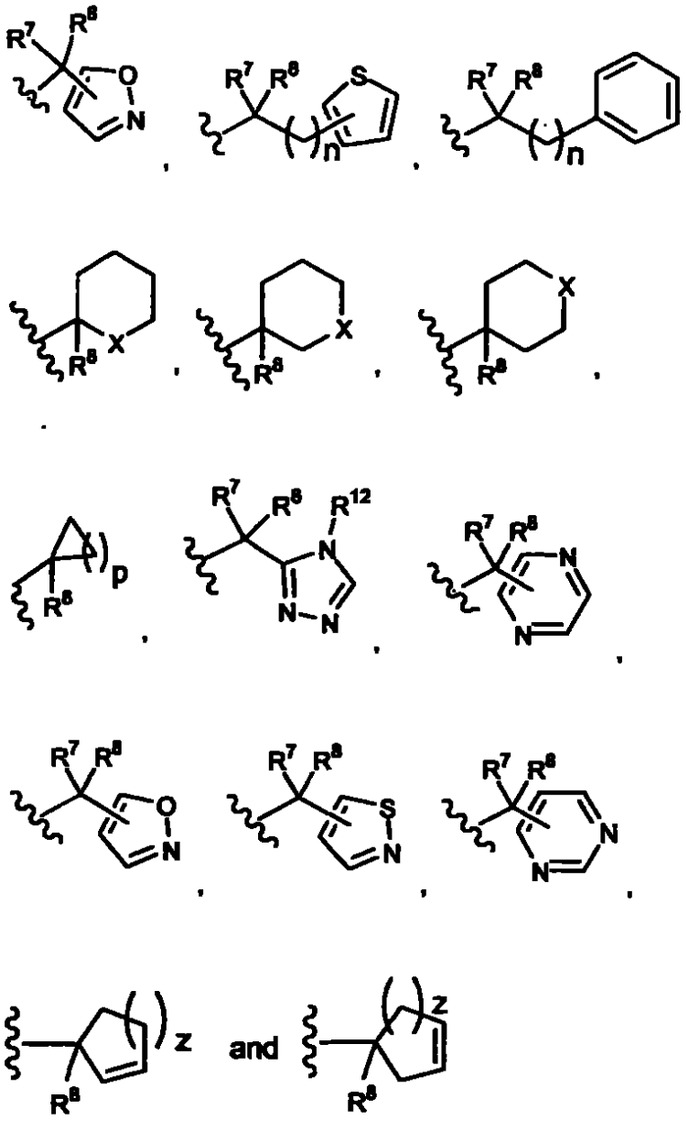




and

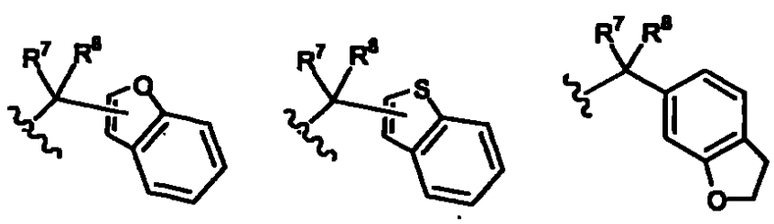
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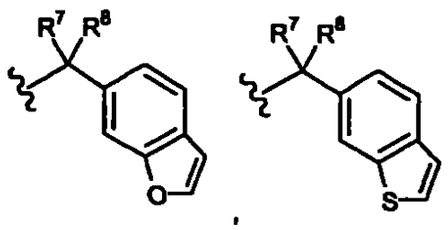


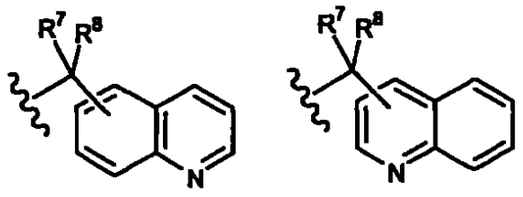


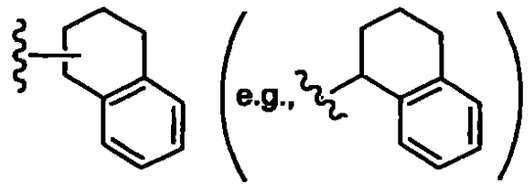
wherein the above rings of said A groups are substituted with 1 to 6 substituents each independently selected from the group consisting of: R^9 groups;

(3)

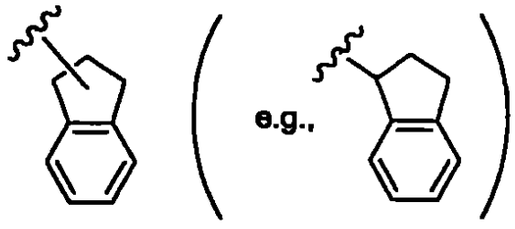






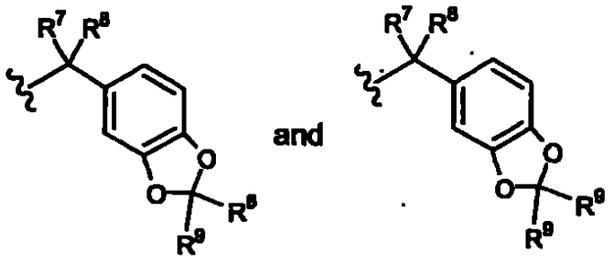


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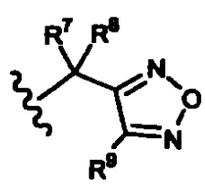
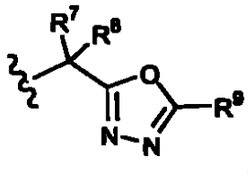
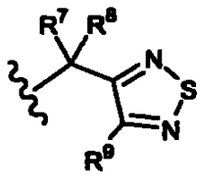
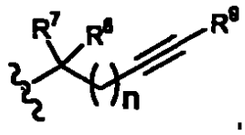
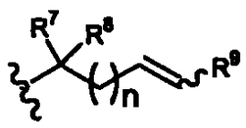
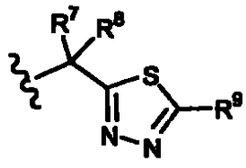
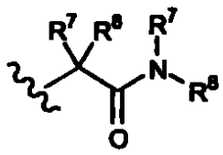
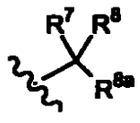
wherein one or both of the above rings of said A groups are substituted with 1 to 6 substituents each independently selected from the group consisting of: R^9 groups;

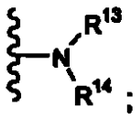
(4)



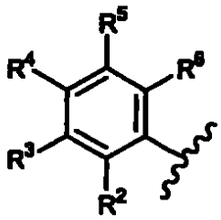
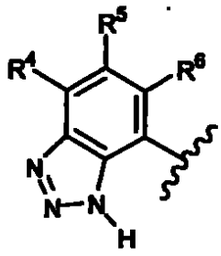
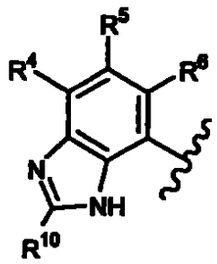
wherein the above phenyl rings of said A groups are substituted with 1 to 3 substituents each independently selected from the group consisting of: R^9 groups; and

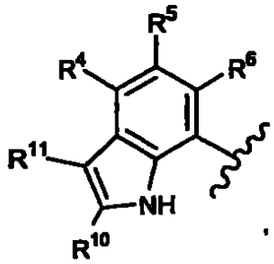
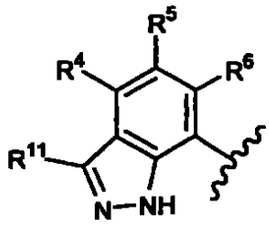
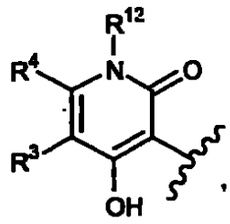
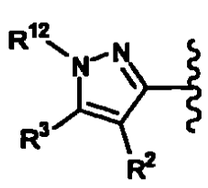
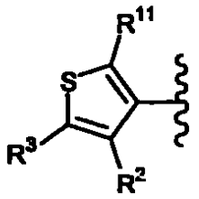
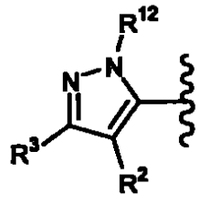
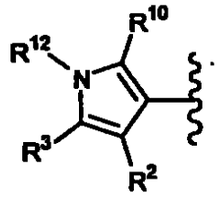
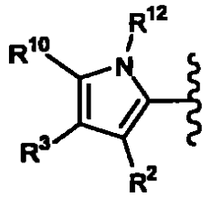
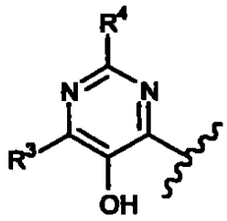
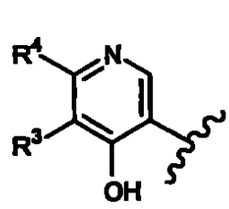
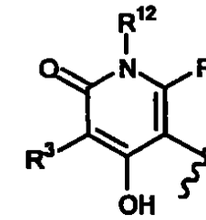
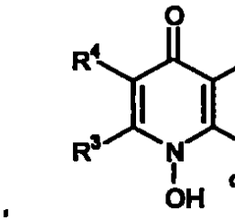
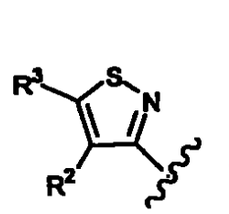
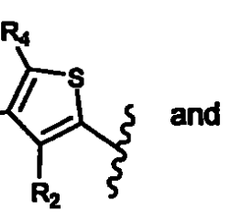
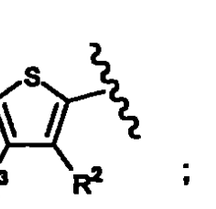
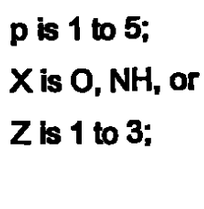
(5)









and


;

B is selected from the group consisting of

and

;

n is 0 to 6;

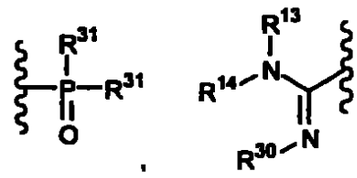
p is 1 to 5;

X is O, NH, or S;

Z is 1 to 3;

R^2 is selected from the group consisting of: hydrogen, OH, -C(O)OH, -SH, $-SO_2NR^{13}R^{14}$, $-NHC(O)R^{13}$, $-NHSO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, $-NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, $-C(O)NHOR^{13}$, $-C(O)NR^{13}OH$, - $S(O_2)OH$, $-OC(O)R^{13}$, an unsubstituted heterocyclic acidic functional group, and a substituted heterocyclic acidic functional group; wherein there are 1 to 6 substituents on said substituted heterocyclic acidic functional group each substituent being independently selected from the group consisting of: R^9 groups;

each R^3 and R^4 is independently selected from the group consisting of: hydrogen, cyano, halogen, alkyl, alkoxy, -OH, $-CF_3$, $-OCF_3$, $-NO_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NHR^{17}$, $-C(O)NR^{13}R^{14}$, $-SO_{(t)}NR^{13}R^{14}$, $-SO_{(t)}R^{13}$, $-C(O)NR^{13}OR^{14}$, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl,



wherein there are 1 to 6 substituents on said substituted aryl group and each substituent is independently selected from the group consisting of: R^9 groups; and wherein there are 1 to 6 substituents on said substituted heteroaryl group and each substituent is independently selected from the group consisting of: R^9 groups;

each R^5 and R^6 are the same or different and are independently selected from the group consisting of hydrogen, halogen, alkyl, alkoxy, $-CF_3$, $-OCF_3$, $-NO_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-SO_{(t)}NR^{13}R^{14}$, $-C(O)NR^{13}OR^{14}$, cyano, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl group; wherein there are 1 to 6 substituents on said substituted aryl group and each substituent is independently selected from the group consisting of: R^9 groups; and wherein there are 1 to 6 substituents on said substituted heteroaryl group and each substituent is independently selected from the group consisting of: R^9 groups;

each R^7 and R^8 is independently selected from the group consisting of: H, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or

substituted cycloalkylalkyl, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, alkynyl, alkenyl, and cycloalkenyl; and wherein there are one or more (e.g., 1 to 6) substituents on said substituted R^7 and R^8 groups, wherein each substitutent is independently selected from the group consisting of:

a) halogen,
b) $-CF_3$,
c) $-COR^{13}$,
d) $-OR^{13}$,
e) $-NR^{13}R^{14}$,
f) $-NO_2$,
g) $-CN$,
h) $-SO_2OR^{13}$,
i) $-Si(alkyl)_3$, wherein each alkyl is independently selected,
j) $-Si(aryl)_3$, wherein each alkyl is independently selected,
k) $-(R^{13})_2R^{14}Si$, wherein each R^{13} is independently selected,
l) $-CO_2R^{13}$,
m) $-C(O)NR^{13}R^{14}$,
n) $-SO_2NR^{13}R^{14}$,
o) $-SO_2R^{13}$,
p) $-OC(O)R^{13}$,
q) $-OC(O)NR^{13}R^{14}$,
r) $-NR^{13}C(O)R^{14}$, and
s) $-NR^{13}CO_2R^{14}$;

(fluoroalkyl is one non-limiting example of an alkyl group that is substituted with halogen);

R^{8a} is selected from the group consisting of: hydrogen, alkyl, cycloalkyl and cycloalkylalkyl;

each R^9 is independently selected from the group consisting of:

a) $-R^{13}$,
b) halogen,
c) $-CF_3$,
d) $-COR^{13}$,
e) $-OR^{13}$,

f) $-NR^{13}R^{14}$,

g) $-NO_2$,

h) –CN,

i) $-SO_2R^{13}$,

j) $-SO_2NR^{13}R^{14}$,

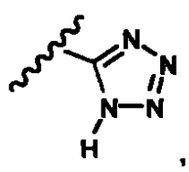
k) $-NR^{13}COR^{14}$,

l) $-CONR^{13}R^{14}$,

m) $-NR^{13}CO_2R^{14}$,

n) $-CO_2R^{13}$,

o)



p) alkyl substituted with one or more (e.g., one) –OH groups (e.g., $-(CH_2)_qOH$, wherein q is 1-6, usually 1 to 2, and preferably 1),

q) alkyl substituted with one or more (e.g., one) $-NR^{13}R^{14}$ group (e.g., $-(CH_2)_qNR^{13}R^{14}$, wherein q is 1-6, usually 1 to 2, and preferably 1), and

r) $-N(R^{13})SO_2R^{14}$ (e.g., R^{13} is H and R^{14} is alkyl, such as methyl);

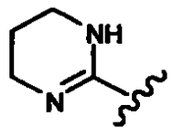
each R^{10} and R^{11} is independently selected from the group consisting of R^{13}, hydrogen, alkyl (e.g., C_1 to C_6, such as methyl), halogen, $-CF_3$, $-OCF_3$, $-NR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, -OH, $-C(O)OR^{13}$, -SH, $-SO_{(t)}NR^{13}R^{14}$, $-SO_2R^{13}$, $-NHC(O)R^{13}$, $-NHSO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, $-C(O)NR^{13}R^{14}$, $-C(O)NR^{13}OR^{14}$, $-OC(O)R^{13}$ and cyano;

R^{12} is selected from the group consisting of: hydrogen, $-C(O)OR^{13}$, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkylalkyl, and unsubstituted or substituted heteroarylalkyl group; wherein there are 1 to 6 substituents on the substituted R^{12} groups and each substituent is independently selected from the group consisting of: R^9 groups;

each R^{13} and R^{14} is independently selected from the group consisting of: H, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl unsubstituted or

substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkylalkyl, unsubstituted or substituted heterocyclic, unsubstituted or substituted fluoroalkyl, and unsubstituted or substituted heterocycloalkylalkyl (wherein "heterocycloalkyl" means heterocyclic); wherein there are 1 to 6 substituents on said substituted R^{13} and R^{14} groups and each substituent is independently selected from the group consisting of: alkyl, $-CF_3$, -OH, alkoxy, aryl, arylalkyl, fluroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, $-N(R^{40})_2$, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-S(O)_tNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ provided that R^{15} is not H, halogen, and $-NHC(O)NR^{15}R^{16}$; or

R^{13} and R^{14} taken together with the nitrogen they are attached to in the groups $-C(O)NR^{13}R^{14}$ and $-SO_2NR^{13}R^{14}$ form an unsubstituted or substituted saturated heterocyclic ring (preferably a 3 to 7 membered heterocyclic ring), said ring optionally containing one additional heteroatom selected from the group consisting of: O, S and NR^{18}; wherein there are 1 to 3 substituents on the substituted cyclized R^{13} and R^{14} groups (i.e., there is 1 to 3 substituents on the ring formed when the R^{13} and R^{14} groups are taken together with the nitrogen to which they are bound) and each substituent is independently selected from the group consisting of: alkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-SO_tNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ provided that R^{15} is not H, $-NHC(O)NR^{15}R^{16}$, $-NHC(O)OR^{15}$, halogen, and a heterocycloalkenyl group (i.e., a heterocyclic group that has at least one, and preferably one, double bond in a ring, e.g.,



;

each R^{15} and R^{16} is independently selected from the group consisting of: H, alkyl, aryl, arylalkyl, cycloalkyl and heteroaryl;

R^{17} is selected from the group consisting of: $-SO_2$alkyl, $-SO_2$aryl, $-SO_2$cycloalkyl, and $-SO_2$heteroaryl;

R^{18} is selected from the group consisting of: H, alkyl, aryl, heteroaryl, $-C(O)R^{19}$, $-SO_2R^{19}$ and $-C(O)NR^{19}R^{20}$;

each R^{19} and R^{20} is independently selected from the group consisting f: alkyl, aryl and heteroaryl;

R^{30} is selected from the group consisting of: alkyl, cycloalkyl, -CN, $-NO_2$, or $-SO_2R^{15}$ provided that R^{15} is not H;

each R^{31} is independently selected from the group consisting of: unsubstituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl and unsubstituted or substituted cycloalkyl; wherein there are 1 to 6 substituents on said substituted R^{31} groups and each substituent is independently selected from the group consisting of: alkyl, halogen and $-CF_3$;

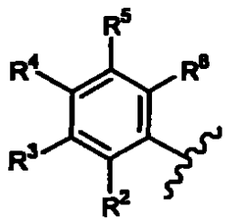
each R^{40} is independently selected from the group consisting of: H, alkyl and cycloalkyl; and

t is 0, 1 or 2.

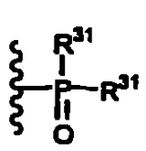
Embodiments of the methods of treatment that use compounds of formula IA, as described above, are described below. The embodiments have been numbered for purposes of reference thereto.

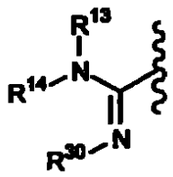
Embodiment No. 1 is directed to the the methods of treatment that use compounds of formula IA wherein B is selected from the group consisting of:

(1)

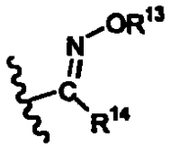


provided that R^3 for this group is selected from the group consisting of: $-C(O)NR^{13}R^{14}$,



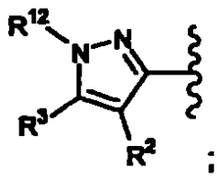


and



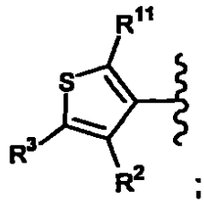
;

(2)



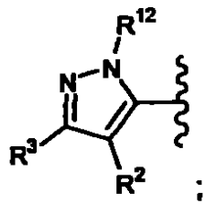
;

(3)



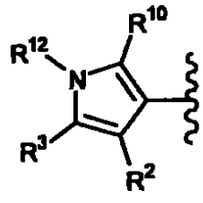
;

(4)



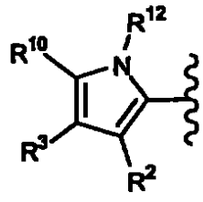
;

(5)



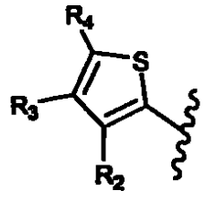
;

(6)



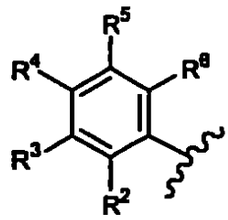
; and

(7)

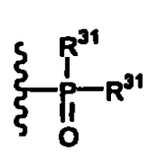
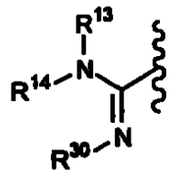
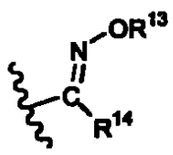


wherein all substituents are as defined for the novel compounds of formula IA.

Embodiment No. 2 is directed to the the methods of treatment that use compounds of formula IA wherein B is:

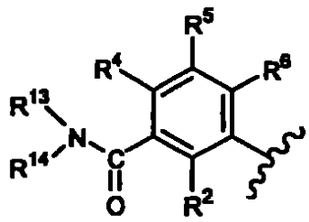


wherein R^3 is selected from the group consisting of: $-C(O)NR^{13}R^{14}$,



and


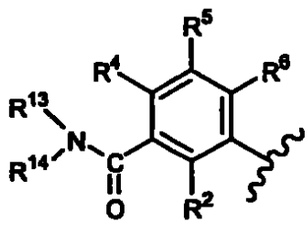
and all other substituents are as defined in formula IA.

Embodiment No. 3 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



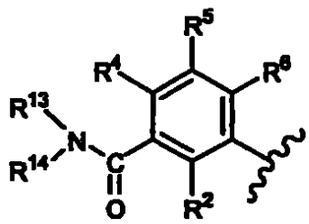
and all other substituents are as defined in formula IA.

Embodiment No. 4 is directed to the the methods of treatment that use compounds of formula IA wherein B is



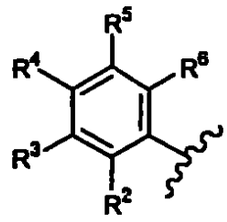
R^{13} and R^{14} are each the same or different alkyl group, and all other substituents are as defined in formula IA.

Embodiment No. 5 is directed to the the methods of treatment that use compounds of formula IA wherein B is

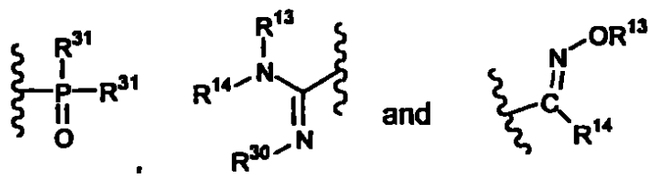


and (1) R^2 is –OH, and all other substituents are as defined in formula IA, or (2) R^2 is –OH, and R^{13} and R^{14} are each the same or different alkyl group, and all other substituents are as defined in formula IA.

Embodiment No. 6 is directed to the the methods of treatment that use compounds of formula IA wherein B is

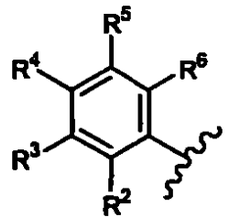


R^3 is selected from the group consisting of:

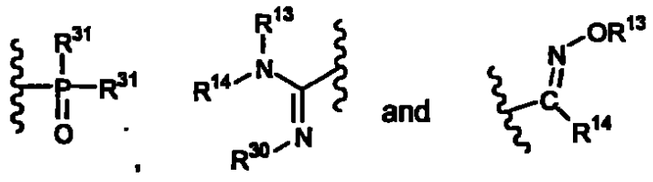


and all other substituents are as defined in formula IA.

Embodiment No. 7 is directed to the the methods of treatment that use compounds of formula IA wherein B is

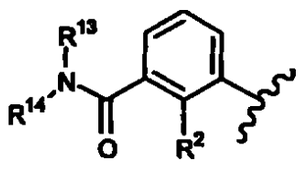


R^3 is selected from the group consisting of:



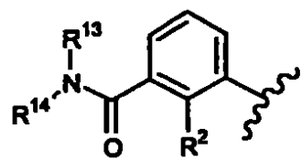
R^2 is –OH, and all other substituents are as defined in formula IA.

Embodiment No. 8 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



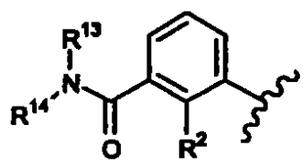
R^2, R^{13}, and R^{14} are as defined for compounds of formula IA, and all other substituents are as defined in formula IA.

Embodiment No. 9 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



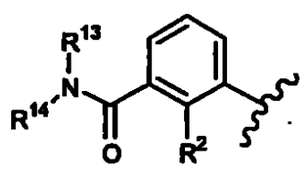
R^2 is –OH, R^{13} and R^{14} are as defined for compounds of formula and all other substituents are as defined in formula IA.

Embodiment No. 10 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



R^2 is as defined for compounds of formula IA, R^{13} and R^{14} are the same or different alkyl group, and all other substituents areas defined for compounds of formula IA.

Embodiment No. 11 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



R^2 is –OH, R^{13} and R^{14} are the same or different alkyl group, and all other substituents areas defined for compounds of formula IA.

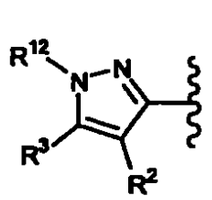
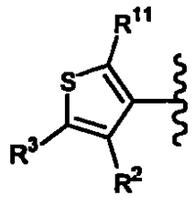
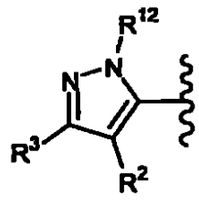
Embodiment No. 12 is directed to the the methods of treatment that use compounds of formula IA wherein B is as described in Embodiment No. 6, R^4 is H, R^5 is H, R^6 is H, and all other substituents areas defined for compounds of formula IA.

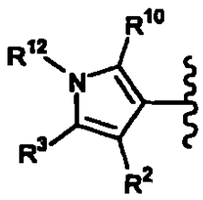
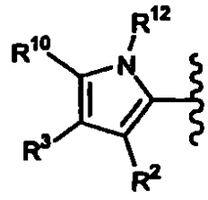
Embodiment No. 13 is directed to the the methods of treatment that use compounds of formula IA wherein B is as described in Embodiment No. 7, R^4 is H, R^5 is H, R^6 is H, and all other substituents areas defined for compounds of formula IA.

Embodiment No. 14 is directed to the the methods of treatment that use compounds of formula IA wherein B is as described in Embodiments Nos. 4, 5, 8 and

9, except that R^{13} and R^{14} are each methyl, and all other substituents are as defined in formula IA.

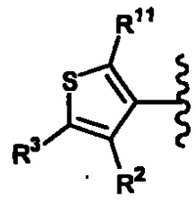
Embodiment No. 15 is directed to the the methods of treatment that use compounds of formula IA wherein B is selected from the group consisting of:


and


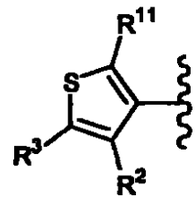
wherein all substituents are as defined for formula IA.

Embodiment No. 16 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



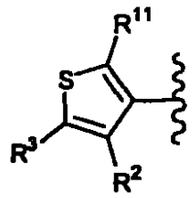
wherein all substituents are as defined for formula IA.

Embodiment No. 17 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



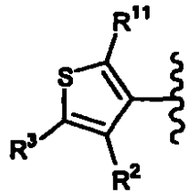
R^{11} is H, and all other substituents are as defined in formula IA.

Embodiment No. 18 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



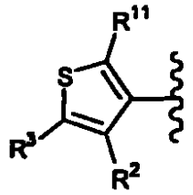
R^2 is –OH, and all other substituents are as defined in formula IA.

Embodiment No. 19 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



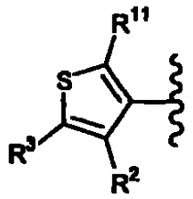
R^3 is $-C(O)NR^{13}R^{14}$, and all other substituents are as defined in formula IA.

Embodiment No. 20 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



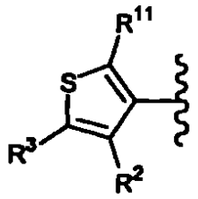
R^3 is $-S(O)_tNR^{13}R^{14}$ (e.g., t is 2), and all other substituents are as defined in formula IA.

Embodiment No. 21 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



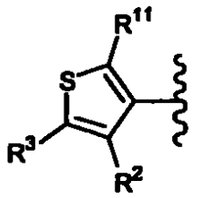
R^2 is –OH, R^3 is $-C(O)NR^{13}R^{14}$, and all other substituents are as defined in formula IA.

Embodiment No. 22 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



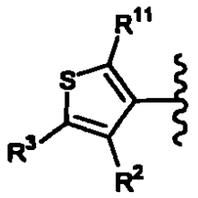
R^2 is –OH, and R^3 is $-S(O)_tNR^{13}R^{14}$ (e.g., t is 2), and all other substituents are as defined in formula IA.

Embodiment No. 23 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



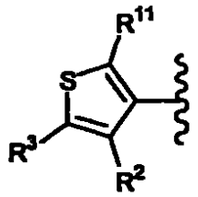
R^2 is –OH, R^3 is $-C(O)NR^{13}R^{14}$, R^{11} is H, and all other substituents are as defined in formula IA.

Embodiment No. 24 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



R^3 is $-S(O)_tNR^{13}R^{14}$ (e.g., t is 2), each R^{13} and R^{14} are the same or different and are selected from the group consisting of: H and alkyl (e.g., methyl, ethyl, isopropyl and t-butyl). In this embodiment, each R^{13} and R^{14} are generally selected from the group consisting of: H and ethyl, and preferably R^{13} and R^{14} are ethyl.and all other substituents are as defined in formula IA.

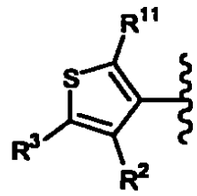
Embodiment No. 25 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



R^3 is $-S(O)_tNR^{13}R^{14}$ (e.g., t is 2), R^{11} is H, and each R^{13} and R^{14} are the same or different and are selected from the group consisting of: H and alkyl (e.g., methyl, ethyl,

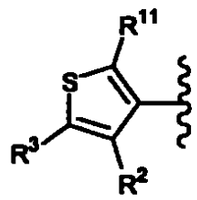
isopropyl and t-butyl). In this embodiment, each R^{13} and R^{14} are generally selected from the group consisting of: H and ethyl, and preferably R^{13} and R^{14} are ethyl.and all other substituents are as defined in formula IA.

Embodiment No. 26 is directed to the the methods of treatment that use compounds of formula IA wherein B is:

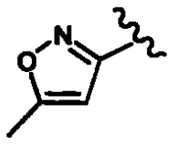


R^2 is –OH, R^3 is $-S(O)_tNR^{13}R^{14}$ (e.g., t is 2), R^{11} is H, and all other substituents are as defined in formula IA.

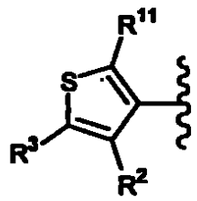
Embodiment No. 27 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



R^2 is –OH, R^3 is $-C(O)NR^{13}R^{14}$, R^{11} is H, and R^{13} and R^{14} are independently selected from the group consisting of: alkyl, unsubstituted heteroaryl and substituted heteroaryl, and all other substituents are as defined in formula IA. In general, one of R^{13} or R^{14} is alkyl (e.g., methyl). An example of a substituted heteroaryl group is



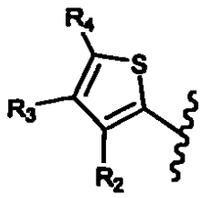
Embodiment No. 28 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



R^2 is –OH, R^3 is $-S(O)_tNR^{13}R^{14}$ (e.g., t is 2), R^{11} is H, and each R^{13} and R^{14} are the same or different and are selected from the group consisting of: H and alkyl (e.g., methyl, ethyl, isopropyl and t-butyl), and all other substituents are as defined in

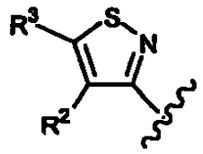
formula IA. In this embodiment, each R^{13} and R^{14} are generally selected from the group consisting of: H and ethyl, and preferably R^{13} and R^{14} are ethyl.

Embodiment No. 29 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



and all substituents are as defined in formula IA.

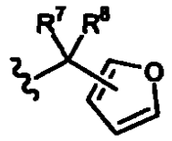
Embodiment No. 30 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



and all substituents are as defined in formula IA.

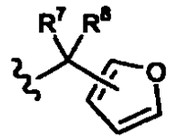
Embodiment No. 31 is directed to the the methods of treatment that use compounds of formula IA wherein B is as described in any one of the Embodiment Nos. 1 to 30, and A is as described in any one of the Embodiment Nos. 39-44 described below.

Embodiment No. 32 is directed to the the methods of treatment that use compounds of formula IA wherein B is as described in any one of the Embodiment Nos. 1 to 30, and A is:



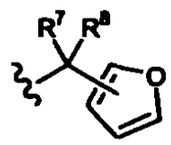
wherein the furan ring is unsubstituted or substituted as described in the definition of A for formula IA, and all other substituents are as defined for formula IA.

Embodiment No. 33 is directed to the the methods of treatment that use compounds of formula IA wherein B is described in any one of the Embodiment Nos. 1 to 30, and A is



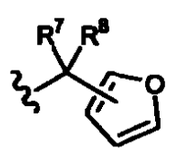
wherein the furan ring is substituted and all other substituents are as defined for formula IA.

Embodiment No. 34 is directed to the the methods of treatment that use compounds of formula IA wherein B is as described in any one of the Embodiment Nos. 1 to 30,and A is



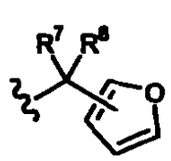
wherein the furan ring is substituted with at least one (e.g., 1 to 3, or 1 to 2) alkyl group and all other substituents are as defined for formula IA.

Embodiment No. 35 is directed to the the methods of treatment that use compounds of formula IA wherein B is as described in any one of the Embodiment Nos. 1 to 30, A is



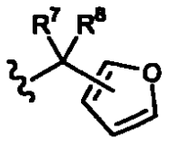
wherein the furan ring is substituted with one alkyl group and all other substituents are as defined for formula IA.

Embodiment No. 36 is directed to the the methods of treatment that use compounds of formula IA wherein B is as described in any one of the Embodiment Nos. 1 to 30, and A is



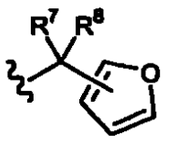
wherein the furan ring is substituted with one C_1 to C_3 alkyl group (e.g., methyl or isopropyl), and all other substituents are as defined for formula IA.

Embodiment No. 37 is directed to the the methods of treatment that use compounds of formula IA wherein B is as described in any one of the Embodiment Nos. 1 to 30, and A is



as defined in any one of the Embodiment Nos. 32 to 36, except that R^7 and R^8 are the same or different and each is selected from the group consisting of: H and alkyl.

Embodiment No. 38 is directed to the the methods of treatment that use compounds of formula IA wherein B is as described in any one of the Embodiment Nos. 1 to 30, and A is

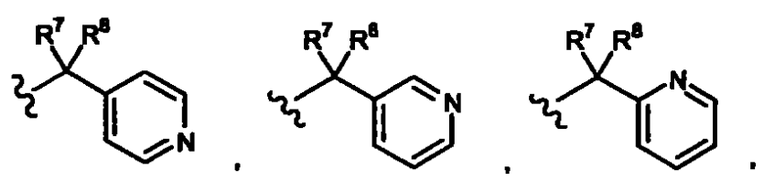


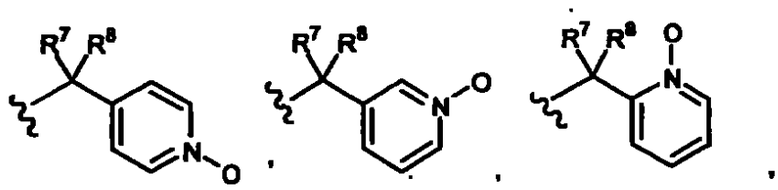
as defined in any one of the Embodiment Nos. 32 to 36, except that R^7 is H, and R^8 is alkyl (e.g., ethyl or t-butyl).

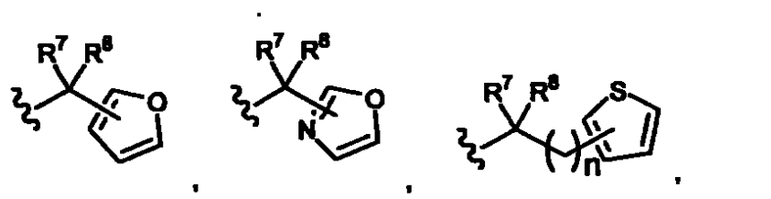
Embodiment No. 39 is directed to the the methods of treatment that use compounds of formula IA wherein:

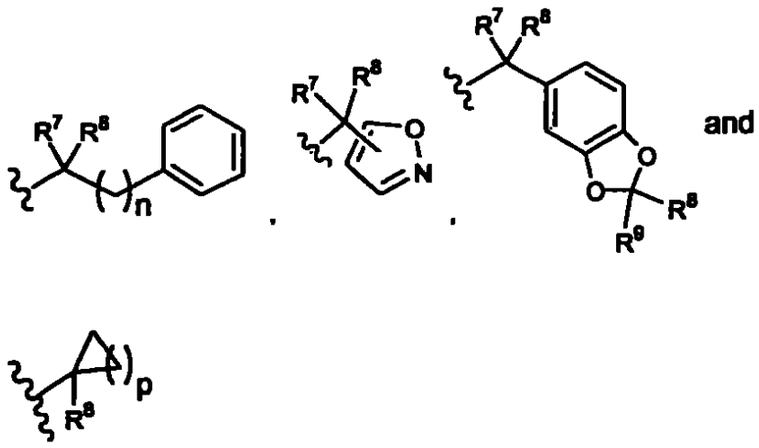
(1) substituent A in formula IA is preferably selected from the group consisting of:

(a)



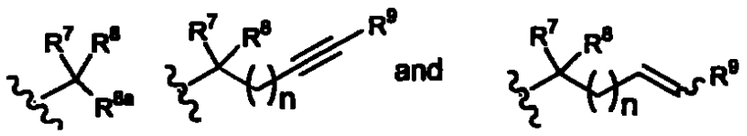






wherein the above rings are unsubstituted or substituted, as described for formula IA: and

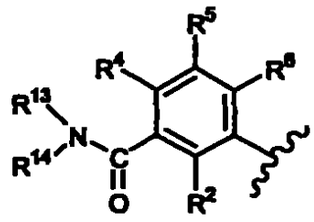
(b)

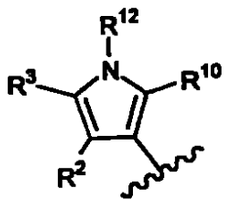
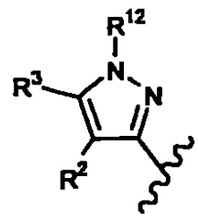
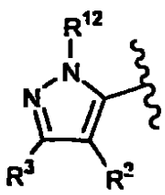


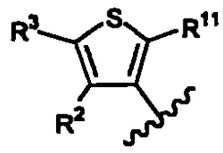
, and

wherein in (a) and (b) above: each R^7 and R^8 is independently selected from the group consisting of: H, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkylalkyl, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, fluoroalkyl, alkynyl, alkenyl, and cycloalkenyl, wherein said substituents on said R^7 and R^8 substituted groups are selected from the group consisting of: a) cyano, b) $-CO_2R^{13}$, c) $-C(O)NR^{13}R^{14}$, d) $-SO_2NR^{13}R^{14}$, e) $-NO_2$, f) $-CF_3$, g) $-OR^{13}$, h) $-NR^{13}R^{14}$, i) $-OC(O)R^{13}$, j) $-OC(O)NR^{13}R^{14}$, and k) halogen; and R^{8a} and R^9 are as defined in formula IA; and

(2) substituent B in formula IA is preferably selected from the group consisting of:



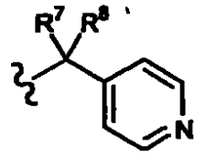
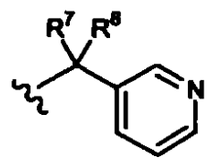
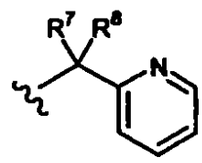
and 

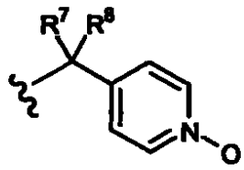
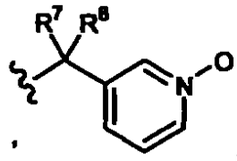
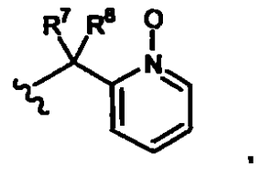
wherein R^2 to R^6 and R^{10} to R^{14} are as defined above for the novel compounds of formula IA .

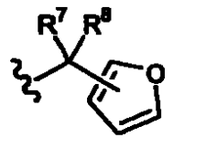
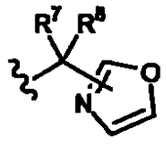
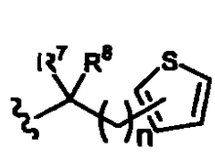
Embodiment No. 40 is directed to the the methods of treatment that use compounds of formula IA wherein:

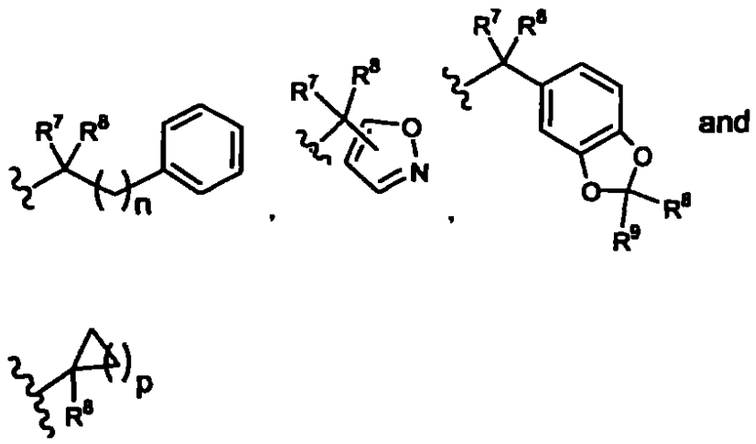
(1) substituent A in formula IA is more preferably selected from the group consisting of:

(a)

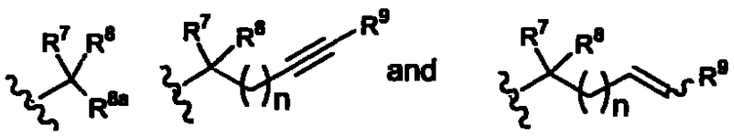






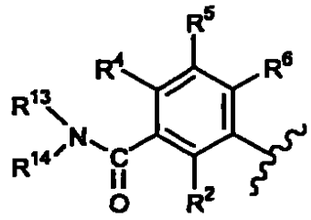
wherein the above rings are unsubstituted, or the above rings are substituted with 1 to 3 substituents independently selected from the group consisting of: halogen, alkyl, cycloalkyl, $-CF_3$, cyano, $-OCH_3$, and $-NO_2$; each R^7 and R^8 is independently selected from the group consisting of: H, alkyl (e.g., methyl, ethyl, t-butyl, and isopropyl), fluoroalkyl (such as, $-CF_3$ and $-CF_2CH_3$), cycloalkyl (e.g.,cyclopropyl, and cyclohexyl), and cycloalkylalkyl (e.g., cyclopropylmethyl); and R^9 is selected from the group consisting of: H, halogen, alkyl, cycloalkyl, $-CF_3$, cyano, $-OCH_3$, and $-NO_2$; and

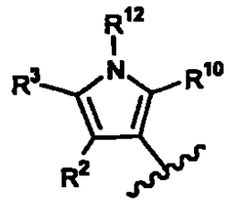
(b)

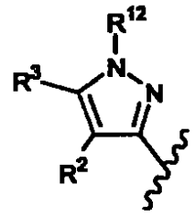


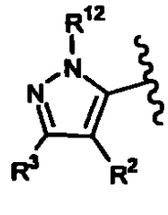
wherein each R^7 and R^8 is independently selected from the group consisting of: H, alkyl (e.g., methyl, ethyl, t-butyl, and isopropyl), fluoroalkyl (such as, $-CF_3$ and $-CF_2CH_3$), cycloalkyl (e.g.,cyclopropyl, and cyclohexyl), and cycloalkylalkyl (e.g., cyclopropylmethyl); wherein R^{8a} is as defined in formula IA, and wherein R^9 is selected from the group consisting of: H, halogen, alkyl, cycloalkyl, $-CF_3$, cyano, $-OCH_3$, and $-NO_2$; each R^7 and R^8 is independently selected from the group consisting of: H, alkyl (e.g., methyl, ethyl, t-butyl, and isopropyl), fluoroalkyl (such as, $-CF_3$ and $-CF_2CH_3$), cycloalkyl (e.g.,cyclopropyl, and cyclohexyl), and cycloalkylalkyl (e.g., cyclopropylmethyl); and

(2) substituent B in formula IA is more preferably selected from the group consisting of:

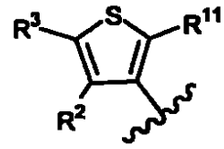








and



wherein

R^2 is selected from the group consisting of: H, OH, $-NHC(O)R^{13}$ and $-NHSO_2R^{13}$;

R^3 is selected from the group consisting of: $-SO_2NR^{13}R^{14}$, $-NO_2$, cyano, $-C(O)NR^{13}R^{14}$, $-SO_2R^{13}$; and $-C(O)OR^{13}$;

R^4 is selected from the group consisting of: H, $-NO_2$, cyano, $-CH_3$, halogen, and $-CF_3$;

R^5 is selected from the group consisting of: H, $-CF_3$, $-NO_2$, halogen and cyano;

R^6 is selected from the group consisting of: H, alkyl and $-CF_3$;

each R^{10} and R^{11} is independently selected from the group consisting of: R^{13}, hydrogen, halogen, $-CF_3$, $-NR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, $-C(O)OR^{13}$, -SH, $-SO_{(t)}NR^{13}R^{14}$, $-SO_2R^{13}$, $-NHC(O)R^{13}$, $-NHSO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, $-C(O)NR^{13}R^{14}$, $-C(O)NR^{13}OR^{14}$, $-OC(O)R^{13}$, $-COR^{13}$, $-OR^{13}$, and cyano;

each R^{13} and R^{14} is independently selected from the group consisting of: H, methyl, ethyl, isopropyl and t-butyl; or

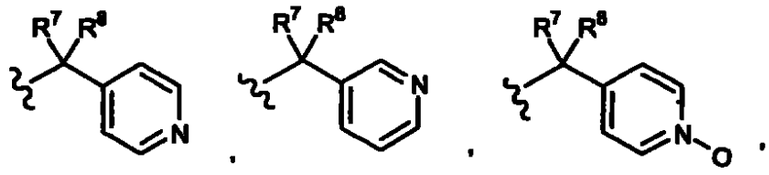
R^{13} and R^{14} when taken together with the nitrogen they are attached to in the groups $-C(O)NR^{13}R^{14}$ and $-SO_2NR^{13}R^{14}$ form an unsubstituted or substituted saturated heterocyclic ring (preferably a 3 to 7 membered ring) optionally having one additional

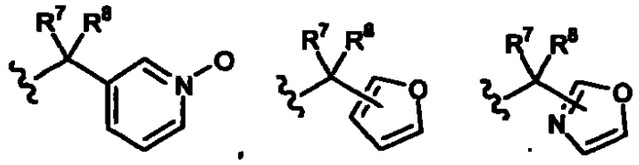
heteroatom selected from the group consisting of: O, S or NR^{18}; wherein R^{18} is selected from the group consisting of: H, alkyl, aryl, heteroaryl, $-C(O)R^{19}$, $-SO_2R^{19}$ and $-C(O)NR^{19}R^{20}$; wherein each R^{19} and R^{20} is independently selected from the group consisting of: alkyl, aryl and heteroaryl; wherein there are 1 to 3 substituents on the substituted cyclized R^{13} and R^{14} groups (i.e., the substituents on the ring formed when R^{13} and R^{14} are taken together with the nitrogen to which they are bound) and each substituent is independently selected from the group consisting of: alkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-SO_nNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ provided that R^{15} is not H, $-NHC(O)NR^{15}R^{16}$ and halogen; and wherein each R^{15} and R^{16} is independently selected from the group consisting: of H, alkyl, aryl, arylalkyl, cycloalkyl and heteroaryl.

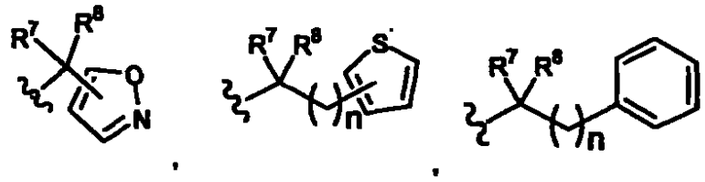
Embodiment No. 41 is directed to the the methods of treatment that use compounds of formula IA wherein:

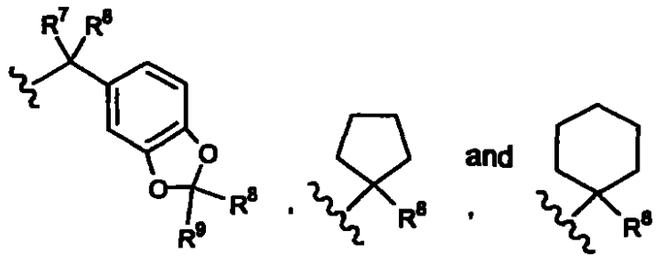
substituent A in formula IA is even more preferably selected from the group consisting of:

(a)



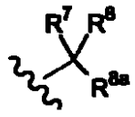






wherein the above rings are unsubstituted, or the above rings are substituted with 1 to 3 substituents independently selected from the group consisting of: H, F, Cl, Br, alkyl, cycloalkyl, and $-CF_3$; R^7 is selected from the group consisting of: H, fluoroalkyl, alkyl and cycloalkyl; R^8 is selected form the group consisting of: H, alkyl, $-CF_2CH_3$ and $-CF_3$; and R^9 is selected from the group consisting of: H, F, Cl, Br, alkyl or $-CF_3$; and

(b)

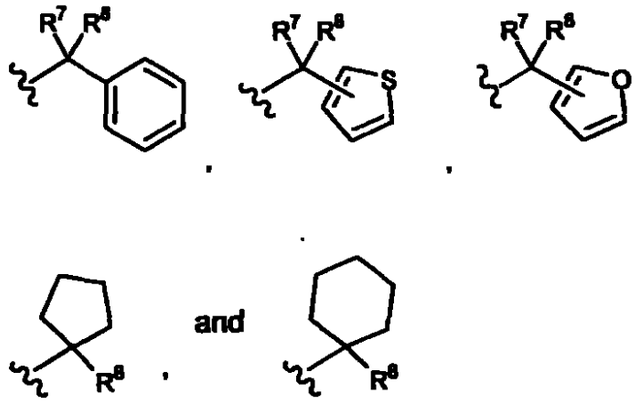


wherein R^7 is selected from the group consisting of: H, fluoroalkyl, alkyl and cycloalkyl; R^8 is selected form the group consisting of: H, alkyl, $-CF_2CH_3$ and $-CF_3$; and R^{8a} is as defined for formula IA.

Embodiment No. 42 is directed to the the methods of treatment that use compounds of formula IA wherein:

(1) substituent A in formula IA is still even more preferably selected from the group consisting of:

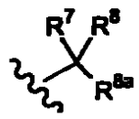
(a)



wherein the above rings are unsubstituted, or the above rings are substituted with 1 to 3 substituents independently selected from the group consisting of: H, F, Cl, Br, alkyl,

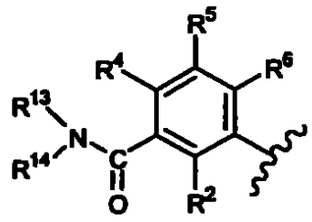
cycloalkyl, and $-CF_3$; R^7 is selected from the group consisting of: H, $-CF_3$, $-CF_2CH_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and

(b)

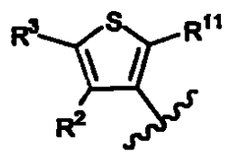


wherein R^7 is selected from the group consisting of: H, $-CF_3$, $-CF_2CH_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and R^{8a} is as defined for formula IA.

(2) substituent B in formula IA is preferably selected from the group consisting of:



and



wherein:

R^2 is selected from the group consisting of: H, OH, $-NHC(O)R^{13}$ and $-NHSO_2R^{13}$;

R^3 is selected from the group consisting of: $-C(O)NR^{13}R^{14}$, $-SO_2NR^{13}R^{14}$, $-NO_2$, cyano, $-SO_2R^{13}$; and $-C(O)OR^{13}$;

R^4 is selected from the group consisting of: H, $-NO_2$, cyano, $-CH_3$ or $-CF_3$;

R^5 is selected from the group consisting of: H, $-CF_3$, $-NO_2$, halogen and cyano; and

R^6 is selected from the group consisting of: H, alkyl and $-CF_3$;

R^{11} is selected from the group consisting of: H, halogen and alkyl; and

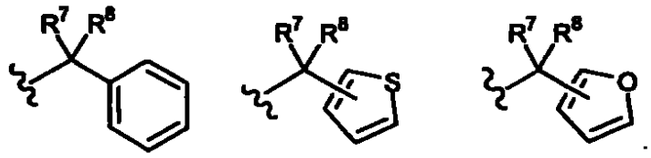
each R^{13} and R^{14} is independently selected from the group consisting of: H, methyl, ethyl, isopropyl and t-butyl; or

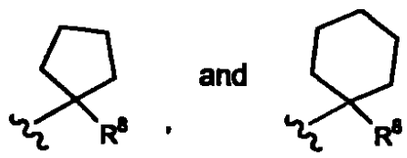
R^{13} and R^{14} when taken together with the nitrogen they are attached to in the groups $-C(O)NR^{13}R^{14}$ and $-SO_2NR^{13}R^{14}$ form an unsubstituted or substituted saturated heterocyclic ring (preferably a 3 to 7 membered ring) optionally having one additional heteroatom selected from O, S or NR^{18} wherein R^{18} is selected from H, alkyl, aryl, heteroaryl, $-C(O)R^{19}$, $-SO_2R^{19}$ and $-C(O)NR^{19}R^{20}$, wherein each R^{19} and R^{20} is independently selected from alkyl, aryl and heteroaryl, wherein there are 1 to 3 substituents on the substituted cyclized R^{13} and R^{14} groups (i.e., on the ring formed when R^{13} and R^{14} are taken together with the nitrogen to which they are bound) and each substituent is independently selected from the group consisting of: alkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-SO_2NR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ provided that R^{15} is not H, $-NHC(O)NR^{15}R^{16}$ and halogen; and wherein each R^{15} and R^{16} is independently selected from the group consisting of: H, alkyl, aryl, arylalkyl, cycloalkyl and heteroaryl.

Embodiment No. 43 is directed to the the methods of treatment that use compounds of formula IA wherein:

(1) substituent A in formula IA is yet even still more preferably selected from the group consisting of:

(a)

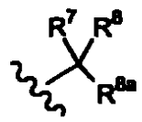




and

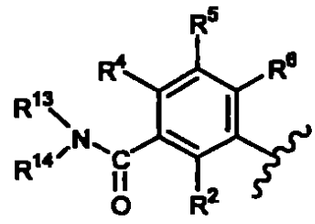
wherein the above rings are unsubstituted, or the above rings are substituted with 1 to 3 substituents independently selected from the group consisting of: F, Cl, Br, alkyl, cycloalkyl, and $-CF_3$; R^7 is selected from the group consisting of: H, $-CF_3$, $-CF_2CH_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and

(b)

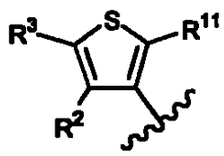


wherein R^7 is selected from the group consisting of: H, $-CF_3$, $-CF_2CH_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and R^{8a} is as defined for formula IA;

(2) substituent B in formula IA is yet even still more preferably selected from the group consisting of:



, and



.

wherein:

R^2 is selected from the group consisting of: H, OH, $-NHC(O)R^{13}$ and $-NHSO_2R^{13}$;

R^3 is selected from the group consisting of: $-C(O)NR^{13}R^{14}$ $-SO_2NR^{13}R^{14}$, $-NO_2$, cyano, and $-SO_2R^{13}$;

R^4 is selected from the group consisting of: H, $-NO_2$, cyano, $-CH_3$ or $-CF_3$;

R^5 is selected from the group consisting of: H, $-CF_3$, $-NO_2$, halogen and cyano; and

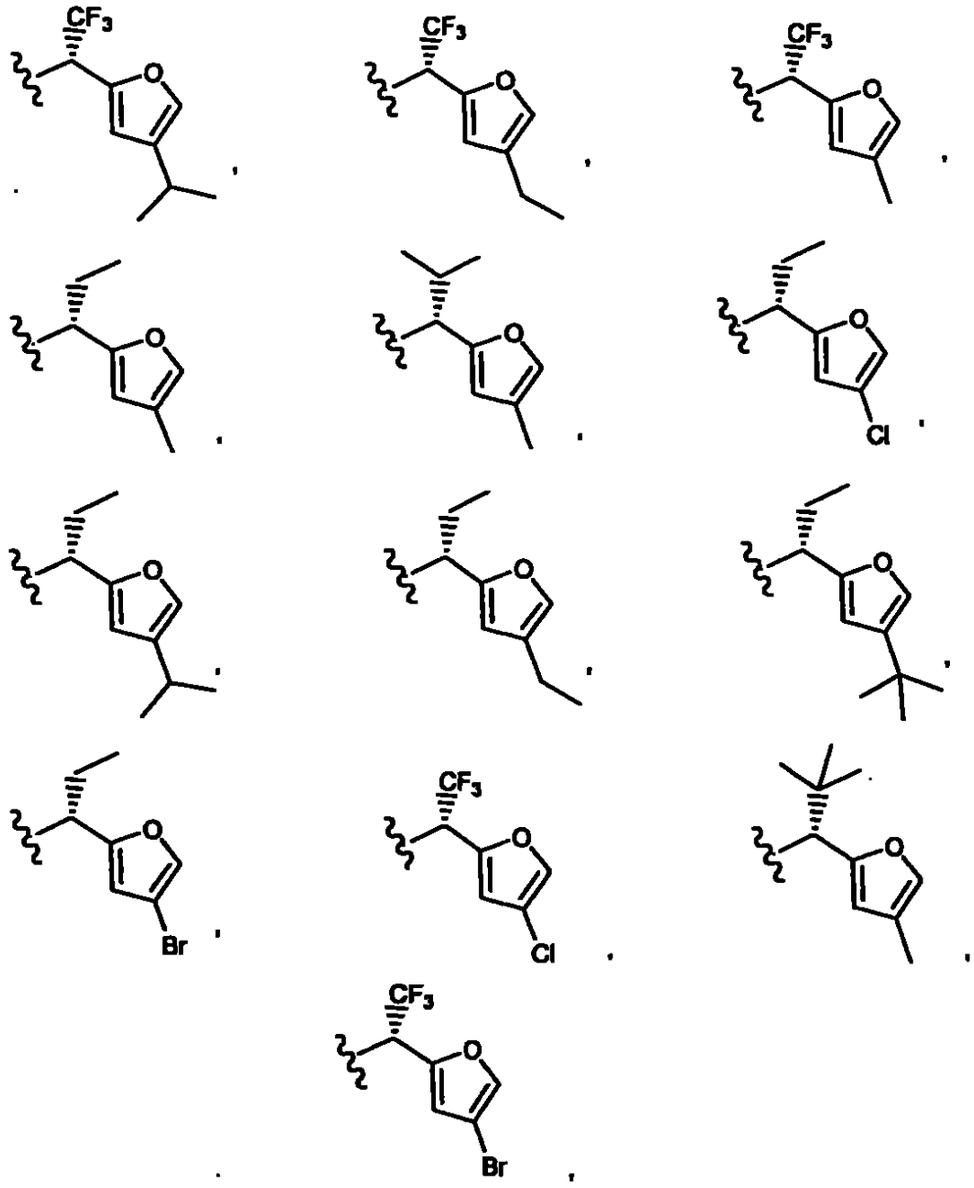
R^6 is selected from the group consisting of: H, alkyl and $-CF_3$;

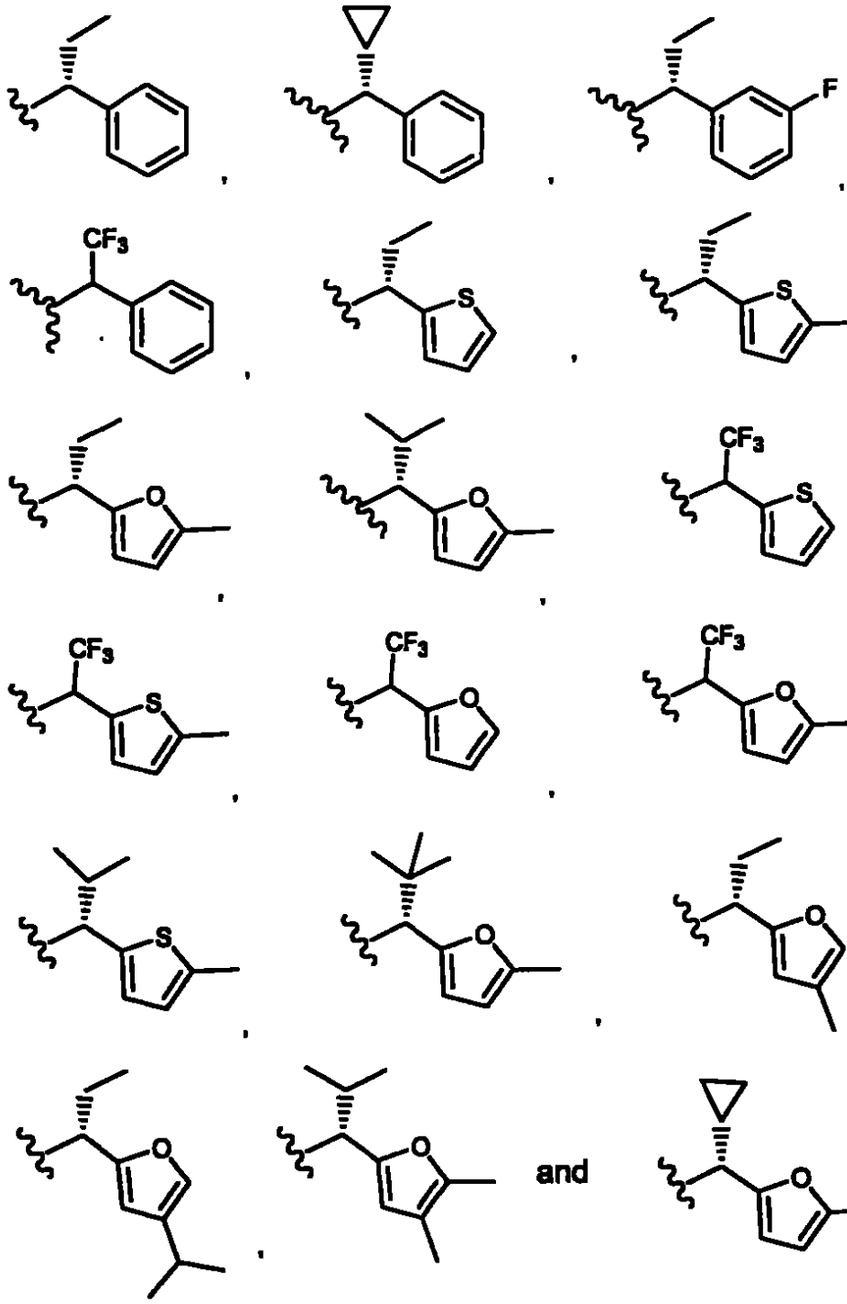
R^{11} is selected from the group consisting of: H, halogen and alkyl; and

each R^{13} and R^{14} is independently selected from the group consisting of: methyl and ethyl.

Embodiment No. 44 is directed to the the methods of treatment that use compounds of formula IA wherein:

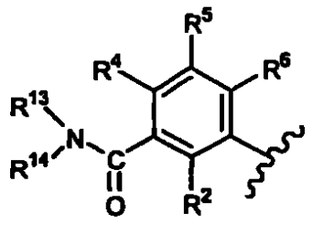
(1) substituent A in formula IA is most preferably selected from the group consisting of:



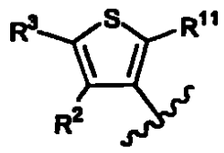


and ; and

(2) substituent B in formula IA is most preferably selected from the group consisting of:



and



wherein:

R^2 is –OH;

R^3 is selected from the group consisting of: $-SO_2NR^{13}R^{14}$ and $-CONR^{13}R^{14}$;

R^4 is selected form the group consisting of: H, $-CH_3$ and $-CF_3$;

R^5 is selected from the group consisting of: H and cyano;

R^6 is selected from the group consisting of: H, $-CH_3$ and $-CF_3$;

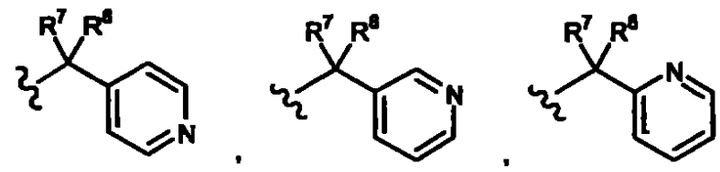
R^{11} is H; and

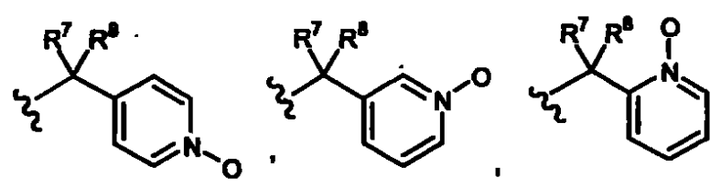
R^{13} and R^{14} are methyl.

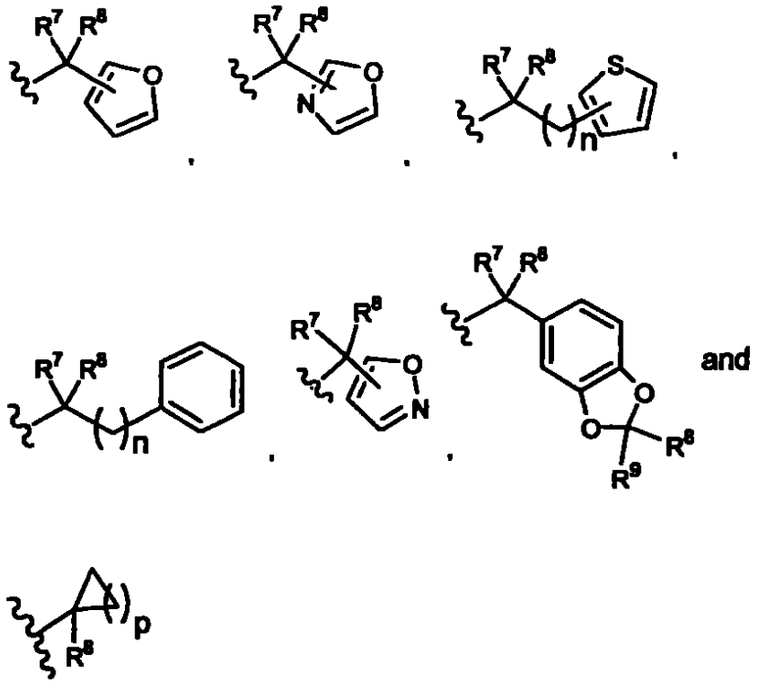
Embodiment No. 45 is directed to the the methods of treatment that use compounds of formula IA wherein:

(1) substituent A in formula IA is selected from the group consisting of:

(a)

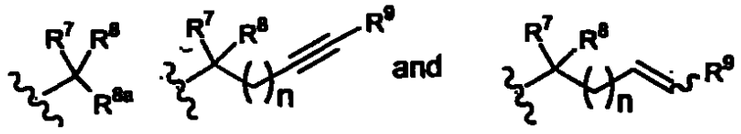






wherein the above rings are unsubstituted or substituted, as described for formula IA: and

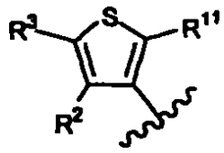
(b)



, and

wherein in (a) and (b) above: each R^7 and R^8 is independently selected from the group consisting of: H, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkylalkyl, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, fluoroalkyl, alkynyl, alkenyl, and cycloalkenyl, wherein said substituents on said R^7 and R^8 substituted groups are selected from the group consisting of: a) cyano, b) $-CO_2R^{13}$, c) $-C(O)NR^{13}R^{14}$, d) $-SO_2NR^{13}R^{14}$, e) $-NO_2$, f) $-CF_3$, g) $-OR^{13}$, h) $-NR^{13}R^{14}$, l) $-OC(O)R^{13}$, j) $-OC(O)NR^{13}R^{14}$, and k) halogen; and R^{8a} and R^9 are as defined in formula IA; and

(2) substituent B in formula IA is:

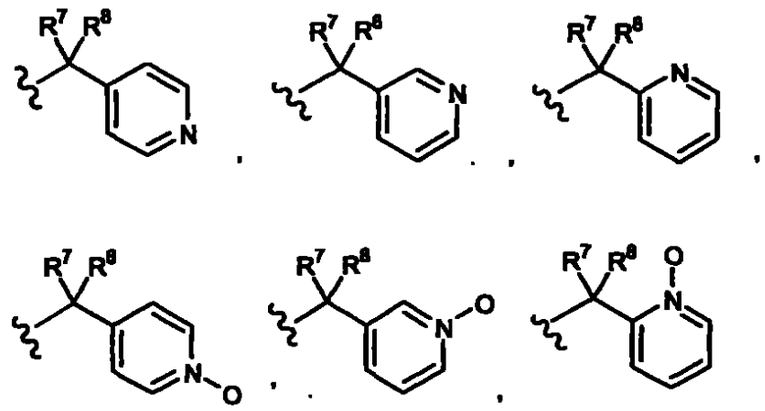


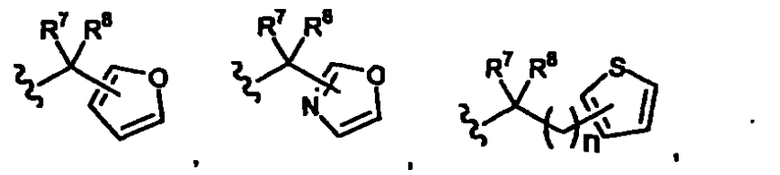
wherein R^2, R^3 and R^{11} are as defined above for the novel compounds of formula IA .

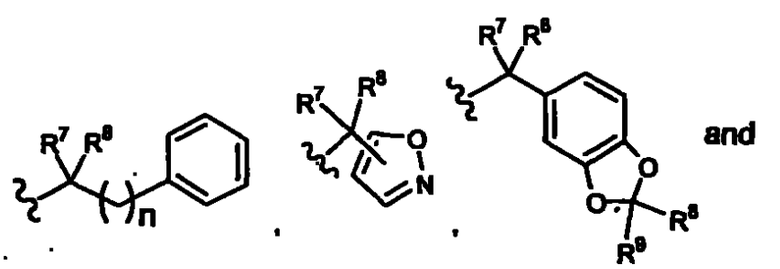
Embodiment No. 46 is directed to the the methods of treatment that use compounds of formula IA wherein:

(1) substituent A in formula IA is selected from the group consisting of:

(a)





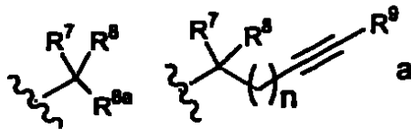


and



wherein the above rings are unsubstituted or substituted, as described for formula IA: and

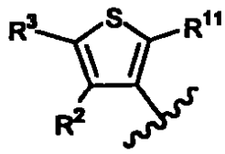
(b)



, and

wherein in (a) and (b) above: each R^7 and R^8 is independently selected from the group consisting of: H, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkylalkyl, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, fluoroalkyl, alkynyl, alkenyl, and cycloalkenyl, wherein said substituents on said R^7 and R^8 substituted groups are selected from the group consisting of: a) cyano, b) $-CO_2R^{13}$, c) $-C(O)NR^{13}R^{14}$, d) $-SO_2NR^{13}R^{14}$, e) $-NO_2$, f) $-CF_3$, g) $-OR^{13}$, h) $-NR^{13}R^{14}$, i) $-OC(O)R^{13}$, j) $-OC(O)NR^{13}R^{14}$, and k) halogen; and R^{8a} and R^9 are as defined in formula IA; and

(2) substituent B in formula IA is:



R^2 is selected from the group consisting of: H, OH, $-NHC(O)R^{13}$ and $-NHSO_2R^{13}$;

R^3 is selected from the group consisting of: $-SO_2NR^{13}R^{14}$, $-NO_2$, cyano, $-C(O)NR^{13}R^{14}$, $-SO_2R^{13}$; and $-C(O)OR^{13}$;

R^{11} is selected from the group consisting of: R^{13}, hydrogen, halogen, $-CF_3$, $-NR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, $-C(O)OR^{13}$, -SH, $-SO_{(t)}NR^{13}R^{14}$, $-SO_2R^{13}$, $-NHC(O)R^{13}$, $-NHSO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, $-C(O)NR^{13}R^{14}$, $-C(O)NR^{13}OR^{14}$, $-OC(O)R^{13}$, $-COR^{13}$, $-OR^{13}$, and cyano;

each R^{13} and R^{14} is independently selected from the group consisting of: H, methyl, ethyl, isopropyl and t-butyl; or

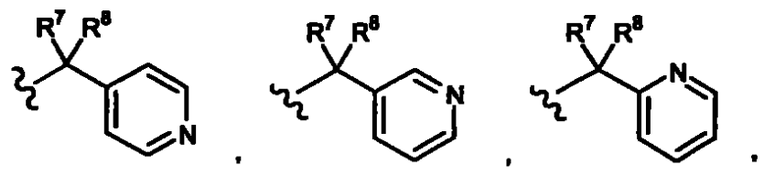
R^{13} and R^{14} when taken together with the nitrogen they are attached to in the groups $-C(O)NR^{13}R^{14}$ and $-SO_2NR^{13}R^{14}$, form an unsubstituted or substituted

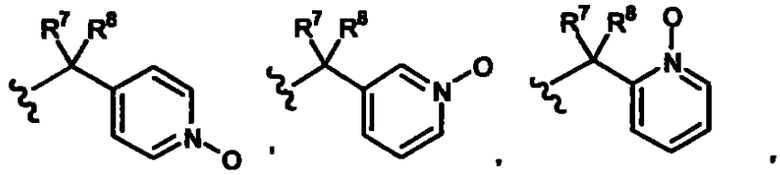
saturated heterocyclic ring (preferably a 3 to 7 membered ring) optionally having one additional heteroatom selected from the group consisting of: O, S or NR^{18}; wherein R^{18} is selected from the group consisting of: H, alkyl, aryl, heteroaryl, $-C(O)R^{19}$, $-SO_2R^{19}$ and $-C(O)NR^{19}R^{20}$; wherein each R^{19} and R^{20} is independently selected from the group consisting of: alkyl, aryl and heteroaryl; wherein there are 1 to 3 substituents on the substituted cyclized R^{13} and R^{14} groups (i.e., the substituents on the ring formed when R^{13} and R^{14} are taken together with the nitrogen to which they are bound) and each substituent is independently selected from the group consisting of: alkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-SO_2NR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ provided that R^{15} is not H, $-NHC(O)NR^{15}R^{16}$ and halogen; and wherein each R^{15} and R^{16} is independently selected from the group consisting: of H, alkyl, aryl, arylalkyl, cycloalkyl and heteroaryl.

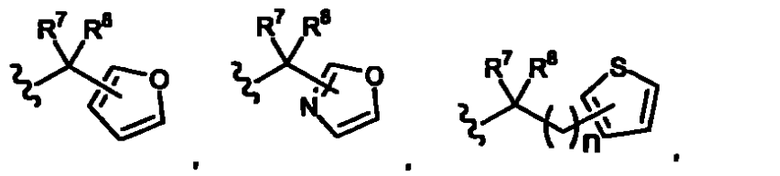
Embodiment No. 47 is directed to the the methods of treatment that use compounds of formula IA wherein:

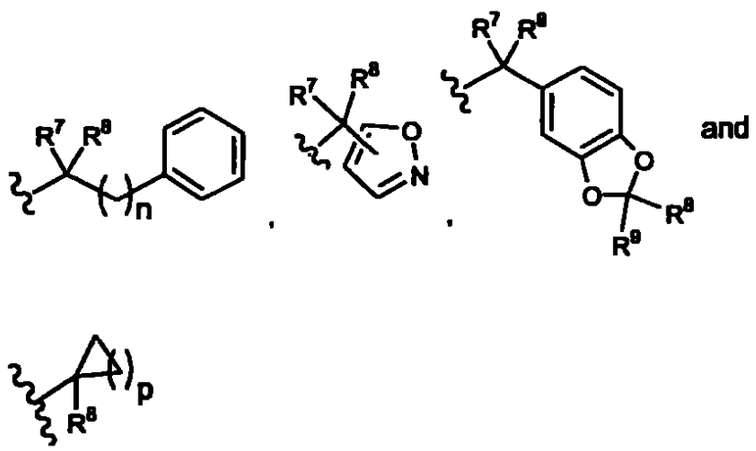
(1) substituent A in formula IA is selected from the group consisting of:

(a)



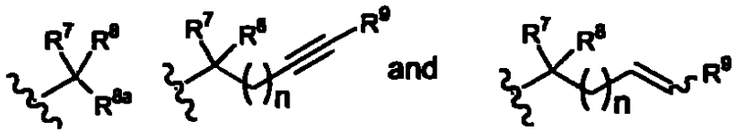






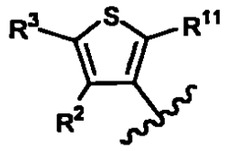
wherein the above rings are unsubstituted, or the above rings are substituted with 1 to 3 substituents independently selected from the group consisting of: halogen, alkyl, cycloalkyl, $-CF_3$, cyano, $-OCH_3$, and $-NO_2$; each R^7 and R^8 is independently selected from the group consisting of: H, alkyl (e.g., methyl, ethyl, t-butyl, and isopropyl), fluoroalkyl (such as, $-CF_3$ and $-CF_2CH_3$), cycloalkyl (e.g.,cyclopropyl, and cyclohexyl), and cycloalkylalkyl (e.g., cyclopropylmethyl); and R^9 is selected from the group consisting of: H, halogen, alkyl, cycloalkyl, $-CF_3$, cyano, $-OCH_3$, and $-NO_2$; and

(b)



wherein each R^7 and R^8 is independently selected from the group consisting of: H, alkyl (e.g., methyl, ethyl, t-butyl, and isopropyl), fluoroalkyl (such as, $-CF_3$ and $-CF_2CH_3$), cycloalkyl (e.g.,cyclopropyl, and cyclohexyl), and cycloalkylalkyl (e.g., cyclopropylmethyl); wherein R^{8a} is as defined in formula IA, and wherein R^9 is selected from the group consisting of: H, halogen, alkyl, cycloalkyl, $-CF_3$, cyano, $-OCH_3$, and $-NO_2$; each R^7 and R^8 is independently selected from the group consisting of: H, alkyl (e.g., methyl, ethyl, t-butyl, and isopropyl), fluoroalkyl (such as, $-CF_3$ and $-CF_2CH_3$), cycloalkyl (e.g.,cyclopropyl, and cyclohexyl), and cycloalkylalkyl (e.g., cyclopropylmethyl); and

(2) substituent B in formula IA is:



wherein

R^2 is selected from the group consisting of: H, OH, -NHC(O)R^{13} or and -NHSO$_2$$R^{13}$;

R^3 is -SO$_2$N$R^{13}$$R^{14}$;

R^{11} is selected from the group consisting of: R^{13}, hydrogen, halogen, -CF$_3$, -N$R^{13}$$R^{14}$, -N$R^{13}$C(O)N$R^{13}$$R^{14}$, -C(O)O$R^{13}$, -SH, -SO$_{(t)}NR^{13}$$R^{14}$,-SO$_2$$R^{13}$, -NHC(O)$R^{13}$, -NHSO$_2NR^{13}$$R^{14}$, -NHSO$_2$$R^{13}$, -C(O)N$R^{13}$$R^{14}$, -C(O)N$R^{13}OR^{14}$, -OC(O)$R^{13}$, -C0$R^{13}$, -O$R^{13}$, and cyano;

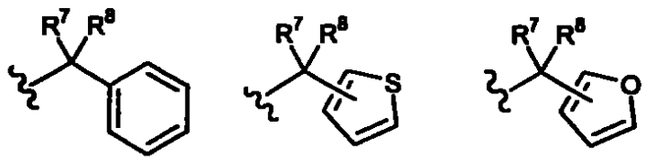
each R^{13} and R^{14} is independently selected from the group consisting of: H, methyl, ethyl, isopropyl and t-butyl; or

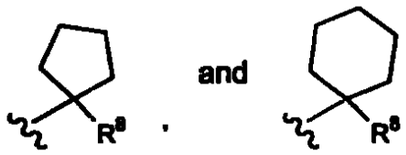
R^{13} and R^{14} when taken together with the nitrogen they are attached to in the group -SO$_2$N$R^{13}$$R^{14}$ form an unsubstituted or substituted saturated heterocyclic ring (preferably a 3 to 7 membered ring) optionally having one additional heteroatom selected from the group consisting of: O, S or NR^{18}; wherein R^{18} is selected from the group consisting of: H, alkyl, aryl, heteroaryl, -C(O)R^{19}, -SO$_2$$R^{19}$ and -C(O)N$R^{19}$$R^{20}$; wherein each R^{19} and R^{20} is independently selected from the group consisting of: alkyl, aryl and heteroaryl; wherein there are 1 to 3 substituents on the substituted cyclized R^{13} and R^{14} groups (i.e., the substituents on the ring formed when R^{13} and R^{14} are taken together with the nitrogen to which they are bound) and each substituent is independently selected from the group consisting of: alkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, -C(O)OR^{15}, -C(O)N$R^{15}$$R^{16}$, -SO$_tNR^{15}$$R^{16}$, -C(O)$R^{15}$, -SO$_2$$R^{15}$ provided that R^{15} is not H, -NHC(O)N$R^{15}$$R^{16}$ and halogen; and wherein each R^{15} and R^{16} is independently selected from the group consisting: of H, alkyl, aryl, arylalkyl, cycloalkyl and heteroaryl.

Embodiment No. 48 is directed to the the methods of treatment that use compounds of formula IA wherein:

(1) substituent A in formula IA is selected from the group consisting of:

(a)





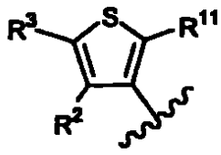
wherein the above rings are unsubstituted, or the above rings are substituted with 1 to 3 substituents independently selected from the group consisting of: H, F, Cl, Br, alkyl, cycloalkyl, and $-CF_3$; R^7 is selected from the group consisting of: H, $-CF_3$, $-CF_2CH_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and

(b)



wherein R^7 is selected from the group consisting of: H, $-CF_3$, $-CF_2CH_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and R^{8a} is as defined for formula IA.

(2) substituent B in formula IA is:



wherein:

R^2 is selected from the group consisting of: H, OH, $-NHC(O)R^{13}$ and $-NHSO_2R^{13}$;

R^3 is selected from the group consisting of: $-C(O)NR^{13}R^{14}$, $-SO_2NR^{13}R^{14}$, $-NO_2$, cyano, $-SO_2R^{13}$; and $-C(O)OR^{13}$;

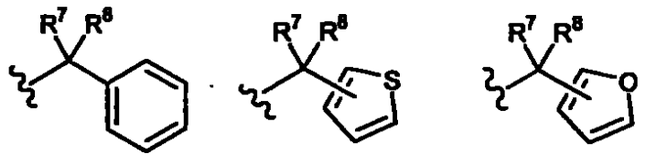
R^{11} is selected from the group consisting of: H, halogen and alkyl; and

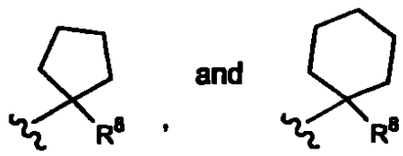
each R^{13} and R^{14} is independently selected from the group consisting of: H, methyl, ethyl, isopropyl and t-butyl.

Embodiment No. 43 is directed to the the methods of treatment that use compounds of formula IA wherein:

(1) substituent A in formula IA is selected from the group consisting of:

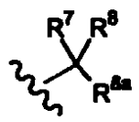
(a)





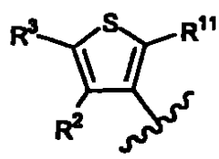
wherein the above rings are unsubstituted, or the above rings are substituted with 1 to 3 substituents independently selected from the group consisting of: F, Cl, Br, alkyl, cycloalkyl, and $-CF_3$; R^7 is selected from the group consisting of: H, $-CF_3$, $-CF_2CH_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and

(b)



wherein R^7 is selected from the group consisting of: H, $-CF_3$, $-CF_2CH_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and R^{8a} is as defined for formula IA;

(2) substituent B in formula IA is:



wherein:

R^2 is selected from the group consisting of: H, OH, $-NHC(O)R^{13}$ and $-NHSO_2R^{13}$ (preferably –OH);

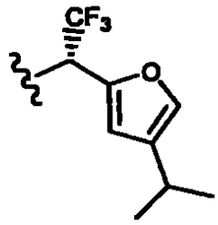
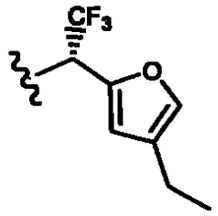
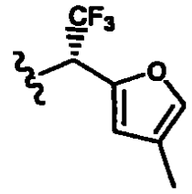
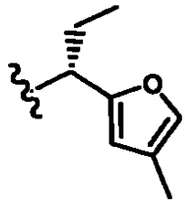
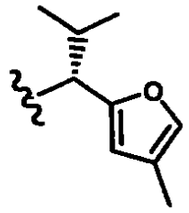
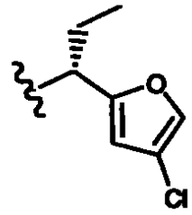
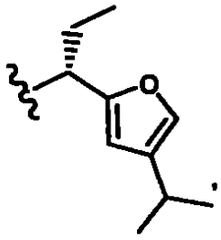
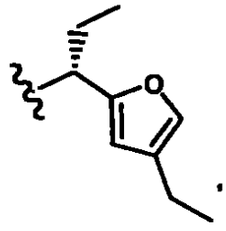
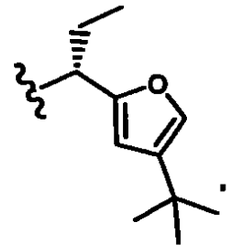
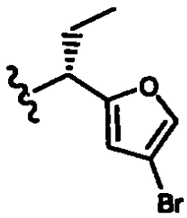
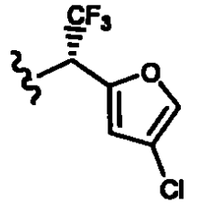
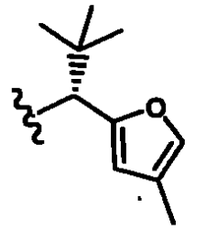
R^3 is $-SO_2NR^{13}R^{14}$;

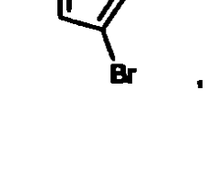
R^{11} is selected from the group consisting of: H, halogen and alkyl (preferably H); and

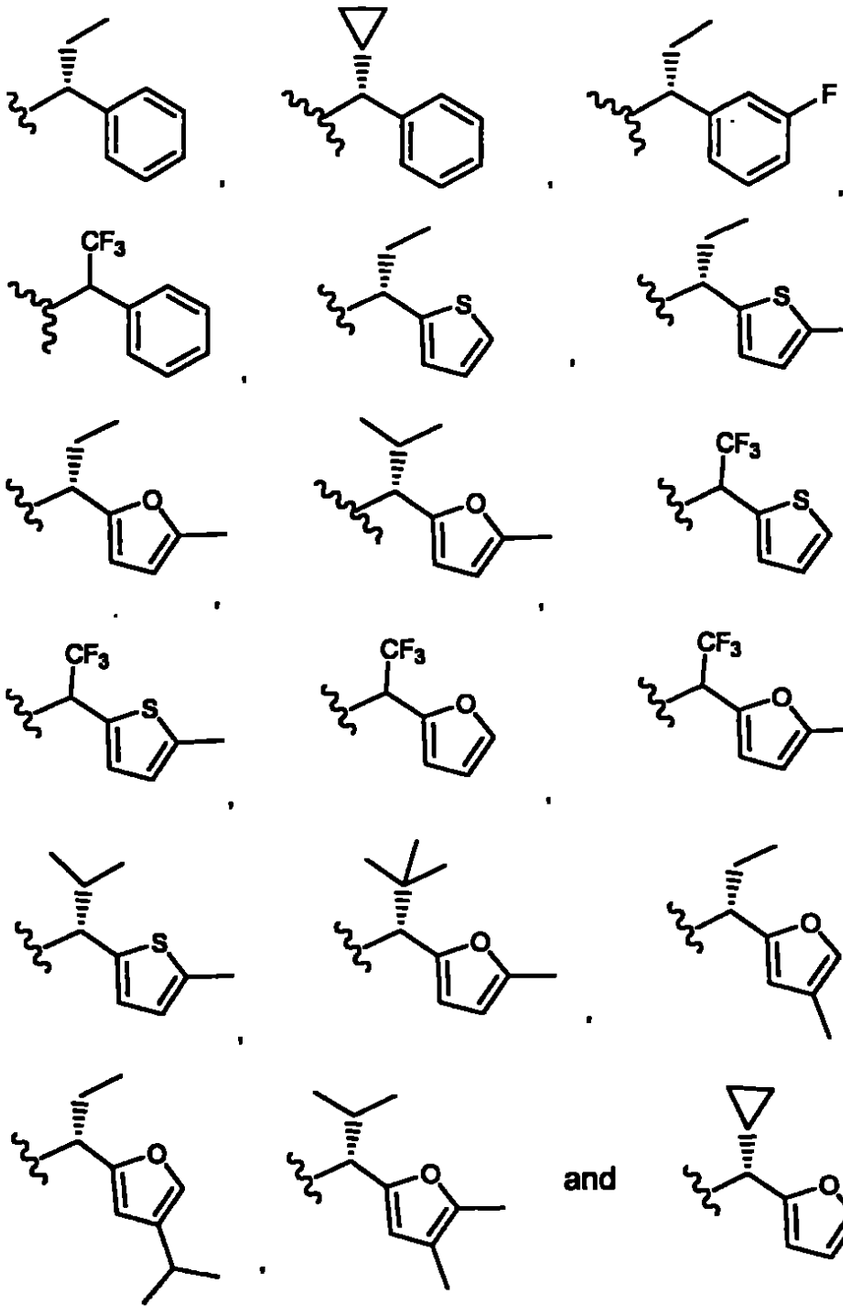
each R^{13} and R^{14} is independently selected from the group consisting of: H and ethyl, preferably R^{13} and R^{14} are ethyl.

Embodiment No. 50 is directed to the the methods of treatment that use compounds of formula IA wherein:

(1) substituent A in formula IA is selected from the group consisting of:

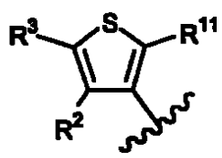




and

; and

(2) substituent B in formula IA is:



wherein:

R^2 is –OH;

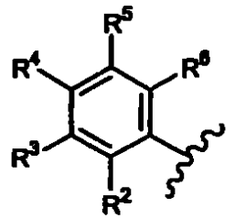
R^3 is: $-SO_2NR^{13}R^{14}$;

R^{11} is H; and

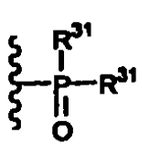
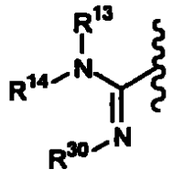
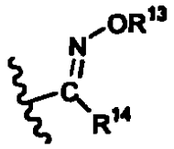
R^{13} and R^{14} are ethyl.

Embodiment No. 51 is directed to the the methods of treatment that use compounds of formula IA wherein B is selected from the group consisting of:

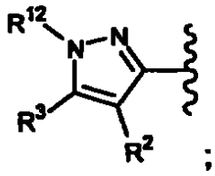
(1)



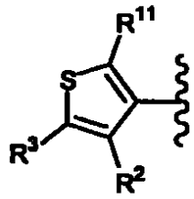
provided that R^3 for this group is selected from the group consisting of: $-C(O)NR^{13}R^{14}$,



and

;

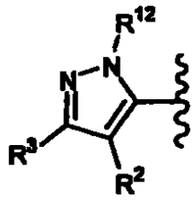
(2)


;

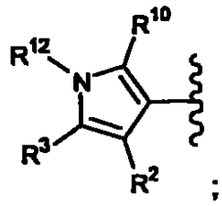
(3)


;

(4)

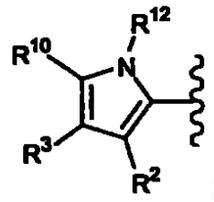

;

(5)



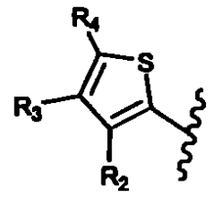
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(6)



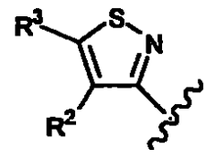
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(7)



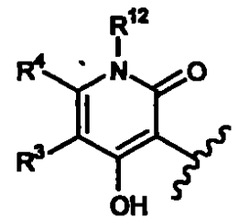
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(8)



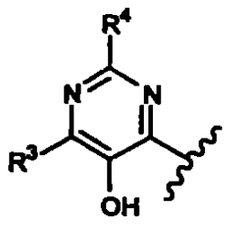
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(9)



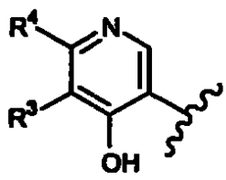
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(10)



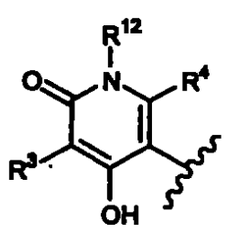
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(11)



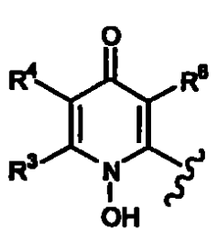
;

(12)



; and

(13)

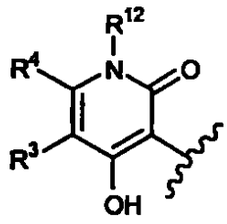


;

wherein all other substituents are as defined for formula IA.

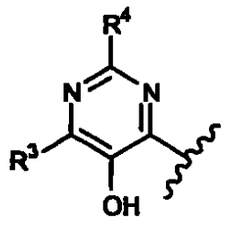
Embodiment No. 52 is directed to the the methods of treatment that use compounds of formula IA wherein B is selected from the group consisting of:

(1)



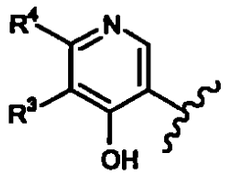
;

(2)



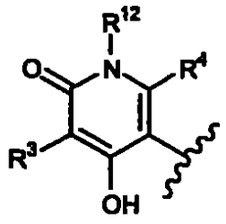
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(3)



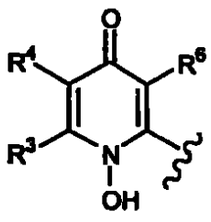
;

(4)



; and

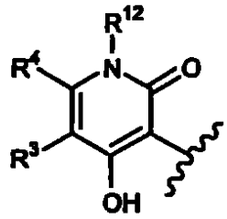
(5)



;

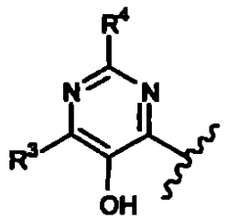
wherein all substituents are as defined for formula IA.

Embodiment No. 53 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



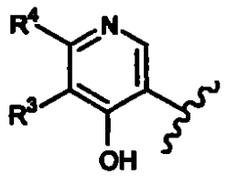
wherein all substituents are as defined for formula IA.

Embodiment No. 54 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



wherein all substituents are as defined for formula IA.

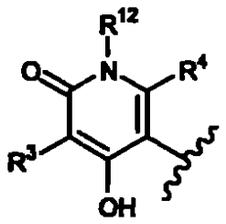
Embodiment No. 55 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



;

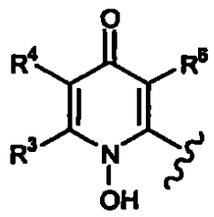
wherein all substituents are as defined for formula IA.

Embodiment No. 56 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



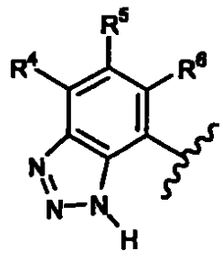
wherein all substituents are as defined for formula IA.

Embodiment No. 57 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



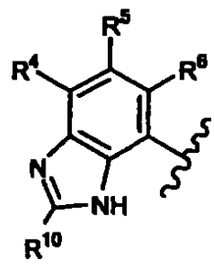
wherein all substituents are as defined for formula IA.

Embodiment No. 58 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



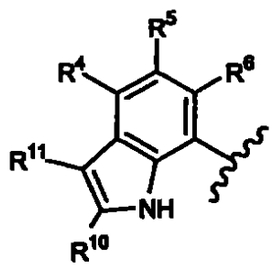
wherein all substituents are as defined for formula IA.

Embodiment No. 59 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



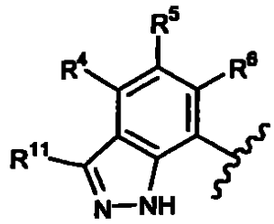
wherein all substituents are as defined for formula IA.

Embodiment No. 60 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



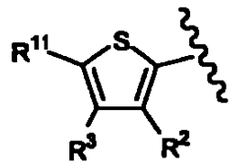
wherein all substituents are as defined for formula IA.

Embodiment No. 61 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



wherein all substituents are as defined for formula IA.

Embodiment No. 62 is directed to the the methods of treatment that use compounds of formula IA wherein B is selected from the group consisting of:



wherein all substituents are as defined for formula IA.

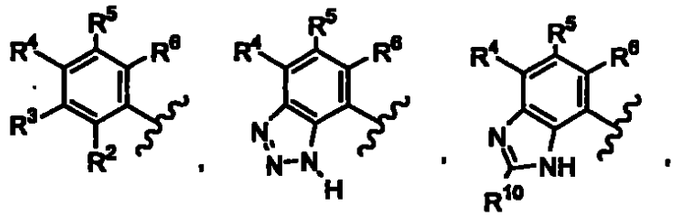
Embodiment No. 63 is directed to the the methods of treatment that use compounds of formula IA wherein B is described in any of Embodiment Nos. 51 to 62 and A is as described in any of Embodiments Nos. 32-44.

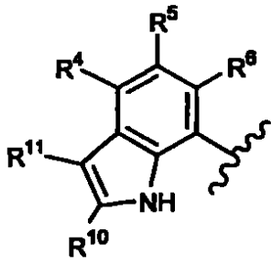
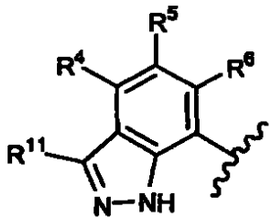
Embodiment No. 64 is directed to any one of the Embodiment Nos. 1 to 63 wherein the compound of formula IA is a pharmaceutically acceptable salt.

Embodiment No. 65 is directed to any one of the Embodiment Nos. 1 to 63 wherein the compound of formula IA is a sodium salt.

Embodiment No. 66 is directed to any one of the Embodiment Nos. 1 to 63 wherein the compound of formula IA is a calcium salt.

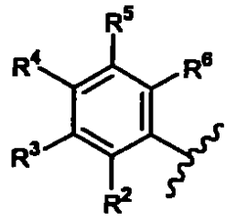
Embodiment No. 67 is directed to the methods of treatment that use compounds of formula IA wherein B is selected from the group consisting of:




and


wherein all substituents are as defined for formula IA.

Embodiment No. 68 is directed to the methods of treatment that use compounds of formula IA wherein B is selected from the group consisting of:



wherein:

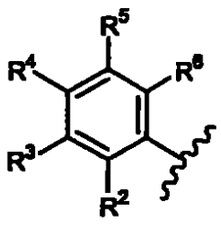
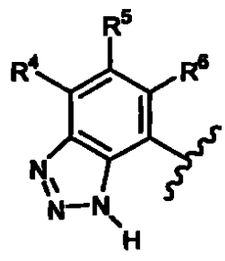
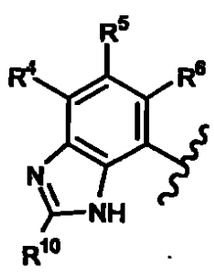
R^2, R^4, R^5 and R^6 are as defined for formula IA; and

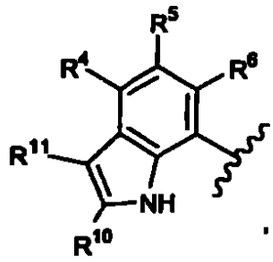
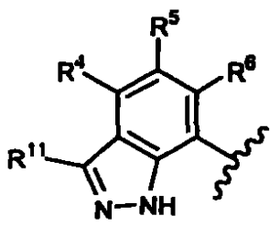
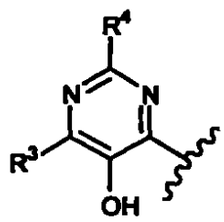
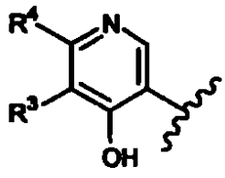
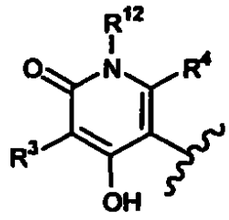
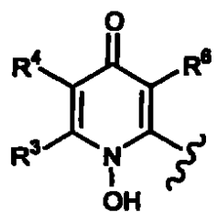
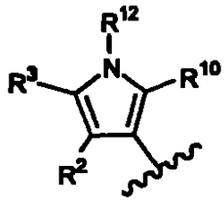
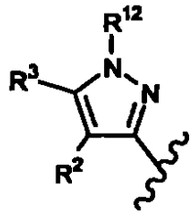
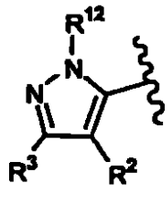
R^3 is selected from the group consisting of: hydrogen, cyano, halogen, alkyl, alkoxy, -OH, $-CF_3$, $-OCF_3$, $-NO_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NHR^{17}$, $-SO_{(t)}NR^{13}R^{14}$, $-SO_{(t)}R^{13}$, $-C(O)NR^{13}OR^{14}$, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, wherein there are 1 to 6 substituents on said substituted aryl group and each substituent is independently selected from the group consisting of: R^9 groups; and wherein there are 1 to 6 substituents on said substituted heteroaryl group and each substituent is independently selected from the group consisting of: R^9 groups.

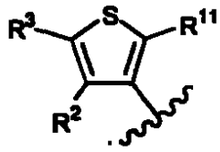
Embodiment No. 69 is directed to the methods of treatment that use compounds of formula IA wherein:

(1) substituent A is as defined in Embodiment No. 39; and

(2) substituent B in formula IA is preferably selected from the group consisting of:


,

,

.

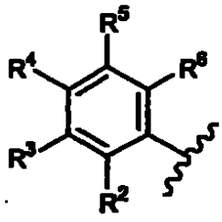
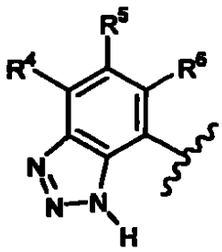
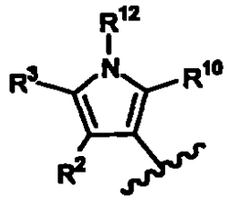
and 

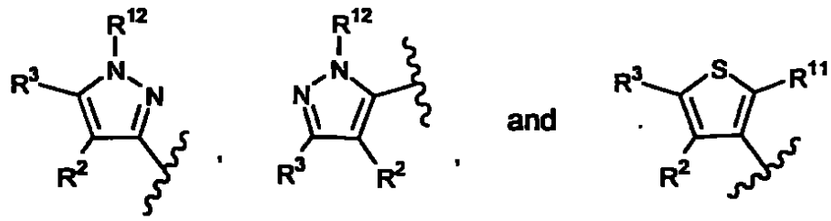
wherein R^2 to R^6 and R^{10} to R^{14} are as defined for formula IA.

Embodiment No. 70 is directed to the methods of treatment that use compounds of formula IA wherein:

(1) substituent A is as defined in Embodiment No. 40; and

(2) substituent B in formula IA is more preferably selected from the group consisting of:



wherein

R^2 is selected from the group consisting of: H, OH, $-NHC(O)R^{13}$ or and $-NHSO_2R^{13}$;

R^3 is selected from the group consisting of: $-SO_2NR^{13}R^{14}$, $-NO_2$, cyano, $-C(O)NR^{13}R^{14}$, $-SO_2R^{13}$; and $-C(O)OR^{13}$;

R^4 is selected from the group consisting of: H, $-NO_2$, cyano, $-CH_3$, halogen, and $-CF_3$;

R^5 is selected from the group consisting of: H, $-CF_3$, $-NO_2$, halogen and cyano;

R^6 is selected from the group consisting of: H, alkyl and $-CF_3$;

each R^{10} and R^{11} is independently selected from the group consisting of: hydrogen, halogen, $-CF_3$, $-NR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, $-C(O)OR^{13}$, -SH, $-SO_{(t)}NR^{13}R^{14}$,$-SO_2R^{13}$, $-NHC(O)R^{13}$, $-NHSO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, $-C(O)NR^{13}R^{14}$, $-C(O)NR^{13}OR^{14}$, $-OC(O)R^{13}$, $-COR^{13}$, $-OR^{13}$, and cyano;

each R^{13} and R^{14} is independently selected from the group consisting of: H, methyl, ethyl, isopropyl and t-butyl; or

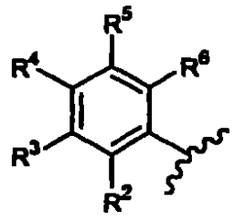
R^{13} and R^{14} when taken together with the nitrogen they are attached to in the groups $-NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, $-SO_2NR^{13}R^{14}$, $-OC(O)NR^{13}R^{14}$, $-CONR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, $-SO_tNR^{13}R^{14}$, $-NHSO_2NR^{13}R^{14}$ form an unsubstituted or substituted saturated heterocyclic ring (preferably a 3 to 7 membered ring) optionally having one additional heteroatom selected from the group consisting of: O, S or NR^{18}; wherein R^{18} is selected from the group consisting of: H, alkyl, aryl, heteroaryl, $-C(O)R^{19}$, $-SO_2R^{19}$ and $-C(O)NR^{19}R^{20}$; wherein each R^{19} and R^{20} is independently selected from the group consisting of: alkyl, aryl and heteroaryl; wherein there are 1 to 3 substituents on the substituted cyclized R^{13} and R^{14} groups (i.e., the substituents on the ring formed when R^{13} and R^{14} are taken together with the nitrogen to which they are bound) and each substituent is independently selected from the group consisting of: alkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, $-C(O)OR^{15}$,

-C(O)NR^{15}R^{16}, -SO$_t$NR^{15}R^{16}, -C(O)R^{15}, -SO$_2$R^{15} provided that R^{15} is not H, -NHC(O)NR^{15}R^{16} and halogen; and wherein each R^{15} and R^{16} is independently selected from the group consisting: of H, alkyl, aryl, arylalkyl, cycloalkyl and heteroaryl.

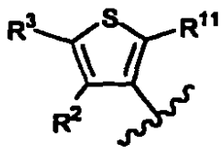
Embodiment No. 71 is directed to the methods of treatment that use compounds of formula IA wherein:

(1) substituent A is as defined in Embodiment No. 42; and

(2) substituent B in formula IA is preferably selected from the group consisting of:



and



wherein:

R^2 is selected from the group consisting of: H, OH, -NHC(O)R^{13} and -NHSO$_2$R^{13};

R^3 is selected from the group consisting of: -C(O)NR^{13}R^{14}, -SO$_2$NR^{13}R^{14}, -NO$_2$, cyano, -SO$_2$R^{13}; and -C(O)OR^{13};

R^4 is selected from the group consisting of: H, -NO$_2$, cyano, -CH$_3$ or -CF$_3$;

R^5 is selected from the group consisting of: H, -CF$_3$, -NO$_2$, halogen and cyano; and

R^6 is selected from the group consisting of: H, alkyl and -CF$_3$;

R^{11} is selected from the group consisting of: H, halogen and alkyl; and

each R^{13} and R^{14} is independently selected from the group consisting of: H, methyl, ethyl, isopropyl and t-butyl; or

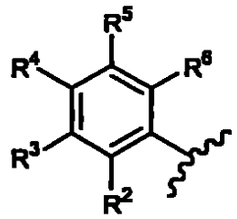
R^{13} and R^{14} when taken together with the nitrogen they are attached to in the groups -NR^{13}R^{14}, -C(O)NR^{13}R^{14}, -SO$_2$NR^{13}R^{14}, -OC(O)NR^{13}R^{14}, -CONR^{13}R^{14}, -NR^{13}C(O)NR^{13}R^{14}, -SO$_t$NR^{13}R^{14}, -NHSO$_2$NR^{13}R^{14} form an unsubstituted or substituted saturated heterocyclic ring (preferably a 3 to 7 membered ring) optionally having one additional heteroatom selected from O, S or NR^{18} wherein R^{18} is selected from H, alkyl, aryl, heteroaryl, -C(O)R^{19}, -SO$_2$R^{19} and -C(O)NR^{19}R^{20}, wherein each R^{19} and R^{20} is independently selected from alkyl, aryl and heteroaryl, wherein there are 1

to 3 substituents on the substituted cyclized R^{13} and R^{14} groups (i.e., on the ring formed when R^{13} and R^{14} are taken together with the nitrogen to which they are bound) and each substituent is independently selected from the group consisting of: alkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-SO_tNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ provided that R^{15} is not H, $-NHC(O)NR^{15}R^{16}$ and halogen; and wherein each R^{15} and R^{16} is independently selected from the group consisting of: H, alkyl, aryl, arylalkyl, cycloalkyl and heteroaryl.

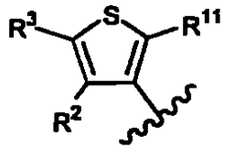
Embodiment No. 72 is directed to the methods of treatment that use compounds of formula IA wherein:

(1) substituent A is as defined in Embodiment No. 43; and

(2) substituent B in formula IA is preferably selected from the group consisting of:



and



wherein:

R^2 is selected from the group consisting of: H, OH, $-NHC(O)R^{13}$ and $-NHSO_2R^{13}$;

R^3 is selected from the group consisting of: $-C(O)NR^{13}R^{14}$ $-SO_2NR^{13}R^{14}$, $-NO_2$, cyano, and $-SO_2R^{13}$;

R^4 is selected from the group consisting of: H, $-NO_2$, cyano, $-CH_3$ or $-CF_3$;

R^5 is selected from the group consisting of: H, $-CF_3$, $-NO_2$, halogen and cyano; and

R^6 is selected from the group consisting of: H, alkyl and $-CF_3$;

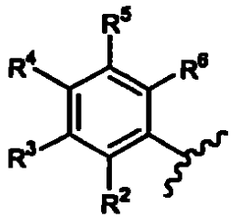
R^{11} is selected from the group consisting of: H, halogen and alkyl; and

each R^{13} and R^{14} is independently selected from the group consisting of: methyl and ethyl.

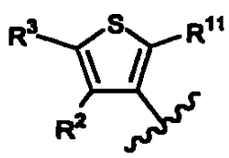
Embodiment No. 73 is directed to the methods of treatment that use compounds of formula IA wherein:

(1) substituent A is as defined in Embodiment No. 44; and

(2) substituent B in formula IA is preferably selected from the group consisting of:



and



wherein:

R^2 is –OH;

R^3 is selected from the group consisting of: $-SO_2NR^{13}R^{14}$ and $-CONR^{13}R^{14}$;

R^4 is selected form the group consisting of: H, $-CH_3$ and $-CF_3$;

R^5 is selected from the group consisting of: H and cyano;

R^6 is selected from the group consisting of: H, $-CH_3$ and $-CF_3$;

R^{11} is H; and

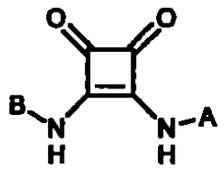
R^{13} and R^{14} are methyl.

Embodiment No. 74 is directed to any one of the Embodiment Nos. 67 to 73 wherein the compound of formula IA is a pharmaceutically acceptable salt.

Embodiment No. 75 is directed to any one of the Embodiment Nos. 67 to 73 wherein the compound of formula IA is a sodium salt.

Embodiment No. 76 is directed to any one of the Embodiment Nos. 1 to 73 wherein the compound of formula IA is a calcium salt.

This invention is also directed to novel compounds of formula IB:

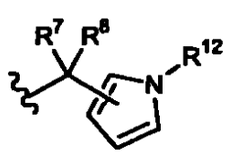


(IB)

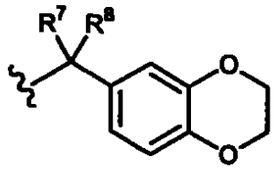
and the pharmaceutically acceptable salts (e.g., sodium or calcium salt) and solvates thereof, wherein:

A is selected from the group consisting of:

(1)

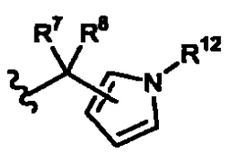


and

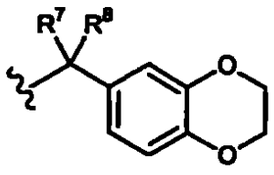


; and

(2)



and



wherein said rings of said A groups are substituted with 1 to 6 substituents each independently selected from the group consisting of: R^9 groups; and

Substituents B, R^7, R^8, R^9 and R^{12} are as defined for formula IA.

Thus, for compounds of formula IB, substituents B, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{30}, R^{31}, R^{40}, q, and t are as defined for formula IA.

In other embodiments of the compounds of formula IB, substituent B is as defined in anyone of Embodiments 1 to 30 described above.

In other embodiments of the compounds of formula IB, substituent B is as defined in anyone of Embodiments 51 to 62 described above.

In other embodiments of the compounds of formula IB, substituent B is as defined in anyone of Embodiments 67 to 73 described above.

Another embodiment of this invention is directed to a pharmaceutical composition comprising at least one (e.g., one) compound of formula IB and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to the calcium salts of the compounds of formula IB.

Another embodiment of this invention is directed to the sodium salts of the compounds of formula IB.

Another embodiment of this invention is directed to a pharmaceutical composition comprising at least one (e.g., one) sodium salt of a compound of formula IB and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising at least one (e.g., one) calcium salt of a compound formula IB and a pharmaceutically acceptable carrier.

The chemokine mediated diseases, that are treated by administering at least one (e.g., one) compound selected from the group consisting of compounds of the formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088, or a pharmaceutically acceptable salt or solvate of said compounds, include: chronic inflammation, acute inflammatory pain, chronic inflammatory pain, acute neuropathic pain, chronic neuropathic pain, psoriasis, atopic dermatitis, asthma, COPD, adult respiratory disease, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, stroke, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer's disease, graft vs. host reaction, allograft rejections, malaria, acute respiratory distress syndrome, delayed type hypersensitivity reaction, atherosclerosis, cerebral and cardiac ischemia, osteoarthritis, multiple sclerosis, restinosis, angiogenesis, osteoporosis, gingivitis, respiratory viruses, herpes viruses, hepatitis viruses, HIV, Kaposi's sarcoma associated virus, meningitis, cystic fibrosis, pre-term labor, cough, pruritis, multi-organ dysfunction, trauma, strains, sprains, contusions, psoriatic arthritis, herpes, encephalitis, CNS vasculitis, traumatic brain injury, CNS tumors, subarachnoid hemorrhage, post surgical trauma, interstitial pneumonitis, hypersensitivity, crystal induced arthritis, acute and chronic pancreatitis, acute alcoholic hepatitis, necrotizing enterocolitis, chronic sinusitis, angiogenic ocular disease, ocular inflammation, retinopathy of prematurity, diabetic retinopathy, macular degeneration with the wet type preferred and corneal neovascularization, polymyositis, vasculitis, acne, gastric and duodenal ulcers, celiac disease, esophagitis, glossitis, airflow obstruction, airway hyperresponsiveness, bronchiectasis, bronchiolitis, bronchiolitis obliterans, chronic bronchitis, cor pulmonae, cough, dyspnea, emphysema, hypercapnea, hyperinflation, hypoxemia, hyperoxia-induced inflammations, hypoxia, surgical lung volume reduction, pulmonary fibrosis, pulmonary hypertension, right ventricular hypertrophy, peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD), granulocytic ehrlichiosis, sarcoidosis, small airway disease, ventilation-perfusion mismatching, wheeze, colds, gout, alcoholic liver disease, lupus, burn therapy,

periodontitis, transplant reperfusion injury and early transplantation rejection, acute inflammation, and rheumatoid arthritis.

The chemokine mediated diseases, that are treated by administering at least one (e.g., one) compound of formula IB, include: chronic inflammation, acute inflammatory pain, chronic inflammatory pain, acute neuropathic pain, chronic neuropathic pain, psoriasis, atopic dermatitis, asthma, COPD, adult respiratory disease, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, stroke, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer's disease, graft vs. host reaction, allograft rejections, malaria, acute respiratory distress syndrome, delayed type hypersensitivity reaction, atherosclerosis, cerebral and cardiac ischemia, osteoarthritis, multiple sclerosis, restinosis, angiogenesis, osteoporosis, gingivitis, respiratory viruses, herpes viruses, hepatitis viruses, HIV, Kaposi's sarcoma associated virus, meningitis, cystic fibrosis, pre-term labor, cough, pruritis, multi-organ dysfunction, trauma, strains, sprains, contusions, psoriatic arthritis, herpes, encephalitis, CNS vasculitis, traumatic brain injury, CNS tumors, subarachnoid hemorrhage, post surgical trauma, interstitial pneumonitis, hypersensitivity, crystal induced arthritis, acute and chronic pancreatitis, acute alcoholic hepatitis, necrotizing enterocolitis, chronic sinusitis, angiogenic ocular disease, ocular inflammation, retinopathy of prematurity, diabetic retinopathy, macular degeneration with the wet type preferred and corneal neovascularization, polymyositis, vasculitis, acne, gastric and duodenal ulcers, celiac disease, esophagitis, glossitis, airflow obstruction, airway hyperresponsiveness, bronchiectasis, bronchiolitis, bronchiolitis obliterans, chronic bronchitis, cor pulmonae, cough, dyspnea, emphysema, hypercapnea, hyperinflation, hypoxemia, hyperoxia-induced inflammations, hypoxia, surgical lung volume reduction, pulmonary fibrosis, pulmonary hypertension, right ventricular hypertrophy, peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD), granulocytic ehrlichiosis, sarcoidosis, small airway disease, ventilation-perfusion mismatching, wheeze, colds, gout, alcoholic liver disease, lupus, burn therapy, periodontitis, transplant reperfusion injury and early transplantation rejection, acute inflammation, and rheumatoid arthritis.

Another embodiment of this invention is directed to a method of treating acute inflammatory pain in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least

one (e.g., 1-3, and usually one) compound of formula IA (or a pharmaceutically acceptable salt or solvate thereof).

Another embodiment of this invention is directed to a method of treating chronic inflammatory pain in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, and usually one) compound of formula IA (or a pharmaceutically acceptable salt or solvate thereof).

Another embodiment of this invention is directed to a method of treating acute neuropathic pain in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, and usually one) compound of formula IA (or a pharmaceutically acceptable salt or solvate thereof).

Another embodiment of this invention is directed to a method of treating chronic neuropathic pain in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, and usually one) compound of formula IA (or a pharmaceutically acceptable salt or solvate thereof).

Another embodiment of this invention is directed to a method of treating acute inflammatory pain in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., one) compound selected from the group consisting of compounds of the formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds).

Another embodiment of this invention is directed to a method of treating chronic inflammatory pain in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., one) compound selected from the group consisting of compounds of the formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds).

Another embodiment of this invention is directed to a method of treating acute neuropathic pain in a patient (e.g., a mammal, preferably a human being) in need of

such treatment comprising administering to said patient an effective amount of at least one (e.g., one) compound selected from the group consisting of compounds of the formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds).

Another embodiment of this invention is directed to a method of treating chronic neuropathic pain in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., one) compound selected from the group consisting of compounds of the formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds).

Another embodiment of this invention is directed to a method of treating COPD in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., one) compound selected from the group consisting of compounds of the formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds).

Another embodiment of this invention is directed to a method of treating acute inflammatory pain in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, and usually one) compound of formula IB (or a pharmaceutically acceptable salt or solvate thereof).

Another embodiment of this invention is directed to a method of treating chronic inflammatory pain in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, and usually one) compound of formula IB (or a pharmaceutically acceptable salt or solvate thereof).

Another embodiment of this invention is directed to a method of treating acute neuropathic pain in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least

one (e.g., 1-3, and usually one) compound of formula IB (or a pharmaceutically acceptable salt or solvate thereof).

Another embodiment of this invention is directed to a method of treating chronic neuropathic pain in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, and usually one) compound of formula IB (or a pharmaceutically acceptable salt or solvate thereof).

Another embodiment of this invention is directed to a method of treating COPD in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, and usually one) compound of formula IB (or a pharmaceutically acceptable salt or solvate thereof).

An embodiment of the present invention is directed to a method of treating cancer in a patient (e.g., a mammal, such as a human being) in need of such treatment, comprising administering to said patient, concurrently or sequentially, a therapeutically effective amount of (a) at least one (e.g., one) compound selected from the group consisting of compounds of the formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds), and (b) a microtubule affecting agent or antineoplastic agent or anti-angiogenesis agent or VEGF receptor kinase inhibitor or antibodies against the VEGF receptor or interferon, and/or c) radiation.

In further embodiments directed to the treatment of cancer, at least one (e.g., one) compound selected from the group consisting of compounds of the 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds), is administered in combination with antineoplastic agents (e.g., one or more, such as one, or such as one or two), selected from the group consisting of: gemcitabine, paclitaxel (Taxol®), 5-Fluorouracil (5-FU), cyclophosphamide (Cytoxan®), temozolomide, taxotere and Vincristine.

In another embodiment the present invention provides a method of treating cancer in a patient (e.g., a mammal, such as a human being) in need of such treatment, comprising administering, concurrently or sequentially, an effective amount

of (a) at least one (e.g., one) compound selected from the group consisting of compounds of the formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds), and (b) a microtubule affecting agent (*e.g.*, paclitaxel).

An embodiment of the present invention is directed to a method of treating cancer in a patient (e.g., a mammal, such as a human being) in need of such treatment, comprising administering to said patient, concurrently or sequentially, a therapeutically effective amount of (a) at least one (e.g., 1-3, and usually one) compound of formula IB (or a pharmaceutically acceptable salt or solvate thereof), and (b) a microtubule affecting agent or antineoplastic agent or anti-angiogenesis agent or VEGF receptor kinase inhibitor or antibodies against the VEGF receptor or interferon, and/or c) radiation.

In further embodiments directed to the treatment of cancer, at least one (e.g., 1-3, and usually one) compound of formula IB (or a pharmaceutically acceptable salt or solvate thereof) is administered in combination with antineoplastic agents (e.g., one or more, such as one, or such as one or two), selected from the group consisting of: gemcitabine, paclitaxel (Taxol®), 5-Fluorouracil (5-FU), cyclophosphamide (Cytoxan®), temozolomide, taxotere and Vincristine.

In another embodiment the present invention provides a method of treating cancer in a patient (e.g., a mammal, such as a human being) in need of such treatment, comprising administering, concurrently or sequentially, an effective amount of (a) at least one (e.g., 1-3, and usually one) compound of formula IB (or a pharmaceutically acceptable salt or solvate thereof), and (b) a microtubule affecting agent (*e.g.*, paclitaxel).

Another embodiment of this invention is directed to a method of treating melanoma, gastric carcinoma, and non-small cell lung cancer in a patient in need of such treatment, said treatment comprising administering to said patient an effective amount of at least one (e.g., one) compound of formula IB (or a pharmaceutically acceptable salt or solvate of said compound).

Another embodiment of this invention is directed to a method of treating melanoma, gastric carcinoma, and non-small cell lung cancer in a patient in need of such treatment, said treatment comprising administering to said patient an effective

amount of at least one (e.g., one) compound of formula IB (or a pharmaceutically acceptable salt or solvate of said compound), in combination with administering at least one anticancer agent.

Another embodiment of this invention is directed to a method of treating melanoma, gastric carcinoma, and non-small cell lung cancer in a patient in need of such treatment, said treatment comprising administering to said patient an effective amount of at least one (e.g., one) compound of formula IB (or a pharmaceutically acceptable salt or solvate of said compound), in combination with administering at least one anticancer agent, wherein said anticancer agent is selected from the group consisting of: alkylating agents, antimetabolites, natural products and their derivatives, hormones, anti-hormones, anti-angiogenic agents and steroids, and synthetics.

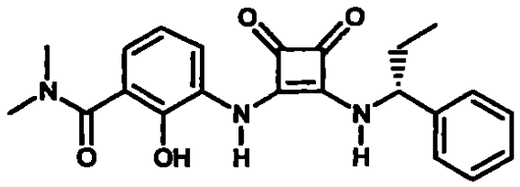
Another embodiment of this invention is directed to a method of treating melanoma, gastric carcinoma, and non-small cell lung cancer in a patient in need of such treatment, said treatment comprising administering to said patient an effective amount of at least one (e.g., one) compound selected from the group consisting of the compounds of formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds).

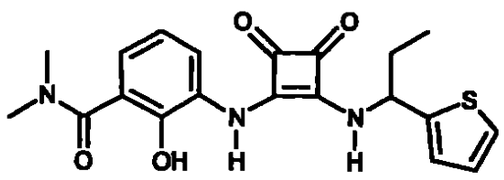
Another embodiment of this invention is directed to a method of treating melanoma, gastric carcinoma, and non-small cell lung cancer in a patient in need of such treatment, said treatment comprising administering to said patient an effective amount of at least one (e.g., one) compound selected from the group consisting of the compounds of formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds), in combination with administering at least one anticancer agent.

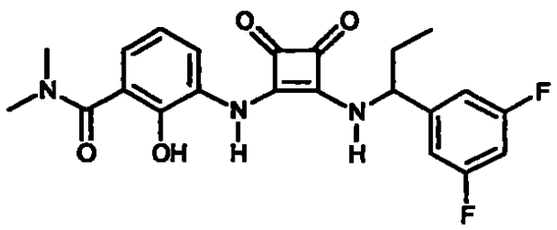
Another embodiment of this invention is directed to a method of treating melanoma, gastric carcinoma, and non-small cell lung cancer in a patient in need of such treatment, said treatment comprising administering to said patient an effective amount of at least one (e.g., one) compound selected from the group consisting of the compounds of formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds), in combination

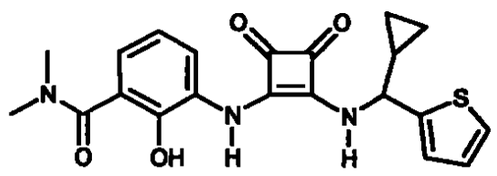
with administering at least one anticancer agent, wherein said anticancer agent is selected from the group consisting of: alkylating agents, antimetabolites, natural products and their derivatives, hormones, anti-hormones, anti-angiogenic agents and steroids, and synthetics.

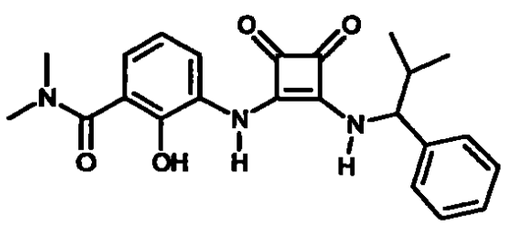
Representative compounds used to treat the chemokine mediated diseases include but are not limited to:

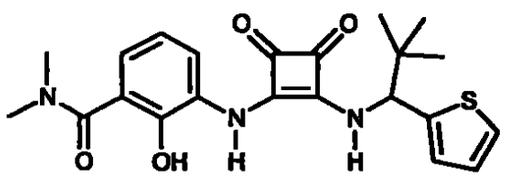


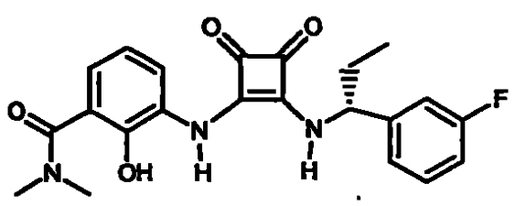


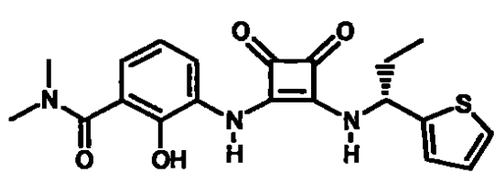


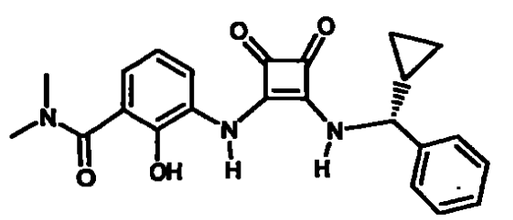




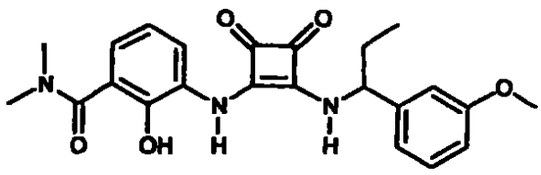


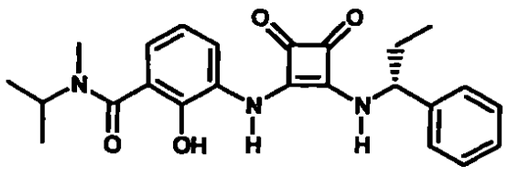


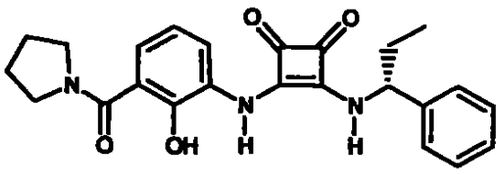


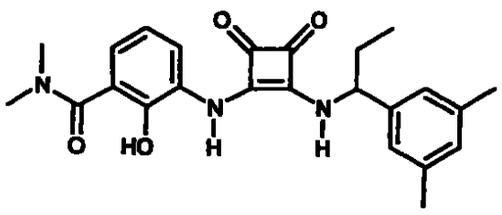


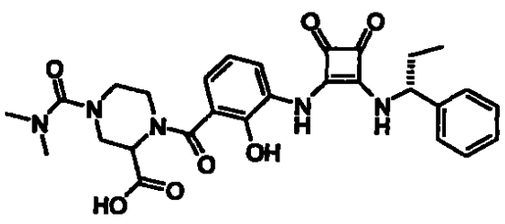


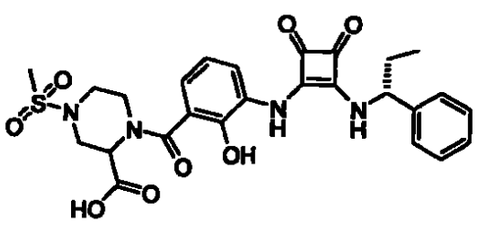


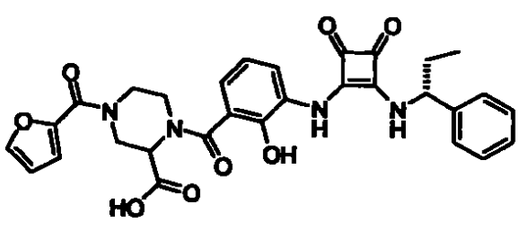


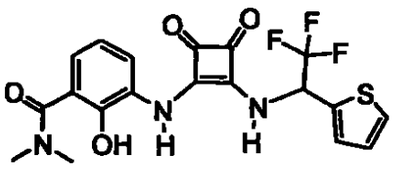


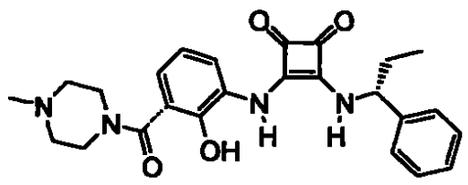


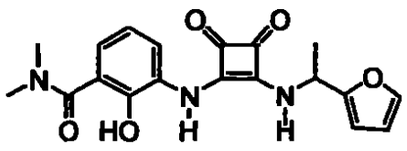


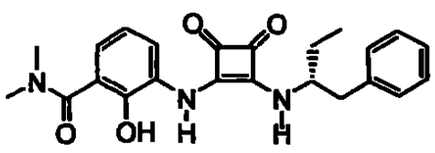


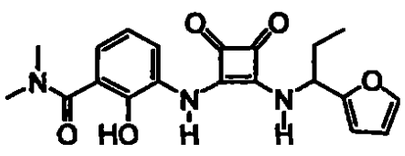


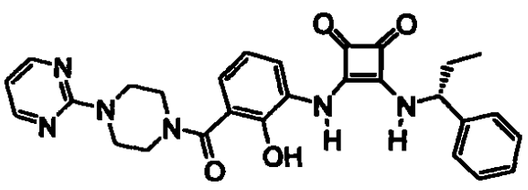


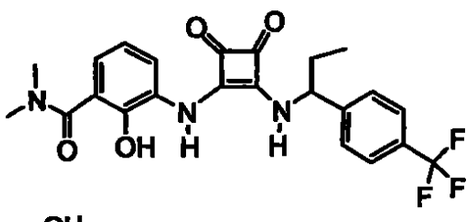


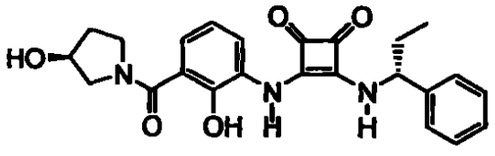


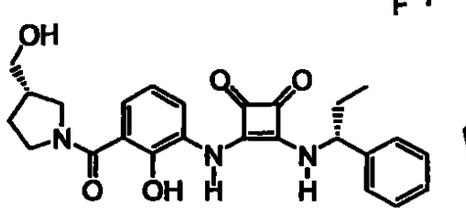


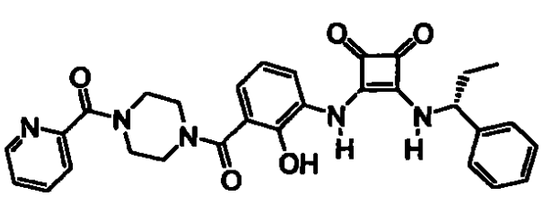


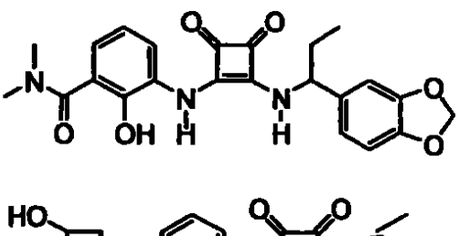


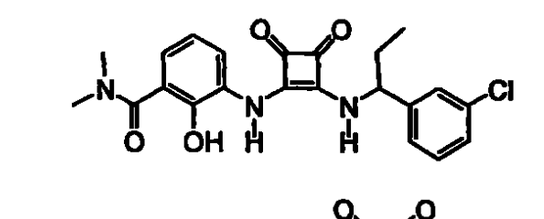


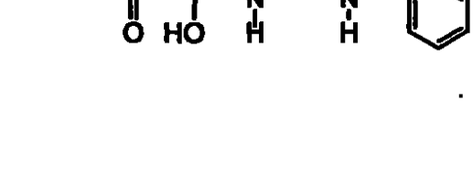


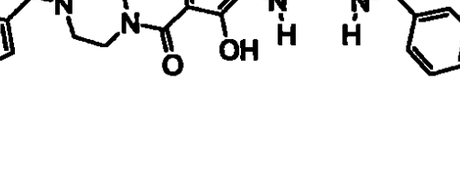


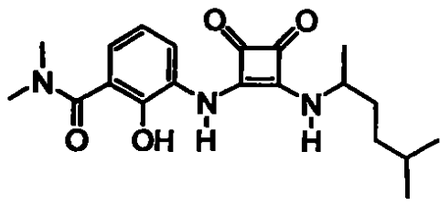


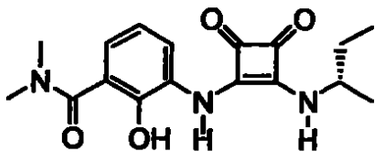


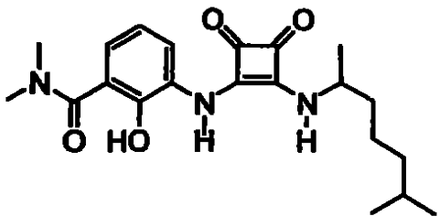


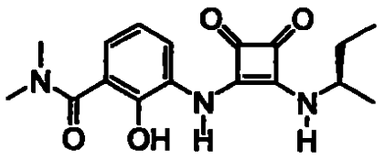


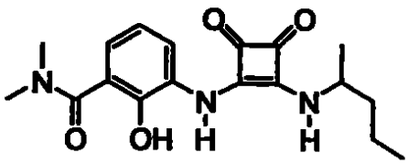


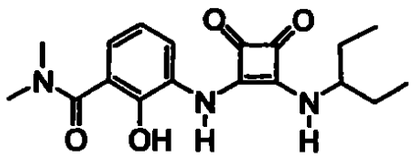


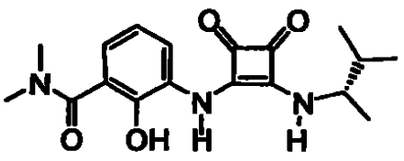


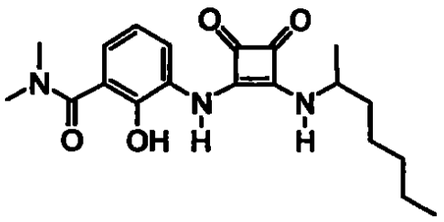


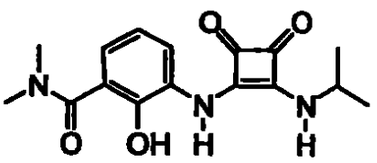


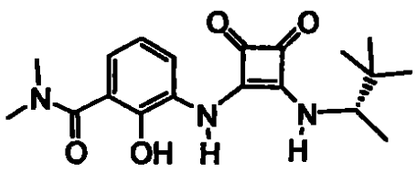


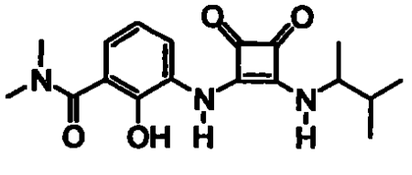


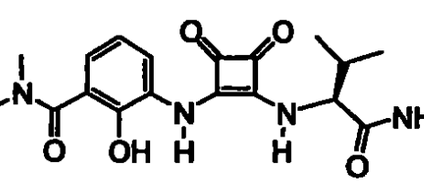


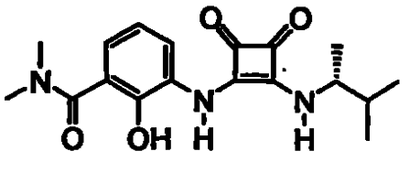


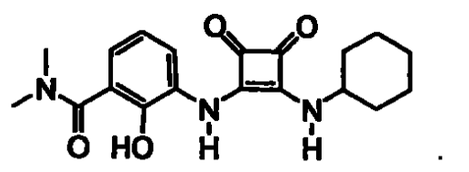


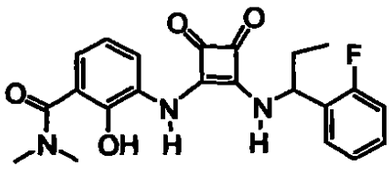


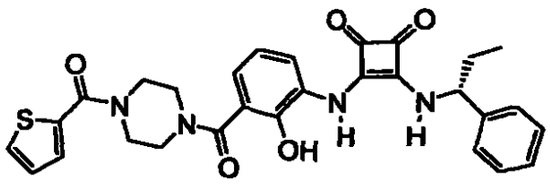


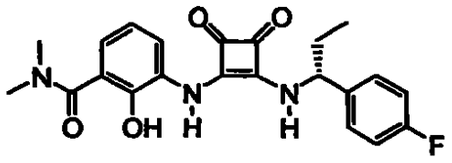


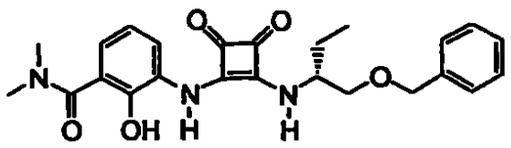


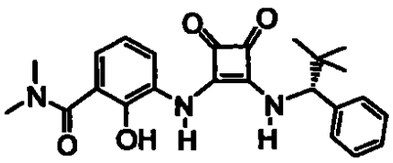


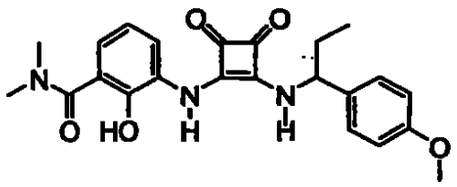


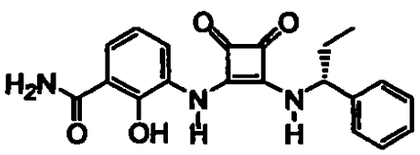


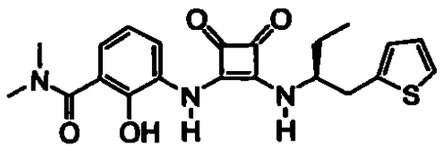


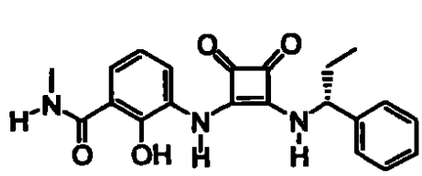


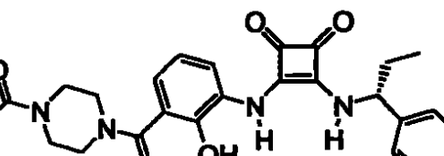


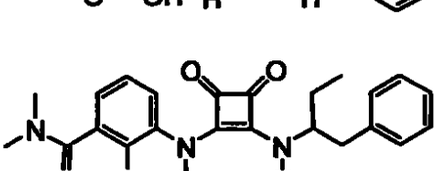


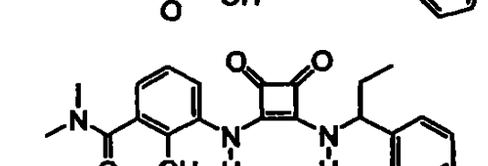


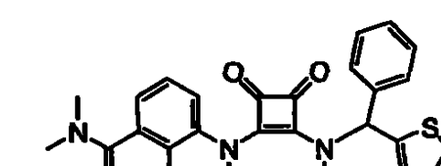


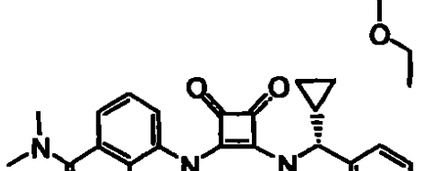


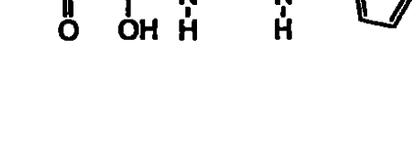


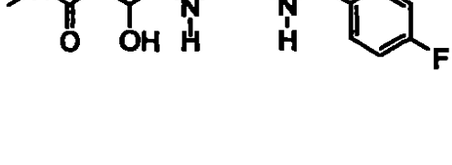




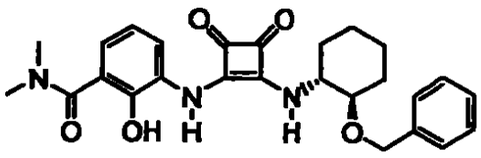


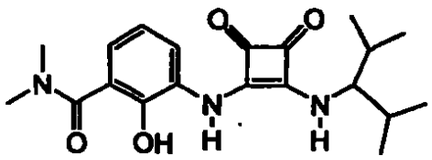


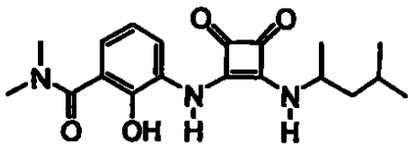


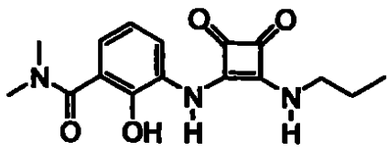


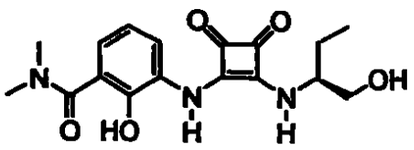


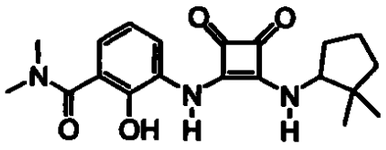


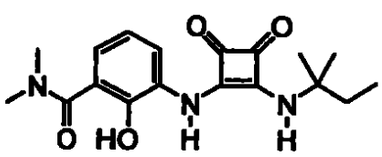


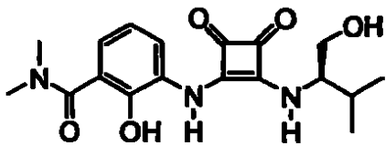


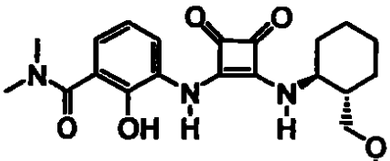


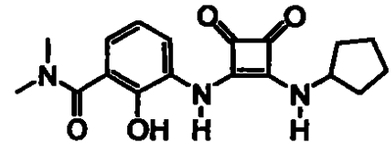


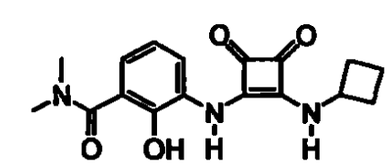


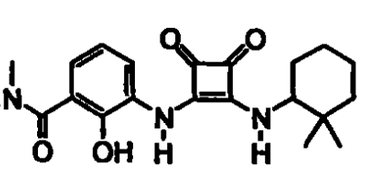


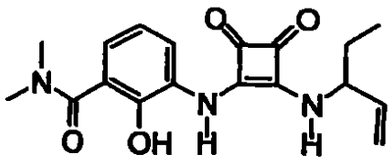


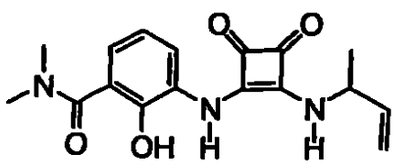


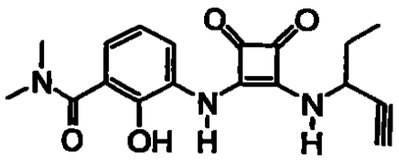


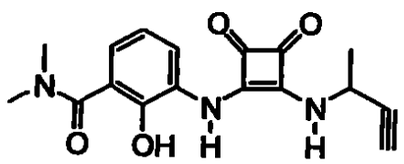


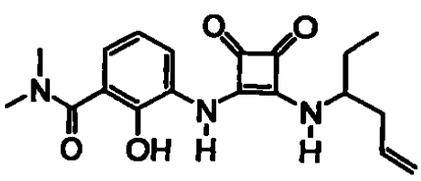


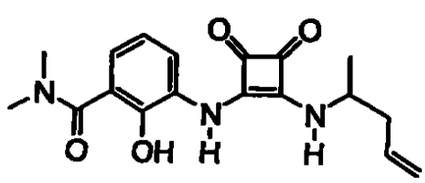


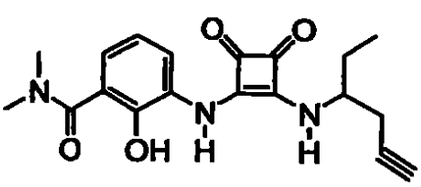


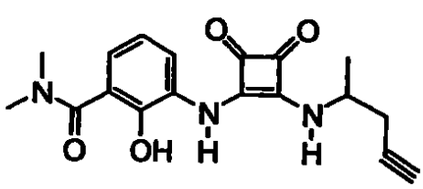


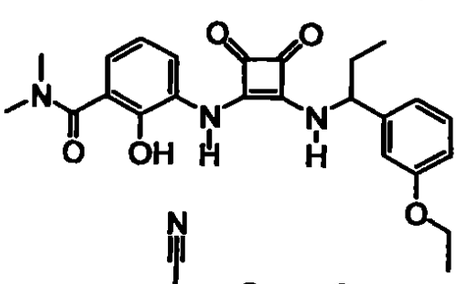


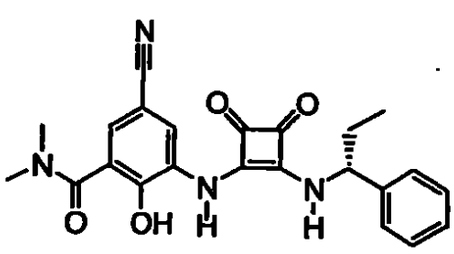


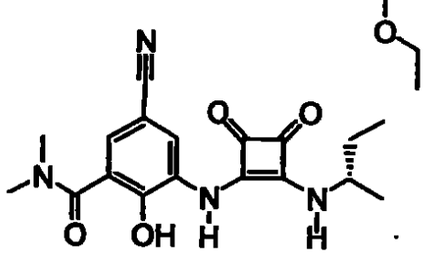


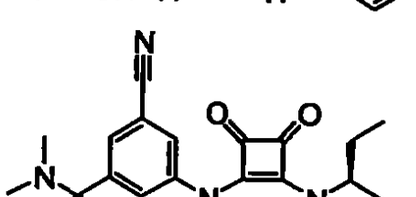


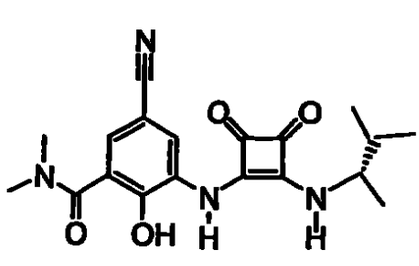


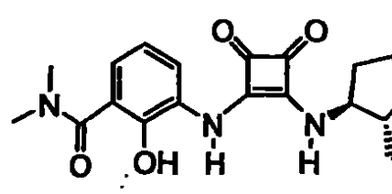


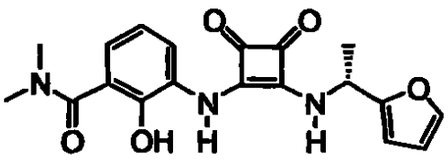


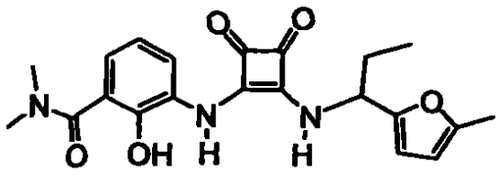


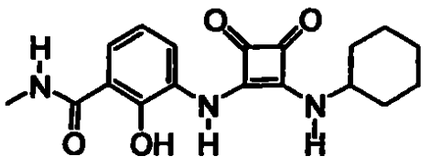


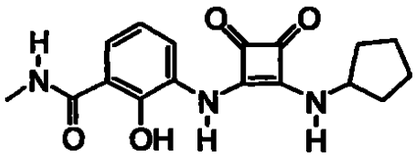


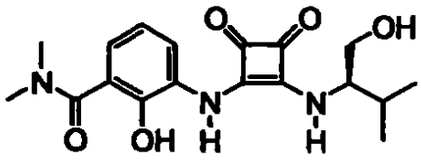


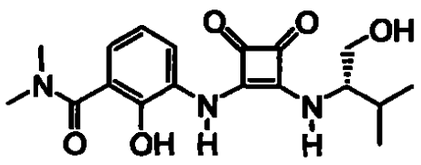


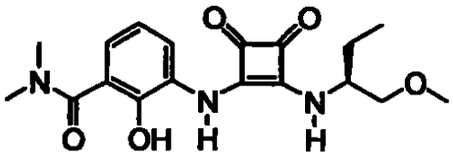


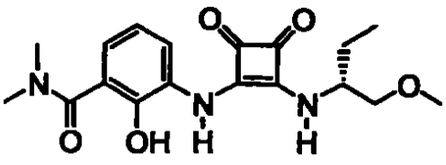


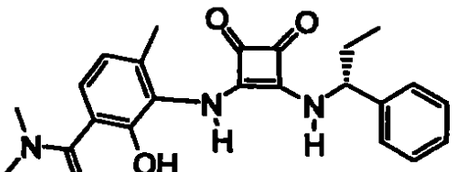


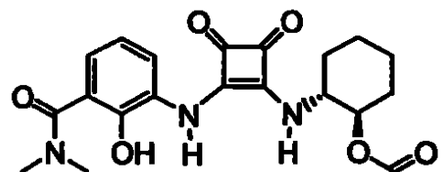


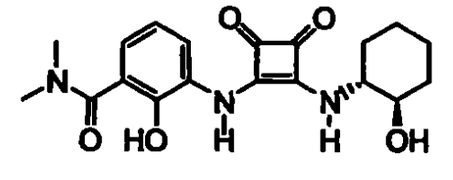


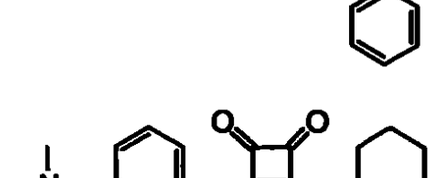


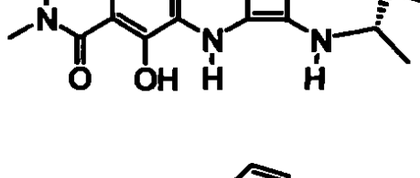


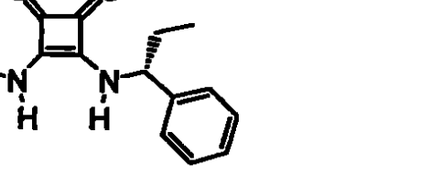


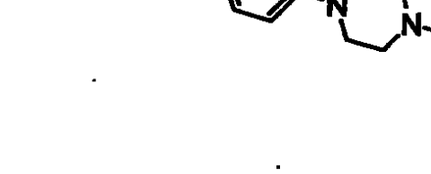


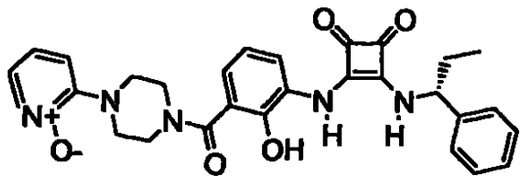


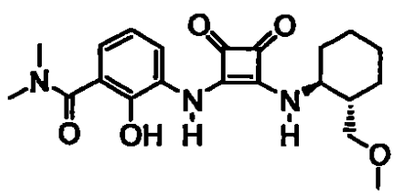


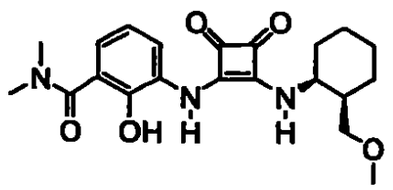


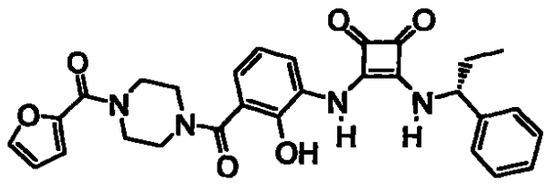


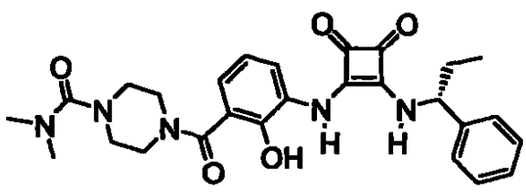


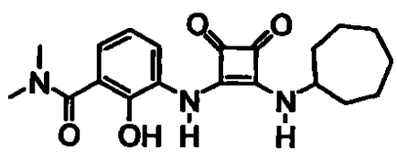


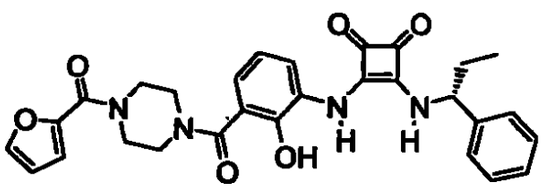


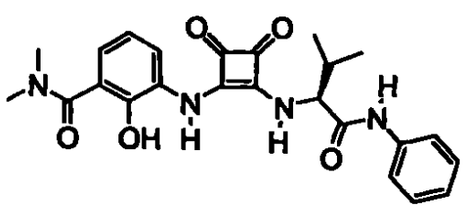


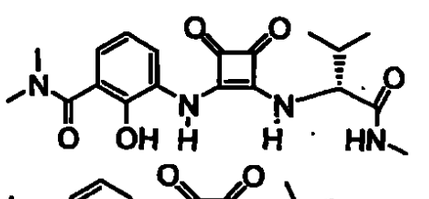


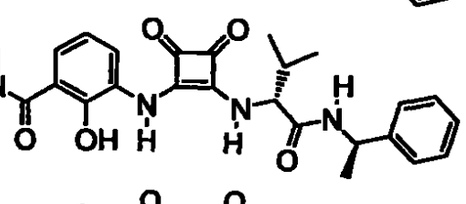


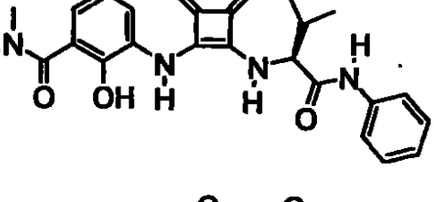


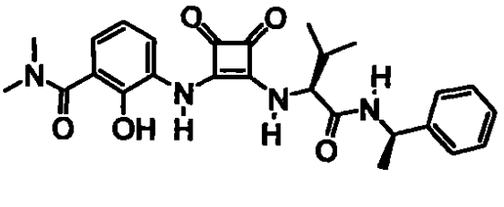


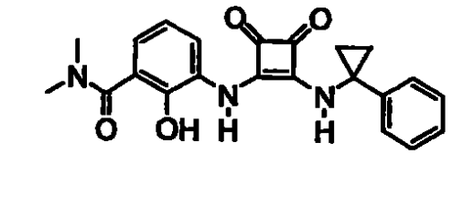


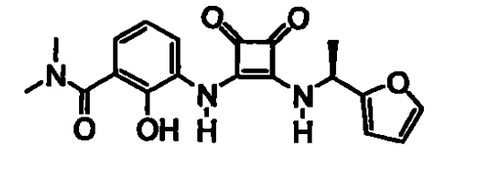


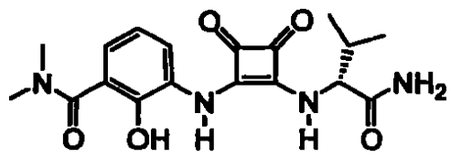


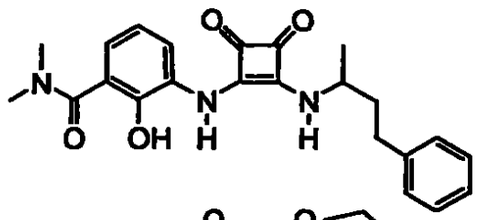


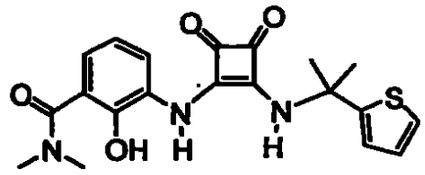


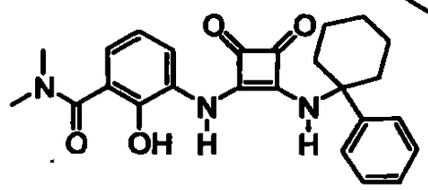


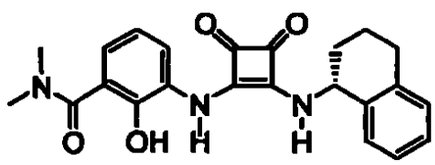


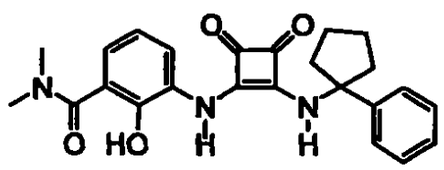


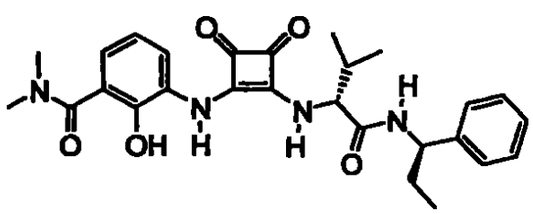


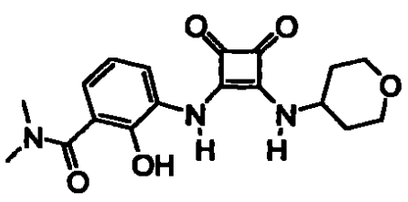


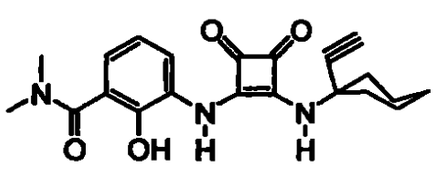


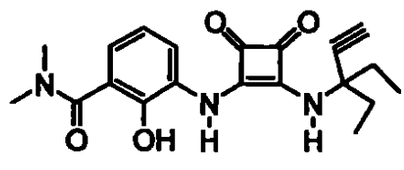


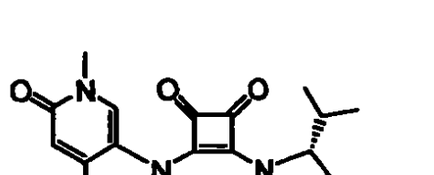


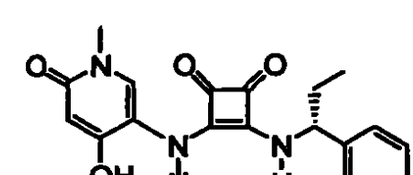


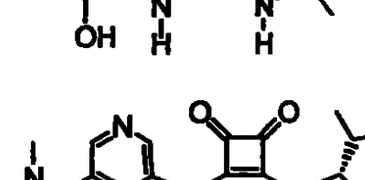


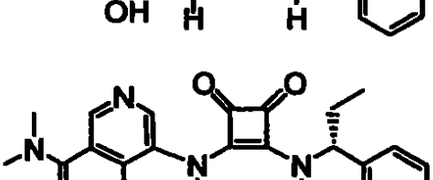


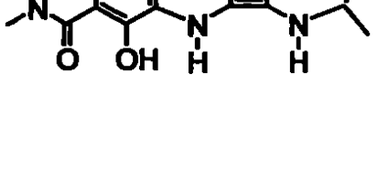


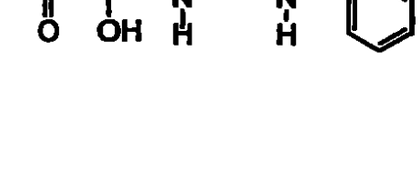


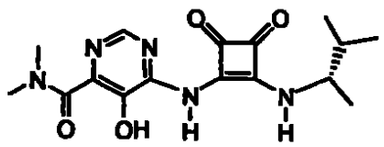


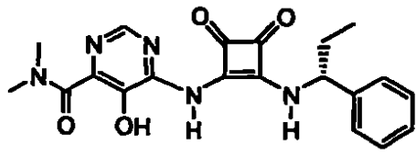


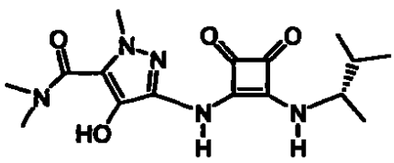


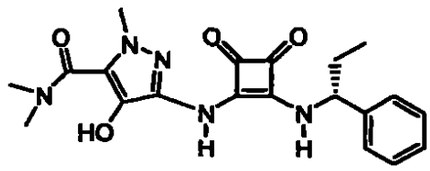


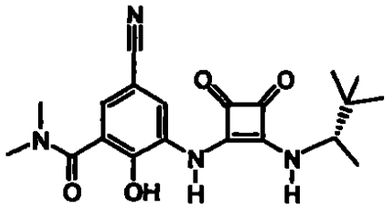


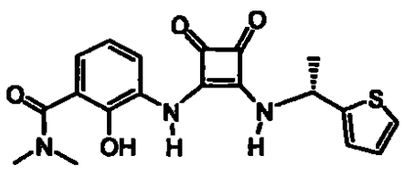


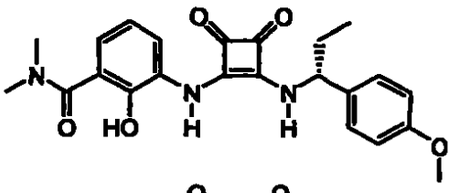


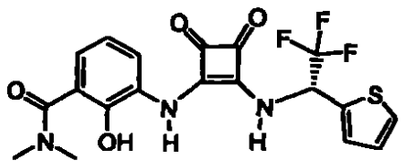


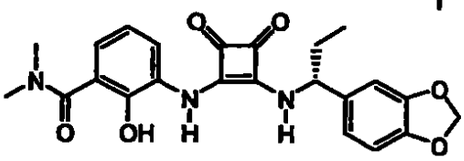


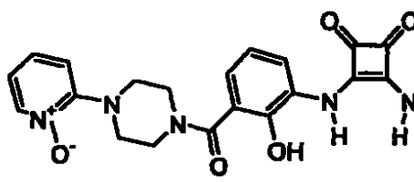


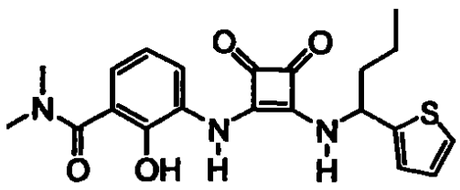


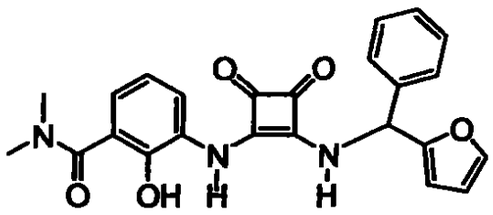


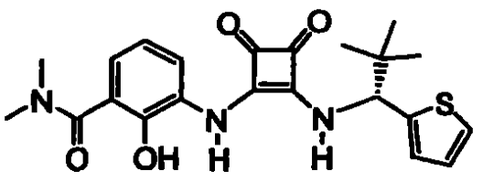


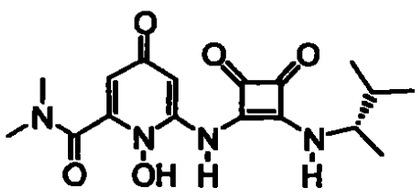


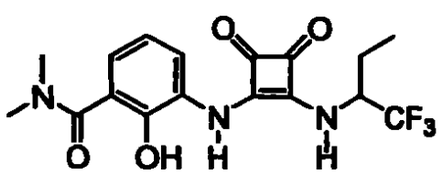


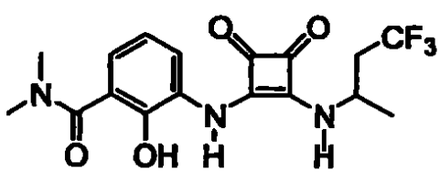


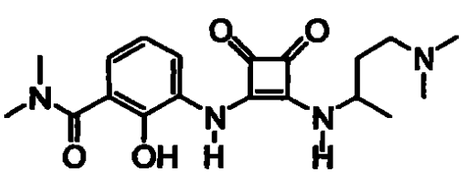


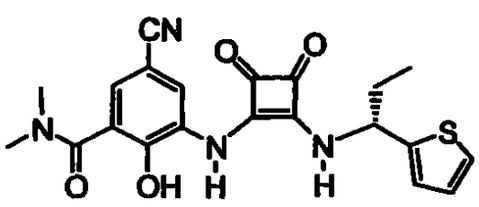


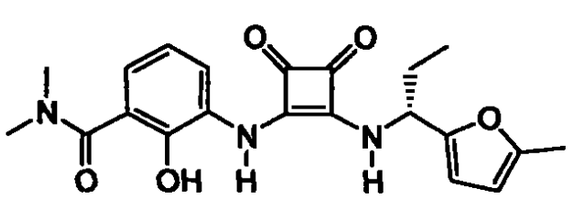


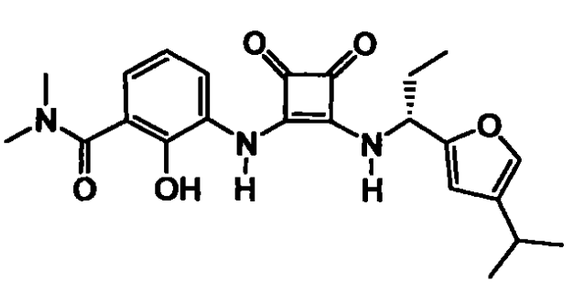




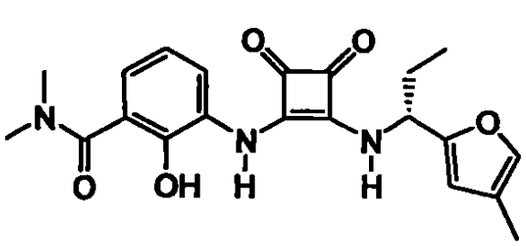


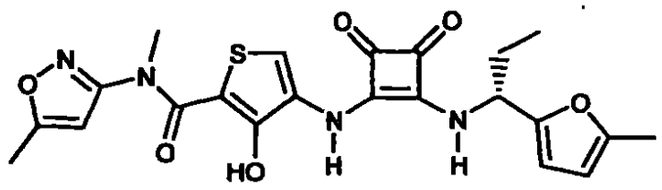


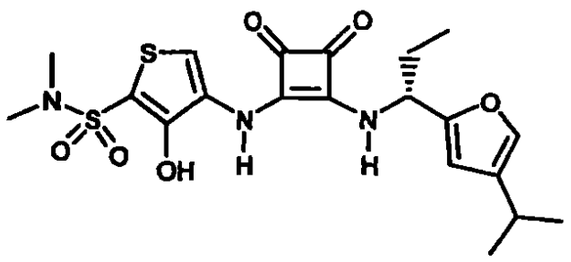


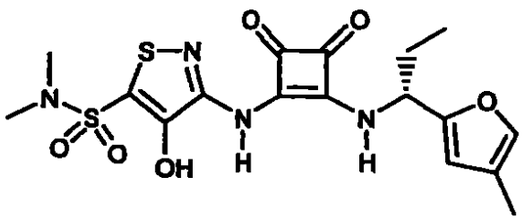


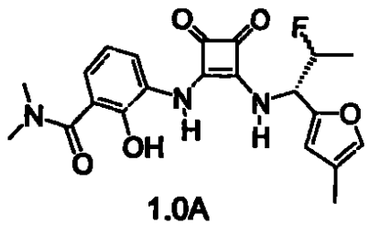
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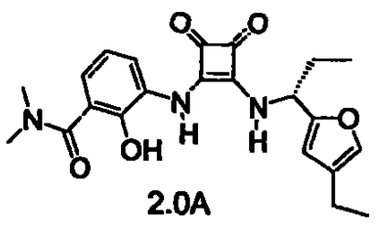




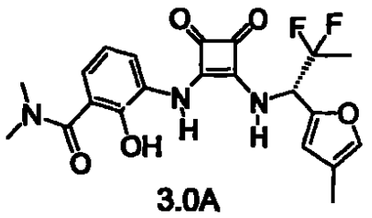




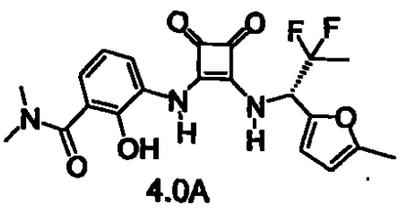
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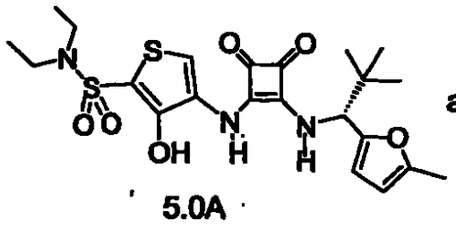
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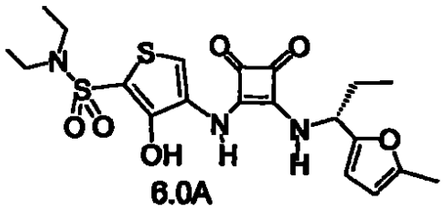


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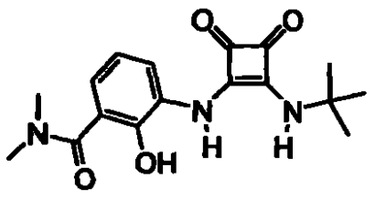
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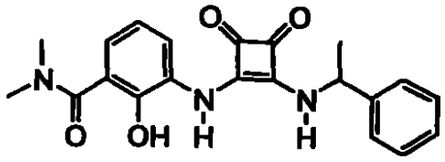
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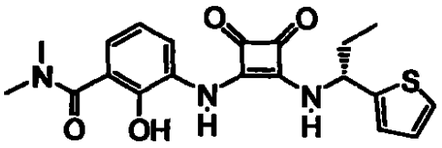


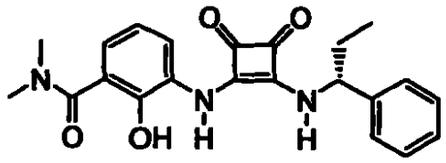
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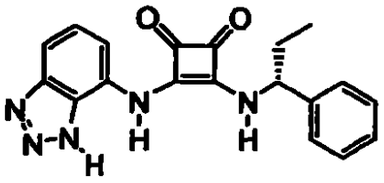
Preferred compounds used to treat the chemokine mediated diseases include but are not limited to:

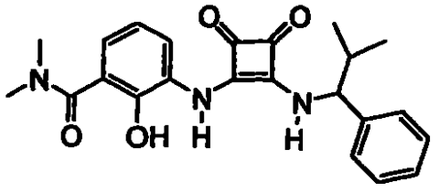


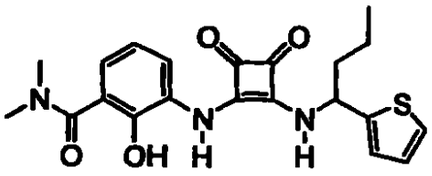


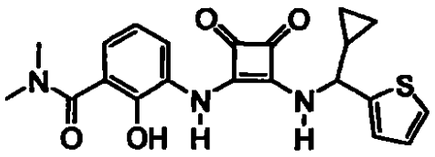


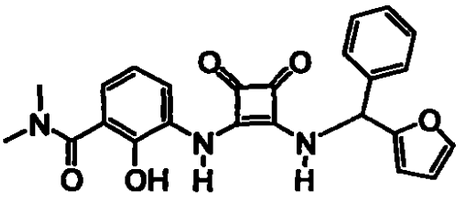


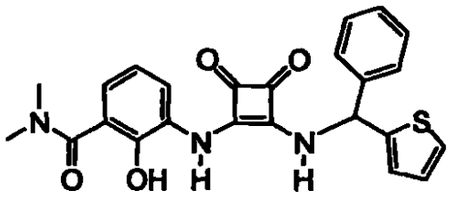


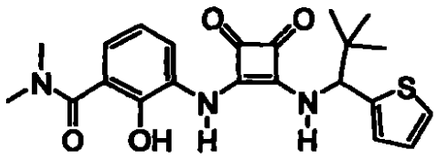


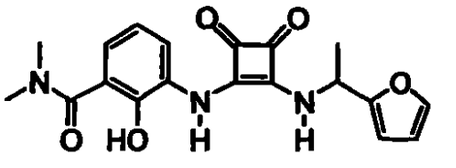


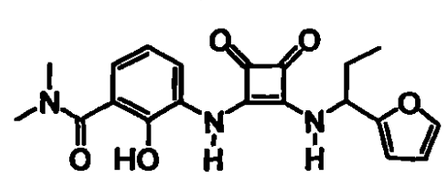


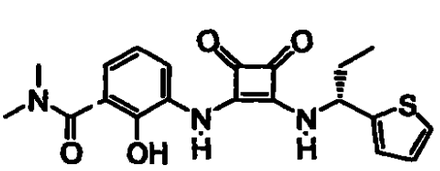




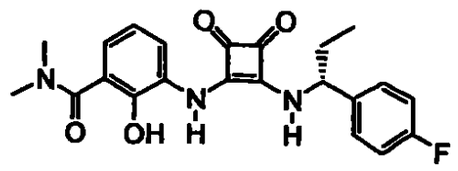


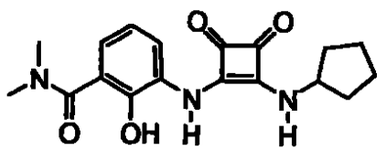


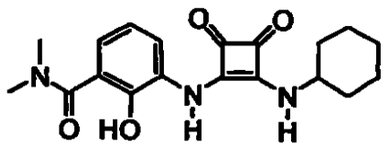


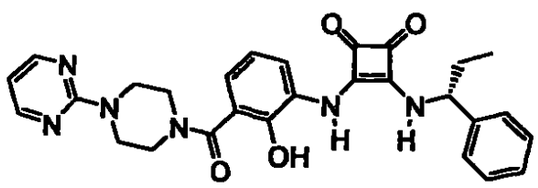


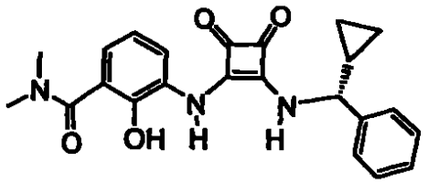
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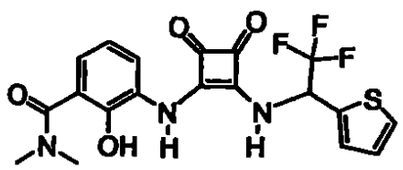


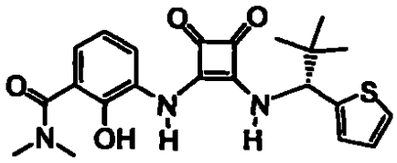


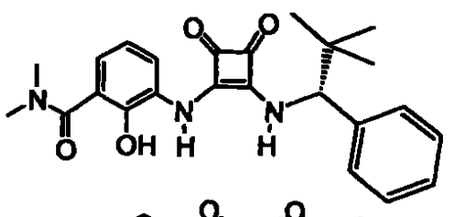


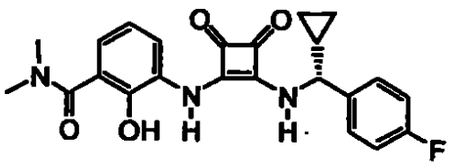


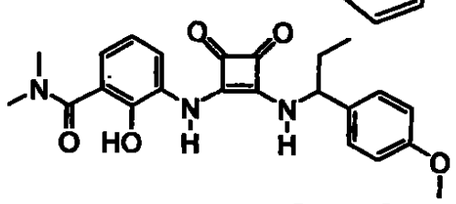


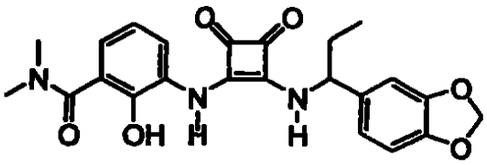


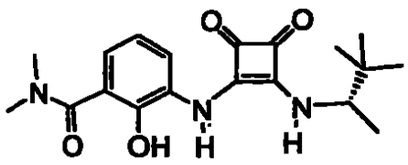


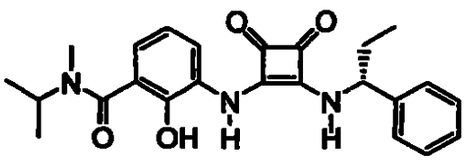


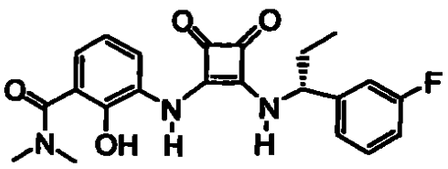


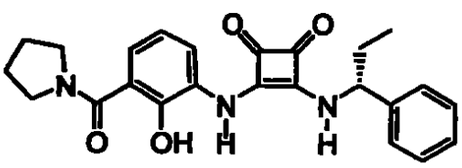


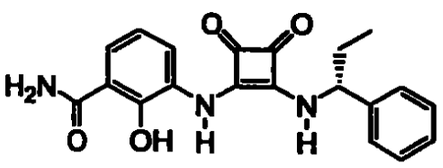


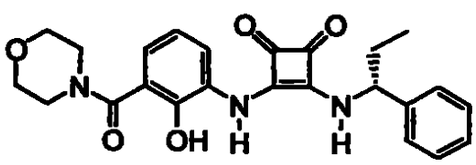


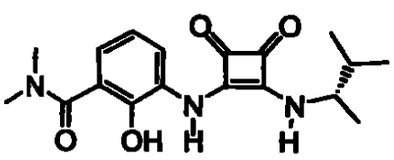


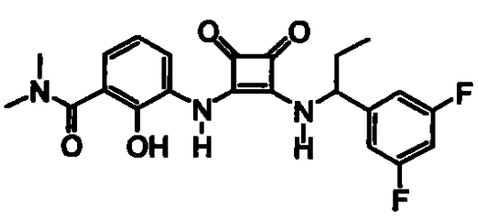


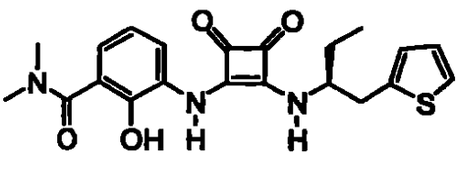


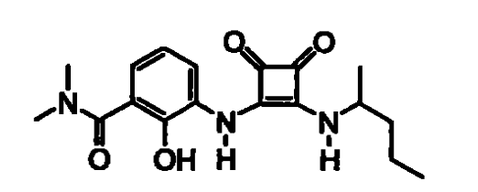


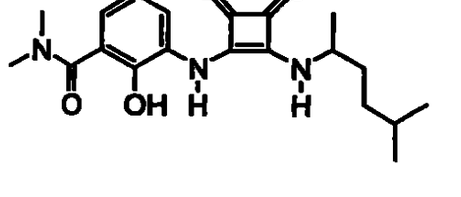


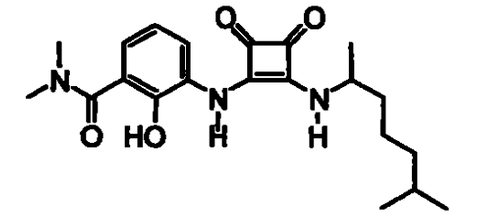


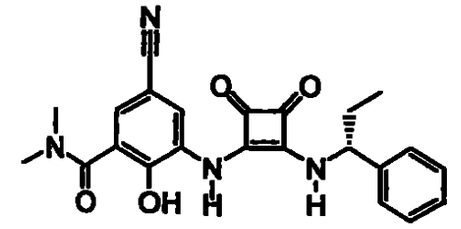


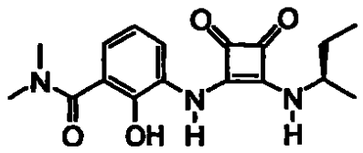


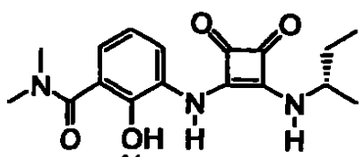


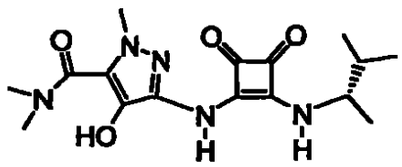


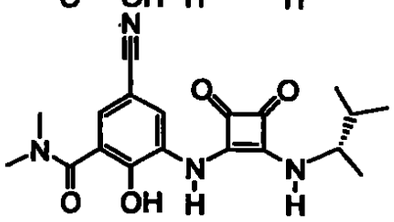


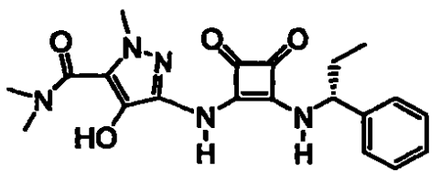


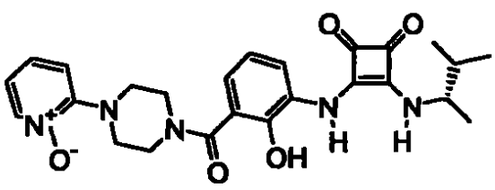


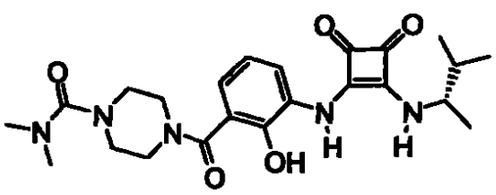


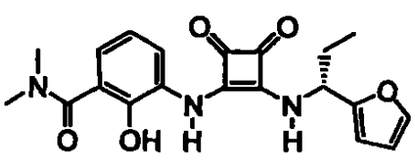


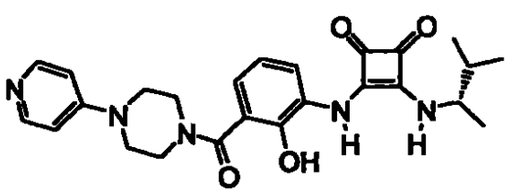


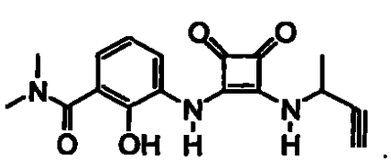


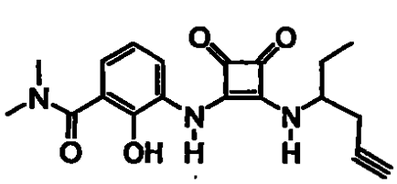


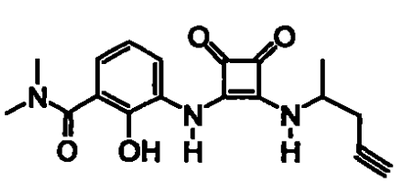


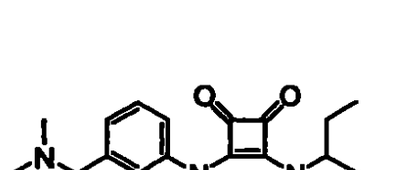


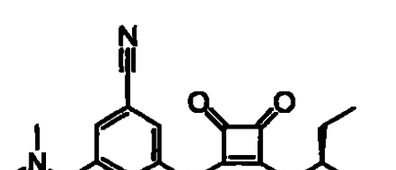


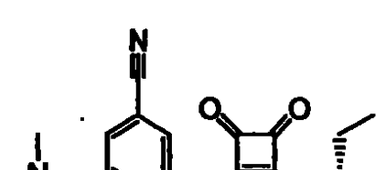


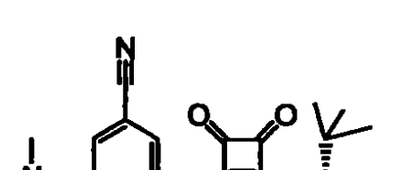


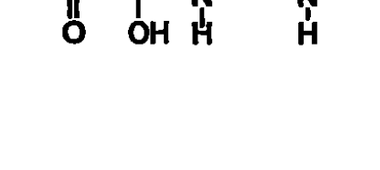


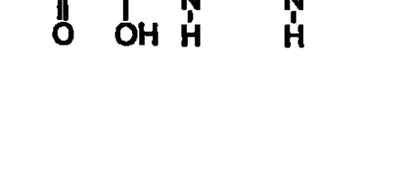


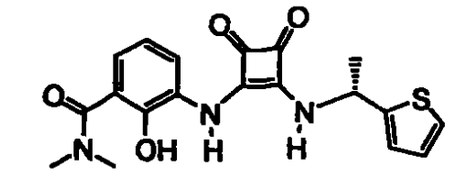


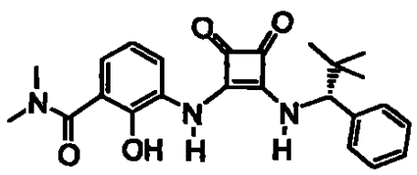


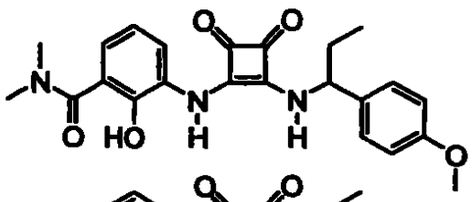


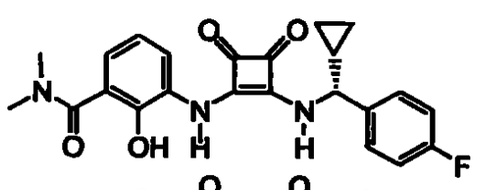


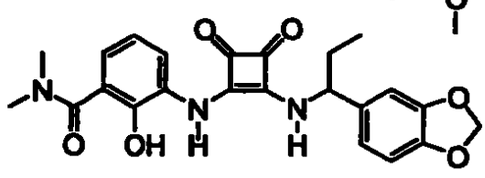


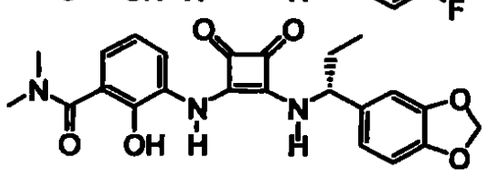


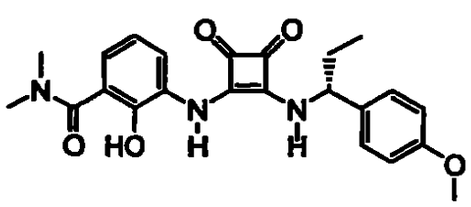


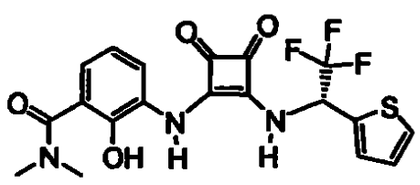


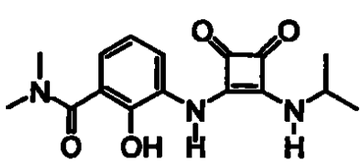


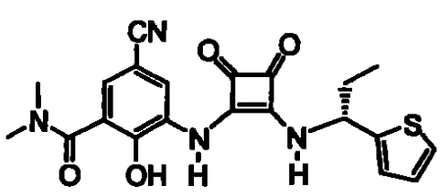


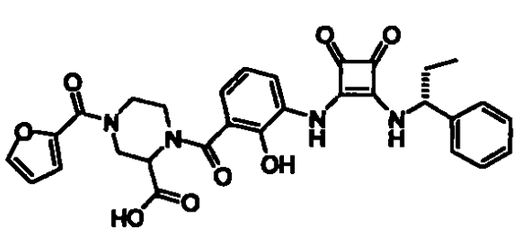


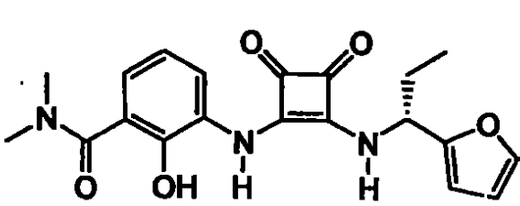




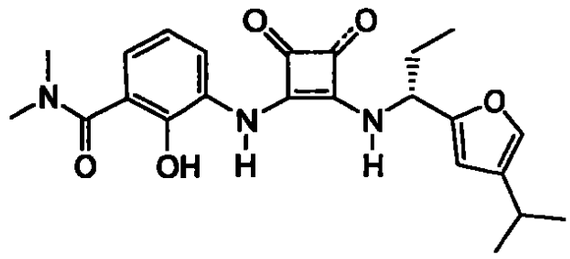


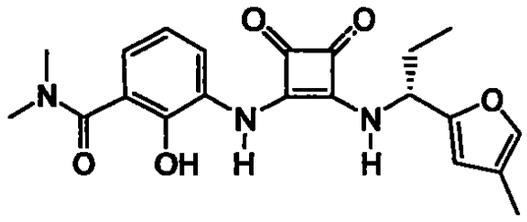


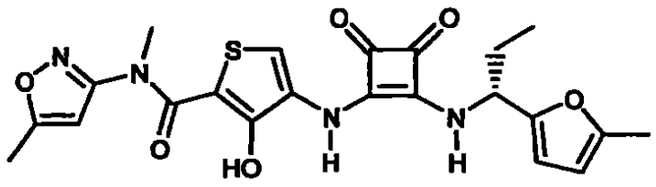


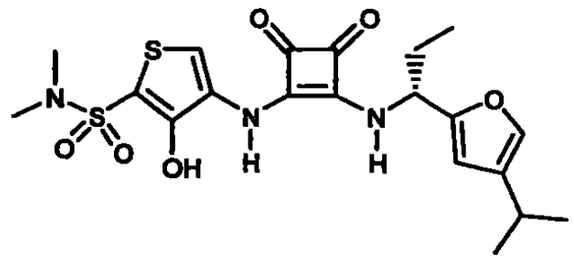


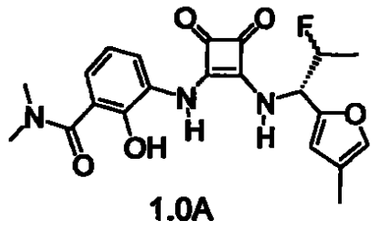
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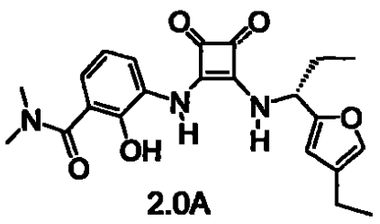




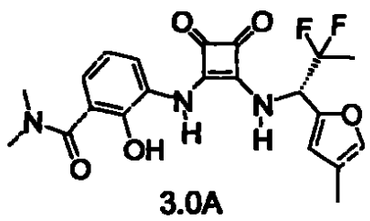




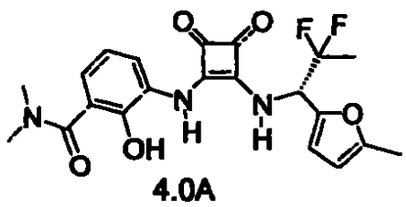
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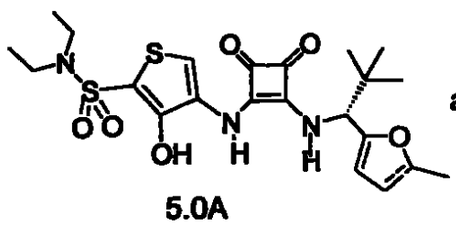
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3.0A

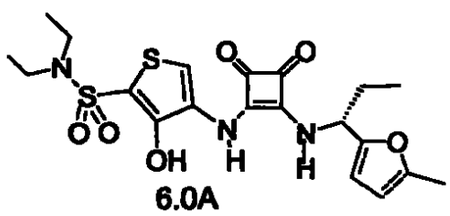


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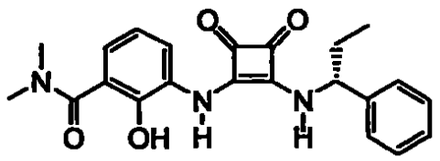
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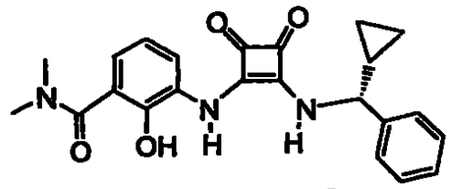
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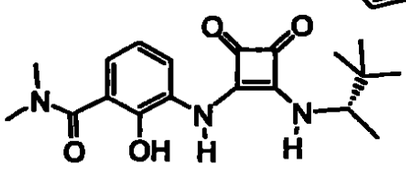


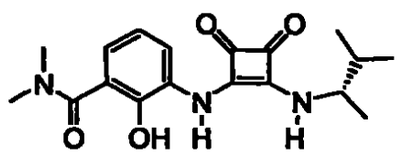
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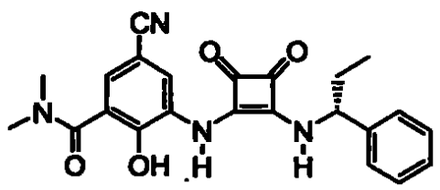
A more preferred group of compounds used to treat the chemokine mediated diseases include but are not limited to

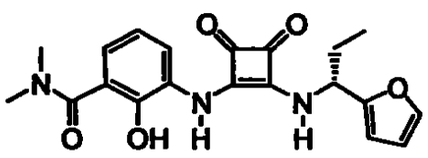


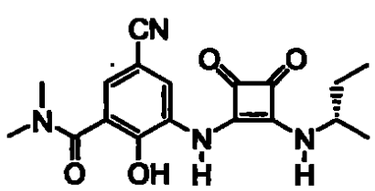


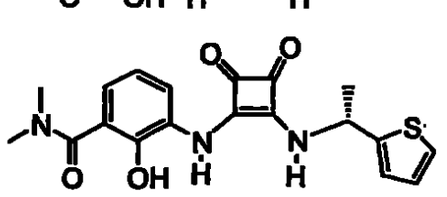


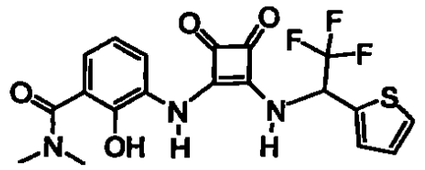


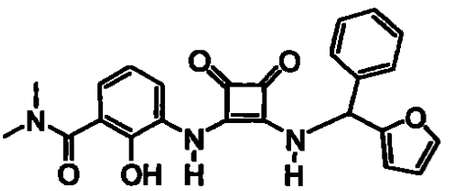


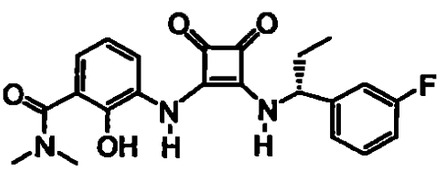


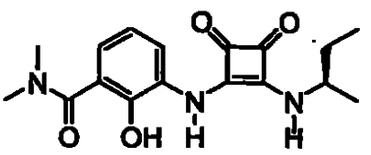


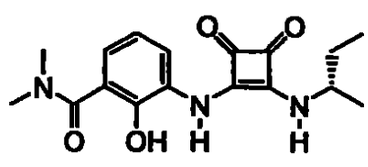


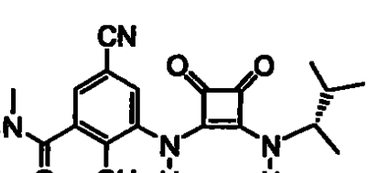


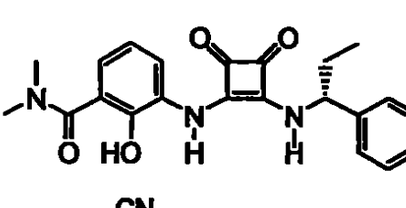


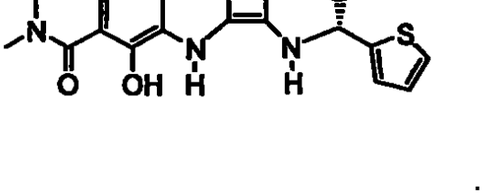


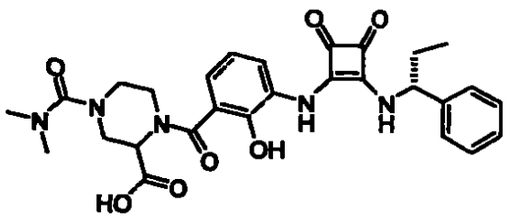


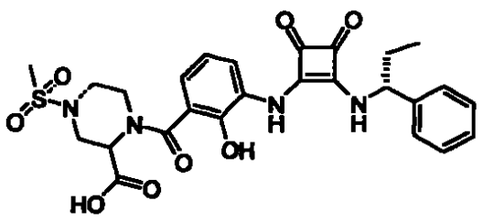


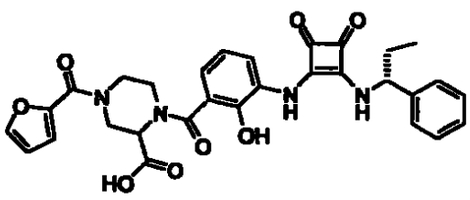


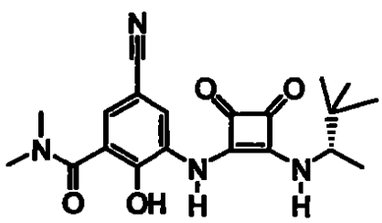


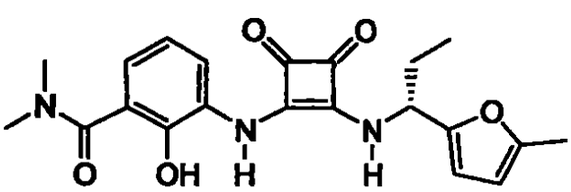


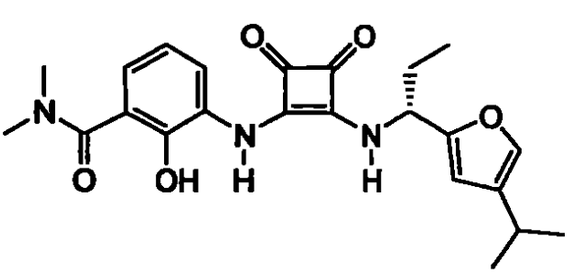


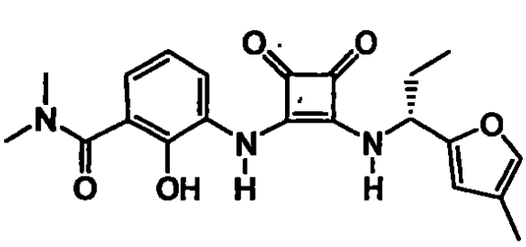


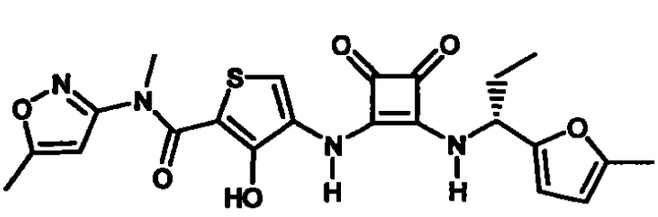


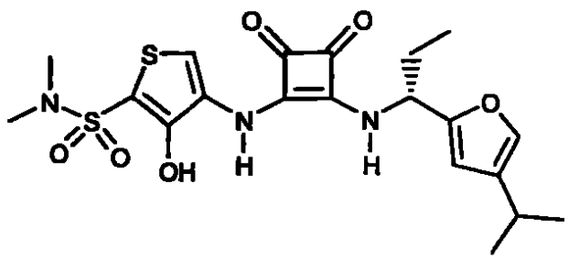


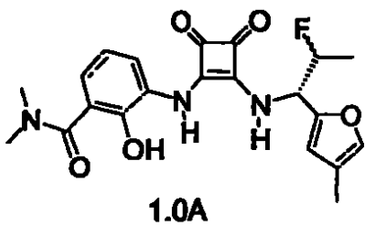




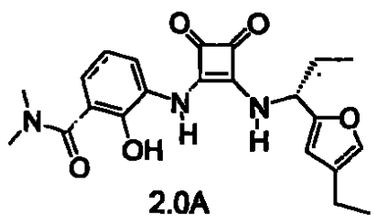




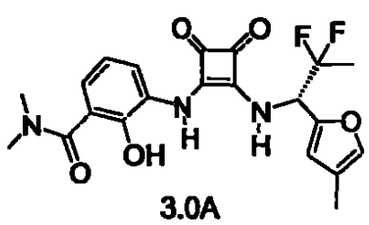




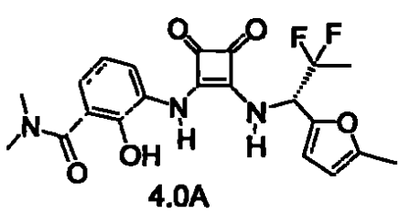
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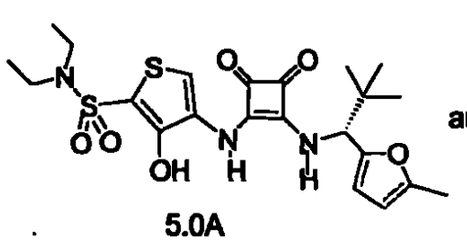
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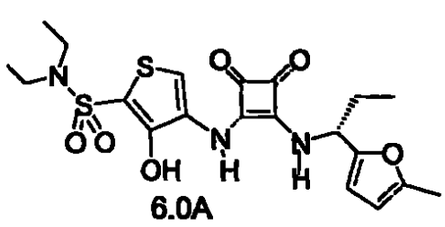


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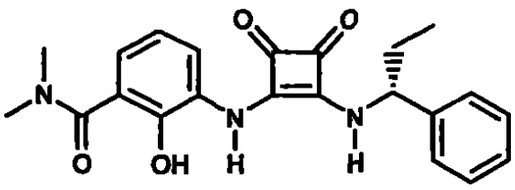
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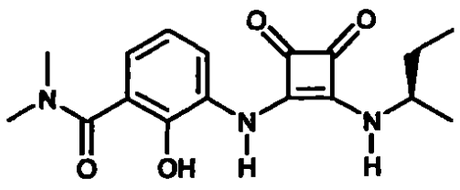
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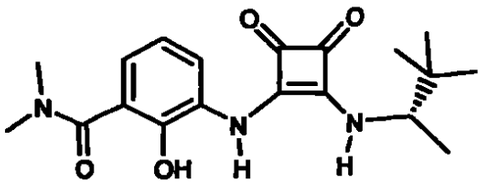


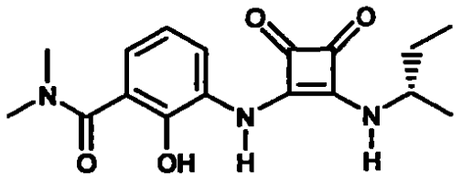
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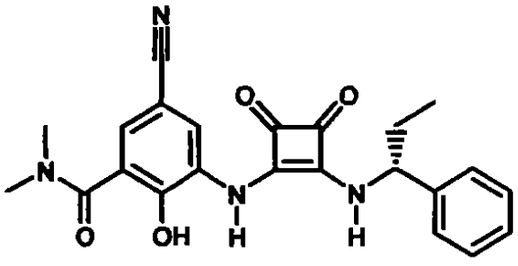
A most preferred group of compounds used to treat the chemokine mediated diseases include but are not limited to

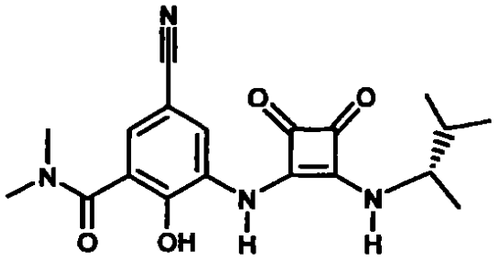


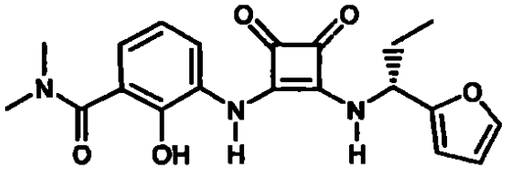


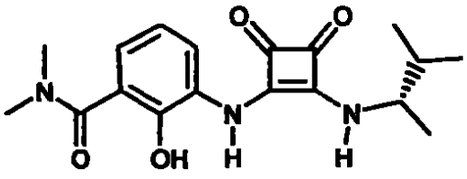


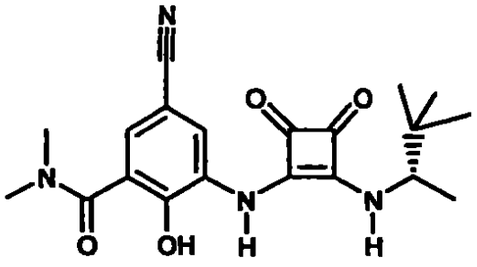


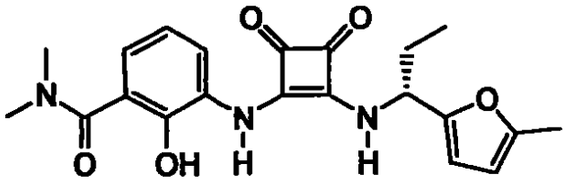


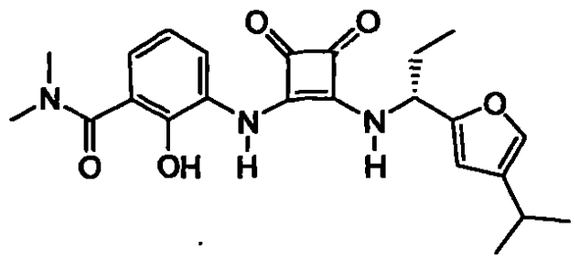


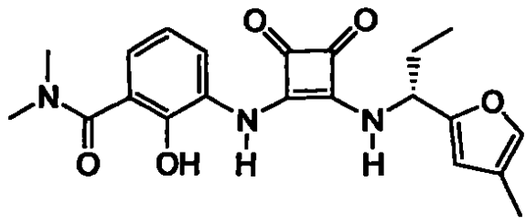


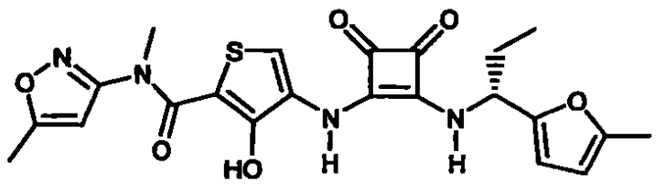


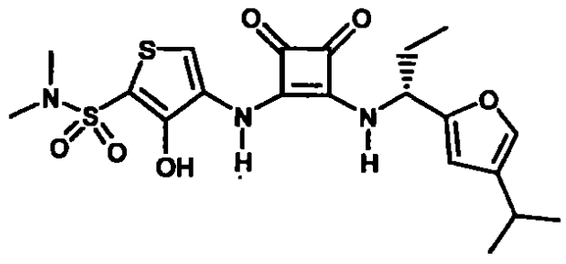


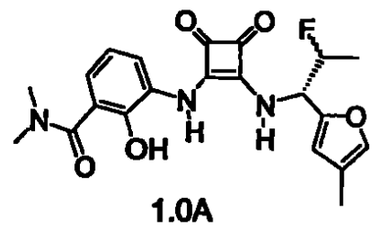




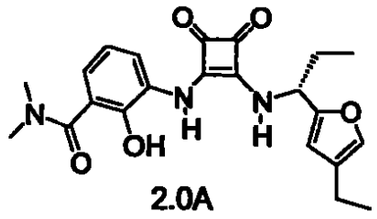




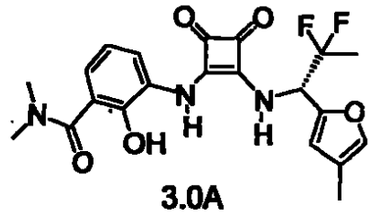




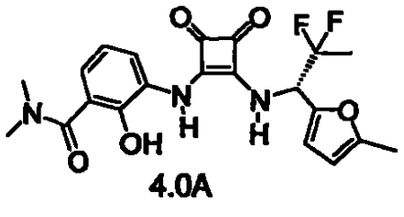
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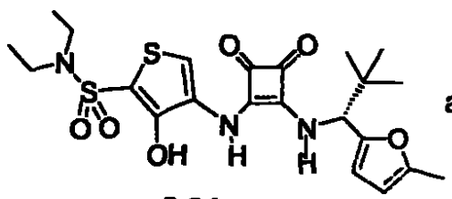
2.0A



3.0A

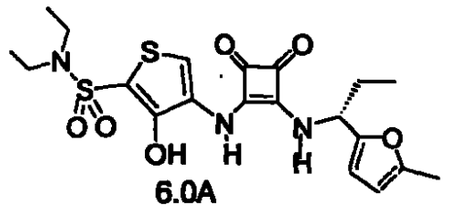


4.0A



5.0A

and



6.0A

Certain compounds of the invention may exist in different stereoisomeric forms (e.g., enantiomers, diastereoisomers and atropisomers). The invention contemplates all such stereoisomers both in pure form and in admixture, including racemic mixtures. Isomers can be prepared using conventional methods.

This invention also includes Prodrugs of the compounds of this invention.

Certain compounds will be acidic in nature, e.g. those compounds that possess a carboxyl or phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts may include sodium, potassium, calcium, aluminum, gold and silver salts. Also contemplated are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

Certain basic compounds also form pharmaceutically acceptable salts, e.g., acid addition salts. For example, the pyrido-nitrogen atoms may form salts with strong acid, while compounds having basic substituents such as amino groups also form salts with weaker acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those skilled in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise equivalent to their respective free base forms for purposes of the invention.

All such acid and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Compounds of the invention can exist in unsolvated and solvated forms, including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like, are equivalent to the unsolvated forms for the purposes of this invention.

In an embodiment of the treatment of cancer, a compound selected from the group consisting of compounds of the formulas IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds) is administered in combination with one of the following antineoplastic agents: gemcitabine, paclitaxel (Taxol®), 5-Fluorourcil (5-FU), cyclophosphamide (Cytoxan®), temozolomide, or Vincristine.

In another embodiment, the present invention provides a method of treating cancer, comprising administering, concurrently or sequentially, and effective amount of a compound selected from the group consisting of compounds of the formulas IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds), and a microtubule affecting agent e.g., paclitaxel.

Another embodiment of the invention is directed to a method treating cancer, comprising administering to a patient in need thereof, concurrently or sequentially, a therapeutically effective amount of (a) a compound selected from the group consisting of compounds of the formulas IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds), and (b) an antineoplastic agent, microtubule affecting agent or anti-angiogenesis agent.

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 which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal composition can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the 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 0.01 mg to about 1000 mg, preferably from about 0.01 mg to about 750 mg, more preferably from about 0.01 mg to about 500 mg, and most preferably from about 0.01 mg to about 250 mg, according to the particular application.

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

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 0.04 mg/day to about 4000 mg/day, in two to four divided doses.

Classes of compounds that can be used as the chemotherapeutic agent (antineoplastic agent) include: alkylating agents, antimetabolites, natural products and their derivatives, hormones and steroids (including synthetic analogs), and synthetics. Examples of compounds within these classes are given below.

Alkylating agents (including nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas and triazenes): Uracil mustard, Chlormethine, Cyclophosphamide (Cytoxan®), Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylene-melamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, and Temozolomide.

Antimetabolites (including folic acid antagonists, pyrimidine analogs, purine analogs and adenosine deaminase inhibitors): Methotrexate, 5-Fluorouracil, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, Pentostatine, and Gemcitabine.

Natural products and their derivatives (including vinca alkaloids, antitumor antibiotics, enzymes, lymphokines and epipodophyllotoxins): Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, paclitaxel (paclitaxel is commercially available as Taxol® and is described in more detail below in the subsection entitled "Microtubule Affecting Agents"), Mithramycin, Deoxyco-formycin, Mitomycin-C, L-Asparaginase, Interferons (especially IFN-a), Etoposide, and Teniposide.

Hormones and steroids (including synthetic analogs): 17α-Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone

propionate, Testolactone, Megestrolacetate, Tamoxifen, Methylprednisolone, Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, Zoladex.

Synthetics (including inorganic complexes such as platinum coordination complexes): Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, and Hexamethylmelamine.

Methods for the safe and effective administration of most of these chemotherapeutic agents are known to those skilled in the art. In addition, their administration is described in the standard literature. For example, the administration of many of the chemotherapeutic agents is described in the "Physicians' Desk Reference" (PDR), e.g., 2002 edition (Medical Economics Company, Montvale, NJ 07645-1742, USA); the disclosure of which is incorporated herein by reference thereto.

As used herein, a microtubule affecting agent is a compound that interferes with cellular mitosis, *i.e.*, having an anti-mitotic effect, by affecting microtubule formation and/or action. Such agents can be, for instance, microtubule stabilizing agents or agents that disrupt microtubule formation.

Microtubule affecting agents useful in the invention are well known to those of skill in the art and include, but are not limited to allocolchicine (NSC 406042), Halichondrin B (NSC 609395), colchicine (NSC 757), colchicine derivatives (e.g., NSC 33410), dolastatin 10 (NSC 376128), maytansine (NSC 153858), rhizoxin (NSC 332598), paclitaxel (Taxol®, NSC 125973), Taxol® derivatives (*e.g.*, derivatives (*e.g.*, NSC 608832), thiocolchicine (NSC 361792), trityl cysteine (NSC 83265), vinblastine sulfate (NSC 49842), vincristine sulfate (NSC 67574), epothilone A, epothilone, and discodermolide (*see* Service, (1996) *Science*, 274:2009) estramustine, nocodazole, MAP4, and the like. Examples of such agents are also described in the scientific and patent literature, see, *e.g.*, Bulinski (1997) *J. Cell Sci.* 110:3055-3064; Panda (1997) *Proc. Natl. Acad. Sci.* USA 94:10560-10564; Muhlradt (1997) Cancer Res. 57:3344-3346; Nicolaou (1997) *Nature* 387:268-272; Vasquez (1997) *Mol. Biol. Cell.* 8:973-985; Panda (1996) *J. Biol. Chem.* 271:29807-29812.

Particularly preferred agents are compounds with paclitaxel-like activity. These include, but are not limited to paclitaxel and paclitaxel derivatives (paclitaxel-like

compounds) and analogues. Paclitaxel and its derivatives are available commercially. In addition, methods of making paclitaxel and paclitaxel derivatives and analogues are well known to those of skill in the art (*see, e.g.,* U.S. Patent Nos: 5,569,729; 5,565,478; 5,530,020; 5,527,924; 5,508,447; 5,489,589; 5,488,116; 5,484,809; 5,478,854; 5,478,736; 5,475,120; 5,468,769; 5,461,169; 5,440,057; 5,422,364; 5,411,984; 5,405,972; and 5,296,506).

More specifically, the term "paclitaxel" as used herein refers to the drug commercially available as Taxol® (NSC number: 125973). Taxol® inhibits eukaryotic cell replication by enhancing polymerization of tubulin moieties into stabilized microtubule bundles that are unable to reorganize into the proper structures for mitosis. Of the many available chemotherapeutic drugs, paclitaxel has generated interest because of its efficacy in clinical trials against drug-refractory tumors, including ovarian and mammary gland tumors (Hawkins (1992) *Oncology*, 6: 17-23, Horwitz (1992) *Trends Pharmacol. Sci.* 13: 134-146, Rowinsky (1990) *J. Natl. Canc. Inst.* 82: 1247-1259).

Additional microtubule affecting agents can be assessed using one of many such assays known in the art, *e.g.,* a semiautomated assay which measures the tubulin-polymerizing activity of paclitaxel analogs in combination with a cellular assay to measure the potential of these compounds to block cells in mitosis (see *Lopes* (1997) *Cancer Chemother. Pharmacol.* 41:37-47).

Generally, activity of a test compound is determined by contacting a cell with that compound and determining whether or not the cell cycle is disrupted, in particular, through the inhibition of a mitotic event. Such inhibition may be mediated by disruption of the mitotic apparatus, *e.g.,* disruption of normal spindle formation. Cells in which mitosis is interrupted may be characterized by altered morphology (*e.g.,* microtubule compaction, increased chromosome number, etc.).

Compounds with possible tubulin polymerization activity can be screened *in vitro*. In a preferred embodiment, the compounds are screened against cultured WR21 cells (derived from line 69-2 wap-ras mice) for inhibition of proliferation and/or for altered cellular morphology, in particular for microtubule compaction. *In vivo* screening of positive-testing compounds can then be performed using nude mice bearing the WR21 tumor cells. Detailed protocols for this screening method are described by Porter (1995) *Lab. Anim. Sci.*, 45(2):145-150.

Other methods of screening compounds for desired activity are well known to those of skill in the art. Typically such assays involve assays for inhibition of microtubule assembly and/or disassembly. Assays for microtubule assembly are described, for example, by Gaskin *et al.* (1974) *J. Molec. Biol.*, 89: 737-758. U.S. Patent No. 5,569,720 also provides *in vitro* and *in vivo* assays for compounds with paclitaxel-like activity.

Methods for the safe and effective administration of the above-mentioned microtubule affecting agents are known to those skilled in the art. In addition, their administration is described in the standard literature. For example, the administration of many of the chemotherapeutic agents is described in the "Physicians' Desk Reference" (PDR), e.g., 1996 edition (Medical Economics Company, Montvale, NJ 07645-1742, USA); the disclosure of which is incorporated herein by reference thereto.

The amount and frequency of administration of the compounds of formulas IA, IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds), and the chemotherapeutic agents and/or radiation therapy will be regulated according to the judgment of the attending clinician (physician) considering such factors as age, condition and size of the patient as well as severity of the disease being treated. A dosage regimen of the compounds of formulas IA, IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds) can be oral administration of from 10 mg to 2000 mg/day, preferably 10 to 1000 mg/day, more preferably 50 to 600 mg/day, in two to four (preferably two) divided doses, to block tumor growth. Intermittant therapy (*e.g.*, one week out of three weeks or three out of four weeks) may also be used.

The chemotherapeutic agent and/or radiation therapy can be administered according to therapeutic protocols well known in the art. It will be apparent to those skilled in the art that the administration of the chemotherapeutic agent and/or radiation therapy can be varied depending on the disease being treated and the known effects of the chemotherapeutic agent and/or radiation therapy on that disease. Also, in accordance with the knowledge of the skilled clinician, the therapeutic protocols (e.g.,

dosage amounts and times of administration) can be varied in view of the observed effects of the administered therapeutic agents (i.e., antineoplastic agent or radiation) on the patient, and in view of the observed responses of the disease to the administered therapeutic agents.

Embodiments of this invention are directed to methods of treatment wherein a compounds of the formulas IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds) are administered concurrently or sequentially with a chemotherapeutic agent and/or radiation. Thus, it is not necessary that, for example, the chemotherapeutic agent and said compounds, or the radiation and said compounds, should be administered simultaneously or essentially simultaneously. The advantage of a simultaneous or essentially simultaneous administration is well within the determination of the skilled clinician.

Also, in general, the compounds of formulas IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds), and the chemotherapeutic agent, do not have to be administered in the same pharmaceutical composition, and may, because of different physical and chemical characteristics, have to be administered by different routes. For example, the compounds formulas IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds) may be administered orally to generate and maintain good blood levels thereof, while the chemotherapeutic agent may be administered intravenously. The determination of the mode of administration and the advisability of administration, where possible, in the same pharmaceutical composition, is well within the knowledge of the skilled clinician. The initial administration can be made according to established protocols known in the art, and then, based upon the observed effects, the dosage, modes of administration and times of administration can be modified by the skilled clinician .

The particular choice of a compound formulas IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said

compounds), and chemotherapeutic agent and/or radiation will depend upon the diagnosis of the attending physicians and their judgement of the condition of the patient and the appropriate treatment protocol.

The compounds of formulas IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds), and chemotherapeutic agent and/or radiation may be administered concurrently (e.g., simultaneously, essentially simultaneously or within the same treatment protocol) or sequentially, depending upon the nature of the proliferative disease, the condition of the patient, and the actual choice of chemotherapeutic agent and/or radiation to be administered in conjunction (i.e., within a single treatment protocol) with the compounds of formulas IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds).

If the compounds of formulas IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds), and the chemotherapeutic agent and/or radiation are not administered simultaneously or essentially simultaneously, then the initial order of administration of the compounds of formulas IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds), and the chemotherapeutic agent and/or radiation, may not be important. Thus, the compounds of formulas IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds) may be administered first, followed by the administration of the chemotherapeutic agent and/or radiation; or the chemo-therapeutic agent and/or radiation may be administered first, followed by the administration of the compounds of formulas IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds). This alternate administration may be repeated during a single treatment protocol. The determination of the order of administration, and the

number of repetitions of administration of each therapeutic agent during a treatment protocol, is well within the knowledge of the skilled physician after evaluation of the disease being treated and the condition of the patient.

For example, the chemotherapeutic agent and/or radiation may be administered first, especially if it is a cytotoxic agent, and then the treatment continued with the administration of the compounds of formulas IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds) followed, where determined advantageous, by the administration of the chemotherapeutic agent and/or radiation, and so on until the treatment protocol is complete.

Thus, in accordance with experience and knowledge, the practicing physician can modify each protocol for the administration of a component (therapeutic agent–*i.e.*, the compounds of formulas IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds), chemotherapeutic agent or radiation) of the treatment according to the individual patient's needs, as the treatment proceeds.

The attending clinician, in judging whether treatment is effective at the dosage administered, will consider the general well-being of the patient as well as more definite signs such as relief of disease-related symptoms, inhibition of tumor growth, actual shrinkage of the tumor, or inhibition of metastasis. Size of the tumor can be measured by standard methods such as radio-logical studies, e.g., CAT or MRI scan, and successive measurements can be used to judge whether or not growth of the tumor has been retarded or even reversed. Relief of disease-related symptoms such as pain, and improvement in overall condition can also be used to help judge effectiveness of treatment.

BIOLOGICAL EXAMPLES

The compounds of the present invention are useful in the treatment of CXC-chemokine mediated conditions and diseases. This utility is manifested in their ability to inhibit IL-8 and GRO-α chemokine as demonstrated by the following *in vitro* assays.

Receptor Binding Assays:

CXCR1 SPA Assay

For each well of a 96 well plate, a reaction mixture of 10 μg hCXCR1-CHO overexpressing membranes (Biosignal) and 200 μg/well WGA-SPA beads (Amersham) in 100 μl was prepared in CXCR1 assay buffer (25 mM HEPES, pH 7.8, 2 mM $CaCl_2$, 1mM $MgCl_2$, 125 mM NaCl, 0.1% BSA) (Sigma). A 0.4 nM stock of ligand, [125I]-IL-8 (NEN) was prepared in the CXCR1 assay buffer. 20X stock solutions of test compounds were prepared in DMSO (Sigma). A 6 X stock solution of IL-8 (R&D) was prepared in CXCR2 assay buffer. The above solutions were added to a 96-well assay plate (PerkinElmer) as follows: 10 μl test compound or DMSO, 40 μl CXCR1 assay buffer or IL-8 stock, 100 μl of reaction mixture, 50 μl of ligand stock (Final [Ligand] = 0.1 nM). The assay plates were shaken for 5 minutes on plate shaker, then incubated for 8 hours before cpm/well were determined in Microbeta Trilux counter (PerkinElmer). % Inhibition of Total binding-NSB (250 nM IL-8) was determined for IC50 values. Compounds of this invention had an IC_{50} of <20μM. The most preferred compounds had a K_i within the range of 3nM to 1120nM.

CXCR2 SPA Assay

For each well of a 96 well plate, a reaction mixture of 4 μg hCXCR2-CHO overexpressing membranes (Biosignal) and 200 μg/well WGA-SPA beads (Amersham) in 100 μl was prepared in CXCR2 assay buffer (25 mM HEPES, pH 7.4, 2 mM $CaCl_2$, 1mM $MgCl_2$). A 0.4 nM stock of ligand, [125I]-IL-8 (NEN), was prepared in the CXCR2 assay buffer. 20X stock solutions of test compounds were prepared in DMSO (Sigma). A 6 X stock solution of GRO-α (R&D) was prepared in CXCR2 assay buffer. The above solutions were added to a 96-well assay plate (PerkinElmer or Corning) as follows: 10 μl test compound or DMSO, 40 ul CXCR2 assay buffer or GRO- α stock, 100 μl of reaction mixture, 50 μl of ligand stock (Final [Ligand] = 0.1 nM). When 40 X stock solutions of test compounds in DMSO were prepared, then the above protocol was used except instead 5 μl test compound or DMSO and 45 μl CXCR2 assay buffer were used. The assay plates were shaken for 5 minutes on a plate shaker, then incubated for 2-8 hours before cpm/well were determined in Microbeta Trilux counter (PerkinElmer). % Inhibition of total binding minus non-specific binding (250 nM Gro-α or 50 μM antagonist) was determined and IC50

values calculated. Compounds of this inventi n had an IC_{50} of <5μM. The most preferred compounds had a K_i within the range of 0.8nM to 40nM. The compound of Example 360.31 had a K_i of 3nM.

Calcium Fluorescence Assay (FLIPR)

HEK 293 cells stably transfected with hCXCR2 and Gαi/q were plated at 10,000 cells per well in a Poly-D-Lysine Black/Clear plate (Becton Dickinson) and incubated 48 hours at 5% CO_2, 37°C. The cultures were then incubated with 4 mM fluo-4, AM (Molecular Probes) in Dye Loading Buffer (1% FBS, HBSS w. Ca & Mg, 20 mM HEPES (Cellgro), 2.5 mM Probenicid (Sigma) for 1 hour. The cultures were washed with wash buffer (HBSS w Ca, & Mg, 20 mM HEPES, Probenicid (2.5 mM)) three times, then 100 μl/well wash buffer was added.

During incubation, compounds were prepared as 4X stocks in 0.4% DMSO (Sigma) and wash buffer and added to their respective wells in the first addition plate. IL-8 or GRO-α (R&D Systems) concentrations were prepared 4X in wash buffer + 0.1% BSA and added to their respective wells in second addition plate.

Culture plate and both addition plates were then placed in the FLIPR imaging system to determine change in calcium fluorescence upon addition of compound and then ligand. Briefly, 50 μl of compound solutions or DMSO solution was added to respective wells and change in calcium fluorescence measured by the FLIPR for 1 minute. After a 3 minute incubation within the instrument, 50 μl of ligand was then added and the change in calcium fluorescence measured by the FLIPR instrument for I minute. The area under each stimulation curve was determined and values used to determine % Stimulation by compound (agonist) and % Inhibition of Total Calcium response to ligand (0.3 nM IL-8 or GRO-α) for IC50 values of the test compounds.

Chemotaxis assays for 293-CXCR2

A chemotaxis assay is setup using Fluorblok inserts (Falcon) for 293-CXCR2 cells (HEK-293 cells overexpressing human CXCR2). The standard protocol used at present is as follows:

1. Inserts are coated with collagenIV (2ug/ml) for 2 hrs at 37°C.
2. The collagen is removed and inserts are allowed to air dry overnight.

3. Cells are labeled with 10uM calcein AM (Molecular Probes) for 2 hrs. Labeling is done in complete media with 2% FBS.
4. Dilutions of compound are made in minimal media (0.1% BSA) and placed inside the insert which is positioned inside the well of a 24 well plate. Within the well is IL-8 at a concentration of 0.25nM in minimal media. Cells are washed and resuspended in minimal media and placed inside the insert at a concentration of 50,000 cells per insert.
5. Plate is incubated for 2hrs and inserts are removed and placed in a new 24 well. Fluorescence is detected at excitation=485 nM and emission=530 nM.

Cytotoxicity Assays

A cytotoxicity assay for CXCR2 compounds is conducted on 293-CXCR2 cells. Concentrations of compounds are tested for toxicity at high concentrations to determine if they may be used for further evaluation in binding and cell based assays. The protocol is as follows:

1. 293-CXCR2 cells are plated overnight at a concentration of 5000 cells per well in complete media.
2. Dilutions of compound are made in minimal media w/0.1% BSA. Complete media is poured off and the dilutions of compound are added. Plates are incubated for 4, 24 and 48hrs. Cells are labeled with 10uM calcein AM for 15 minutes to determine cell viability. Detection method is the same as above.

Soft Agar Assay

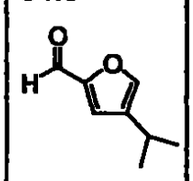
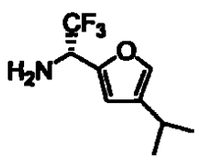
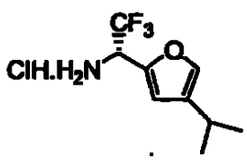
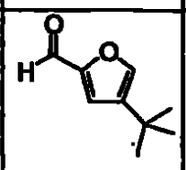
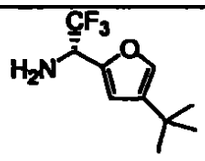
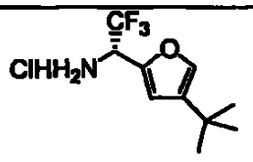
10,000 SKMEL-5 cells/well are placed in a mixture of 1.2% agar and complete media with various dilutions of compound. Final concentration of agar is 0.6%. After 21 days viable cell colonies are stained with a solution of MTT (1mg/ml in PBS). Plates are then scanned to determine colony number and size. IC_{50} is determined by comparing total area vs. compound concentration.

Compounds of formulas IA, IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 may be produced by processes known to those skilled in the art, by the processes disclosed in WO 02/083624 published October 24, 2002, and by the preparations and examples below.

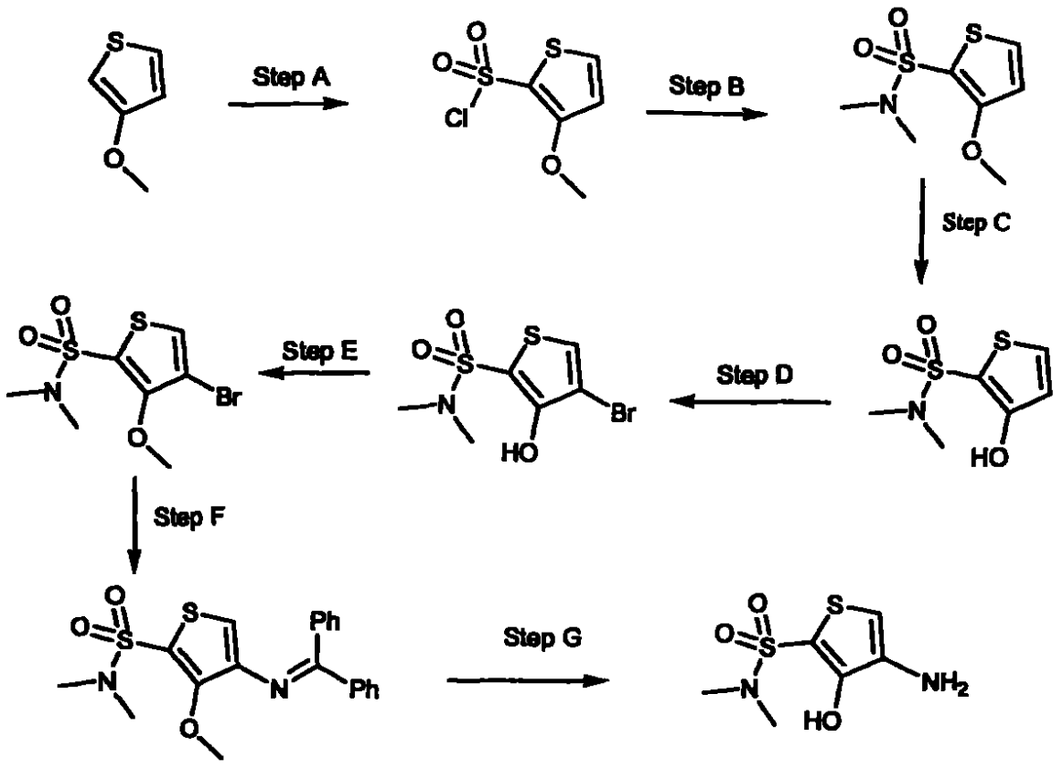
The invention disclosed herein is exemplified by the following preparations and examples that should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures may be apparent to those skilled in the art.

PREPARATIVE EXAMPLES 13.17A-13.17B

Following the procedure set forth in Preparative Example 13.13 of WO 02/083624 published October 24, 2002, but using the prepared or commercially available aldehydes, the optically pure amine products in the Table below were obtained. The number "34.8" in the "Aldehyde" column refers to Preparative Example 34.8 in WO 02/083624.

Prep Ex.	Aldehyde	Amine	Product	Yield (%)
13.17A	34.8 			38%
13.17B				31%

PREPARATIVE EXAMPLE 13.29



Step A

To a solution of 3-methoxythiophene (3 g) in dichloromethane (175 mL) at –78°C was added chlorosulfonic acid (8.5 mL) dropwise. The mixture was stirred for 15 min at –78°C and 1.5 h at room temp. Afterwards, the mixture was poured carefully into crushed ice, and extracted with dichloromethane. The extracts were washed with brine, dried over magnesium sulfate, filtered through a 1-in silica gel pad. The filtrate was concentrated in vacuo to give the desired compound (4.2 g).

Step B

The product from Step A above (4.5 g) was dissolved in dichloromethane (140 mL) and added with triethylamine (8.8 mL) followed by diethyl amine in THF (2*M*, 21 mL). The resulting mixture was stirred at room temperature overnight. The mixture was washed with brine and saturated bicarbonate (aq) and brine again, dried over sodium sulfate, filtered through a 1-in silica gel pad. The filtrate was concentrated in vacuo to give the desired compound (4.4 g).

Step C

The product from Step B above (4.3 g) was dissolved in dichloromethane (125 mL) and cooled in a -78°C bath. A solution of boron tribromide (1.0 M in dichloromethane, 24.3 mL) was added. The mixture was stirred for 4 h while the temperature was increased slowly from -78°C to 10°C. H_2O was added, the two layers were separated, and the aqueous layer was extracted with dichloro- methane. The combined organic layer and extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to give 3.96 g of the desired hydroxy-compound.

Step D

The product from step C above (3.96 g) was dissolved in 125 mL of dichloromethane, and added with potassium carbonate (6.6 g) followed by bromine (2 mL). The mixture was stirred for 5 h at room temperature, quenched with 100 mL of H_2O. The aqueous mixture was addjusted to pH ~ 5 using a 0.5N hydrogen chloride aqueous solution, and extracted with dichloromethane. The extracts were washed with a 10 % $Na_2S_2O_3$ aqueous solution and brine, dried over sodium sulfate, and filtered through a celite pad. The filtrate was concentrated in vacuo to afford 4.2 g of the desired bromo-compound.

Step E

The product from Step D (4.2 g) was dissolved in 100 mL of acetone and added with potassium carbonate (10 g) followed by iodomethane (9 mL). The mixture was heated to reflux and continued for 3.5 h. After cooled to room temperature, the mixture was filtered through a Celite pad. The filtrate was concentrated in vacuo to a dark brown residue, which was purified by flash column chromatography eluting with dichloromethane-hexanes (1:1, v/v) to give 2.7 g of the desired product.

Step F

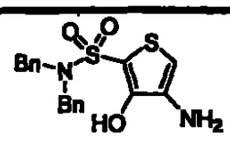
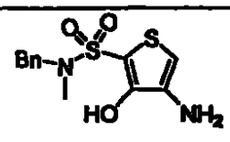
The product from step E (2.7 g) was converted to the desired imine compound (3 g), following the similar procedure to that of Preparative Example 13.19 step D.

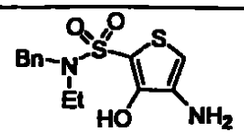
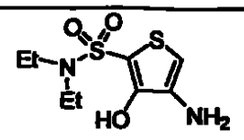
Step G

The imine product from step F (3 g) was dissolved in 80 mL of dichloromethane and cooled in a –78°C bath. A solution of boron tribromide (1.0 M in dichloromethane, 9.2 mL) was added dropwise. The mixture was stirred for 4.25 h from -78°C to 5°C. H_2O (50 mL) was added, and the layers were separated. The aqueous layer was extracted with dichloromethane. The organic layer and extracts were combined, washed with brine, and concentrated to an oily residue. The residue was dissolved in 80 mL of methanol, stirred with sodium acetate (1.5 g) and hydroxyamine hydrochloride (0.95 g) at room temperature for 2 h. The mixture was poured into an aqueous mixture of sodium hydroxide (1.0 M aq, 50 mL) and ether (100 mL). The two layers were separated. The aqueous layer was washed with ether three times. The combined ether washings were re-extracted with H_2O once. The aqueous layers were combined, washed once with dichloromethane, adjusted to pH ~ 6 using 3.0 M and 0.5 M hydrogen chloride aqueous solutions, and extracted with dichloromethane. The organic extracts were combined, washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 1.2 g of desired amine compound.

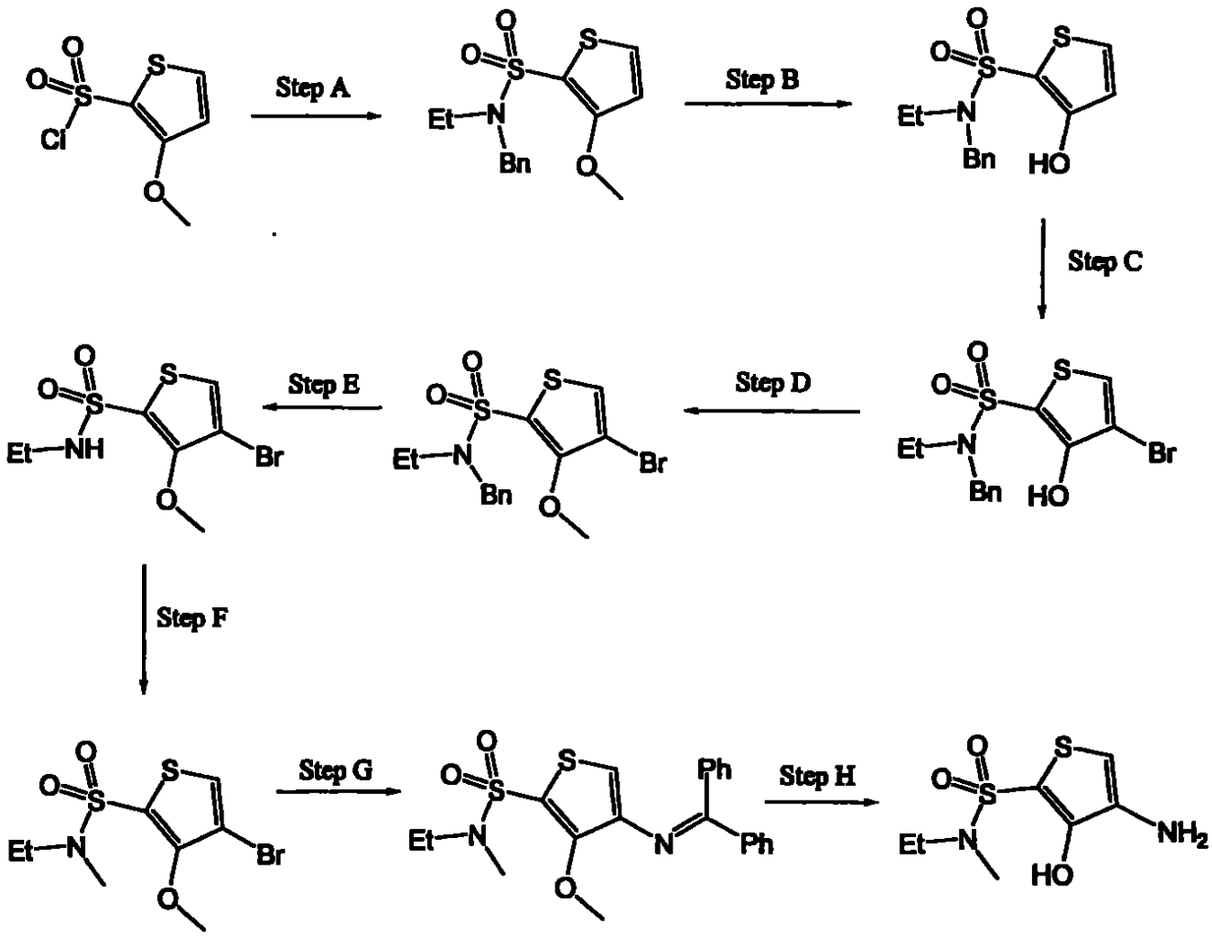
PREPARATIVE EXAMPLES 13.30-13.32

Following the procedures set forth in Preparative Example 13.29, but using commercially available amines, hydroxy-amino-thiophene products in the Table below were obtained.

Prep Ex.	Amine	Product	Yield (%) MH^+
13.30	Bn_2NH		10% 375.1
13.31	MeBnNH		14% 299.0

13.32	EtBnNH		22%
13.32A	$(Et)_2NH$		25%

PREPARATIVE EXAMPLE 13.33



Step A

2-Chlorosulfonyl-3-methoxy-thiophene (4.0 g, 18.8 mmol), the product from Step A of Preparative Example 13.29, was converted to 3-methoxy-2-ethylbenzylsulfonyl-thiophene (5.5 g, 94%, MH^+ = 312.1) by using ethylbenzylamine, following the procedure set forth in Preparative Example 13.29, Step B.

Step B

The product from Step A above (5.5 g, 17.70 mmol) was demethylated following the procedure set forth in Preparative Example 13.29, Step C. The alcohol product was obtained in 4.55 g (87%, MH^+ = 298.0).

Step C

The product from Step B above (4.55 g, 15.30 mmol) was brominated using the procedure set forth in Preparative Example 13.29, Step D. The corresponding bromide was obtained in 4.85 g (84%).

Step D

The bromo-alcohol from Step C above (4.84 g, 12.86 mmol) was methylated using the procedure set forth in Preparative Example 13.29, Step E. The product was obtained in 4.82 g (96%).

Step E

The product from Step D above (4.82 g, 12.36 mmol) was stirred with concentrated sulfuric acid (5 mL) at room temperature for 3 h. Ice water (30 mL) was added to the mixture followed by CH_2Cl_2 (50 mL). The aqueous mixture was adjusted to pH ~ 6 using a 1.0 M NaOH aqueous solution. The layers were separated. Th aqueous layer was extracted with CH_2Cl_2 (50 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to a dark brown oil, which was purified by flash column chromatography, eluting with CH_2Cl_2-hexanes (1:1, v/v). Removal of solvents afforded 3.03 g (82%) of the debenzylated product (M^+ = 300.0, M+2 = 302.0).

Step F

The product from Step E (1.34 g, 4.45 mmol) was methylated using the procedure set forth in Preparative Example 13.29, Step E. The desired product was obtained in 1.36 g (97%, M^+ = 314.1, M+2 = 316.0).

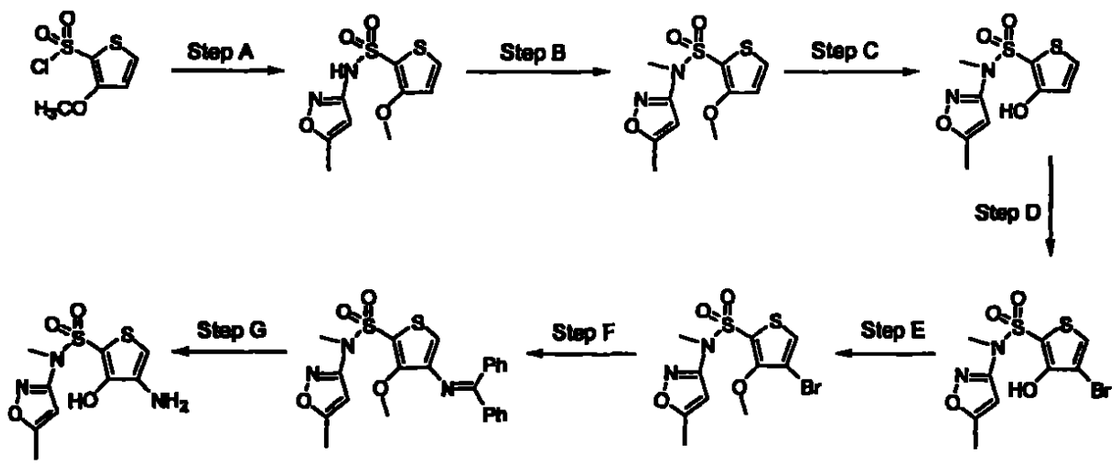
Step G

The product from Step F (1.36 g, 4.33 mmol) was converted to imine product (1.06 g, 55%, MH^+ = 415.1) using the procedure set forth in Preparative Example 13.29, Step F.

Step H

The imine product from Step G (1.06 g, 2.56 mmol) was converted to the desired hydroxy-amino thiophene compound (0.26 g, 43%) using the procedure set forth in Preparative Example 13.29, Step G.

PREPARATIVE EXAMPLE 13.34



Step A

2-Chlorosulfonyl-3-methoxy-thiophene (3.8 g, 17.87 mmol), the product from step A of Preparative Example 13. 29, was dissolved in 100 mL of CH_2Cl_2 and 20 mL of pyridine. 3-Amino-5-methyl-isoxazole (3.5 g, 35.68 mmol) was added. The mixture was stirred for 20 h at room temperature, diluted with 100 mL of CH_2Cl_2, and washed with a 0.5 N HCl aqueous solution (50 mL x 2), H_2O (50 mL), and brine (50 mL). The organic solution was dried with Na_2SO_4, and concentrated in vacuo to a brown oil.

This oil was dissolved in 100 mL of CH_2Cl_2, washed again with a 0.5 M HCl aqueous solution (30 mL x 3) and brine. After dried over Na_2SO_4, the organic solution was concentrated in vacuo to a yellow solid, 4.48 g (91%, MH^+= 275.0) of the desired product.

Step B

The product from Step A above (4.48 g, 16.33 mmol) was dissolved in acetone (100 mL), added with potassium carbonate (5.63 g, 40.80 mmol) and iodomethane (10.1 mL, 163.84 mmol). The mixture was stirred at room temperature for 1.5 h, diluted with 100 mL of hexanes and 50 mL of CH2Cl2, and filtered through a 1-in silica gel pad, rinsing with CH_2Cl_2. The filtrate was concentrated under reduced pressure to give 4.23 g (90%, MH^+= 289.0) of the desired product as a light yellow solid.

Step C

To a stirred suspension of sodium hydride (130 mg, 95%, 5.4 mmol) in 8 mL of *N*, *N'*-dimethylforamide at room temperature was added ethanethiol (0.45 mL, 6.0 mmol) dropwise. After 5 min, the mixture became a clear solution, and was added to a stirred solution of the product obtained from Step B above (0.45 g, 1.56 mmol) in 2 mL of *N*, *N'*-dimethylforamide in a round bottom flask. The flask was sealed with a ground glass stopper, and the mixture was heated at 90-95°C for 4 h. After cooled to room temperature, the mixture was poured into 20 mL of a 1.0 M NaOH aqueous solution, further rinsed with 20 mL of H_2O. The aqueous mixture was washed with diethyl ether (30 mL x 2), adjusted to PH ~5 using a 0.5 M HCl aqueous solution, and extracted with CH_2Cl_2 (50 mL x4). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated to a dark yellow solution. This was dissolved in 50 mL of ethyl acetate, washed with H_2O (30 mL x2) and brine (30 mL), dried over Na_2SO_4. Evaporation of solvent gave 0.422 g of the alcohol product (99%, MH^+ = 275.0).

Step D

The alcohol obtained from Step C above (0.467 g, 1.70 mmol) was brominated using the procedure set forth in Preparative Example 13.29, Step D, to afford the corresponding bromide in 0.607 g (100%).

Step E

The bromide obtained from Step D above (0.607 g, 1.72 mmol) was methylated using the procedure set forth in Preparative Example 13.29, Step E, to give the desired product in 0.408 g (65%, M^+ = 367, M+2 = 369.1).

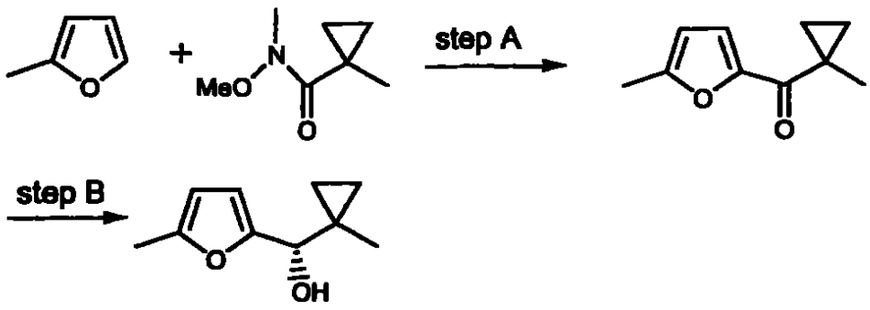
Step F

The product (0.405 g, 1.103 mmol) from Step E above was converted to the imine compound (0.29 g, 56%) using the procedure set forth in Preparative Example 13.29, Step F.

Step G

The imine product obtained from Step F above (0.29 g, 0.61 mmol) was demethylated using the procedure set forth in Step C above to give the corresponding alcohol as a dark yellow oil, which was dissolved in 5 mL methanol and added with sodium acetate (0.12 g, 1.46 mmol) and hydroxyamine hydrochloride (0.075 g, 1.08 mmol). The resulting mixture was stirred at room temperature for 3 h, and poured into 10 mL of 1.0 M NaOH aqueous solution. 30 mL of H_2O was used as rinsing and combined to the aqueous layer. The aqueous mixture was washed with diethyl ether (40 mL x 3), adjusted to pH ~ 6 using a 1.0 M HCl aqueous solution, and extracted with ethyl acetate (40 mL x 3). The organic extracts were washed with H_2O (20 mL x2), brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo to give 0.112 g of the desired hydroxy-amino thiophene sulfonamide (64%, MH^+ = 290).

PREPARATIVE EXAMPLE 13.35



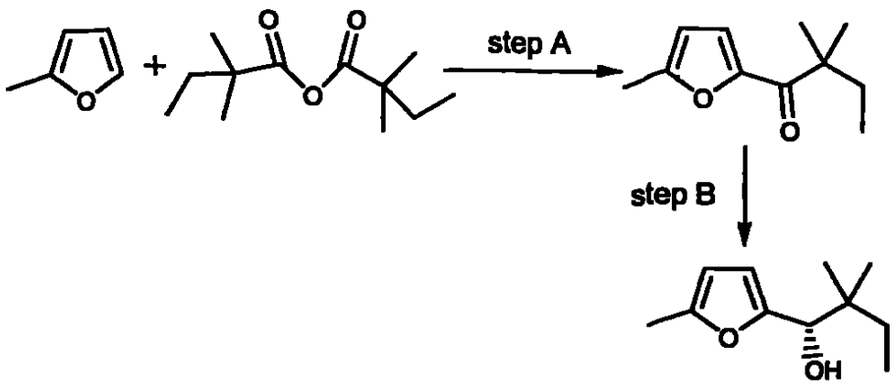
Step A

To a solution of 2-methyl furan (1.72g) in ether was added BuLi (8.38mL) at –78°C and stirred at room temperature for half an hour. The reaction mixture again cooled to –78°C and quenched with cyclopropyl amide 1 and stirred for two hours at –78°C and slowly warmed to room temperature. The reaction mixture stirred for three hours at room temperature and quenched with the addition of saturated ammonium chloride solution. The mixture was taken to a separatory funnel, washed with water, brine and dried over anhydrous sodium sulfate. Filtration and removal of solvent afforded the crude ketone, which was purified by using column chromatography to afford the ketone 3.0g (87%) as a pale yellow oil.

Step B

To a solution of ketone (1.0g) in THF (5.0mL) at 0°C was added R-methyl oxazoborolidine (1.2Ml, 1M in toluene) dropwise followed by addition of a solution of borane complexed with dimethyl sulfide (1.85mL, 2M in THF). The reaction mixture was stirred for 30minutes at 0°C and than at room temperature for one hour. The reaction mixture was cooled to 0°C and MeOH was added carefully. The mixture was stirred for 20 minutes and was concentrated under reduced pressure. The residue was extracted with ether, washed with water, 1M HCl (10mL), saturated sodium bicarbonate (10.0mL) water and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and removal of solvent afforded the crude alcohol which was purified by silica gel chromatography to afford the pure alcohol 0.91g (91%) as yellow oil.

PREPARATIVE EXAMPLE 13.36



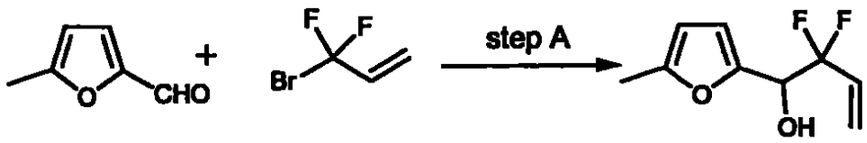
Step A

An equimolar mixture of 2-methylfuran (1.0g) and anhydride (2.6g) was mixed with $SnCl_4$ (0.05mL) and heated at 100^{0}C for 3 hours. After cooling the reaction mixture, water (10mL) was added, followed by saturated sodium carbonate solution until it becomes alkaline. The reaction mixture was extracted with ether several times and the combined ether layer was washed with water, brine and dried over anhydrous sodium sulfate. Filtration and removal of solvent afforded the crude ketone, which was purified by using silica gel chromatography to afford the ketone 0.9g (43%) as a yellow oil.

Step B

The Step B alcohol was obtained following a similar procedure set forth in the Preparative Eexample 13.35 Step B.

PREPARATIVE EXAMPLE 13.37

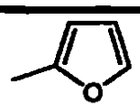
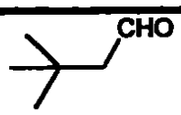
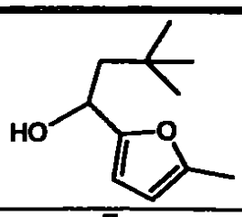
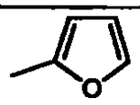
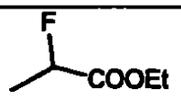
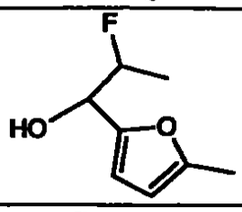
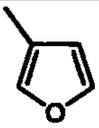
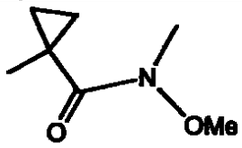
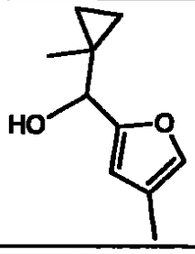
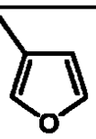
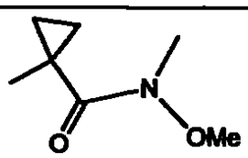
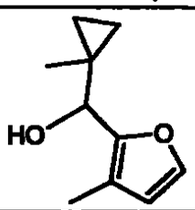
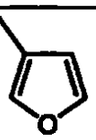
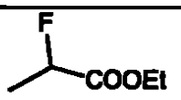
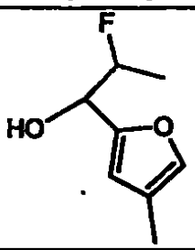
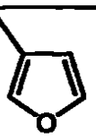
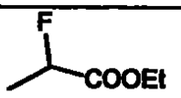
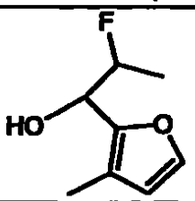


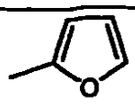
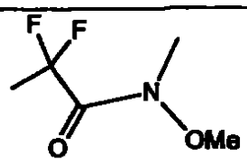
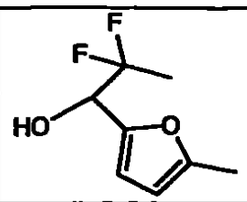
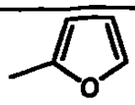
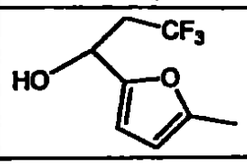
Step A:

To a solution of 5-methyl furan-2-aldehyde (1.0g) and 3-bromo-3,3-difluoropropene (2.24g) in DMF (30mL) was added indium powder (1.66g) and lithium iodide (50.0mg). The reaction mixture was stirred over night, diluted with water and extracted with ether. The ether layer was washed with water, brine and purified by silicagel chromatography to afford the pure alcohol 2.8g (92%).

PREPARATIVE EXAMPLES 13.38-13.45

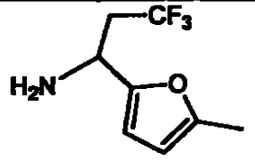
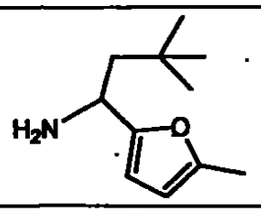
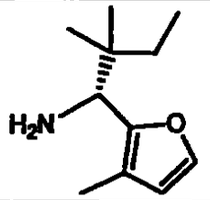
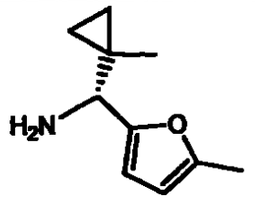
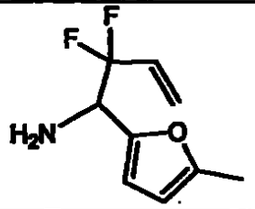
Following a similar procedure set forth in Preparative Example 13.25 of WO 02/083624 published October 24, 2002, and Preparative Example 13.35, and using the indicated Furan and Electrophile, the following Alcohols in the Table below were prepared.

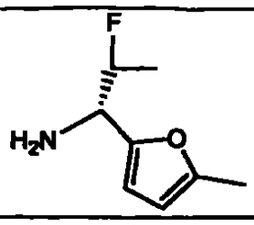
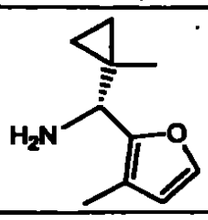
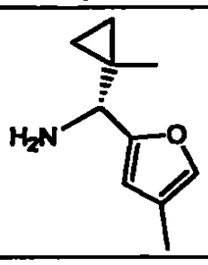
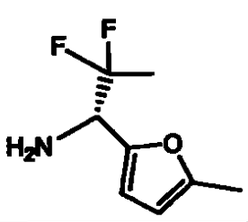
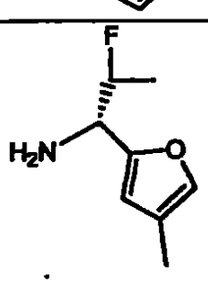
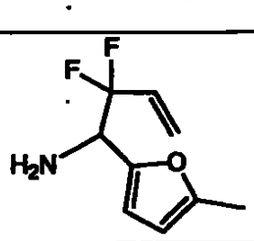
Prep. Ex	Furan	Electrophile	Alcohol	Yield
13.38				86%
13.39				69%
13.40				84%
13.41				82%
13.42				60%
13.43				65%

13.44				82%
13.45				89%

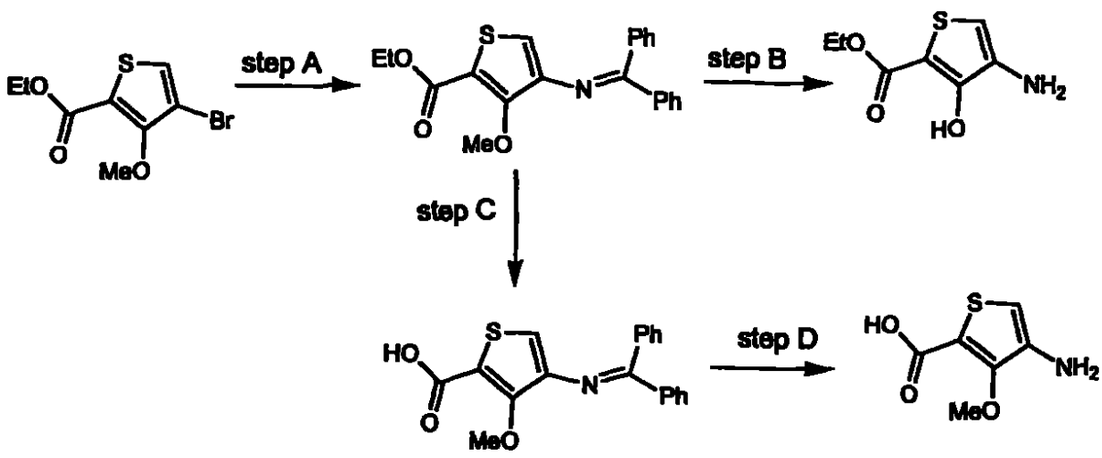
PREPARATIVE EXAMPLES 13.50-13.61

Following a similar procedure set forth in Preparative Examples 13.25 of WO 02/083624 published October 24, 2002, and using the indicated Alcohol, the following Amines in the Table below were prepared.

PREP. EX.	ALCOHOL	AMINE	% YIELD
13.50	13.45		28%
13.51	13.38		58%
13.52	13.36		69%
13.53	13.35		81%
13.54	13.37		82%

13.55	13.39		45%
13.56	13.41		57%
13.57	13.40		58%
13.58	13.44		54%
13.59	13.42		53%
13.61	13.37		82%

PREPARATIVE EXAMPLE 13.70



Step A

The imine was prepared following the procedure set forth in the Preparative Example 13.19 of WO 02/083624 published October 24, 2002, from the known bromoester (1.0g) as a yellow solid, Step A to yield 1.1g (79%).

Step B

The Step A product (0.6g) was reacted following the procedure set forth in the Preparative Example 13.19 of WO 02/083624 published October 24, 2002, to give the amine product 0.19g (64%).

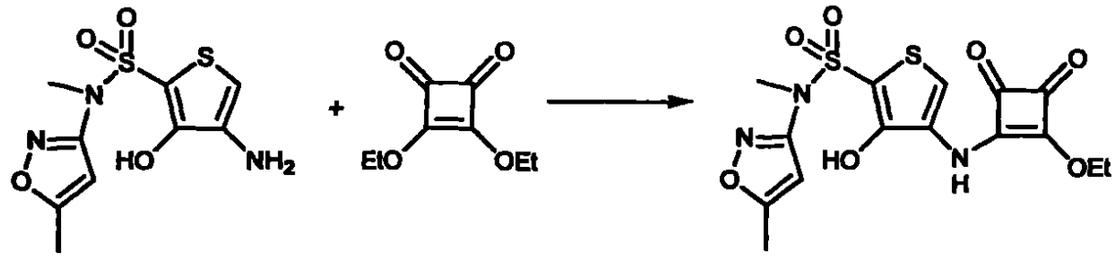
Step C

The Step B product (1.0g) was reacted following the procedure set forth in the Preparative Example 13.19 of WO 02/083624 published October 24, 2002, to give the acid as yellow solid 0.9g (94%)

Step D

The Step C product (0.35g) was reacted following the procedure set forth in the Preparative Example 13.19 of WO 02/083624 published October 24, 2002, to give the amino acid as yellow solid 0.167g (93%).

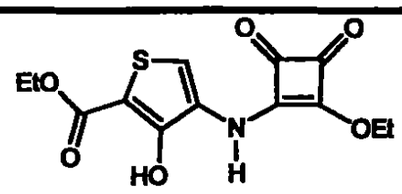
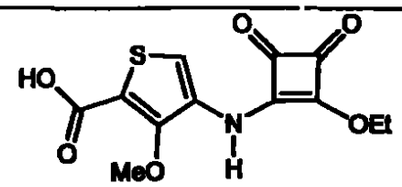
PREPARATIVE EXAMPLE 19.2



The hydroxy thiophene amine from Preparative Example 13.34 (108 mg, 0.37mmol) was dissolved in 5 mL of ethanol and stirred with diethoxysquarate (0.14 mL, 0.95 mmoL) and potassium carbonate (52 mg, 0.38 mmol) at room temperature overnight. The mixture was diluted with H2O (25 mL), adjusted to pH ~ 6 using a 1.0 M HCl aqueous solution, and extracted with ethyl acetate (40 mL x 3). The combined organic extracts were washed with brine, dried over Na2SO4, and concentrated to an oil, which was purified by flash column chromatography, eluting with CH2Cl2-MeOH (100:1, v/v). Removal of solvents afforded 83.5 mg of the titled product (MH+ = 414).

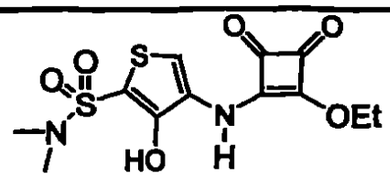
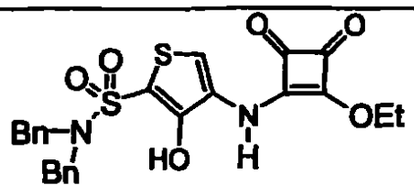
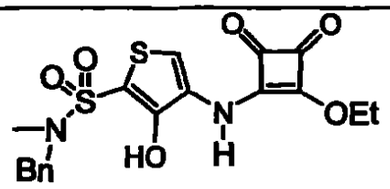
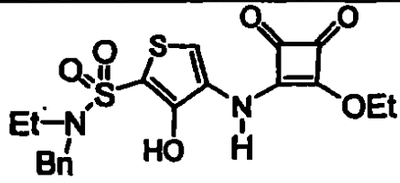
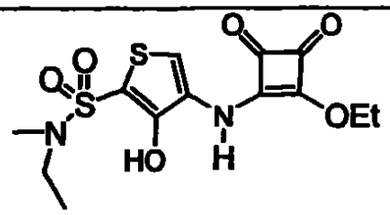
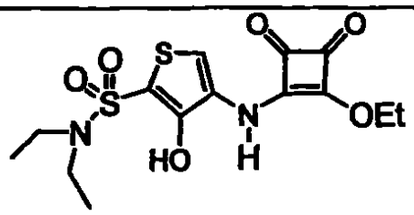
PREPARATIVE EXAMPLES 23.14A and 23.14B

Following the procedures set forth in Preparative Example 19 of WO 02/083624 published October 24, 2002, but using the amine from the Preparative Example indicated in the Table below, the cyclobutenedione intermediates were obtained.

Prep Ex.	Amine from Prep Ex.	Product	1. Yield (%) 2. MH^+
23.14A	13.70 Step B		1. 60% 2. 138
23.14B	13.70 Step D		1. 65%

PREPARATIVE EXAMPLE 23.15A –23.15F

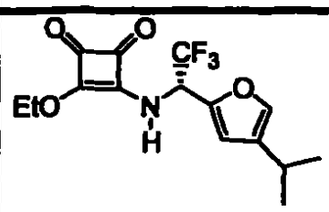
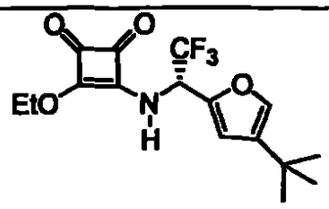
Following the procedures set forth in Preparative Example 19.2 but using the amines from the Preparative Example indicated in the Table below, the corresponding cyclobutenedione intermediates were prepared.

Prep Ex.	Amine from Prep Ex.	Product	1. Yield (%) 2. MH^+
23.15A	13.29		1. 66 % 2. 347
23.15B	13.30		1. 21% 2. 499
23.15C	13.31		1. 41% 2. 423
23.15D	13.32		1. 26% 2. 437
23.15E	13.33		1. 48% 2. 361.1
23.15F	13.32A		1. 68% 2. 375.1

PREPARATIVE EXAMPLE 23.16-23.26

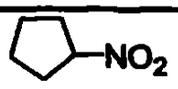
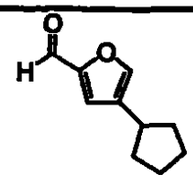
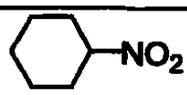
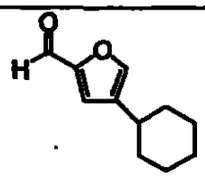
Following the procedures set forth in Preparative Example 19 of WO 02/083624 published October 24, 2002, but using the amine from the Preparative Example

indicated in the Table below, the cyclobutenedione intermediate products were obtained.

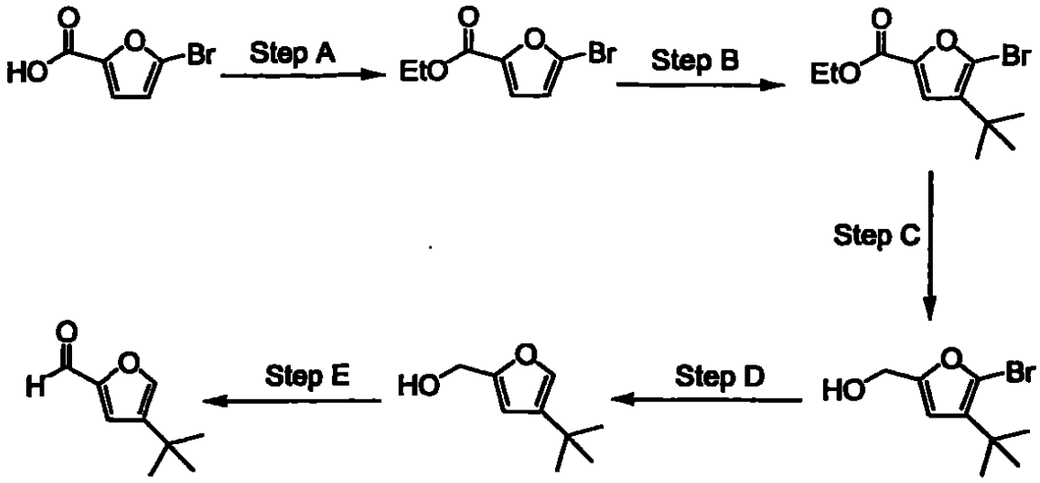
Prep Ex.	Amine from Prep Ex.	Product	Yield (%)
23.25	13.17A		48%
23.26	13.17B		66%

PREPARATIVE EXAMPLE 34.15-34.16

Following the procedures set forth in Preparative Example 34.8 of WO 02/083624 published October 24, 2002, but using the nitroalkanes indicated in the table below, the aldehydes were prepared.

Prep. Ex.	Nitroalkane	Aldehyde	Yield
34.15			17%
34.16			21%

PREPARATIVE EXAMPLE 34.17



Step A

To a stirred suspension of 5-bromo-2-furoic acid (15.0 g, 78.54 mmol) in 225 mL of CH_2Cl_2 at room temperature was added oxalyl chloride followed by a catalytic amount of *N,N'*-dimethylforamide. After 1 h, ethanol (20 mL) was added followed by triethylamine (22 mL). Reaction was continued for 15 h. The mixture was concentrated under reduced pressure to a residue, which was extracted with excess volume of hexanes, and hexanes-CH_2Cl_2 (3:1, v/v). The extracts were filtered, the filtrated was concentrated to a yellow oil, dried on high vacuum, yielding 17.2 g (93%) of the desired ester.

Step B

The ester product obtained from Step A above (17.2 g, 73.18 mmol) was converted to 2-ethyl-4-tertbutyl-5-bromo-furoate (7.9 g, 37%) using the literature procedure: *J. Am. Chem.Soc.*, **1939**, *61*, 473-478.

Step C

The ester product obtained from Step B above (7.9 g, 27.13 mol) was reduced to the alcohol (6.32 g) using the procedure set forth in Preparative Example 34.8, Step C, of WO 02/083624 published October 24, 2002.

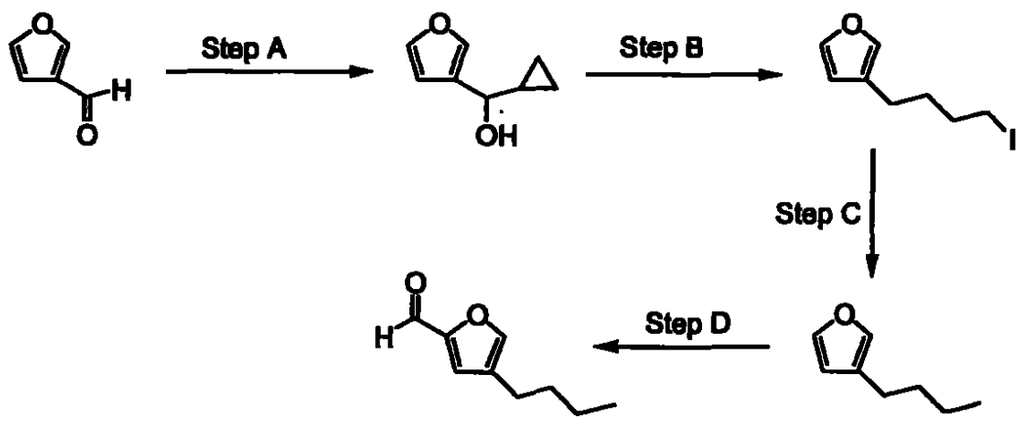
Step D

The product obtained from Step C above (6.32 g) was dissolved in 140 mL of THF and cooled in a –78°C bath. A 2.5 M solution of n-butyllithium in hexanes (22 mL, 55.0 mmol) was added dropwise along the side wall of the flask. After 15 min, H_2O (~70 mL) was added. Cooling bath was removed, the mixture was stirred for an additional 1h. Brine (50 mL) and CH_2Cl_2 (300 mL) were added, the two layers were separated, the aqueous layer was extracted with CH_2Cl_2 (100 mL), and the combined organic layers ere dried by Na_2SO_4. Evaporation of solvents afforded 5.33 g (crude) of the debrominated product as a reddish brown oil.

Step E

The alcohol product obtained from Step D above (5.33g) was oxidized to the corresponding aldehyde (3.06 g, 74% over three steps) using the procedure set forth in Preparative Example 34.8, Step D.

PREPARATIVE EXAMPLE 34.18



Step A

To a stirred solution of cyclopropyl bromide (4.0 mL, 50 mmol) in 120 mL of ether at –78°C was added dropwise a 1.7M solution of t-butyllithium in pentane (44.5 mL, 75.7 mmol). After 10 min, cooling bath was removed, stirring was continued for 1.5 h. The mixture was cooled again in a –78°C bath, and 3-furaldehyde (3.5 mL, 41.9 mmol) was added. Reaction was continued for 1 h, and quenched with a saturated NH4Cl aqueous solution. The aqueous mixture was extracted with CH_2Cl_2

(100 mL x 3). The organic extracts were washed with brine, dried by Na_2SO_4, filtered, and concentrated in vacuo to give 5.3 g (91%) of the alcohol product as a yellow oil.

Step B

Chloro trimethylsilane (27.2 mL, 214.2 mmol) was added dropwise to a vigorously stirred suspension of sodium iodide (32 g, 213.5 mmol) in 100 mL of acetonitrile. After 5 min, a solution of the alcohol obtained from Step A above (4.93 g, 35.68 mmol) in 100 mL of acetonitrile was added dropwise. Stirring was continued for 5 min. H_2O (100 mL) was added, the layers were separated, and the aqueous layer was extracted with ether (100 mL x 2). The organic layers were combined, washed with a 10 % $Na_2S_2O_3$ aqueous solution and brine, and dried over Na_2SO_4. Evaporation of solvents gave a dark brown oil, which was filtered through a 5-in silica gel column, eluting with CH_2Cl_2-hexanes (1:3.5, v/v). Removal of solvents afforded 4.22 g (47%) of the iodo product as a light yellow oil.

Step C

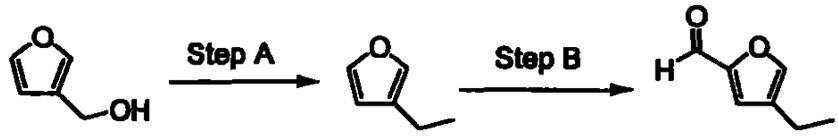
The iodo-product obtained from Step B above (2.2 g, 8.8 mmol) was dissolved in 60 mL of ether, and stirred in a –78°C bath. A 1.7 M solution of t-butyllithium in pentane (10.4 mL, 17.7 mmol) was added dropwise. After 20 min, cooling bath was removed. Reaction was continued for 2.5 h, and quenched with H_2O (20 mL). The aqueous mixture was stirred overnight and separated. The aqueous layer was extracted with ether (30 mL). The combined organic layers were washed with brine, dried by Na_2SO_4, and filtered through a Celite pad. Removal of solvent gave 1.10 g (100%) of 3-butylfuran as a reddish-yellow oil.

Step D

3-Butylfuran (1.1 g, 8.8 mmol), obtained from Step C above, was dissolved in 60 mL of ether, and stirred in a –78°C bath. A 1.7 M solution of t-butyllithium in pentane (6.0 mL, 10.2 mmol) was added dropwise along the side wall of the flask. The mixture was stirred for 3 h from –78°C to 0°C, and continued for 1 h at room temperature. A solution of *N,N'*-dimethylforamide (1.1 mL, 14.23 mmol) was added. Reaction was continued overnight, and quenched with a saturated NH_4Cl aqueous solution. The two layers were separated, the aqueous layer was extracted with

CH_2Cl_2 (30 mL x 2). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated to an oil, which was purified by preparative TLC (CH_2Cl_2-hexanes = 1:1.5, v/v) to give 0.48 g (36%) of the aldehyde (contaminated by some 3-butyl-2-furaldehyde).

PREPARATIVE EXAMPLE 34.19



Step A

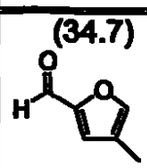
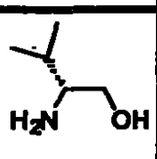
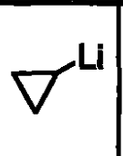
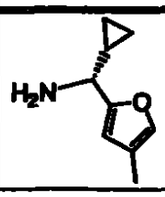
3-Ethylfuran was prepared from 3-hydroxymethylfuran according to literature procedure: *J. Org. Chem.*, **1983**, *48*, 1106-1107.

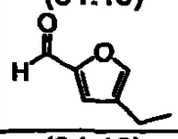
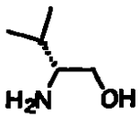
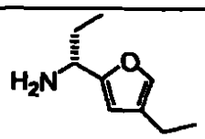
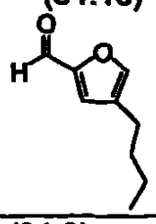
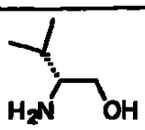
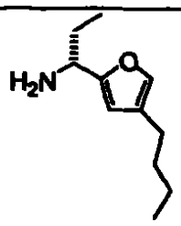
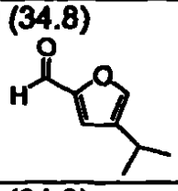
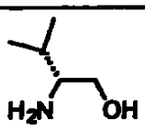
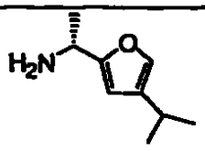
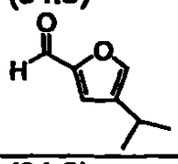
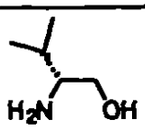
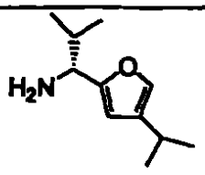
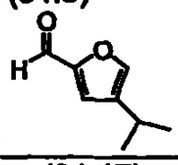
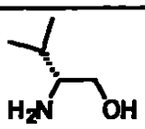
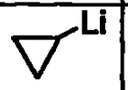
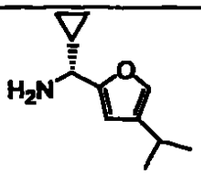
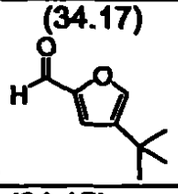
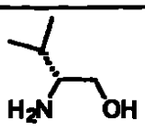
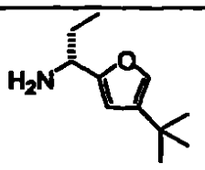
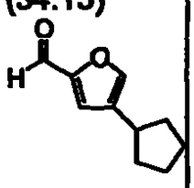
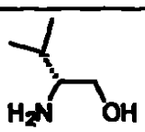
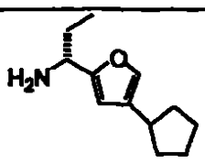
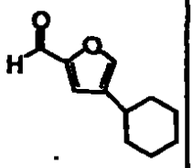
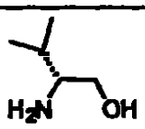
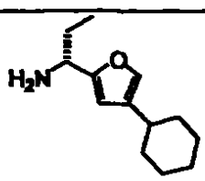
Step B

3-Ethylfuran obtained from Step A above was converted to 4-ethyl-2-furaldehyde using the procedure set forth in Preparative Example 34.32, Step D, of WO 02/083624 published October 24, 2002.

PREPARATIVE EXAMPLES 75.10A-75.10J

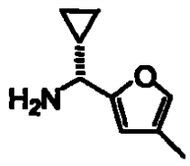
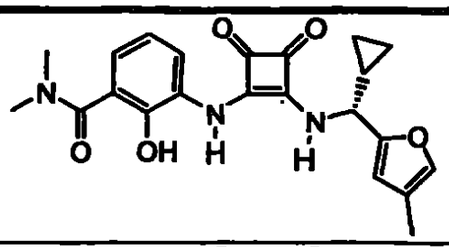
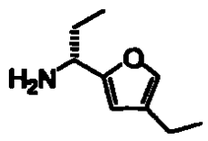
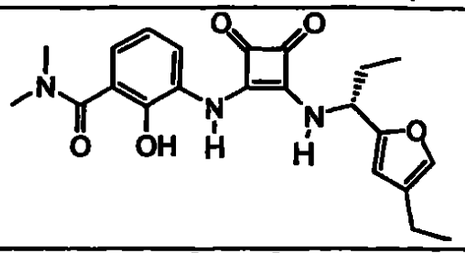
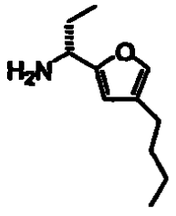
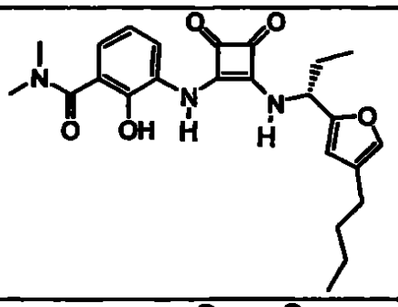
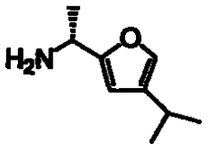
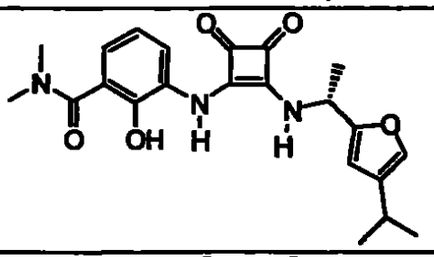
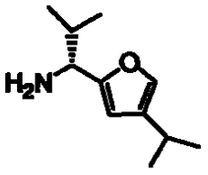
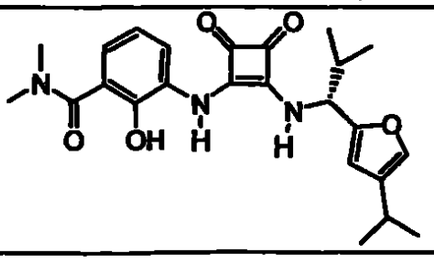
Following the procedure set forth in Preparative Example 64 of WO 02/083624 published October 24, 2002, but using the commercially available aldehydes, amino alcohols, and organolithium reagents in the Table below, the optically pure amine products in the Table below were obtained. The numbers in the "Aldehyde" column refer to preparative examples herein or in WO 02/083624.

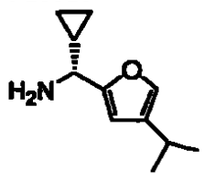
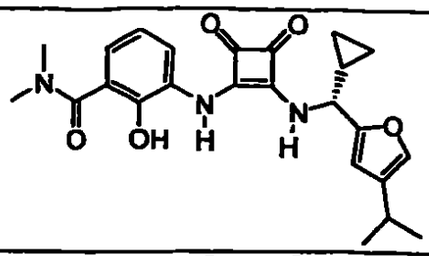
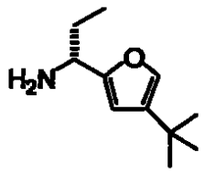
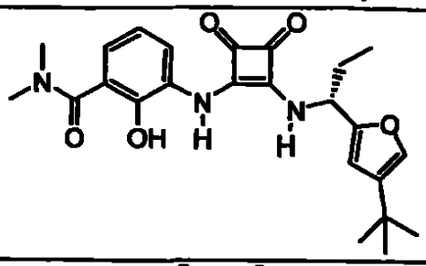
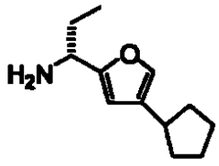
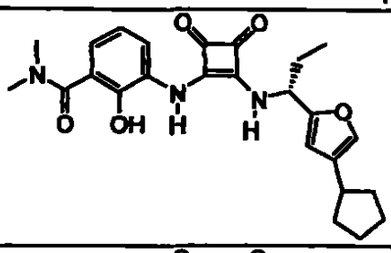
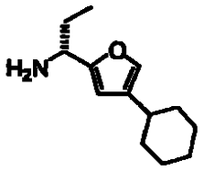
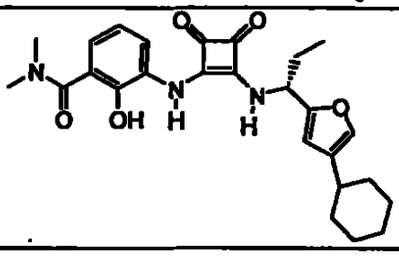
Prep Ex.	Aldehyde	Amino Alcohol	Organo lithium	Product	1.Yield 2. MH^+
75.10A	(34.7) 				1. 61% 2. 135 $[M-NH_2]^+$

75.10B	(34.19) 		EtLi		1. 24% 2. 154
75.10C	(34.18) 		EtLi		1. 32% 2. 165 $[M-NH_2]^+$
75.10D	(34.8) 		MeLi		1. 47% 2. 137 $[M-NH_2]^+$
75.10E	(34.8) 		iPrLi		1. 30% 2. 165 $[M-NH_2]^+$
75.10F	(34.8) 				1. 67% 2. 163.0 $[M-NH_2]^+$
75.10G	(34.17) 		EtLi		1. 24% 2. 165 $[M-NH_2]^+$
75.10H	(34.15) 		EtLi		1. 70% 2. 194
75.10J	(34.16) 		EtLi		1. 54% 2. 208

EXAMPLES 360.109-360.117

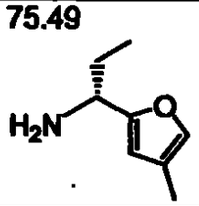
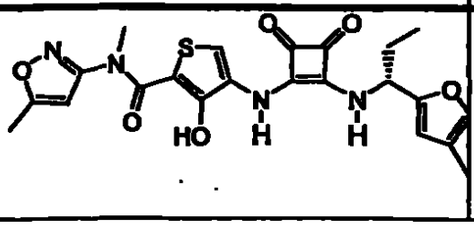
Following the procedure set forth in Example 261 of WO 02/083624 published October 24, 2002, but using the commercially available amine or the prepared amine from the Preparative Example indicated in the table below, the following cyclobutenedione products were obtained.

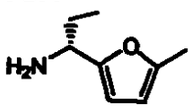
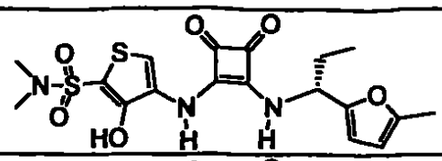
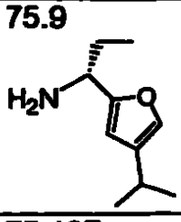
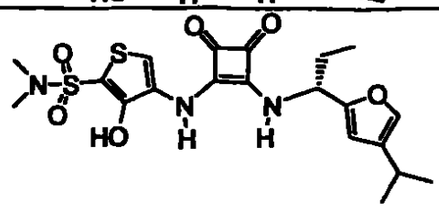
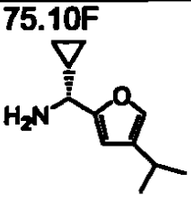
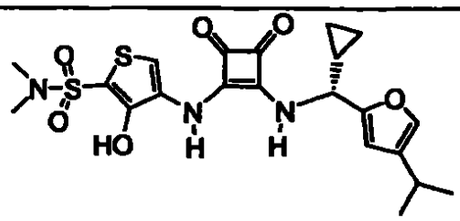
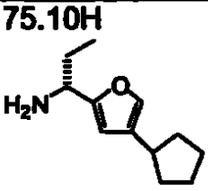
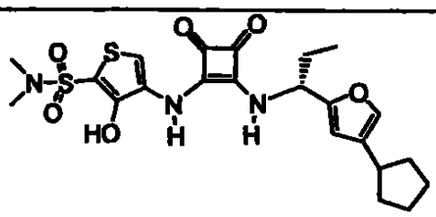
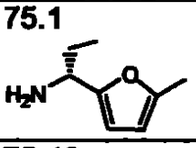
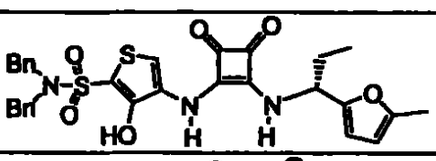
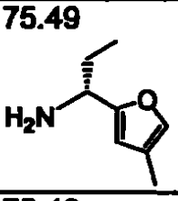
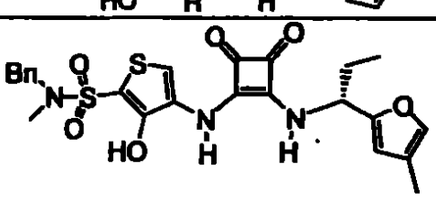
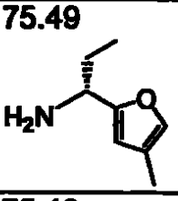
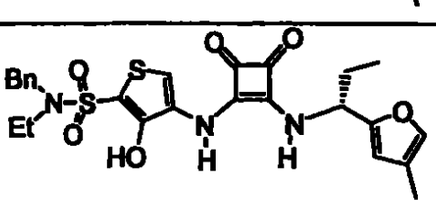
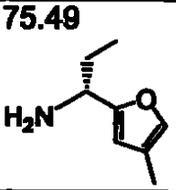
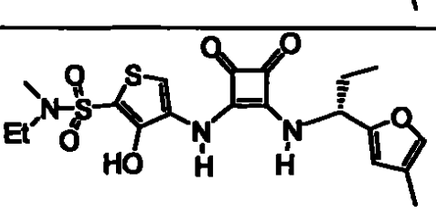
Ex.	Amine	Product	1.Yield 2. MH^+ 3. mp (°C)
360.109	75.10A 		1. 67% 2. 410.1 3. 119-121
360.110	75.10B 		1. 71% 2. 412 3. 102
360.111	75.10C 		1. 64% 2. 440.1 3. 91-93
360.112	75.10D 		1. 79% 2. 412 3. 111-113
360.113	75.10E 		1. 20% 2. 440.1 3. 130 (DEC)

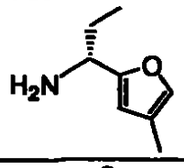
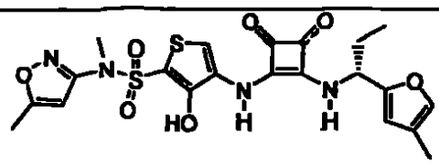
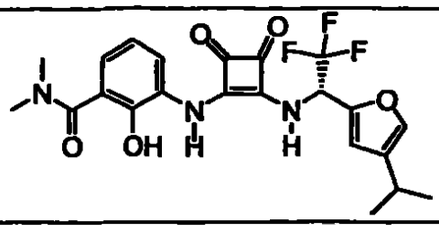
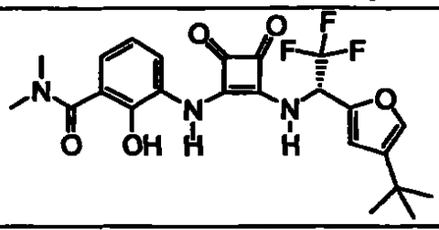
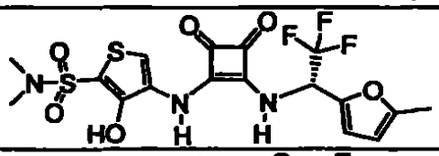
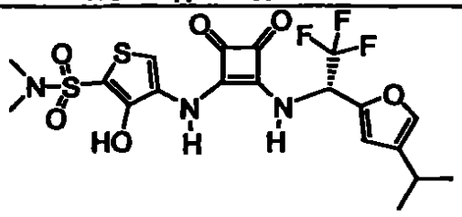
360.114	75.10F 		1. 61% 2. 438.1 3. 117-119
360.115	75.10G 		1. 61% 2. 440.1 3. 117-119
360.116	75.10H 		1. 81% 2. 452 3. 118
360.117	75.10J 		1. 65% 2. 466 3. 109

EXAMPLES 368.32-368.45

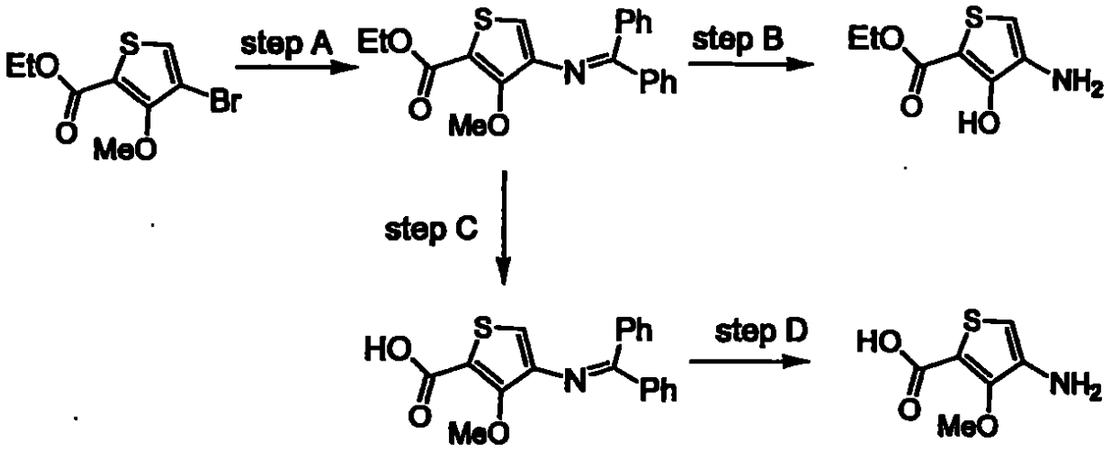
Following the procedure set forth in Example 261 of WO 02/083624 published October 24, 2002, but using the commercially available amine in the table below and the cyclobutenedione intermediate from the Preparative Example indicated, the following cyclobutenedione products were obtained. The numbers in the "Amine" and "Prep. Ex." columns refer to preparative examples herein or in WO 02/083624.

Ex.	Amine	Prep. Ex.	Product	1.Yield (%) 2. MH^+ 3. mp (°C)
368.32	75.49 	23.14		1. 58% 2. 471.1 3. 149

368.33	75.1 	23.15A		1. 33% 2. 440.1 3. 181
368.34	75.9 	23.15A		1. 56% 2. 468 3. 180
368.35	75.10F 	23.15A		1. 28% 2. 480 3. 186
368.36	75.10H 	23.15A		1. 48% 2. 494 3. 112.5
368.37	75.1 	23.15B		1. 58% 2. 592 3. 177-179
368.38	75.49 	23.15C		1. 69% 2. 516 3. 88-90
368.39	75.49 	23.15D		1. 80% 2. 530 3. 134-137
368.40	75.49 	23.15E		1. 57% 2. 454 3. 138-140

368.41	75.49 	19.2		1. 26% 2. 507 3. 162-164
368.42	3	23.25		1. 82% 2. 466 3. 141-143
368.43	3	23.26		1. 67% 2. 480 3. 139 dec
368.44	13.29	23.16		1. 29% 2. 480 3. 112-114
368.45	13.29	23.26		1. 88% 2. 508 3. 190 dec

PREPARATIVE EXAMPLES 600



Step A

Following the procedure set forth in Preparative Example 13.19, Step D, of WO 02/083624, published October 24, 2002, the imine was prepared from the known bromoester (1.0g) to yield 1.1g (79%) as a yellow solid.

Step B

The product of step A (0.6g) was reacted following the procedure set forth in Preparative Example 13.19, Step E, of WO 02/083624, published October 24, 2002, to give the amine product 0.19g (64%).

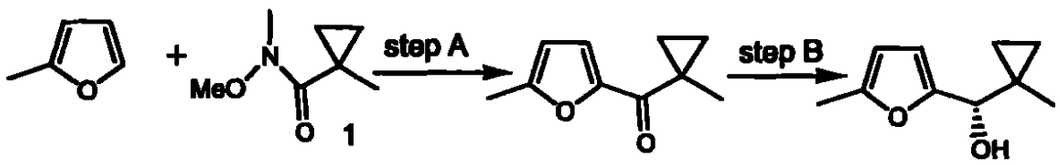
Step C

The product of Step B (1.0g) was reacted following the procedure set forth in Preparative Example 13.19, Step B, of WO 02/083624, published October 24, 2002, to give the acid as yellow solid 0.9g (94%).

Step D

The product of Step C (0.35g) was reacted following the procedure set forth in Preparative Example 13.19, Step E, of WO 02/083624, published October 24, 2002, to give the amino acid as yellow solid 0.167g (93%).

PREPARATIVE EXAMPLES 601



Step A

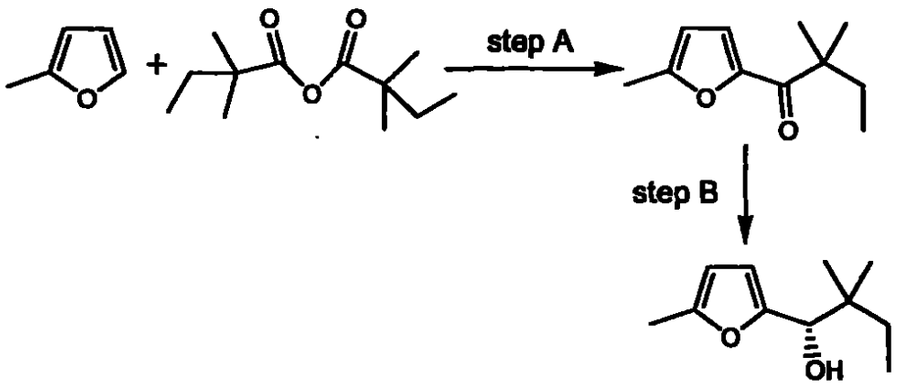
To a solution of 2-methyl furan (1.72g) in ether was added BuLi (8.38mL) at –78^{0}C and stirred at room temperature for half an hour. The reaction mixture again cooled to –78^{0}C and quenched with cyclopropyl amide 1 and stirred for two hours at –78^{0}C and slowly warmed to room temperature. The reaction mixture stirred for three hours at room temperature and quenched with the addition of saturated ammonium chloride solution. The mixture was taken to a separatory funnel, washed with water, brine and dried over anhydrous sodium sulfate. Filtration and removal of solvent

afforded the crude ketone, which was purified by using column chromatography to afford the ketone 3.0g (87%) as a pale yellow oil.

Step B

To a solution of ketone (1.0g) from Step A above in THF (5.0mL) at 0^0C was added *R*-methyl oxazoborolidine (1.2Ml, 1M in toluene) dropwise followed by addition of a solution of borane complexed with dimethyl sulfide (1.85mL, 2M in THF). The reaction mixture was stirred for 30 minutes at 0^0C and than at room temperature for one hour. The reaction mixture was cooled to 0^0C and MeOH was added carefully. The mixture was stirred for 20 minutes and was concentrated under reduced pressure. The residue was extracted with ether, washed with water, 1M HCl (10mL), saturated sodium bicarbonate (10.0mL) water and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and removal of solvent afforded the crude alcohol which was purified by silica gel chromatography to afford the pure alcohol 0.91g (91%) as yellow oil.

PREPARATIVE EXAMPLES 602



Step A

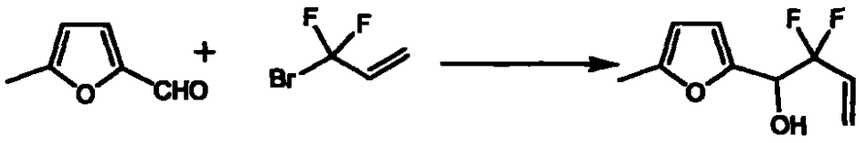
An equimolar mixture of 2-methylfuran (1.0g) and anhydride (2.6g) was mixed with $SnCl_4$ (0.05mL) and heated at 100^0C for 3 hours. After cooling the reaction mixture, water (10mL) was added, followed by saturated sodium carbonate solution until it becomes alkaline. The reaction mixture was extracted with ether several times and the combined ether layer was washed with water, brine and dried over anhydrous sodium sulfate. Filtration and removal of solvent afforded the crude ketone, which was

purified by using silica gel chromatography to afford the ketone 0.9g (43%) as a yellow oil.

Step B

The title alcohol was obtained following a similar procedure set forth in Preparative Example 601.

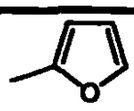
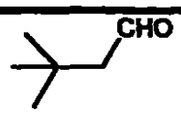
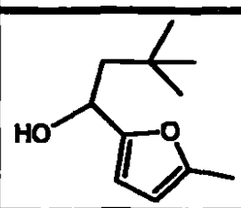
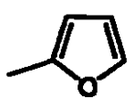
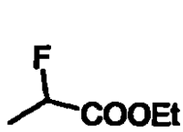
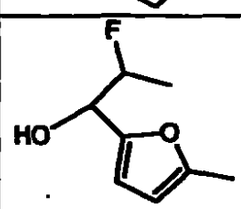
PREPARATIVE EXAMPLES 603

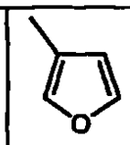
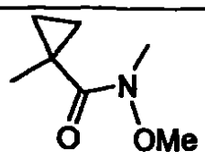
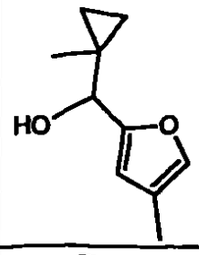
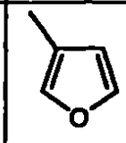
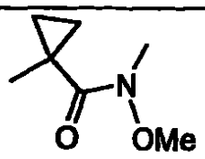
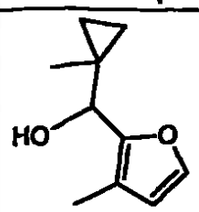
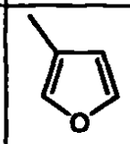
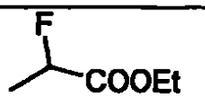
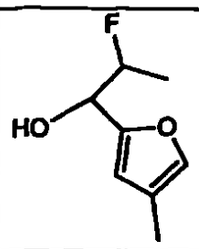
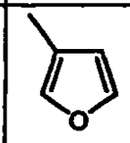
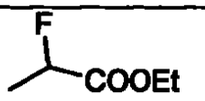
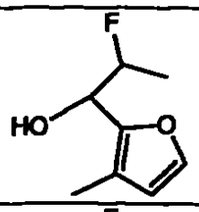
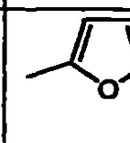
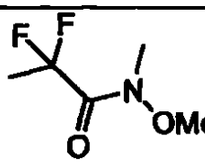
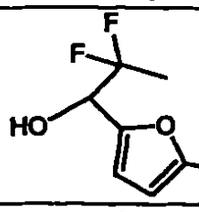
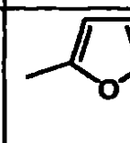
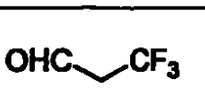
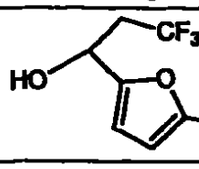


To a solution of 5-methyl furan-2-aldehyde (1.0g) and 3-bromo-3,3-difluoropropene (2.24g) in DMF (30mL) was added indium powder (1.66g) and lithium iodide (50.0mg). The reaction mixture was stirred over night, diluted with water and extracted with ether. The ether layer was washed with water, brine and purified by silica gel chromatography to afford the pure alcohol 2.8g (92%).

PREPARATIVE EXAMPLES 604-611

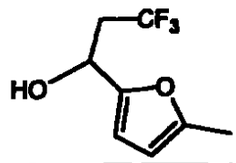
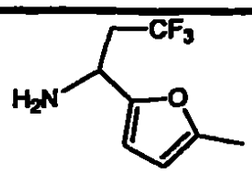
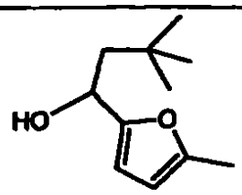
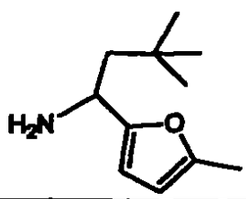
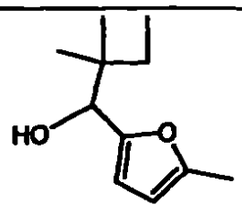
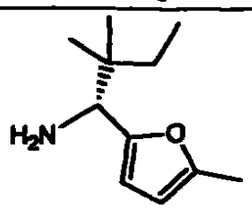
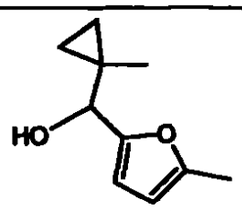
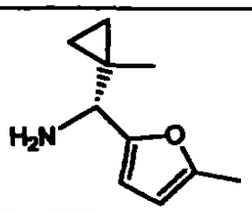
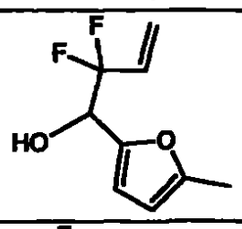
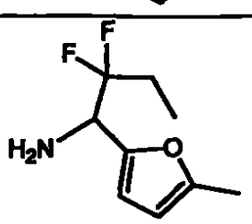
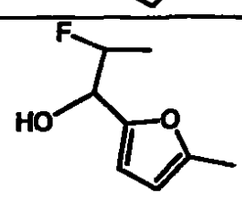
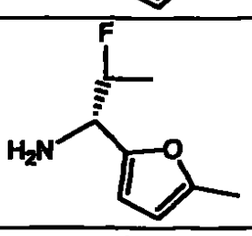
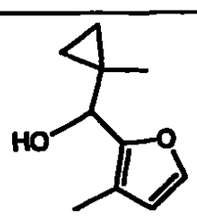
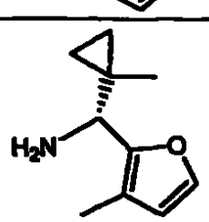
Following a similar procedure set forth in Preparative Example 13.25 of WO 02/083624 published October 24, 2002, or Preparative Example 601, the following Alcohols were prepared.

Prep Ex	Furan	Electrophile	Alcohol	Yield
604				86%
605				69%

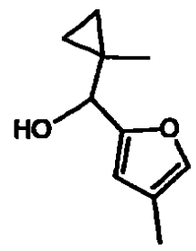
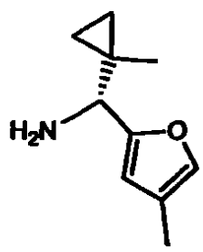
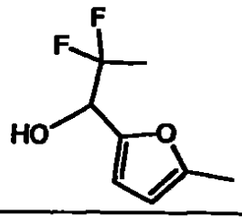
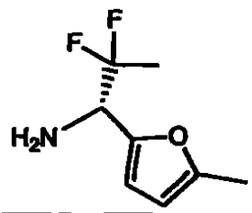
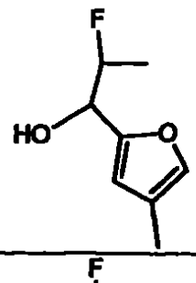
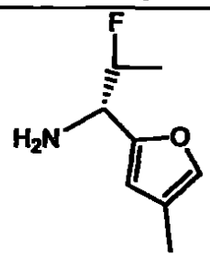
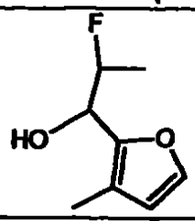
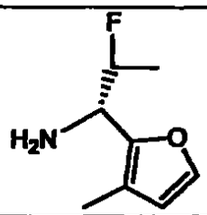
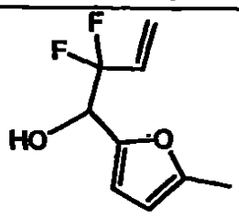
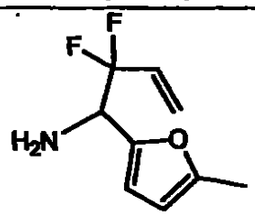
606				84%
607				82%
608				60%
609				65%
610				82%
611				89%

PREPARATIVE EXAMPLES 620-631

Following a similar procedure set forth in Preparative Examples 13.25 the following Amines were prepared from the corresponding Alcohols.

Prep Ex	ALCOHOL	AMINE	YIELD
620			28%
621			58%
622			69%
623			81%
624			82%
625			45%
626			57%

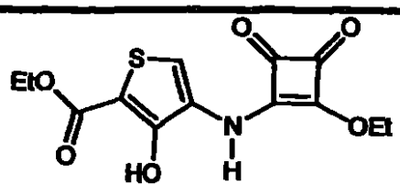
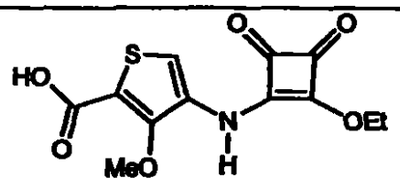
87
88

627			58%
628			54%
629			53%
630			50%
631			82%

5

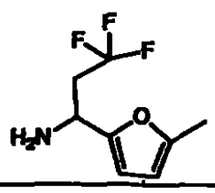
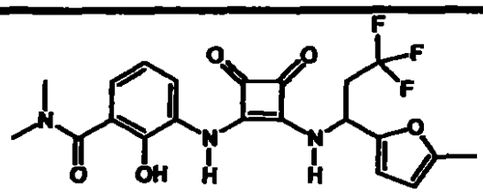
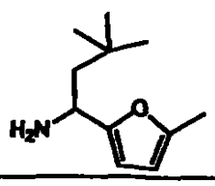
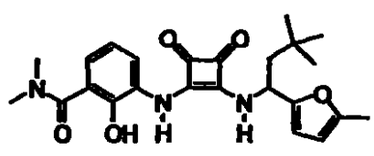
PREPARATIVE EXAMPLE 640-641

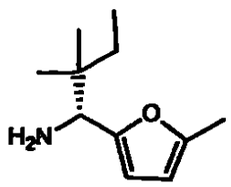
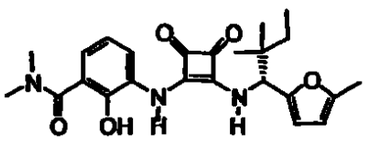
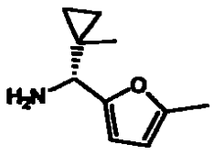
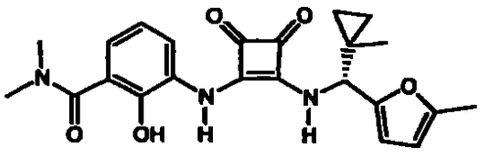
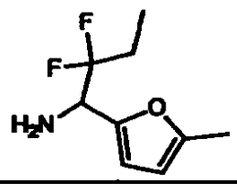
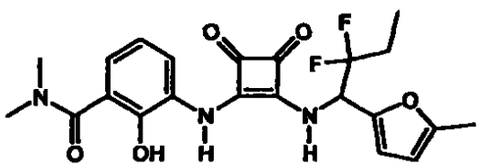
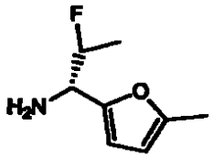
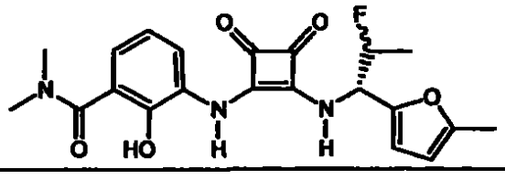
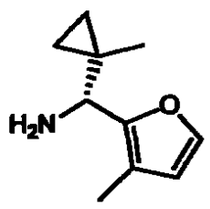
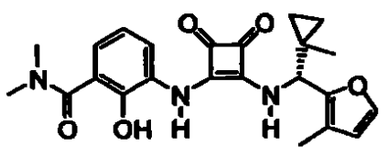
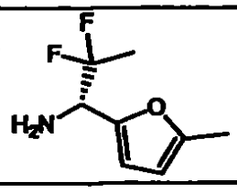
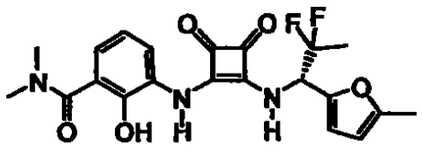
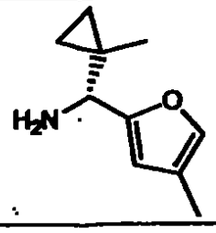
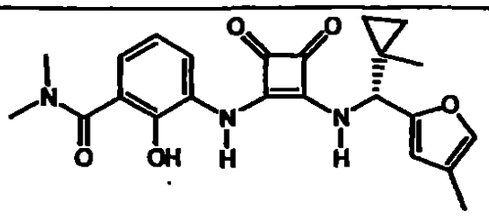
Following the procedures set forth in Preparative Example 19 of WO 02/083624, published October 24, 2002, but using the amine from the Preparative Example indicated in the Table below, the cyclobutenedione intermediates were obtained.

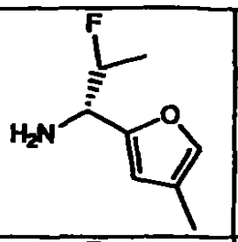
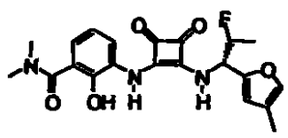
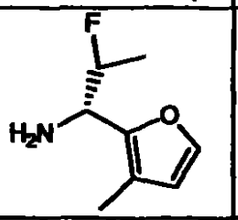
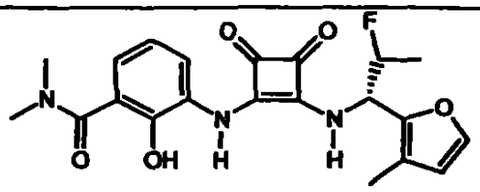
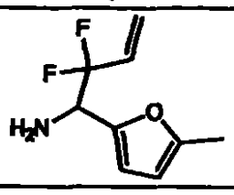
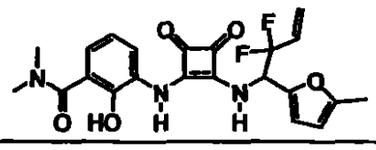
Prep Ex.	Amine from Prep Ex.	Product	1. Yield (%) 2. MH^+
640	600 Step B		1. 60% 2. 138
641	600 Step D		1. 66 2. 138

EXAMPLES 1200-1211

Following the procedure set forth in Example 261 of WO 02/083624, published October 24, 2002, but using the commercially available amine or the prepared amine from the Preparative Example indicated in the table below, the following cyclobutenedione products were obtained.

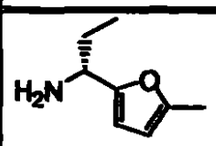
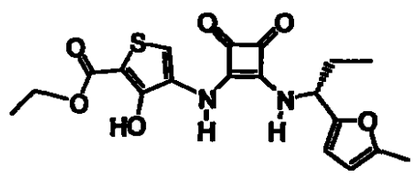
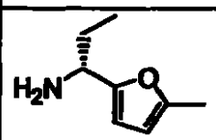
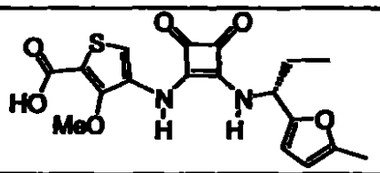
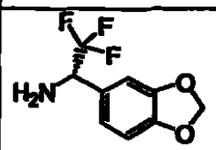
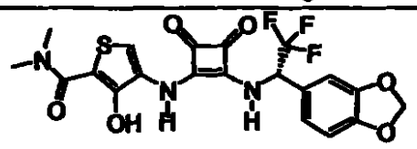
Ex.	Amine	Product	1.Yield (%) 2. MH^+ 3. mp (°C)
1200			1. 61.3 2. 451.4 3. 108.6
1201			1. 54 2. 439.5 3. 117.8

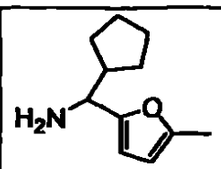
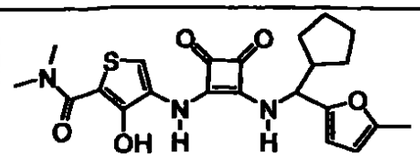
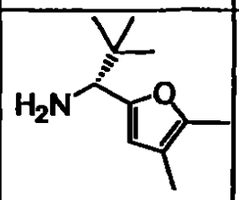
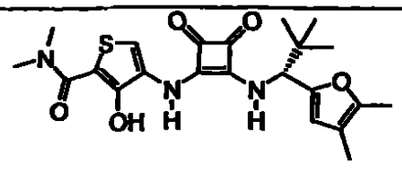
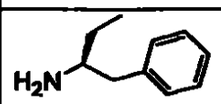
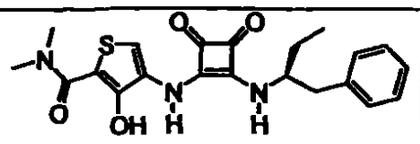
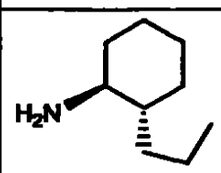
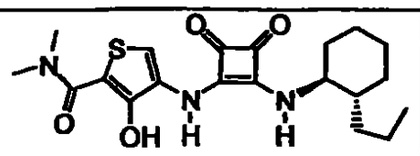
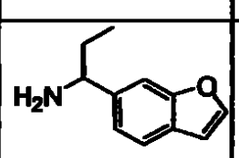
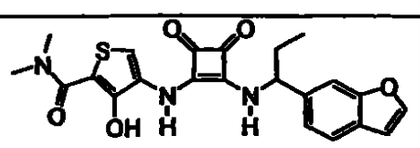
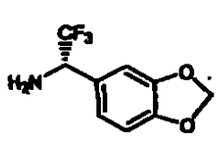
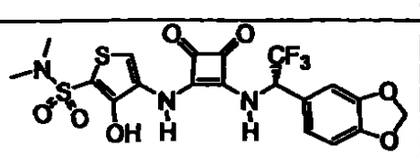
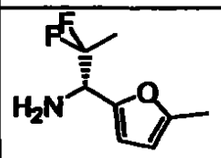
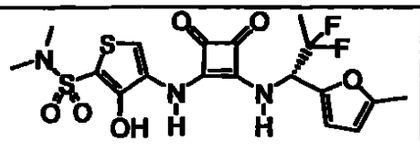
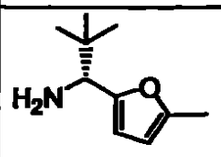
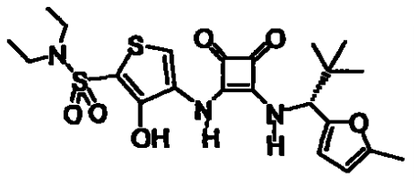
1202			1. 80 2. 439.5 3. 128-131.8
1203			1. 75 2. 423.4 3. 118-119
1204			1. 74 2. 447.4 3. 108-111
1205			1. 42 2. 415.42 3. 136-140
1206			1. 46 2. 423.4 3. 114-117
1207			1. 35 2. 433.1 3. 123-128
1208			1. 42 2. 423.4 3. 118-121

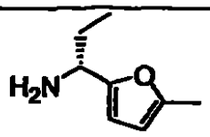
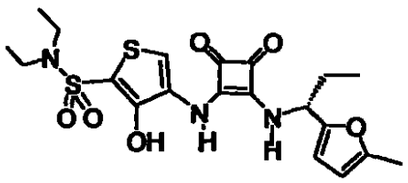
1209			1. 51 2. 415.4 3. 112-117
1210			1. 44 2. 415.4% 3. 115-120
1211			1. 48 2. 445.4 3. 105-110

EXAMPLES 1300-1311

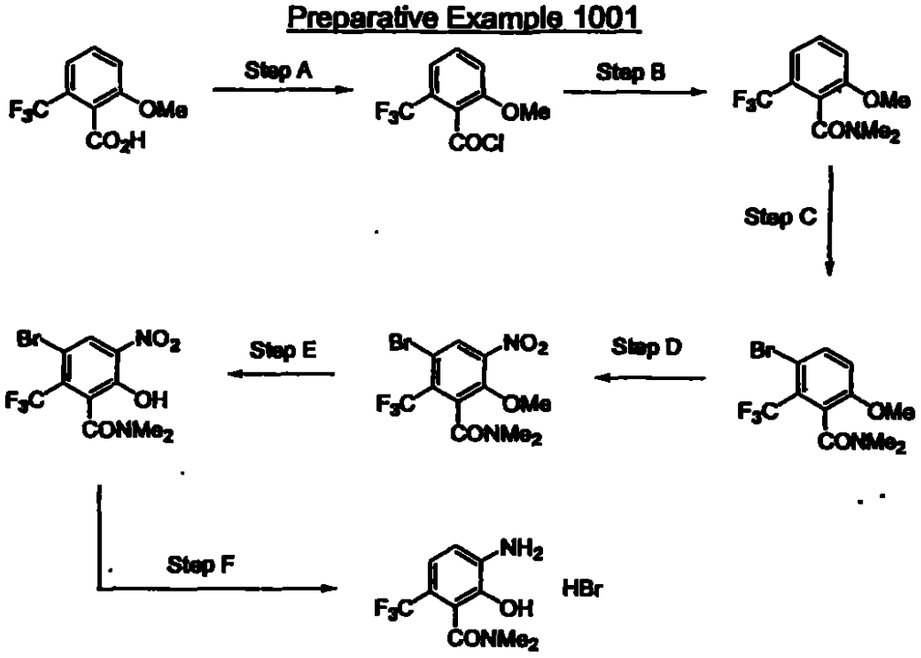
Following the procedure set forth in Example 261, of WO 02/083624, published October 24, 2002, but using the commercially available amine in the table below and the cyclobutenedione intermediate from the Preparative Example indicated, the following cyclobutenedione products were obtained. Preparative Example 23.9 is in WO 02/083624, published October 24, 2002.

Ex.	Amine	Prep. Ex.	Product	1.Yield (%) 2. MH^+ 3. mp (°C)
1300		640		1. 35% 2. 390.4 3. 100
1301		641		1.78% 2. 390.4 3. 130
1302		23.9		1. 48% 2. 483.4 3. 116

1303		23.9		1. 46% 2. 443.5 3. 106
1304		23.9		1. 40% 2. 445.54 3. 102
1305		23.9		1. 51% 2. 413.4 3. 98
1306		23.9		1.78% 2. 405.5 3. 246
1307		23.9		1.. 83% 2. 439.5 3. 129
1308		23.15A		1. 11% 2. 519.47 3. 123
1309		23.15A		1. 47% 2. 475 3. 113
1310		640		1. 55% 2. 496.1 3. 123- 125

1311		640		1. 74% 2. 468.1 3. 116-118

Preparative Example 1001



Step A

Oxalyl chloride (3 mL, 34.27 mmol) was added dropwise to a mixture of 2-methoxy-6-(trifluoromethyl)benzoic acid (1.5 g, 6.81 mmol) (prepared according to known method, see: EP0897904B1), *N,N*-dimethylformamide (0.3 mL), and dichloromethane (40 mL) with stirring at rt. The reaction mixture was stirred overnight. Evaporation of solvent and excess oxalyl chloride and drying under vacuum afforded 2-methoxy-6-(trifluoromethyl)benzoyl chloride as a solid, which was used without purification.

Step B

A solution of 2-methoxy-6-(trifluoromethyl)benzoyl chloride (ca. 6.81 mmol) from Step A above in dichloromethane (20 mL) was added dropwise to a mixture of 4-(dimethylamino)pyridine (42 mg, 0.34 mmol), triethylamine (2.8 mL, 20.09 mmol), and 2 M dimethylamine solution in tetrahydrofuran (7 mL, 14 mmol), and dichloromethane

(30 mL) with stirring at rt. The reaction mixture was stirred overnight. A mixture of dichloromethane and water was added. The organic phase was separated, washed with 1N HCl solution, water, and saturated sodium bicarbonate solution and concentrated. The residue was purified by column chromatography (ethyl acetate:hexanes, 3:1 v/v) to give the product as a white solid (1.24 g, 74% over two steps).

Step C

A mixture of the amide from Step B above (1.8 g, 7.28 mmol), carbon tetrachloride (25 mL), and iron powder (305 mg, 5.46 mmol) was cooled to 0 °C. Bromine (0.94 mL, 18.34 mmol) was added dropwise with stirring. After addition, the mixture was stirred at rt for 1 h and at 50 °C for 3 h. The mixture was cooled to rt, diluted with dichloromethane, and slowly poured to a cold 10% $NaHSO_3$ solution. After stirring at rt for 0.5 h, the organic layer was separated and concentrated to give the product as a white solid (2.26 g, 95%).

Step D

Concentrated sulfuric acid (10 mL) was added dropwise to a flask charged with the bromide from Step C above (600 mg, 1.84 mmol) at 0 °C with stirring. A mixture of nitric acid (0.2 mL, 4.76 mmol) and concentrated sulfuric acid (0.3 mL) was then added dropwise. After addition, the mixture was stirred at rt for 3 h. The mixture was added to ice-water, neutralized with 15% NaOH solution to pH 7, and extracted with dichloromethane. The organic layer was concentrated to give the product as a white solid (621 mg, 91%). mp 92 °C, *m/e* 371 (MH^+).

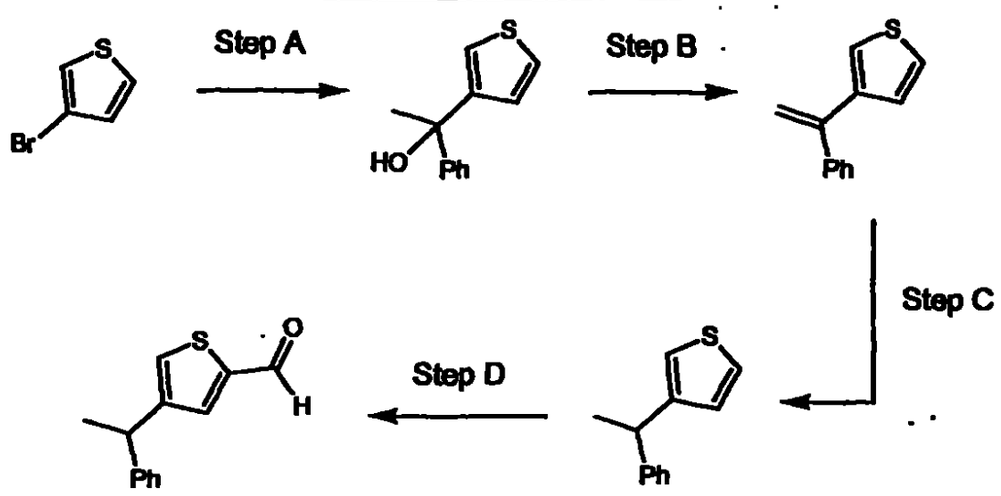
Step E

A solution of the compound from Step D above (1.2 g, 3.23 mmol) in dichloromethane (50 mL) was cooled to –75 °C. 1 M BBr_3 solution in dichloromethane (7.5 mL, 7.5 mmol) was added dropwise with stirring. The mixture was stirred at –75 °C for 2 h. The mixture was added to ice-water. After stirring at rt for 0.5 h, the mixture was extracted with dichloromethane. The organic was concentrated and the residue was purified by column chromatography (dichloromethane-methanol, 9:1 v/v) to give the product as a yellow solid (1.05 g, 91%). *m/e* 357 (MH^+).

Step F

A mixture of the compound from Step E above (1.08 g, 3.02 mmol), methanol (30 mL), and 10% Pd-C (250 mg) was subjected to hydrogenation at 50 psi at rt for 6 h. The mixture was filtered through a layer of Celite. The filtrate was concentrated to give the title compound as a pale yellow solid (930 mg, 96%). mp 132 °C, *m/e* 249.

Preparative Example 1002



Step A

To a cooled (-70°C) etherial (45 mL dry) solution of 3-bromothiophene (3.8 mL) was added BuLi (30 mL of 1.6M in hexane) dropwise, and the mixture was stirred at -70°C for 20 min. Acetophenone (4.6 mL) in ether (6 mL) was added dropwise with stirring at -70°C. After 3 hrs, the mixture was warmed to RT and sat. NH_4Cl (aq) was added and the mixture was extracted with ether. The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give the title compound which was used in Step B without further purification.

Step B

The crude product from Step A above was stirred with oxalic acid (0.375 g) at 70°C under reduced pressure for 3 hr, then cooled to RT and extracted with ether. The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give the product as a pale yellow liquid (5.7 g, 78% for Steps A-B).

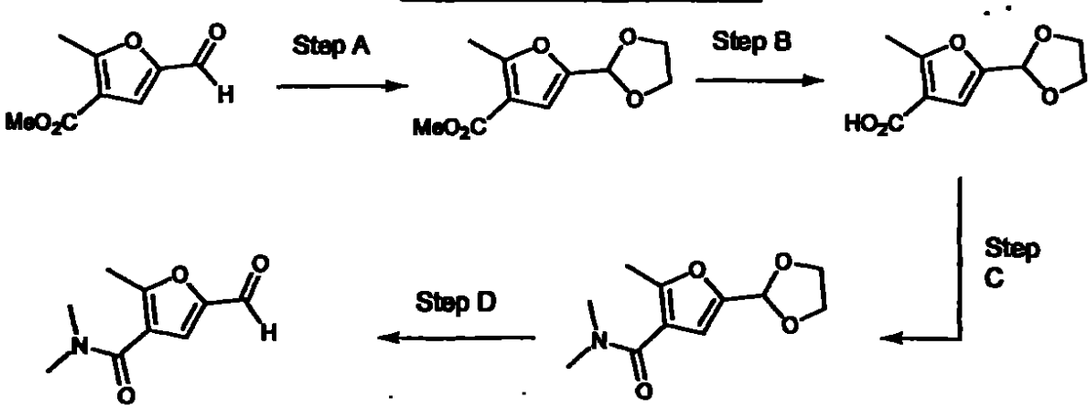
Step C

To the product from Step B above (4.2 g) diluted with dichloromethane (30 mL) and containing triethylsilane (6 mL) was added TFA (3 mL) in dichloromethane (7.5 mL). After stirring at RT for 10 min, the mixture was concentrated in vacuo to give the product as a colorless liquid (4.61 g, 80%).

Step D

To an etherial (3.5 mL dry) solution of the thiophene product (1.5 g) from Step C above was added BuLi (3.2 mL of 2.5M), and the mixture was heated at reflux for 15 min, cooled to RT, and DMF (0.8 mL) in ether (3.5 mL) was added dropwise. After stirring for 30 min, sat. NH_4Cl (aq) was added and the mixture was extracted with ether. The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give the title compound (1.71 g, 98%).

Preparative Example 1003



Step A

The aldehyde (0.50 g) was combined with ethylene glycol (1 mL), benzene (40 mL) and pTSA monohydrate (30 mg) and stirred at reflux for 20 hr. Cool to room temperature, add EtOAc and sat. $NaHCO_3$ (aq) solution, separate the organic phase, concentrate in vacuo, and purify by silica gel chromatography (EtOAc-Hex, 1:4) to give a colorless liquid (60 mg)

Step B

The product from Step A above (0.607 g) was stirred at 45°C overnight with 1N NaOH (aq), then cooled to room temperature, acidified with 3N HCl and extracted with EtOAc. Washing with brine and concentration in vacuo gave a solid (5.0 g).

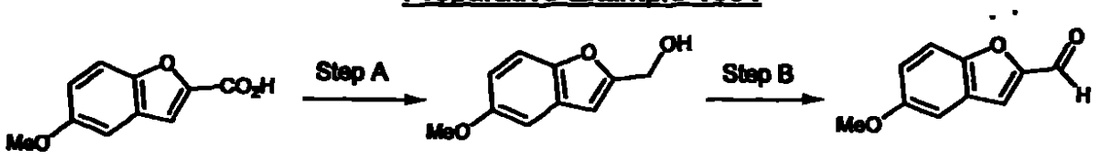
Step C

Following a similar procedure as that used in Preparative Example 1, except using the product from Step B above and dimethylamine in THF (2M), the product was obtained (1.21g crude).

Step D

The product from Step C above was dissolved in THF and stirred with 0.3N HCl (aq) and stirred at RT for 4 hr. Concentration in vacuo gave a pale yellow oil (1.1 g, 67%).

Preparative Example 1004



Step A

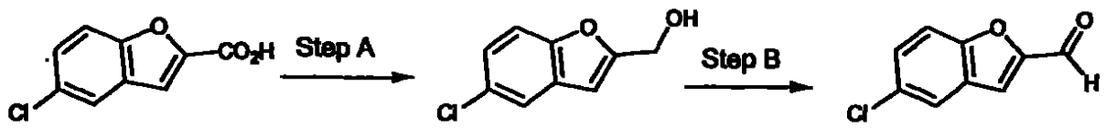
To a cooled (-78°C) solution of methoxybenzofuran-2-carboxylic acid (1 g) was added DIBAL (30 mL, 1M in THF). After stirring for 20 min, the mixture was warmed to RT and stirred for 4 hr, then poured into sat. NH4Cl (aq) (35 mL). After stirring at RT for 20 min, 6M HCl (aq) was added and the mixture was extracted with EtOAc, the organic phase dried and then concentrated in vacuo. Purification by silica gel chromatography (EtOAc-hexane, 3:7) afforded the alcohol as a solid (0.4 g, 97%).

Step B

A mixture of the product from Step A above (0.9 g), EtOAc (50 mL) and MnO2 (5.2 g) was stirred at RT for 22 h, then filtered and concentrated in vacuo. The solid was redissolved in EtOAc (50 mL), MnO2 (5.2 g) was added and the mixture was

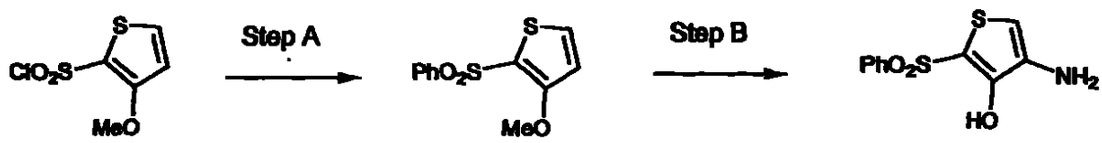
stirred for 4 additional hrs. Filtration, concentration and silica gel purification (EtOAc-Hexane, 1:3) gave the title compound as a solid (0.60 g, 67%).

Preparative Example 1005



Following a similar procedure as that detailed in Preparative Example 1004, except using 5-chlorobenzofuran-2-carboxylic acid (1.5 g), the title compound was obtained (solid, 0.31 g, 24%).

Preparative Example 1006



Step A

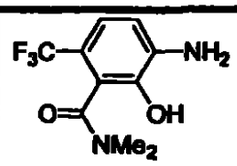
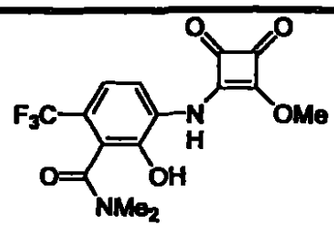
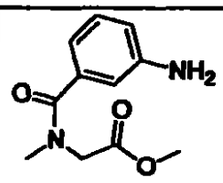
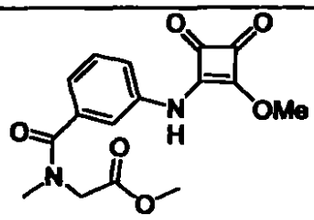
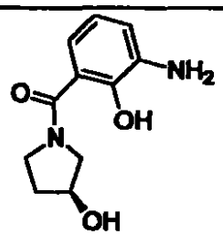
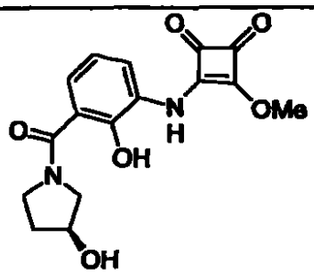
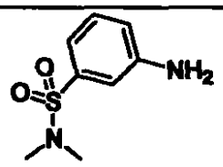
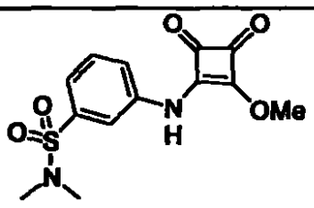
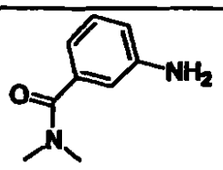
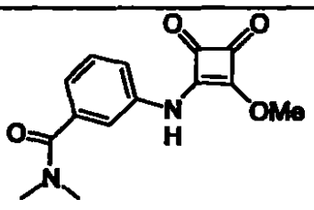
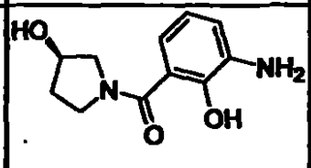
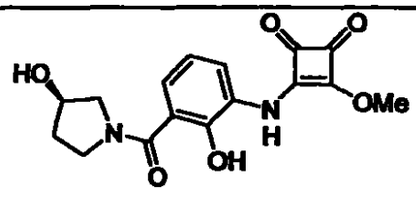
The sulfonyl chloride from Preparative Example 13.29 Step A (1.5 g) was stirred with AlCl3 and benzene for 15 min at 20 °C. Treatment with NaOH, extraction with Et_2O, concentration in vacuo, and purification by column chromatography (silica, hexane-EtOAc, 5:2) gave the phenylsulfone (1.5g, 84%, MH^+ = 255).

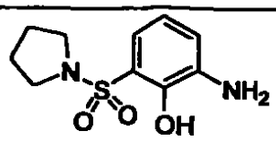
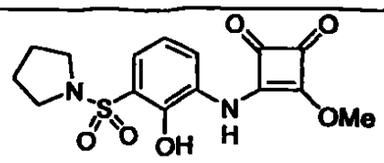
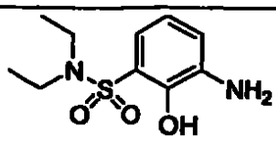
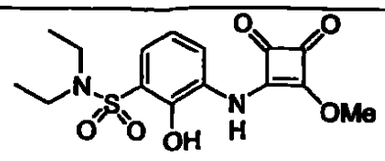
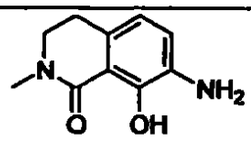
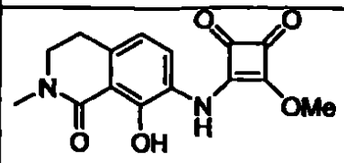
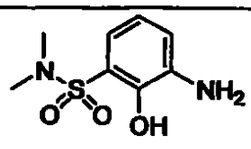
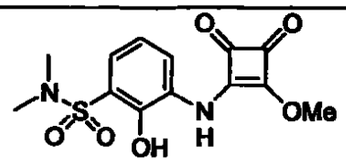
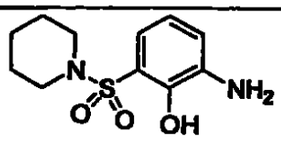
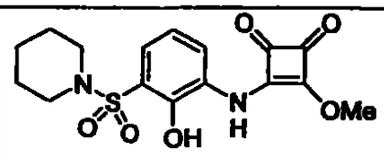
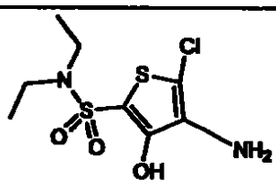
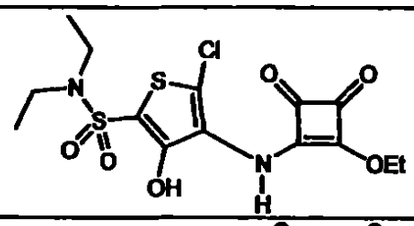
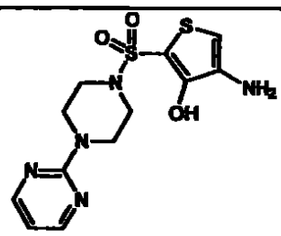
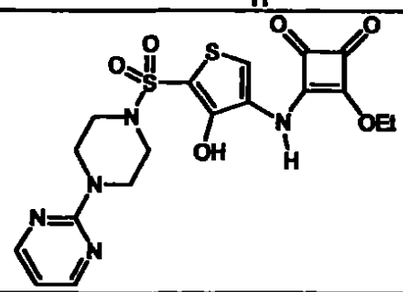
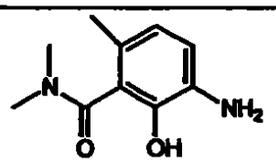
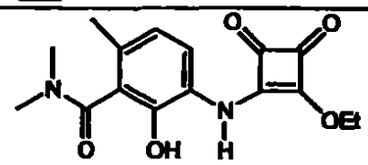
Step B

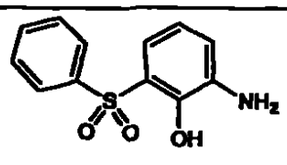
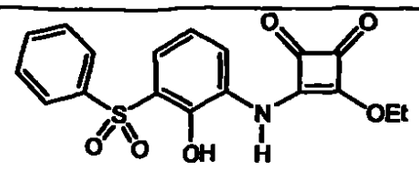
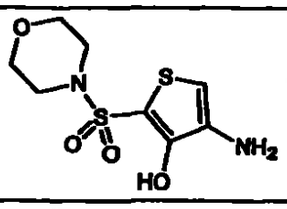
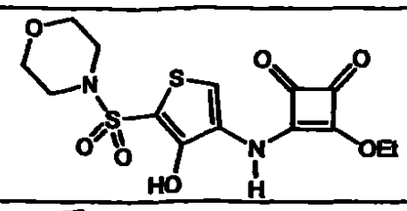
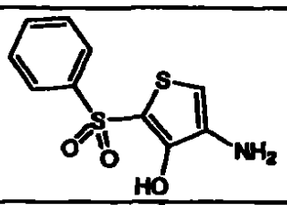
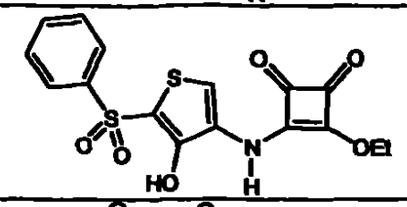
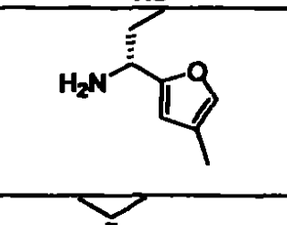
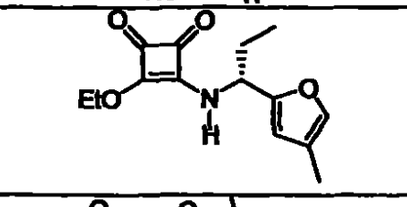
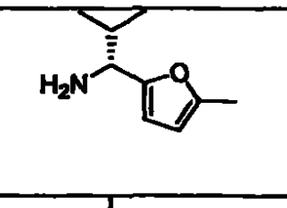
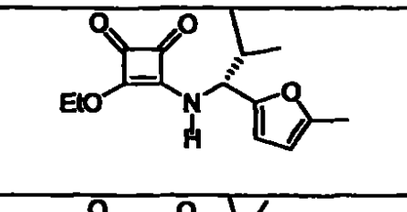
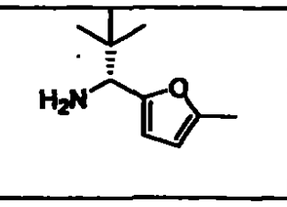
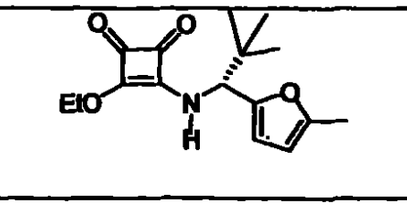
Following similar procedures as those used in Preparative Example 13.29 Steps C-G, except using the sulfone from Step A above, the title compound was prepared (0.04 g, 27%, MH^+ = 256).

Preparative Example 1007-1029

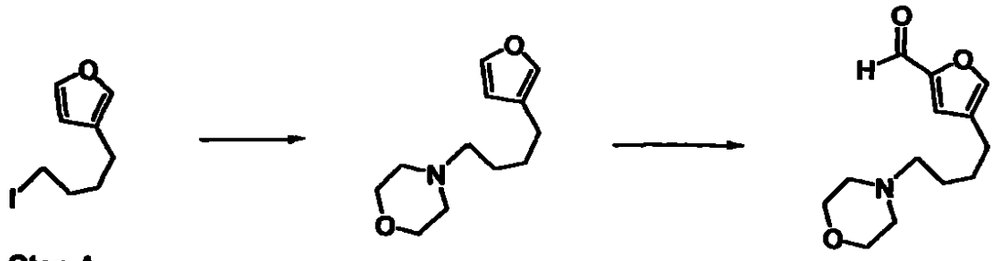
Following a similar procedure set forth in Preparative Example 19.1 of WO 02/083624, published October 24, 2002, or Preparative Example 19.2, but using the Amine (Anilines) listed in the Table below, the following squarate intermediates were prepared.

Example	Amine/Aniline	Product	1.Yield (%) 2. $(M+1)^+$
1007			1. 95% 2. 359
1008			1. 99% 2. 333
1009			1. 99% 2. 333
1010			1. 99% 2. 311
1011			1. 99% 2. 275
1012			1. 99% 2. 333

1013			1. 72% 2. 353.0
1014			1. 60% 2. 355.1
1015			1. 70% 2. 303.1
1016			1. 45% 2. 327.0
1017			1. 70% 2. 367.0
1019			1. 32% 2. 409
1020			1. 48% 2. 466
1021			1. ~60% (crude)

1022			1. 21%
1023			1. 45% 2. 389
1024			1. 30% 2. 380
1027			1. 44% 2. 264
1028			1. 56% 2. 278
1029			1. 47% 2. 292

Preparative Example 1030



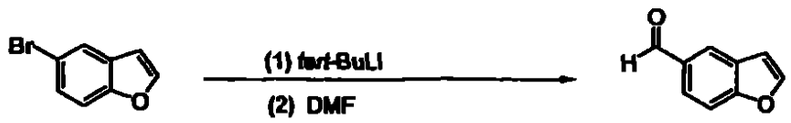
Step A

The product of Preparative Example 34.18 Step B (2 g, 8 mmol) was stirred with morpholine (0.9 mL, 10.29 mmol) and K2CO3 (2.2 g, 15.9 mmol) in 50 mL of acetone at RT to obtain th morpholinobutylfuran derivative (1.22 g,73%).

Step B

Following a similar procedure as in Preparative Example 34.18 Step D, but using the product (1.2 g) from Step A above, the title aldehyde was prepared (0.9 g,66%, 1:0.7 regioisomeric mixture).

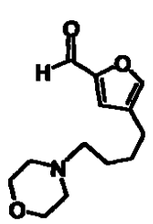
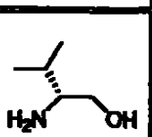
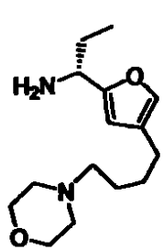
Preparative Example 1031

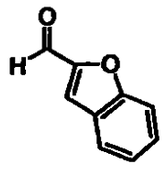
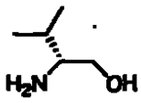
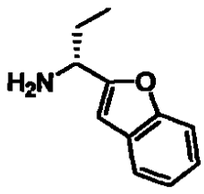
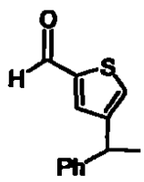
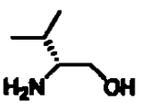
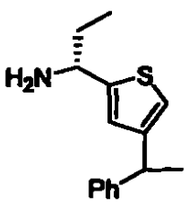
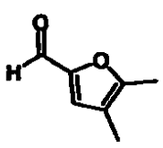
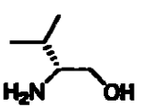
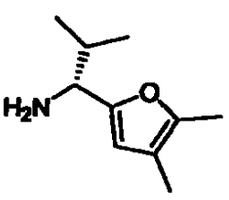
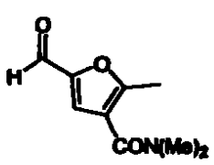
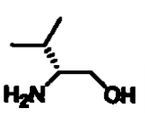
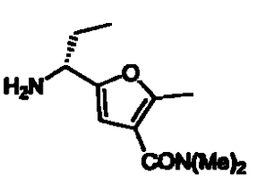
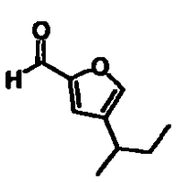
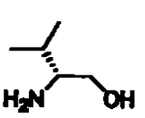
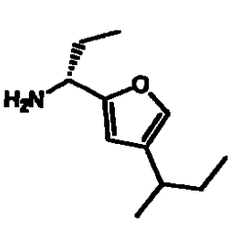
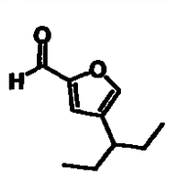
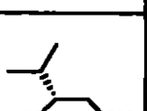
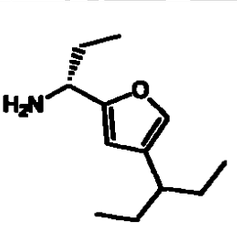
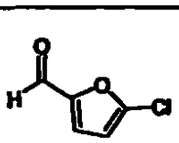
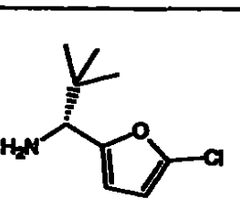


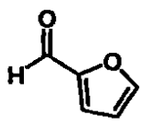
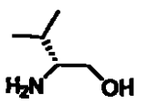
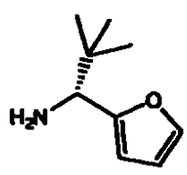
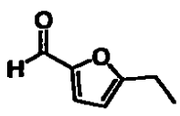
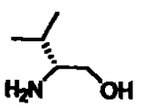
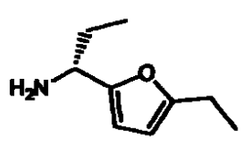
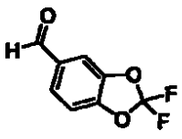
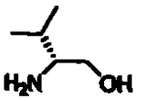
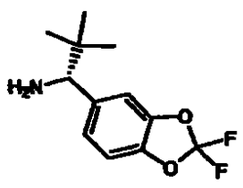
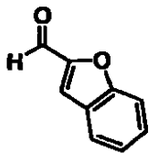
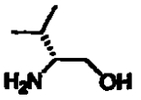
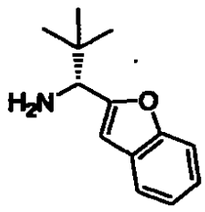
A solution of 5-bromobenzofuran (950 mg, 4.82 mmol) in anhydrous ether (12 mL) was cooled to –78 °C. 1.7 M *tert*-BuLi solution in pentane (6 ml, 10.2 mmol) was added dropwise under argon. After addition, the mixture was stirred at –78 °C for 20 min, followed by addition of a mixture of DMF (0.8 mL) and ether (1 mL). The mixture was allowed to warm to rt and stirred for 0.5 h. Ethyl acetate was added. The mixture was poured to saturated ammonium chloride solution. The organic layer was separated and concentrated. The residue was purified by column chromatography (ethyl acetate-hexanes, 1:5 v/v) to give the title compound as a pale yellow solid (490 mg, 70%).

PREPARATIVE EXAMPLES 1040-1054

Following the procedure set forth in Preparative Example 64 of WO 02/083624, published October 24, 2002, but using the commercially available (or prepared) aldehyde, aminoalcohols, and organolithium reagents in the Table below, the optically pure amine products in the Table below were obtained.

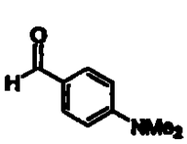
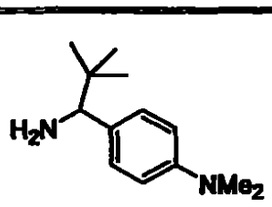
Prep. Ex.	Aldehyde	Amino Alcohol	Organo-lithium	Product	1.Yield (%) 2. $(M+1)^+$
1040			EtLi		1. 24% 2. 267

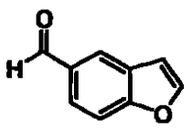
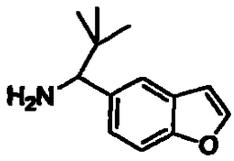
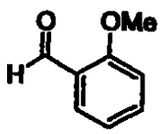
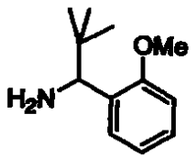
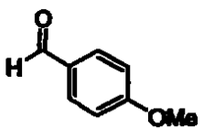
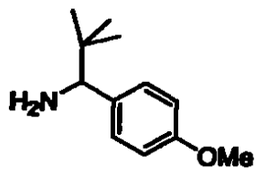
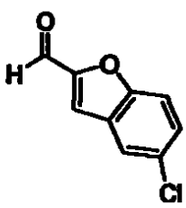
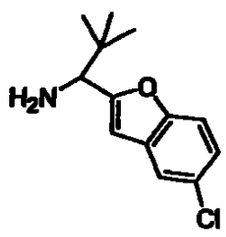
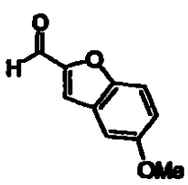
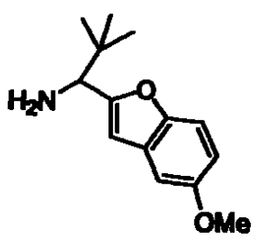
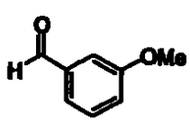
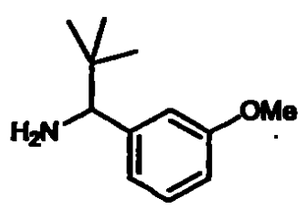
1041			EtLi		1. 94% 2. 176 (m/e)
1042			EtLi		1. 67% 2. 229 (M-16)
1043			i-PrLi		1. 60% 2. 151 [M-16]
1044			EtLi		1. 74% 2. 194 (M-18)
1045			EtLi		1. 33% 2. 165 $[M-NH_2]^+$
1048			EtLi		1. 31 2. 179 $[M-NH_2]^+$
1047			t-BuLi		1. 31% 2. 188

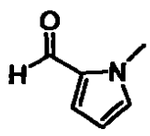
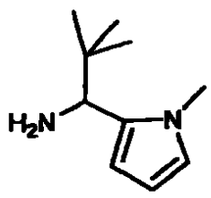
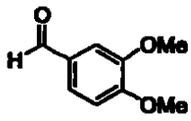
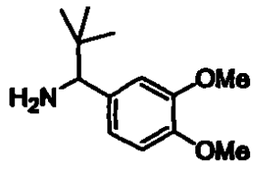
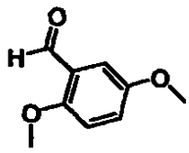
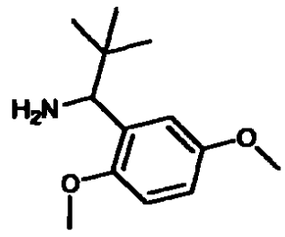
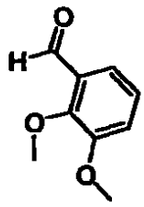
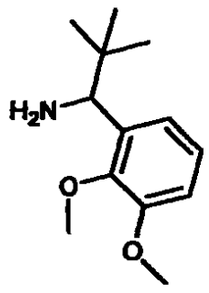
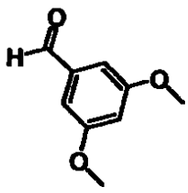
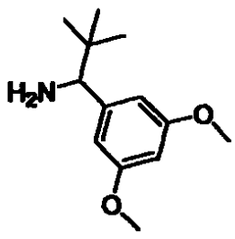
1048			t-BuLi		1. 10% 2. 154
1049			EtLi		1. 73% 2. 137 [M-NH2]$^+$
1051			t-BuLi		1. 17%
1054			t-BuLi		1. 79% 2. 151 (M-16)

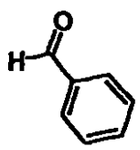
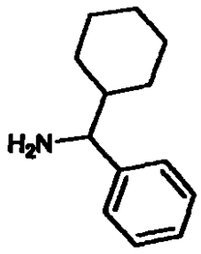
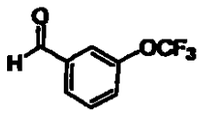
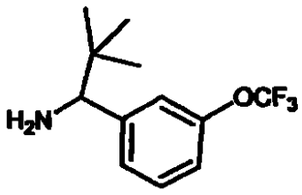
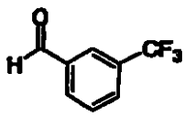
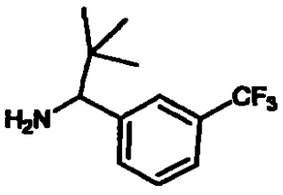
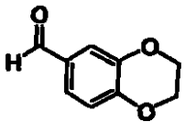
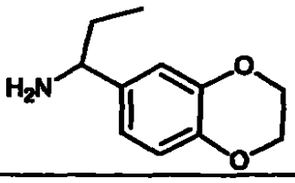
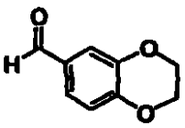
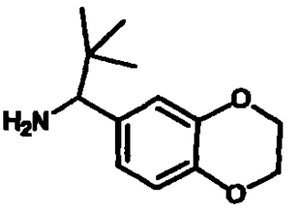
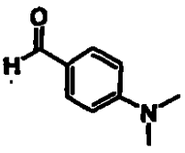
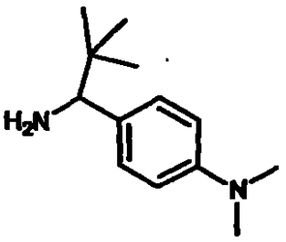
PREPARATIVE EXAMPLES 1100-1126

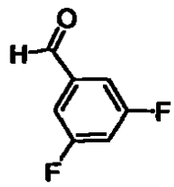
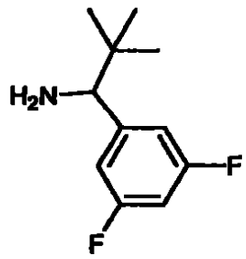
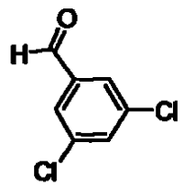
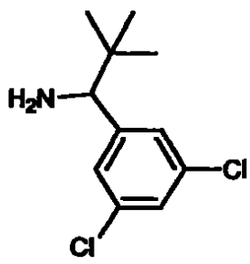
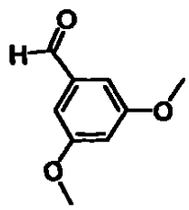
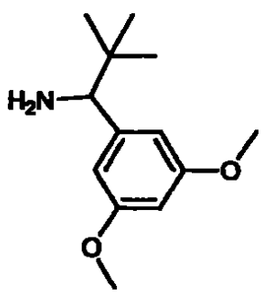
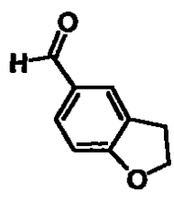
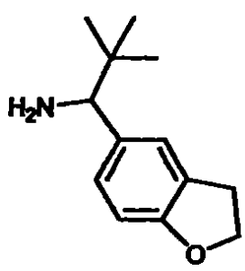
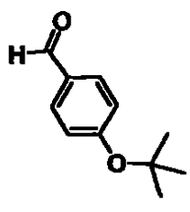
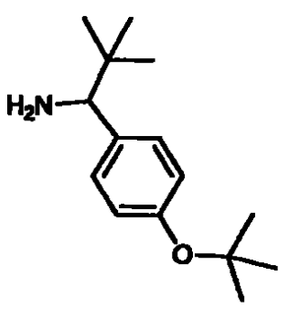
Following the procedure set forth in Preparative Example 34 of WO 02/083624, published October 24, 2002, but using the commercially available aldehydes and Grignard/Organolithium reagents listed in the Table below, the amine products were obtained.

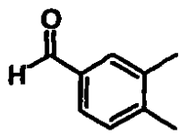
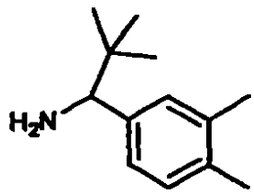
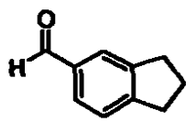
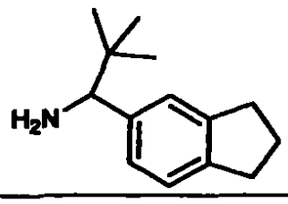
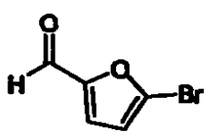
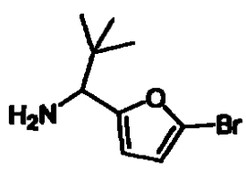
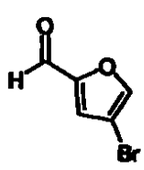
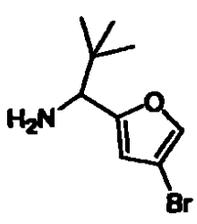
Prep. Ex.	Aldehyde	Organo-metallic Reagent	Product	1.Yield (%) 2. (M+1)$^+$
1100		t-BuLi		1. 83% 2. 190 (M-16)

1101		t-BuLi		1. 46% 2. 204
1102		t-BuLi		1. 48% 2. 194
1103		t-BuLi		1. 51% 2. 194
1104		t-BuLi		1. 12% 2. 238
1105		t-BuLi		1. 39% 2. 234
1106		t-BuLi		1. 44% 2. 194 (m/e)

1107		t-BuLi		1. 57% 2. 150 (M-16)
1108		t-BuLi		1. 31% 2. 224
1109		t-BuLi		1. 11% 2. 224
1110		t-BuLi		1. 57% 2. 224
1111		t-BuLi		1. 21% 2. 224

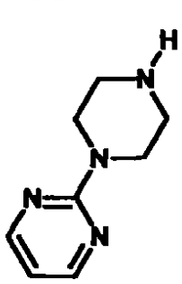
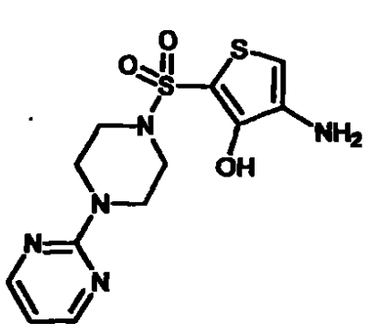
1112		c-Pentyl-Li		1. 58% 2. 190
1113		t-BuLi		1. 20% 2. 248
1114		t-BuLi		1. 24% 2. 232
1115		EtLi		1. 32% 2. 177 (M-NH2)
1116		t-BuLi		1. 26% 2. 205 (M-NH2)
1117		t-BuLi		1. 50% 2. 190 (M-NH2)

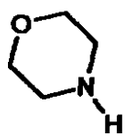
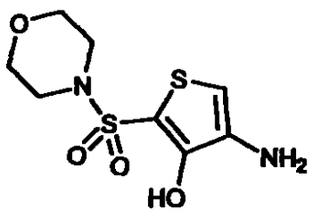
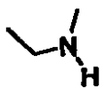
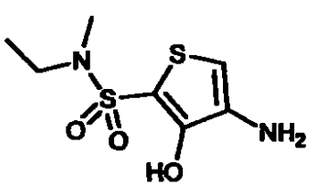
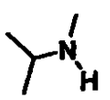
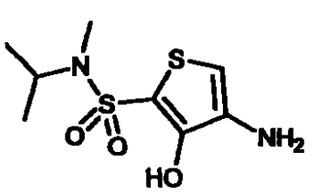
1118		t-BuLi		1. 29% 2. 200
1119		t-BuLi		1. 28% 2. 232
1120		t-BuLi		1. 76% 2. 224
1121		t-BuLi		1. 40% 2. 206
1122		t-BuLi		1. 38% 2. 236

1123		t-BuLi		1. 70% 2. 192
1124		t-BuLi		1. 81% 2. 204
1125		t-BuLi		33%
1126		t-BuLi		50%

PREPARATIVE EXAMPLES 1200-1203

Following the procedure set forth in Preparative Example 13.29 but using the commercially available amines, the hydroxyaminothiophene products listed in the Table below were obtained.

Prep. Ex.	Amine	Product	1.Yield (%) 2. $(M+1)^+$
1200			1. 3% 2. 342

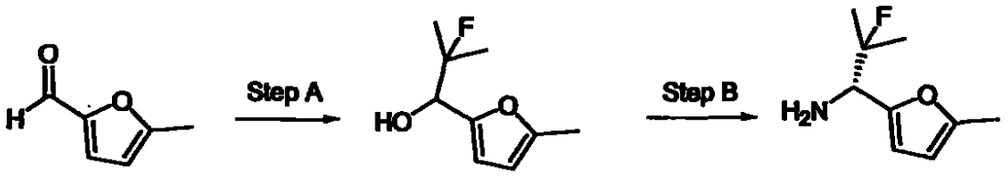
1201			1. 41% 2. 265
1202			1. 17% 2. 237
1203			1. 1%

PREPARATIVE EXAMPLE 1300



The title compound from Preparative Example 13.32 (0.35 g) was treated with concentrated sulfuric acid (3 mL) for 6 hrs, then poured on ice, and the pH adjusted to 4 with NaOH. Extraction with EtOAc, and drying of the organic phase over Na_2SO_4 gave the title compound (159 mg, 64%, $MH^+ = 223$).

PREPARATIVE EXAMPLE 1301



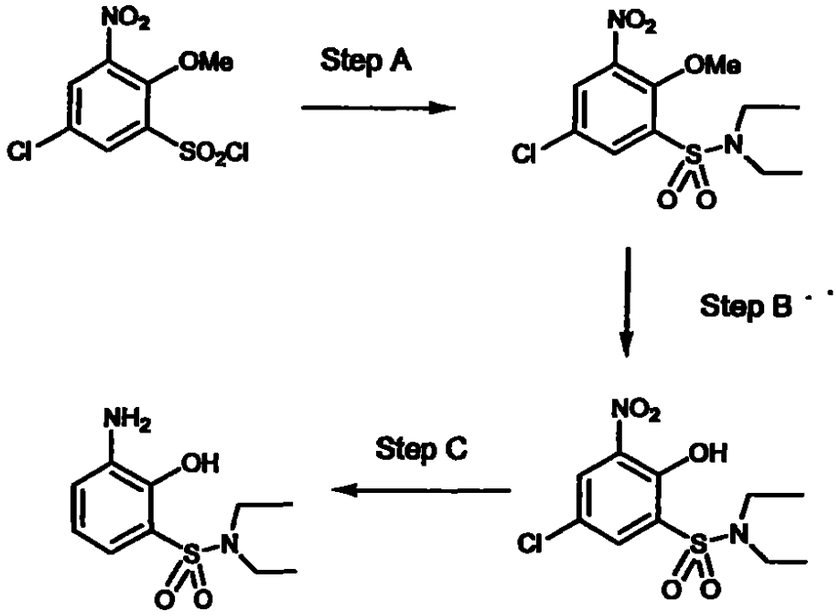
Step A

Following the procedure set forth in Preparative Example 605 but using the commercially available fluoroisopropylester, the alcohol product was obtained (1.2 g, 84%, M-OH = 155).

Step B

Following the procedure set forth in Preparative Example 625 but using the alcohol from Step A above, the amine product was obtained (350 mg, 35%, M-NH2 = 155).

PREPARATIVE EXAMPLE 1302



Step A

Following a similar procedure as that used in Preparative Example 13.29 Step B, except using the commercially available arylsulfonylchloride (0.15 g) and diethylamine (2.2 eq), the dimethylsulfonamide was obtained (0.12 g, 71%, MH^+ = 323).

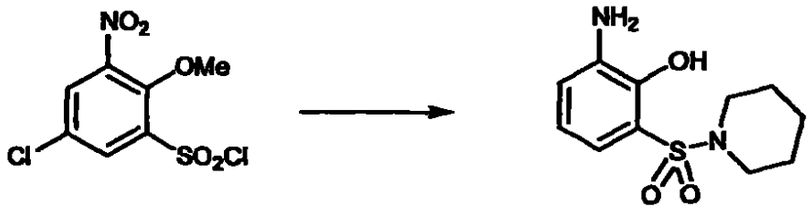
Step B

Following a similar procedure as that used in Preparative Example 13.29 Step C, except using the product from Step A above (0.12 g), the phenol was obtained (0.112 g, 98%).

Step C

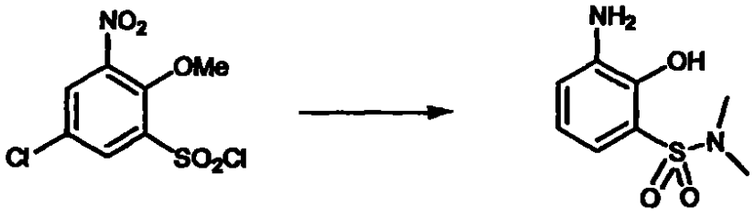
Following a similar procedure as that used in Preparative Example 10.55 Step C, of WO 02/083624, published October 24, 2002, except using the product from Step B above (0.112 g), the title compound was obtained (0.1 g, 99%, MH^+ = 245).

PREPARATIVE EXAMPLE 1303



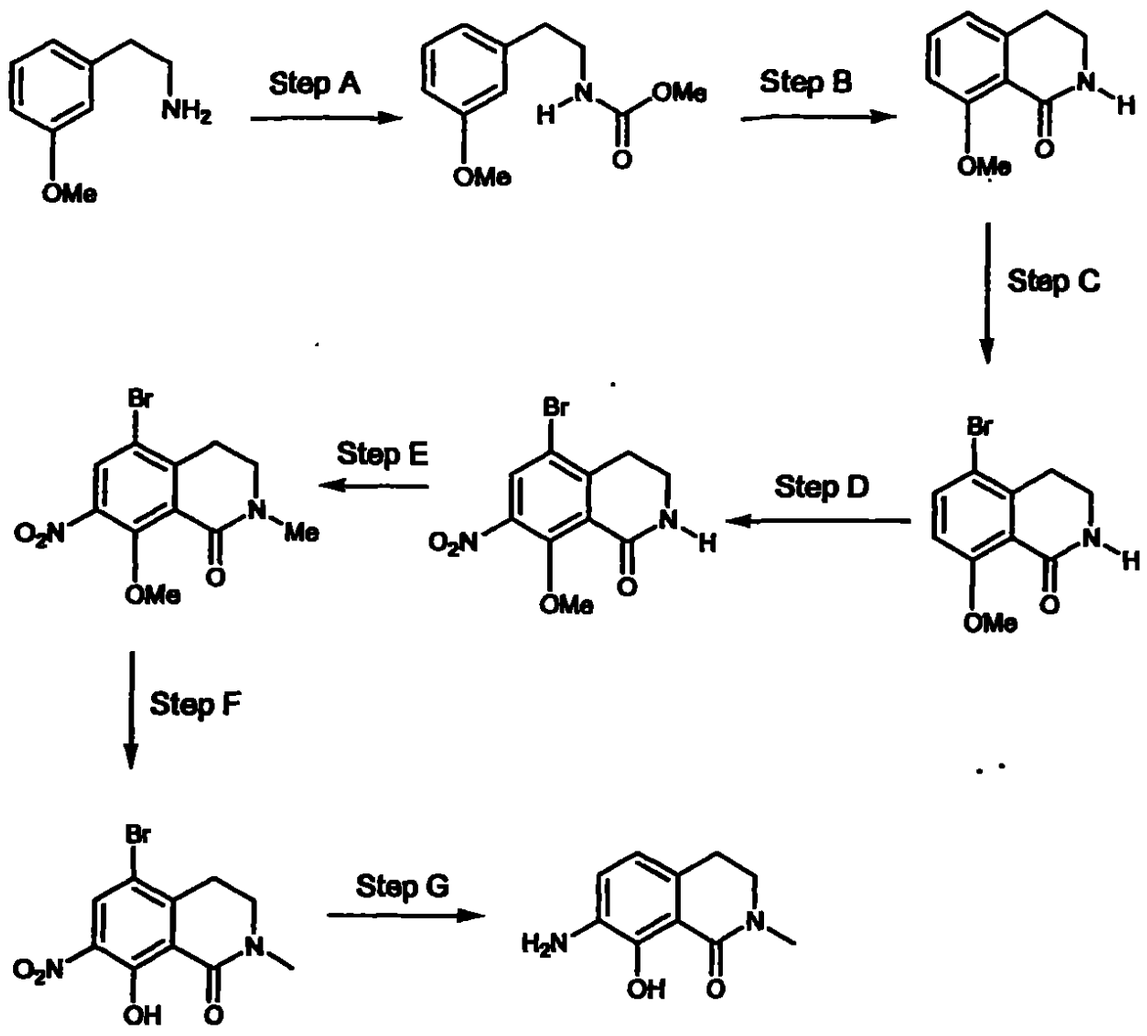
Following a similar procedure as that used in Preparative Example 1302 Steps A-C, except using piperidine in Step A (0.078 g) instead of diethylamine, the title compound was obtained (0.070 g, 35%, MH^+ = 257).

PREPARATIVE EXAMPLE 1304



Following a similar procedure as that used in Preparative Example 1302 Steps A-C, except using dimethylamine (2*M* in THF) in Step A instead of diethylamine, the title compound was obtained (1.92g, 72%, MH^+ = 217).

PREPARATIVE EXAMPLE 1305



Step A

Following a similar procedure as that used in Preparative Example 1302 Step A, except using the phenethylamine indicated (4.99 g), the product was obtained (5.96 g, 86%, MH^+ = 210).

Step B

The compound from Step A above (5.0 g) was added to 30 g of PPA at 150°C and the resulting mixture stirred for 20 min, before being poured on ice and extracted with dichloromethane. The organic phase was dried over MgSO4, concentrated in vacuo and purified by silica gel chromatography (EtOAc:MeOH, 95:5) to give the product (0.5 g, 9%).

100
101

Step C

Following a similar procedure as that used in Preparative Example 13.3 Step D, of WO 02/083624, published October 24, 2002, except using the compound from Step B above (0.14 g), the product was obtained (0.18 g, 87%, MH^+ = 256).

Step D

Following a similar procedure as that used in Preparative Example 11 Step B, of WO 02/083624, published October 24, 2002, except using the compound from Step C above (0.18 g), the product was obtained (0.17 g).

Step E

Following a similar procedure as that used in Preparative Example 13.3 Step B, of WO 02/083624, published October 24, 2002, except using the compound from Step D above (0.17 g), the product was obtained (0.17 g, 95%, MH^+ = 315).

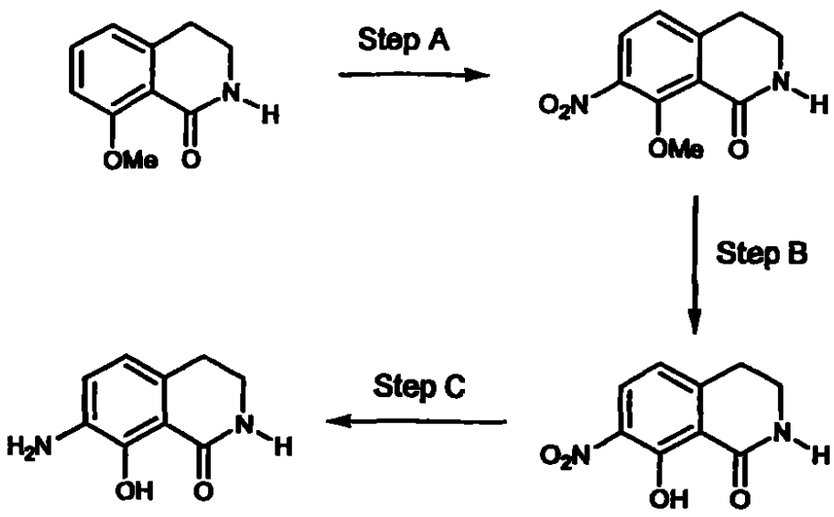
Step F

Following a similar procedure as that used in Preparative Example 13.29 Step C, except using the product from Step E above (0.17 g), the nitrophenol was obtained (0.165 g, 99%, MH^+ = 303).

Step G

Following a similar procedure as that used in Preparative Example 10.55 Step C, of WO 02/083624, published October 24, 2002, except using the product from Step F above (0.165 g), the title compound was obtained (0.128 g, 86%, MH^+ = 193).

PREPARATIVE EXAMPLE 1306



Step A

Following a similar procedure as that used in Preparative Example 11 Step B, of WO 02/083624, published October 24, 2002, except using the lactam (0.179 g), the title compound was obtained (0.25 g, 25%).

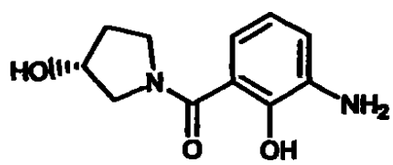
Step B

Following a similar procedure as that used in Preparative Example 13.29 Step C, except using the product from Step A above (0.055 g), the phenol was obtained (0.045 g, 99%).

Step C

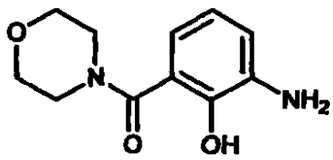
Following a similar procedure as that used in Preparative Example 10.55 Step C, of WO 02/083624, published October 24, 2002, except using the product from Step B above (0.045 g), the title compound was obtained (0.022 g, 57%, MH^+ = 179).

PREPARATIVE EXAMPLE 1307



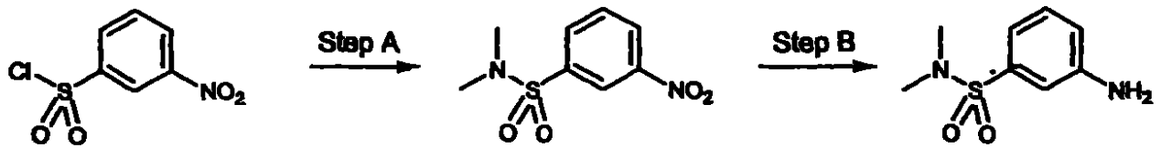
Following a similar procedure as that used in Preparative Example 2, of WO 02/083624, published October 24, 2002, except using 3(*R*)-hydroxypyrrolidine HCl (1.36 g), the title compound was obtained (2.25 g, 89%).

PREPARATIVE EXAMPLE 1308



Following a similar procedure as that used in Preparative Example 2, of WO 02/083624, published October 24, 2002, except using morpholine, the title compound was obtained (3.79 g).

PREPARATIVE EXAMPLE 1309



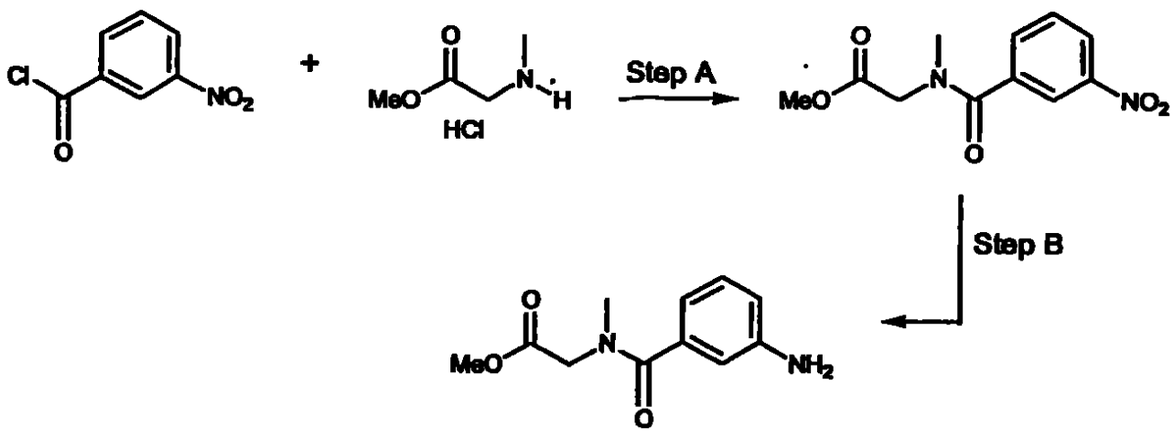
Step A

Following a similar procedure as that used in Preparative Example 13.29 Step B, except using the commercially available nitrophenylsulfonylchloride and diethylamine (2.2 eq), the dimethylsulfonamide was obtained (90%, $MH^+ = 231$).

Step B

Following a similar procedure as that used in Preparative Example 10.55 Step C, of WO 02/083624, published October 24, 2002, except using the product from Step B above, the title compound was obtained (45%, $MH^+ = 201$).

PREPARATIVE EXAMPLE 1310



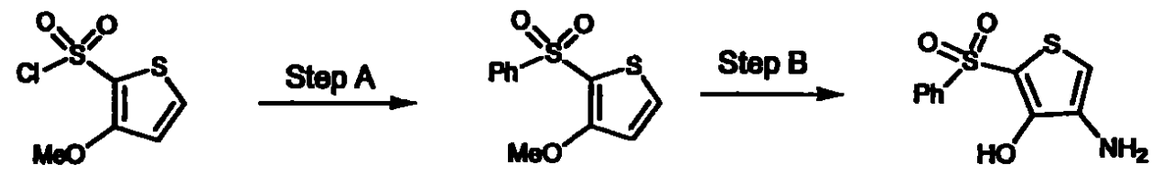
Step A

Following a similar procedure as that used in Preparative Example 13.29 Step B, except using the commercially available nitrobenzoylchloride and the commercially available amine indicated, the benzamide was obtained (13%, MH^+ = 253).

Step C

Following a similar procedure as that used in Preparative Example 10.55 Step C, of WO 02/083624, published October 24, 2002, except using the product from Step B above, the title compound was obtained (94%, MH^+ = 223).

PREPARATIVE EXAMPLE 1311



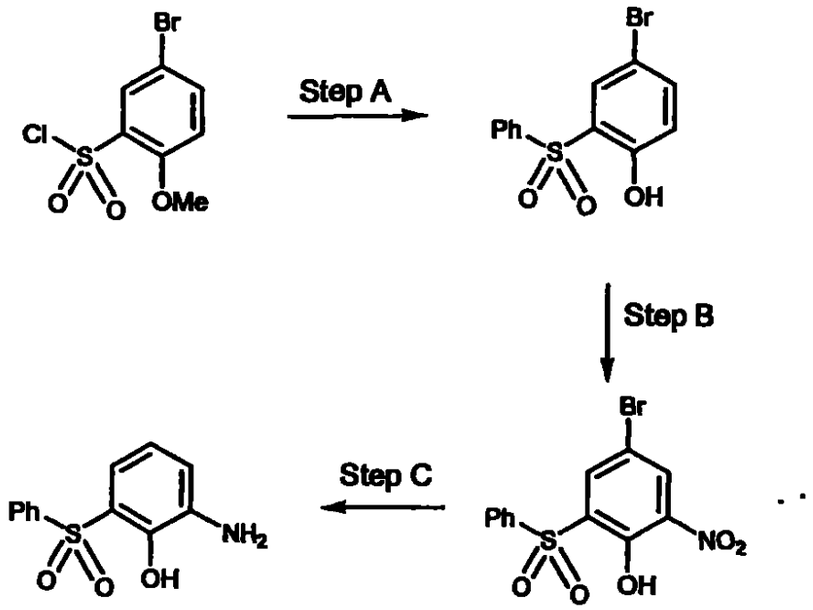
Step A

To a benzene (20 mL) solution of methoxythiophenesulfonylchloride (1.5 g) was added $AlCl_3$ (2.0 g) at RT. After 15 min, the mixture was added to 0.1N HCl (aq) with stirring, then extracted with Et_2O. Washing the organic phase with bring, drying over $MgSO_4$, concentration in vacuo and purification by silica gel chromatography (Hexane:EtOAc, 5:2) gave the title compound (1.5 g, 84%).

Step B

Following a similar procedure as that used in Preparative Example 13.29 Steps C-G, except using the product from Step A above, the title compound was obtained (3%, MH^+ = 380).

PREPARATIVE EXAMPLE 1312



Step A

Following a similar procedure as that used in Preparative Example 1311 Step A, except using the commercially available sulfonylchloride, the diphenylsulfone was obtained (880 mg, 80%).

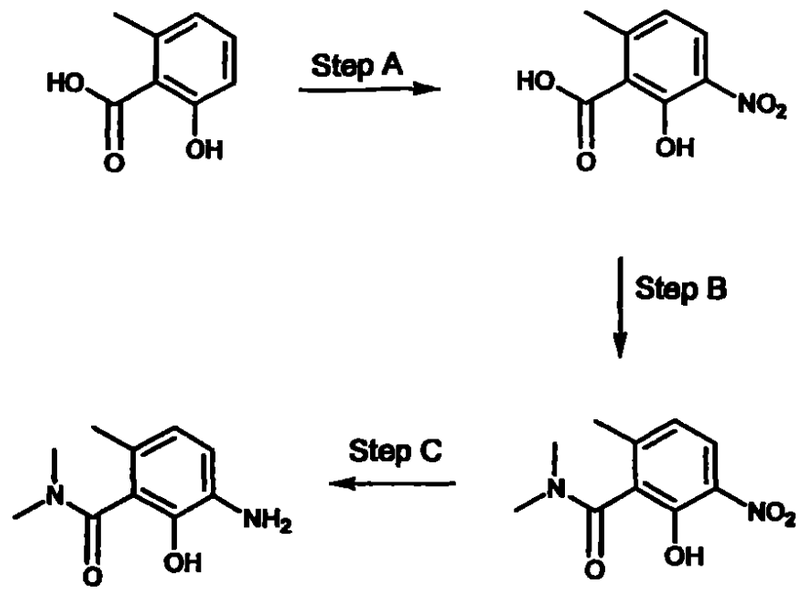
Step B

Following a similar procedure as that used in Preparative Example 11 Step B, of WO 02/083624, published October 24, 2002, except using the product from Step A above, the title compound was obtained (0.90 g, 97%).

Step C

Following a similar procedure as that used in Preparative Example 10.55 Step C, of WO 02/083624, published October 24, 2002, except using the product from Step B above (0.16 g), the title compound was obtained (0.106 g, 95%).

PREPARATIVE EXAMPLE 1313



Step A

Following a similar procedure as that used in Preparative Example 1311 Step A, except using the commercially available phenol (2 g), the nitroacid was obtained (~ 13 mmol).

Step B

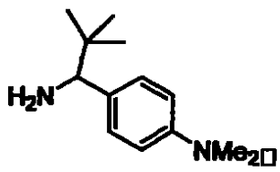
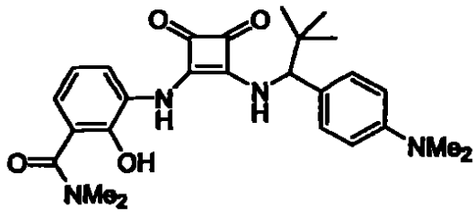
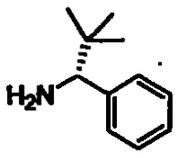
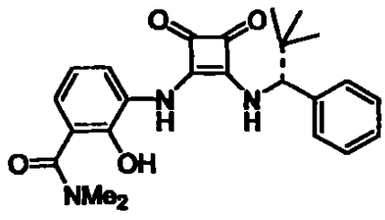
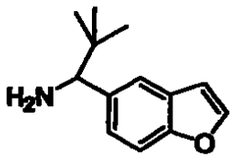
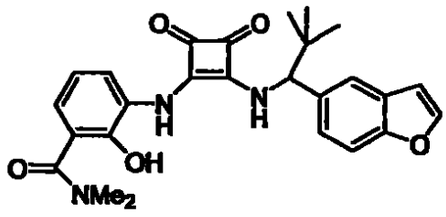
Oxallyl chloride (3.5 mL) and two drops of DMF was added to the product from Step A above (~ 13 mmol) dissolved in dichloromethane (100 mL). After stirring at RT overnight, the mixture was concentrated in vacuo, diluted with dichloromethane (50 mL), cooled to 0°C. Dimethylamine in THF (20 mL of 2N) and TEA (8 mL) were added. After 3 hr of stirring, the mixture was concentrated in vacuo, aq NaOH (1M) was added, and the mixture was extracted with dichloromethane. The pH of the aq layer was adjusted to pH = 2 using 6N HCl (aq), and extracted with dichloromethane. The combined organic extracts were washed with brine, dried, concentrated in vacuo, and the product purified by silica gel chromatography (700 mL dichloromethane/20 mL MeOH/ 1 mL AcOH) to give the title compound (800 mg, 27% for two steps).

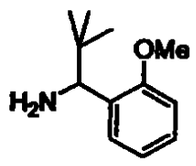
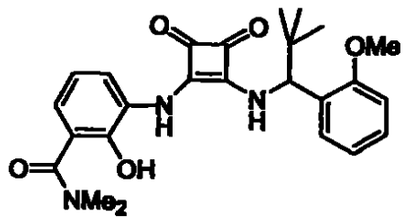
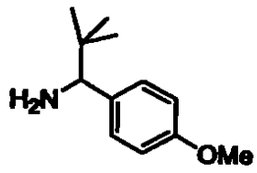
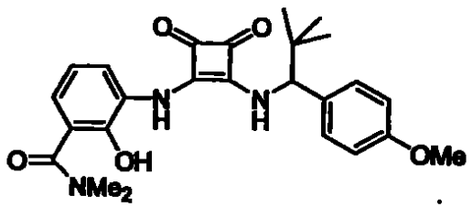
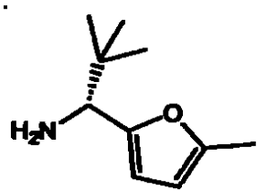
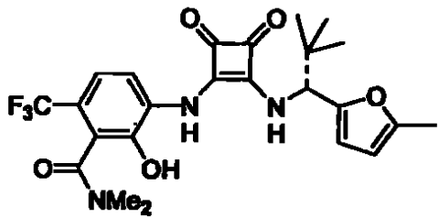
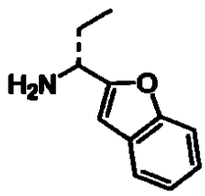
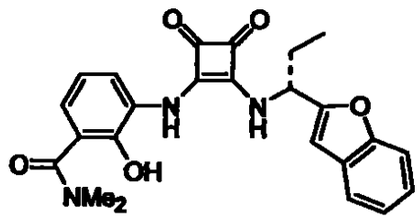
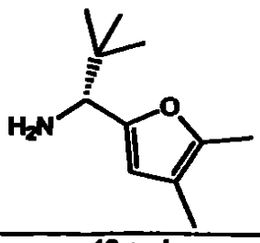
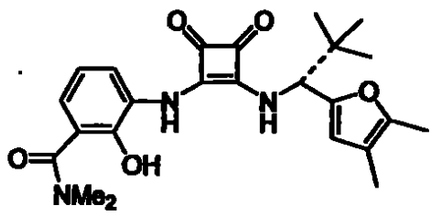
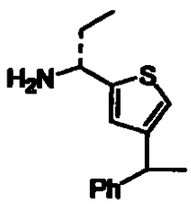
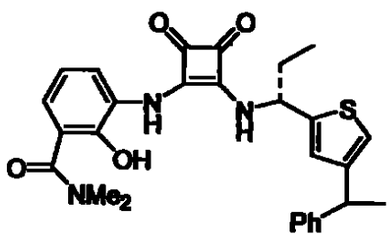
Step C

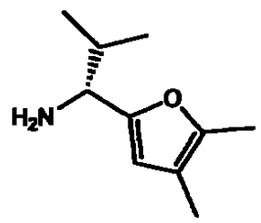
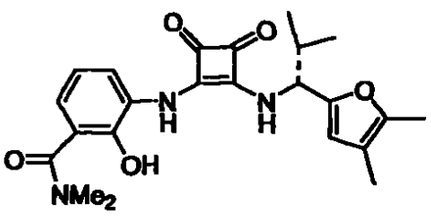
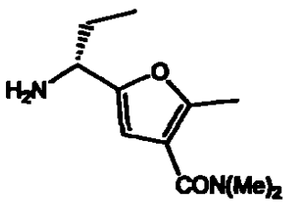
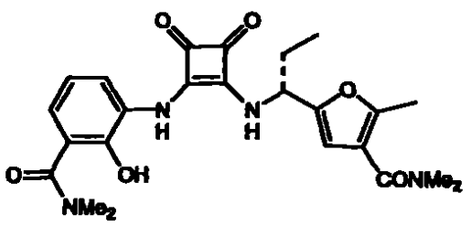
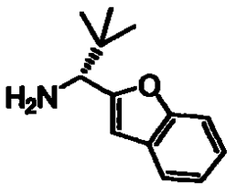
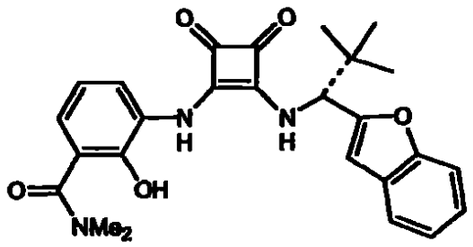
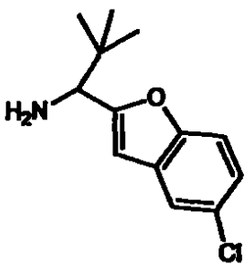
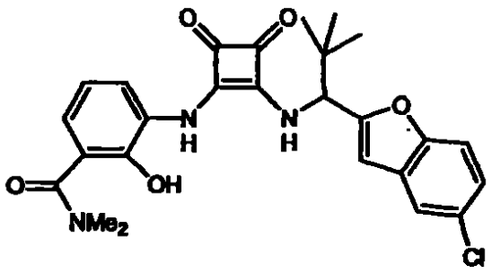
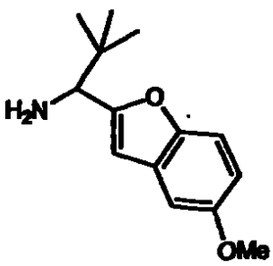
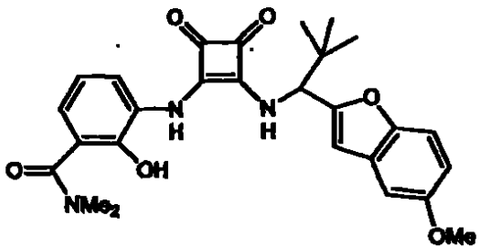
Following a similar procedure as that used in Preparative Example 10.55 Step C, of WO 02/083624, published October 24, 2002, except using the product from Step B above (780 mg), the title compound was obtained (0.46 g, 68%).

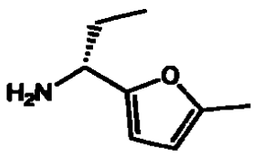
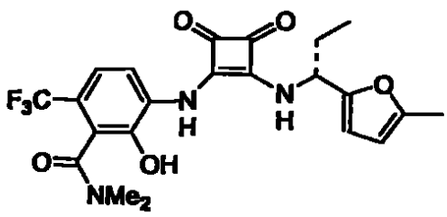
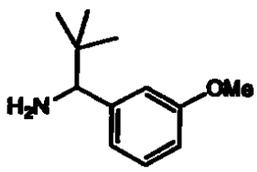
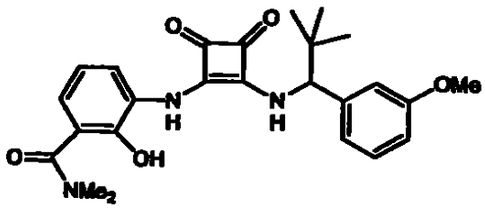
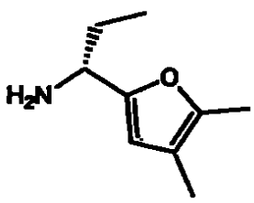
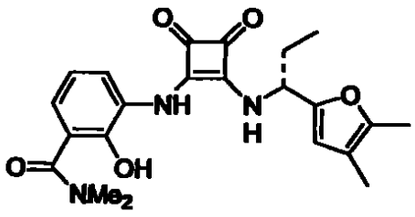
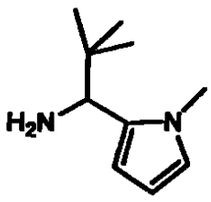
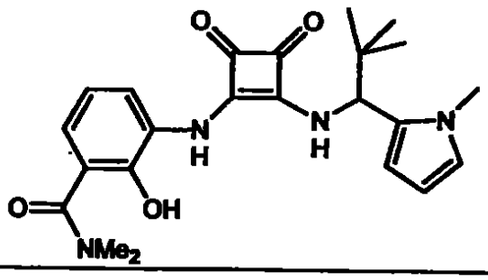
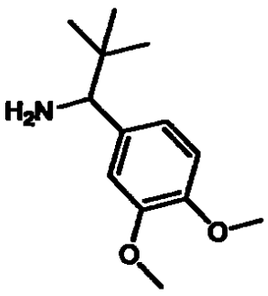
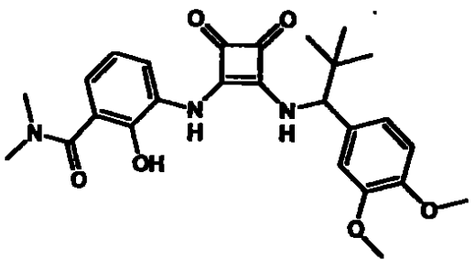
Examples 2001-2088

Following a similar procedure set forth in Example 210, of WO 02/083624, published October 24, 2002, but using the cyclobutenedione intermediate and amine indicated in the Table below, the following cyclobutenedione products were obtained. See WO 02/083624, published October 24, 2002, for Preparative Examples 19, 19.2, 22, 23.14 and 87.1.

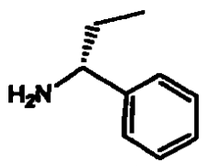
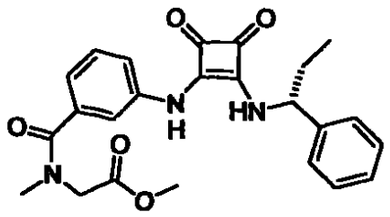
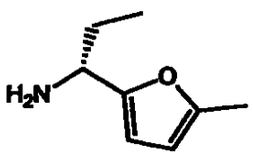
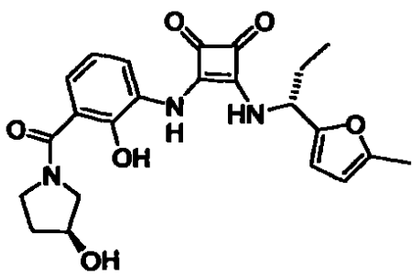
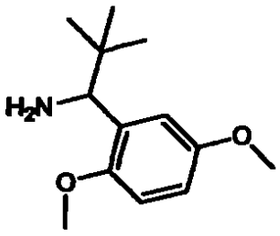
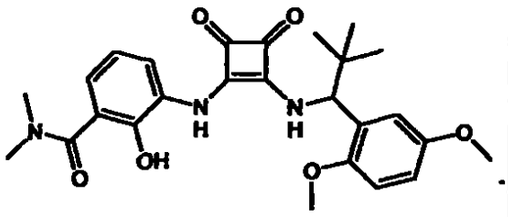
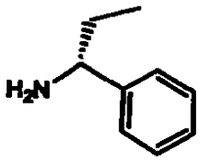
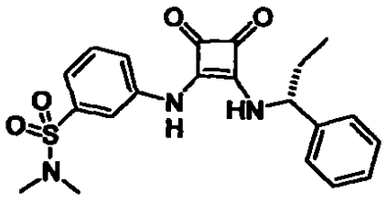
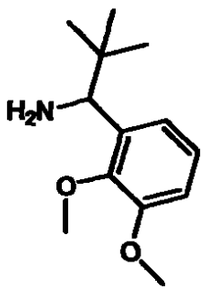
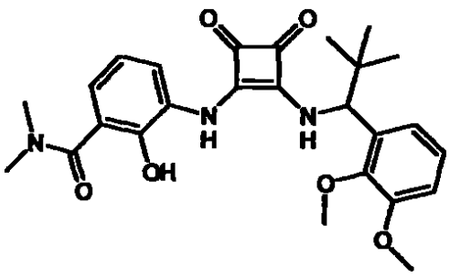
Example	Prep Ex of intermediate and Amine	Product	1.Yield (%) 2. $(M+1)^+$
2001	19 and 		3. 65% 4. 465
2002	19 and 		1. 5% 2. 422
2003	19 and 		1. 47% 2. 462

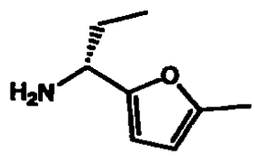
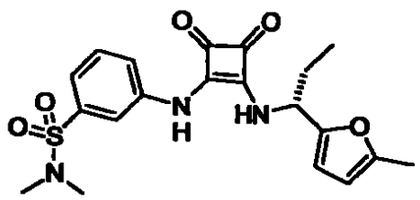
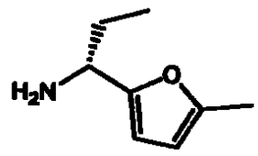
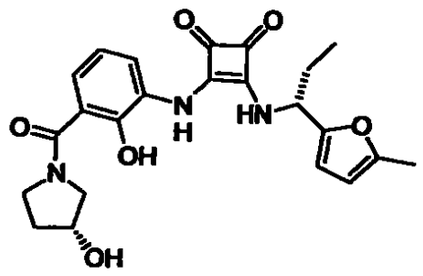
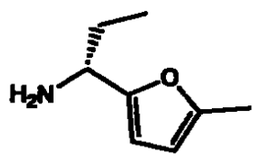
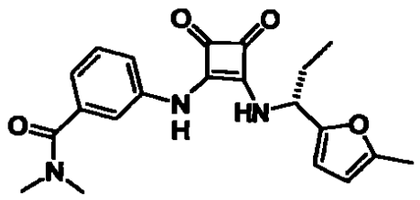
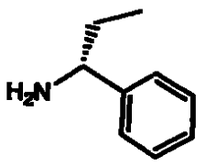
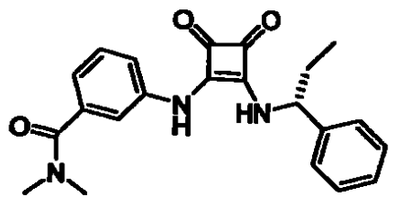
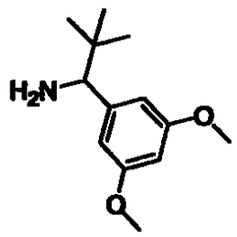
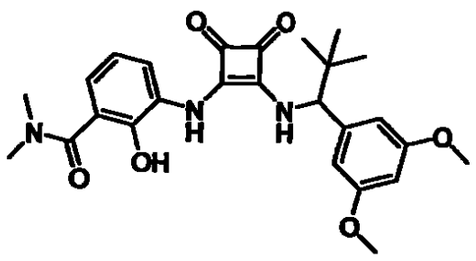
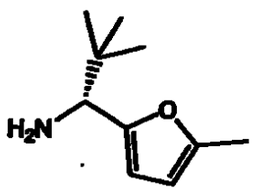
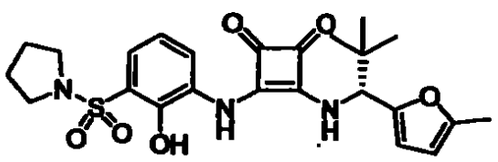
2004	19 and 		1. 74% 2. 452
2005	19 and 		1. 71% 2. 452
2006	1007 and 		1. 18% 2. 494
2007	19 and 		1. 36% 2. 434
2008	19 and 		1. 19% 2. 440
2009	19 and 		1. 45% 2. 504

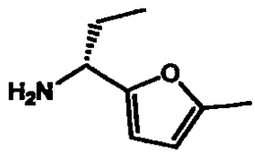
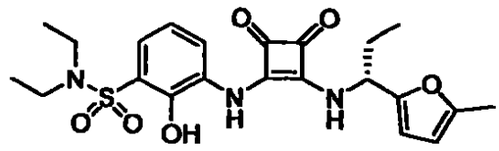
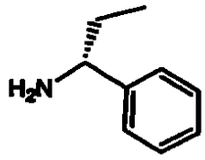
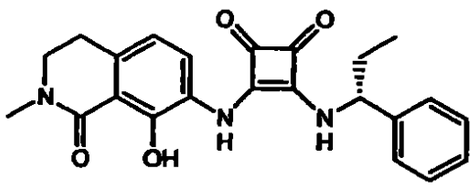
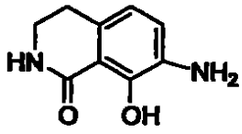
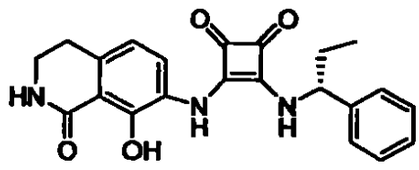
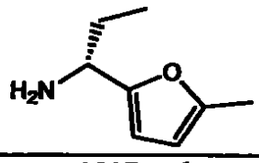
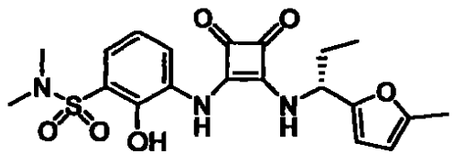
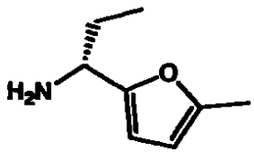
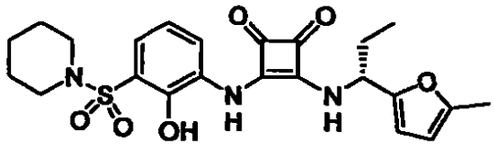
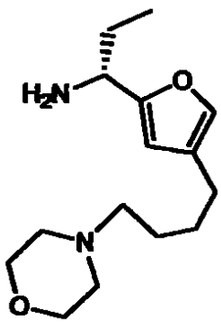
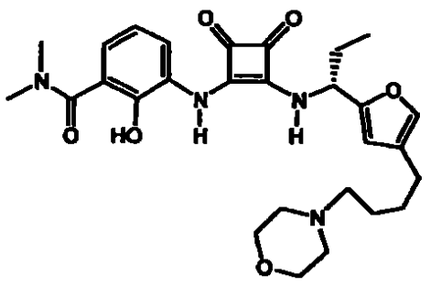
2010	19 and 		1. 57% 2. 426
2011	19 and 		1. 6% 2. 469
2012	19 and 		1. 4% 2. 462
2013	19 and 		1. 29% 2. 496
2014	19 and 		1. 17% 2. 492

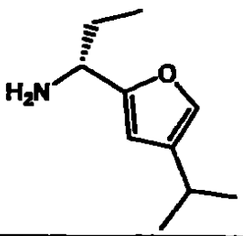
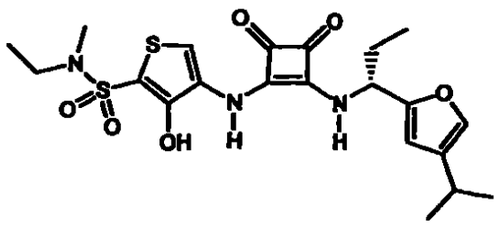
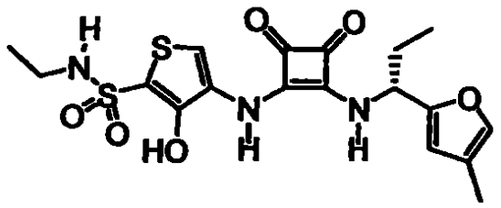
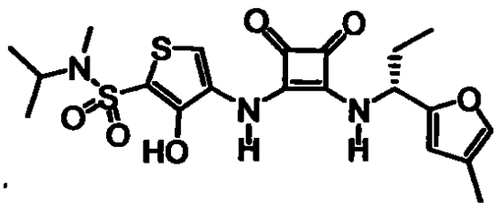
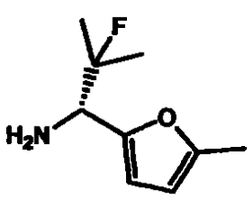
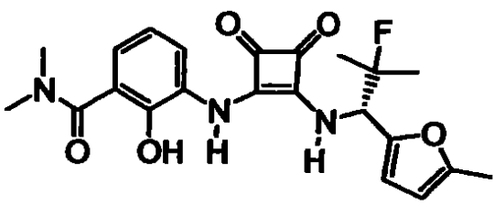
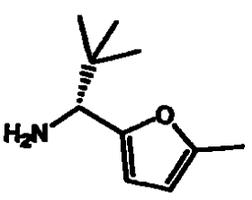
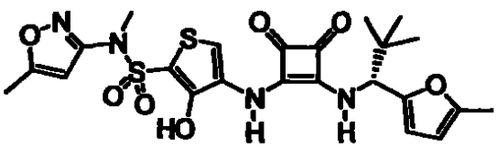
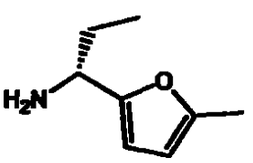
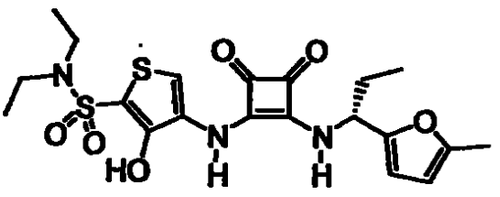
2015	1007 and 		1. 65% 2. 466
2016	19 and 		1. 72% 2. 452
2017	19 and 		1. 22% 2. 412
2018	19 and 		1. 5% 2. 425
2019	19 and 		1. 82% 2. 482

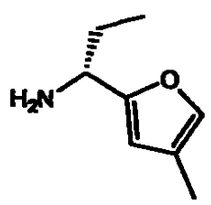
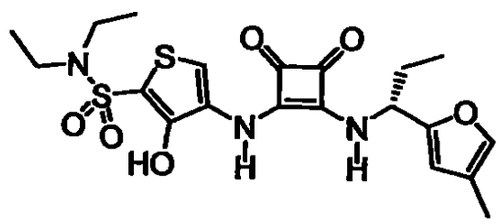
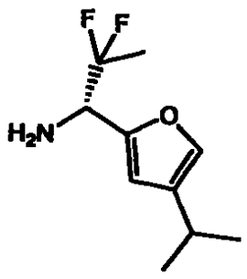
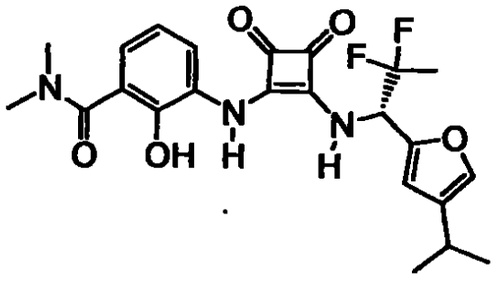
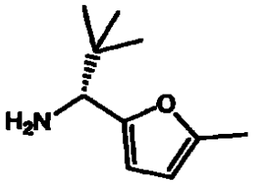
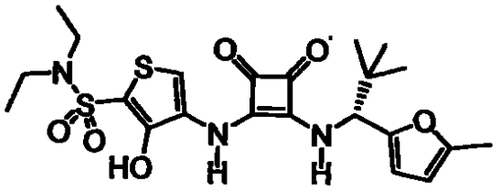
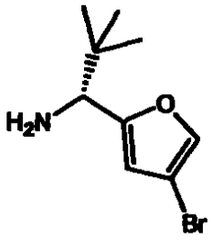
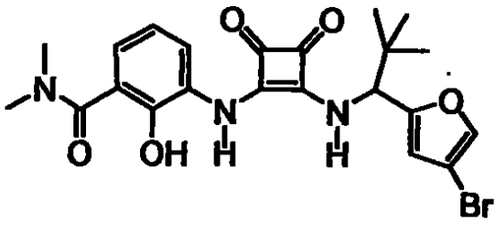
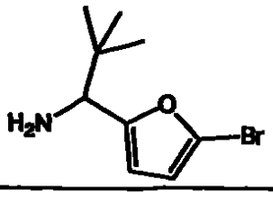
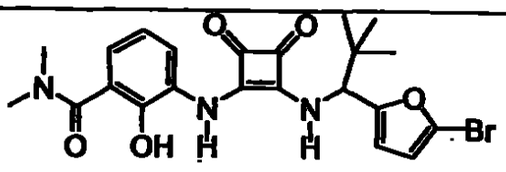
105
106

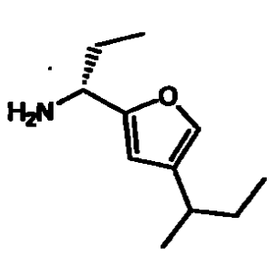
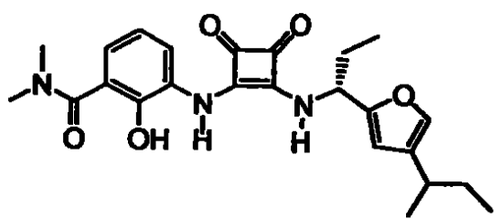
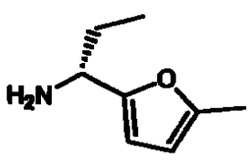
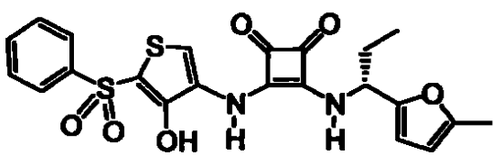
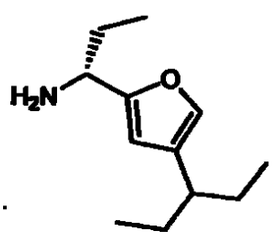
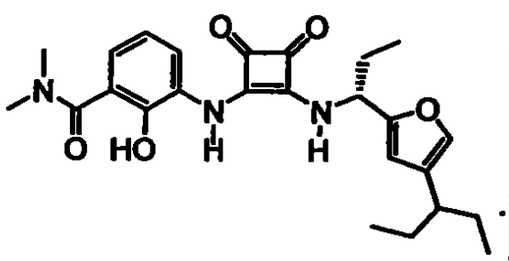
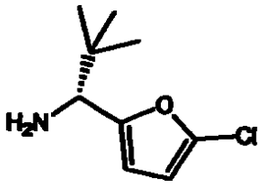
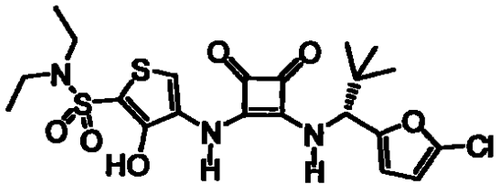
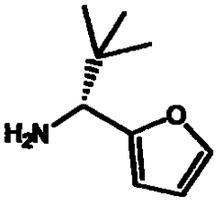
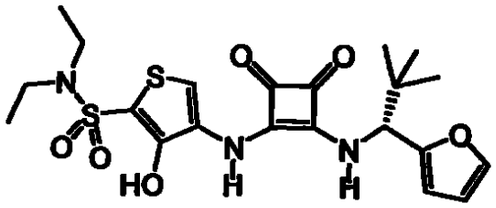
2020	1008 and 		1. 49% 2. 436
2021	22 and 		1. 45% 2. 440
2022	19 and 		1. 35% 2. 482
2024	1010 and 		1. 16% 2. 414
2026	19 and 		1. 46% 2. 482

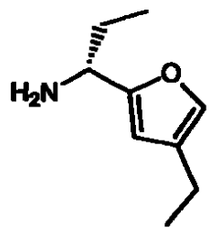
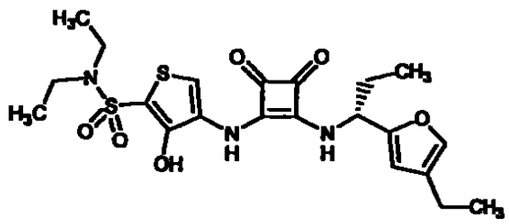
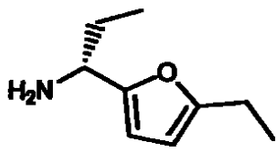
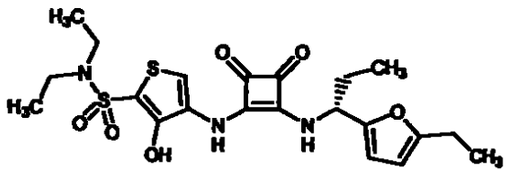
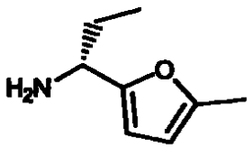
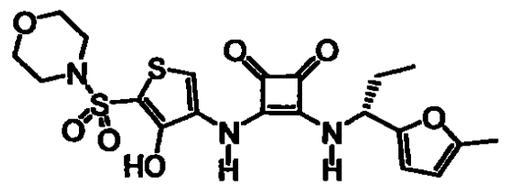
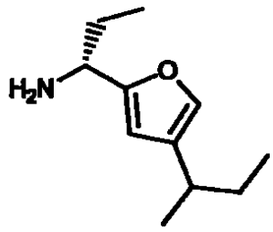
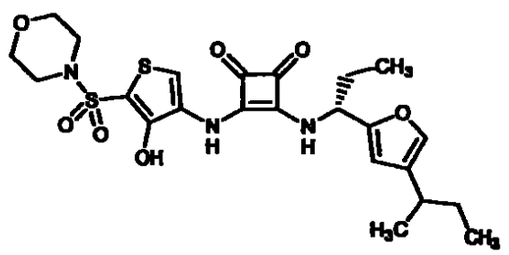
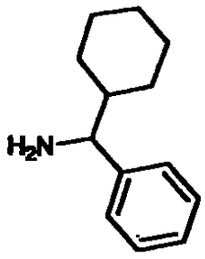
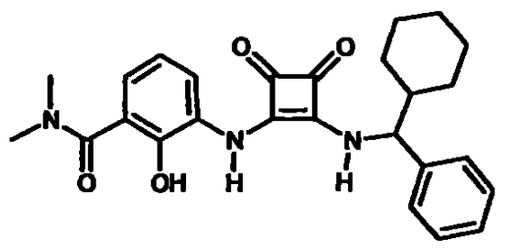
2027	1010 and 		1. 13% 2. 418
2028	1012 and 		1. 39% 2. 440
2029	19 and 		1. 55% 2. 382
2030	19 and 		1. 39% 2. 378
2033	19 and 		1. 71% 2. 482
2034	1013 and 		1. 45% 2. 487.9

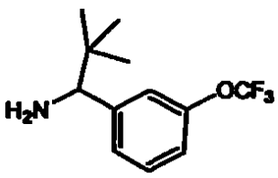
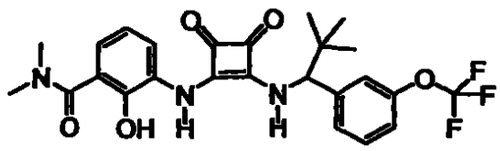
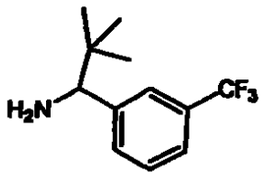
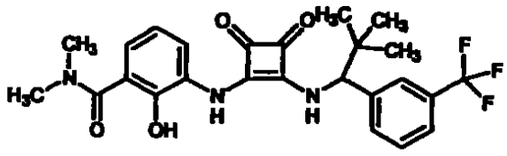
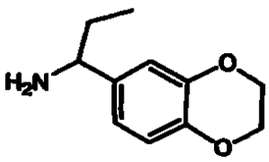
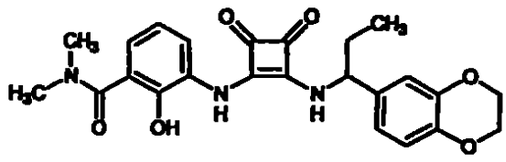
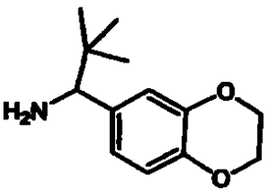
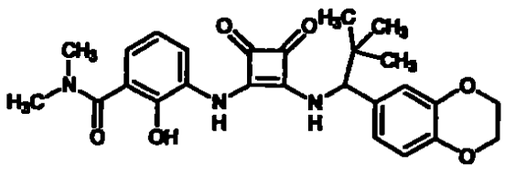
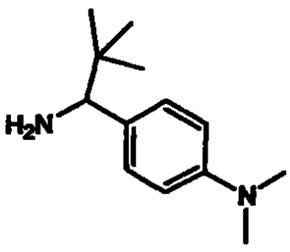
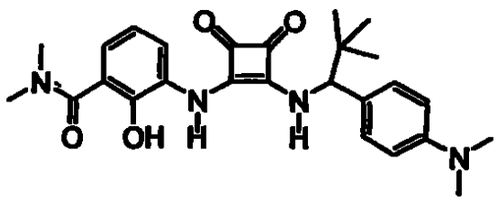
2035	1014 and 		1. 22% 2. 461.8
2036	1015 and 		1. 27% 2. 405.9
2037	87.1 and 		1. 26% 2. 392.0
2038	1016 and 		1. 28% 2. 433.8
2039	1017 and 		1. 34% 2. 473.9
2040	19 and 		1. 34% 2. 525

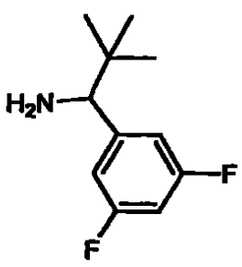
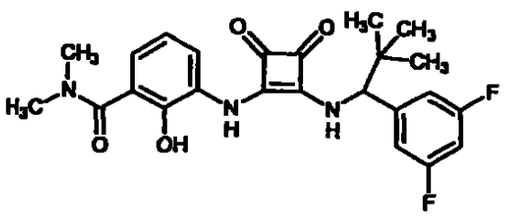
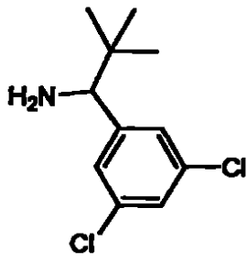
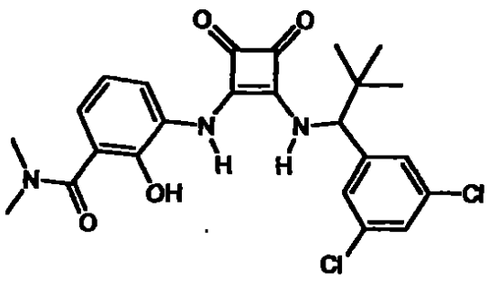
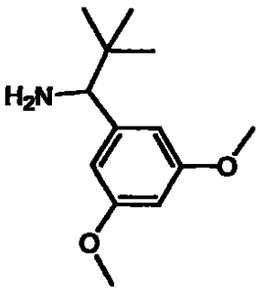
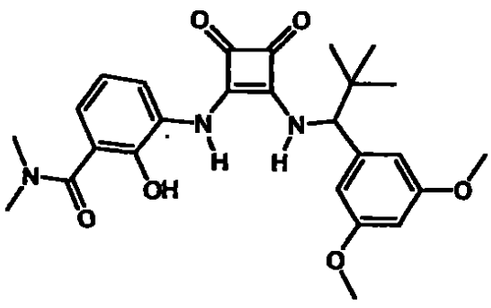
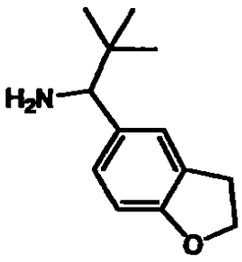
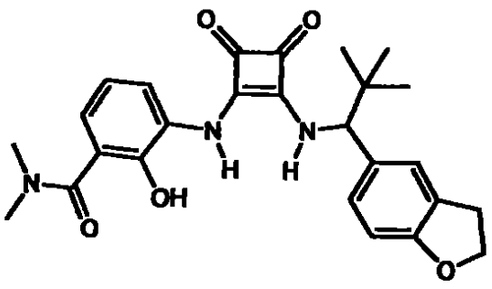
2041	23.15E and 		1. 67% 2. 482
2042	1300 and 1027		1. 33% 2. 440
2043	1203 and 1027		1. 24% 2. 468
2044	19 and 		1. 26% 2. 466
2046	19.2 and 		1. 27% 2. 535
2047	23.15F and 		1. 74% 2. 468

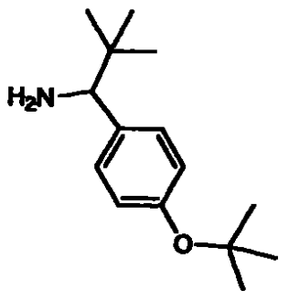
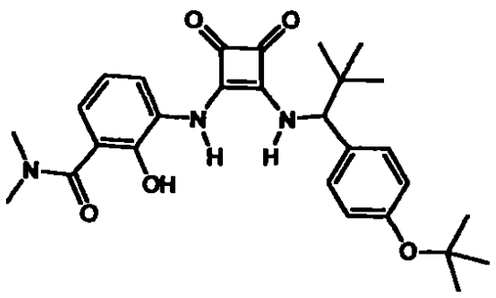
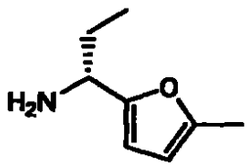
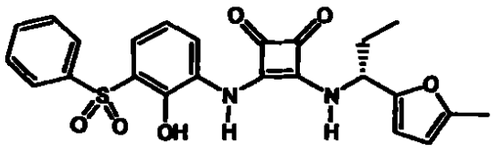
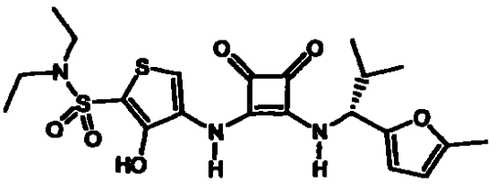
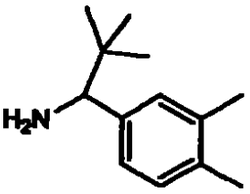
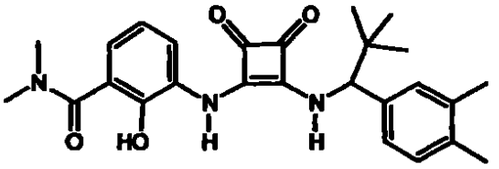
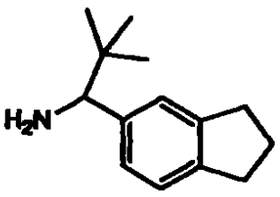
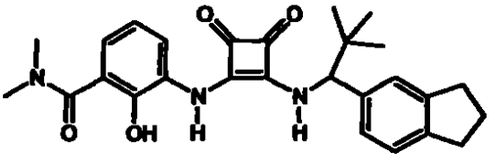
2048	23.15F and 		1. 68% 2. 468
2049	19 and 		1. 31% 2. 462
2050	23.15F and 		1. 41% 2. 496
2051	19 and 		1. 66% 2. 490
2052	19 and 		1. 43% 2. 490

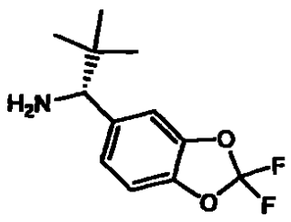
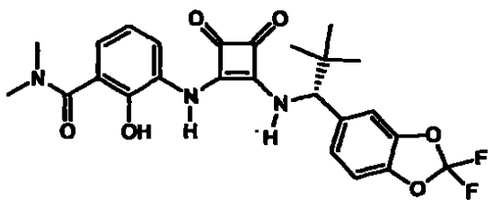
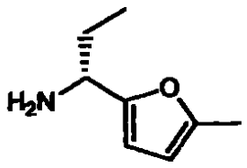
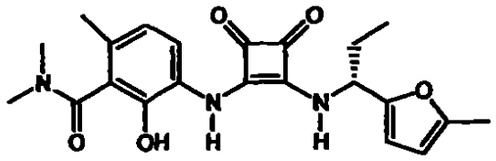
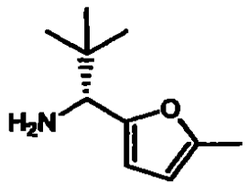
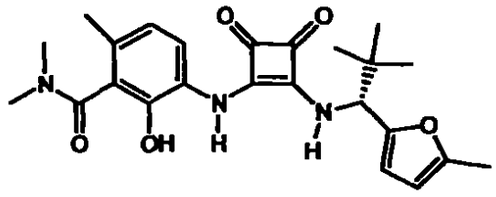
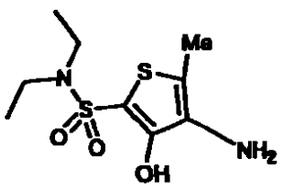
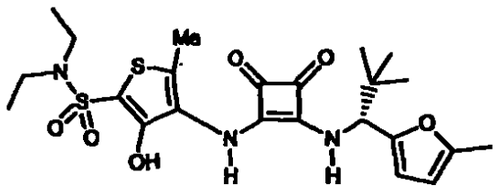
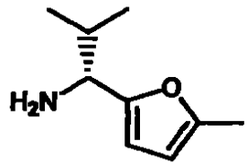
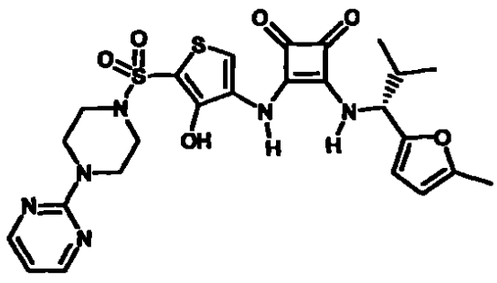
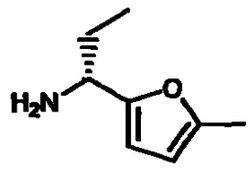
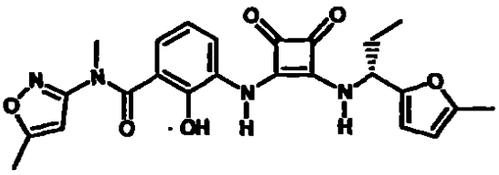
2053	19 and 		1. 76% 2. 440
2054	1024 and 		1. 15% 2. 473
2055	19 and 		1. 87% 2. 454
2056	23.15F and 		1. 52% 2. 516
2056A	23.15F and 		1. 62% 2. 482

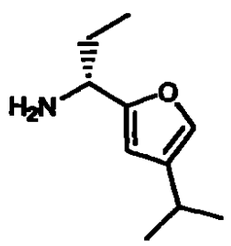
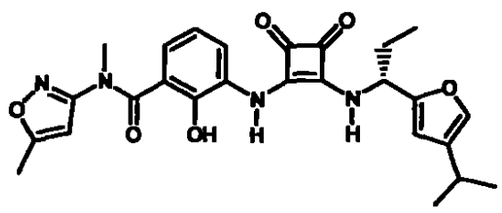
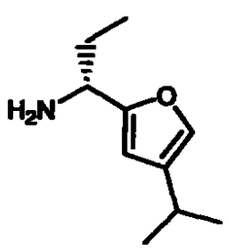
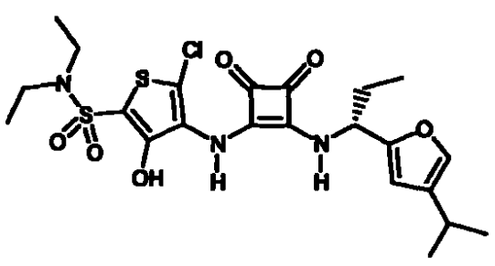
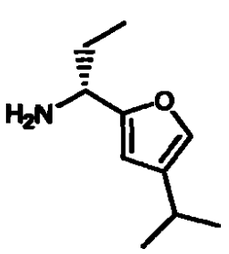
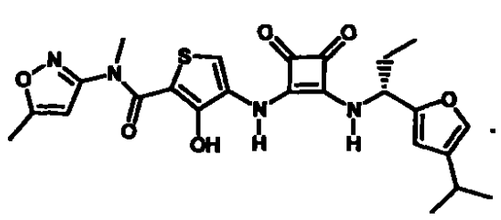
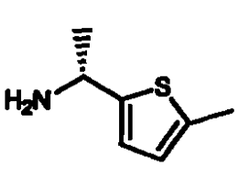
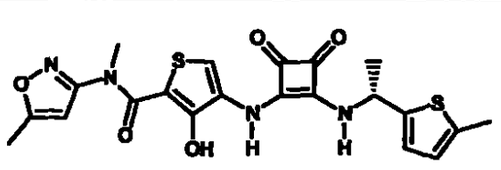
2057	23.15F and 		1. 40% 2. 482
2058	23.15F and 		1. 71% 2. 482
2059	1023 and 		1. 67% 2. 482
2060	1023 and 		1. 60% 2. 524
2061	19 and 		1. 34% 2. 448

2062	19 and 		1. 43% 2. 506
2063	19 and 		1. 53% 2. 490
2064	19 and 		1. 25% 2. 452
2065	19 and 		1. 24% 2. 480
2066	19 and 		1. 37% 2. 465

2067	19 and 		1. 38% 2. 458
2068	19 and 		1. 35% 2. 490
2069	19 and 		1. 73% 2. 482
2070	19 and 		1. 69% 2. 464

2071	19 and 		1. 71% 2. 494
2072	1022 and 		1. 54% 2. 467
2074	13.32A and 1028		1. 42% 2. 482
2075	19 and 		1. 78% 2. 450
2076	19 and 		1. 25% 2. 402

2077	19 and 		1. 33% 2. 502
2079	1021 and 		1. 23% 2. 440
2080	1021 and 		1. 15% 2. 476
2081	1029 and 		1. 17% 2. 510
2083	1020 and 		1. 46% 2. 573
2084	23.14 and 		1. 80% 2. 465

2085	23.14 and 		1. 62% 2. 493
2086	1019 and 		1. 29% 2. 530
2087	23.14 and 		1. 30% 2. 499
2088	23.14 and 		1. 13% 2. 473

Another embodiment of this invention is directed to the use of any of the compounds described above (e.g., the compounds of formulas IA, IB, 1.0A, 3.0A and the final compounds of examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088, or a pharmaceutically acceptable salt (e.g., calcium or sodium) or solvate thereof) for the manufacture of a medicament for the treatment of acute inflammation.

Another embodiment of this invention is directed to the use of any of the compounds described above (e.g., the compounds of formulas IA, IB, 1.0A, 3.0A and the final compounds of examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-

1311, and 2001-2088, or a pharmaceutically acceptable salt (e.g., calcium or sodium) or solvate thereof) for the manufacture of a medicament for the treatment of acute inflammation.

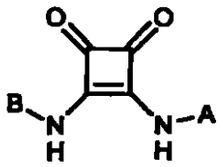
Another embodiment of this invention is directed to the use of any of the compounds described above (e.g., the compounds of formulas IA, IB, 1.0A, 3.0A and the final compounds of examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088, or a pharmaceutically acceptable salt (e.g., calcium or sodium) or solvate thereof) for the manufacture of a medicament for the treatment of rheumatoid arthritis.

Another embodiment of this invention is directed to a final compound of Examples 2006, 2010, 2015, 2029, 2034, 2035, 2038, 2039, 2047, 2050, 2074, 2079 and 2087, or a pharmaceutically acceptable salt (e.g., calcium or sodium) or solvate thereof. Other embodiments are directed to the use of these compounds for the manufacture of a medicament for the treatment of acute inflammation, or for the manufacture of a medicament for the treatment of chronic inflammation, or for the manufacture of a medicament for the treatment of rheumatoid arthritis, or for the manufacture of a medicament for the treatment of acute inflammatory pain, or for the manufacture of a medicament for the treatment of chronic inflammatory pain, or for the manufacture of a medicament for the treatment of acute neuropathic pain, or for the manufacture of a medicament for the treatment of chronic neuropathic pain, or for the manufacture of a medicament for the treatment of COPD.

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

WHAT IS CLAIMED IS:

1. A compound of the formula:

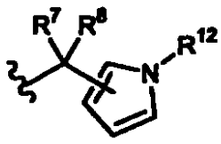


(IB)

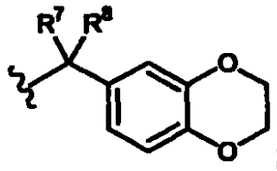
and the pharmaceutically acceptable salts and solvates thereof, wherein:

A is selected from the group consisting of:

(1)

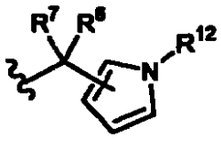


and

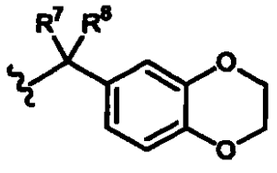


; and

(2)



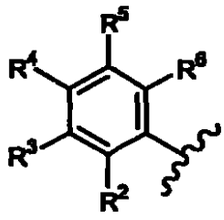
and



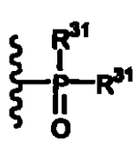
wherein said rings of said A groups are substituted with 1 to 6 substituents each independently selected from the group consisting of: R^9 groups; and

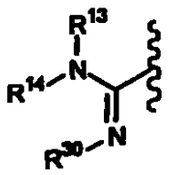
B is selected from the group consisting of:

(1)

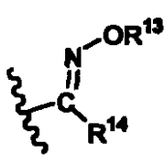


provided that R^3 for this group is selected from the group consisting of: $-C(O)NR^{13}R^{14}$,



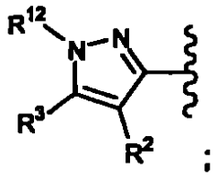


and



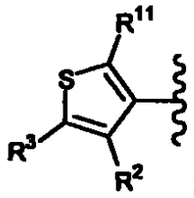
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(2)



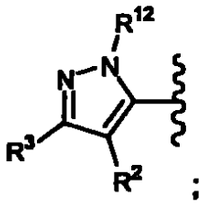
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(3)



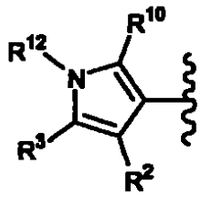
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(4)



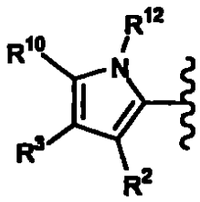
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(5)



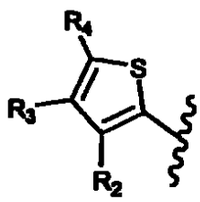
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(6)



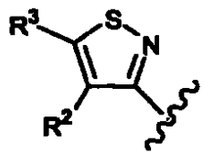
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(7)



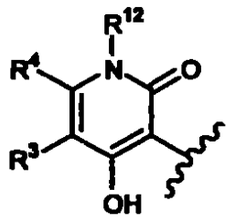
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(8)



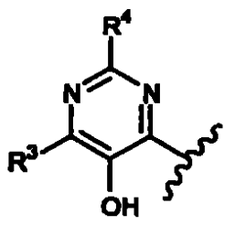
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(9)



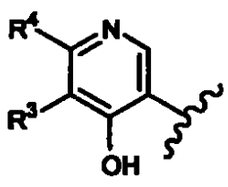
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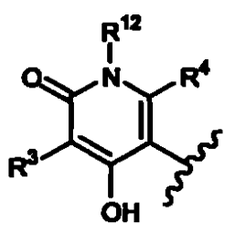
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(11)



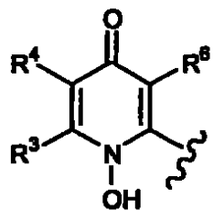
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(12)



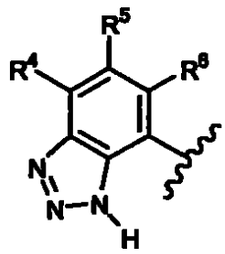
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(13)



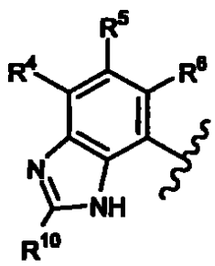
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(14)



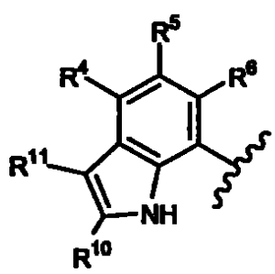
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(15)



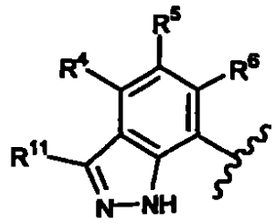
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(16)



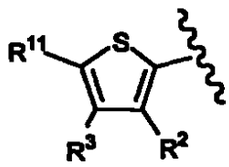
;

(17)



; and

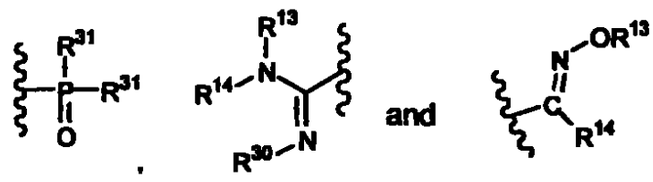
(18)



;

R^2 is selected from the group consisting of: hydrogen, OH, -C(O)OH, -SH, $-SO_2NR^{13}R^{14}$, $-NHC(O)R^{13}$, $-NHSO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, $-NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, $-C(O)NHOR^{13}$, $-C(O)NR^{13}OH$, $-S(O_2)OH$, $-OC(O)R^{13}$, an unsubstituted heterocyclic acidic functional group, and a substituted heterocyclic acidic functional group; wherein there are 1 to 6 substituents on said substituted heterocyclic acidic functional group each substituent being independently selected from the group consisting of: R^9 groups;

each R^3 and R^4 is independently selected from the group consisting of: hydrogen, cyano, halogen, alkyl, alkoxy, -OH, $-CF_3$, $-OCF_3$, $-NO_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NHR^{17}$, $-C(O)NR^{13}R^{14}$, $-SO_{(t)}NR^{13}R^{14}$, $-SO_{(t)}R^{13}$, $-C(O)NR^{13}OR^{14}$, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl,



wherein there are 1 to 6 substituents on said substituted aryl group and each substituent is independently selected from the group consisting of: R^9 groups; and wherein there are 1 to 6 substituents on said substituted heteroaryl group and each substituent is independently selected from the group consisting of: R^9 groups;

each R^5 and R^6 are the same or different and are independently selected from the group consisting of hydrogen, halogen, alkyl, alkoxy, $-CF_3$, $-OCF_3$, $-NO_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-SO_{(t)}NR^{13}R^{14}$, $-C(O)NR^{13}OR^{14}$, cyano, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl group; wherein there are 1 to 6 substituents on said substituted aryl group and each substituent is independently selected from the group consisting of: R^9 groups; and wherein there are 1 to 6 substituents on said substituted heteroaryl group and each substituent is independently selected from the group consisting of: R^9 groups;

each R^7 and R^8 is independently selected from the group consisting of: H, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkylalkyl, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, alkynyl, alkenyl, and cycloalkenyl; and wherein there are one or more substituents on said substituted R^7 and R^8 groups, wherein each substitutent is independently selected from the group consisting of:

a) halogen,
b) $-CF_3$,
c) $-COR^{13}$,
d) $-OR^{13}$,
e) $-NR^{13}R^{14}$,
f) $-NO_2$,
g) $-CN$,
h) $-SO_2OR^{13}$,
i) $-Si(alkyl)_3$, wherein each alkyl is independently selected,
j) $-Si(aryl)_3$, wherein each alkyl is independently selected,
k) $-(R^{13})_2R^{14}Si$, wherein each R^{13} is independently selected,
l) $-CO_2R^{13}$,
m) $-C(O)NR^{13}R^{14}$,
n) $-SO_2NR^{13}R^{14}$,
o) $-SO_2R^{13}$,
p) $-OC(O)R^{13}$,
q) $-OC(O)NR^{13}R^{14}$,
r) $-NR^{13}C(O)R^{14}$, and

s) $-NR^{13}CO_2R^{14}$;

each R^9 is independently selected from the group consisting of:

a) $-R^{13}$,

b) halogen,

c) $-CF_3$,

d) $-COR^{13}$,

e) $-OR^{13}$,

f) $-NR^{13}R^{14}$,

g) $-NO_2$,

h) $-CN$,

i) $-SO_2R^{13}$,

j) $-SO_2NR^{13}R^{14}$,

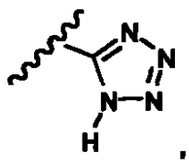
k) $-NR^{13}COR^{14}$,

l) $-CONR^{13}R^{14}$,

m) $-NR^{13}CO_2R^{14}$,

n) $-CO_2R^{13}$,

o)



p) alkyl substituted with one or more –OH groups,

q) alkyl substituted with one or more $-NR^{13}R^{14}$ group, and

r) $-N(R^{13})SO_2R^{14}$;

each R^{10} and R^{11} is independently selected from the group consisting of R^{13}, hydrogen, alkyl, halogen, $-CF_3$, $-OCF_3$, $-NR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, $-OH$, $-C(O)OR^{13}$, $-SH$, $-SO_{(t)}NR^{13}R^{14}$, $-SO_2R^{13}$, $-NHC(O)R^{13}$, $-NHSO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, $-C(O)NR^{13}R^{14}$, $-C(O)NR^{13}OR^{14}$, $-OC(O)R^{13}$ and cyano;

R^{12} is selected from the group consisting of: hydrogen, $-C(O)OR^{13}$, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkylalkyl, and unsubstituted or substituted heteroarylalkyl group; wherein there are 1 to 6 substituents on the

substituted R^{12} groups and each substituent is independently selected from the group consisting of: R^9 groups;

each R^{13} and R^{14} is independently selected from the group consisting of: H, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkylalkyl, unsubstituted or substituted heterocyclic, unsubstituted or substituted fluoroalkyl, and unsubstituted or substituted heterocycloalkylalkyl; wherein there are 1 to 6 substituents on said substituted R^{13} and R^{14} groups and each substituent is independently selected from the group consisting of: alkyl, $-CF_3$, -OH, alkoxy, aryl, arylalkyl, fluroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, $-N(R^{40})_2$, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-S(O)_tNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ provided that R^{15} is not H, halogen, and $-NHC(O)NR^{15}R^{16}$; or

R^{13} and R^{14} taken together with the nitrogen they are attached to in the groups $-C(O)NR^{13}R^{14}$ and $-SO_2NR^{13}R^{14}$ form an unsubstituted or substituted saturated heterocyclic ring, said ring optionally containing one additional heteroatom selected from the group consisting of: O, S and NR^{18}; wherein there are 1 to 3 substituents on the substituted cyclized R^{13} and R^{14} groups and each substituent is independently selected from the group consisting of: alkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-SO_tNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ provided that R^{15} is not H, $-NHC(O)NR^{15}R^{16}$, $-NHC(O)OR^{15}$, halogen, and a heterocycloalkenyl group

each R^{15} and R^{16} is independently selected from the group consisting of: H, alkyl, aryl, arylalkyl, cycloalkyl and heteroaryl;

R^{17} is selected from the group consisting of: $-SO_2$alkyl, $-SO_2$aryl, $-SO_2$cycloalkyl, and $-SO_2$heteroaryl;

R^{18} is selected from the group consisting of: H, alkyl, aryl, heteroaryl, $-C(O)R^{19}$, $-SO_2R^{19}$ and $-C(O)NR^{19}R^{20}$;

each R^{19} and R^{20} is independently selected from the group consisting of: alkyl, aryl and heteroaryl;

R^{30} is selected from the group consisting of: alkyl, cycloalkyl, -CN, $-NO_2$, or $-SO_2R^{15}$ provided that R^{15} is not H;

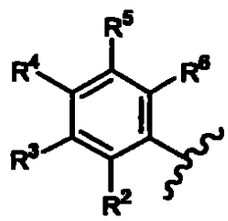
each R^{31} is independently selected from the group consisting of: unsubstituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl and unsubstituted or substituted cycloalkyl; wherein there are 1 to 6 substituents on said substituted R^{31} groups and each substituent is independently selected from the group consisting of: alkyl, halogen and $-CF_3$;

each R^{40} is independently selected from the group consisting of: H, alkyl and cycloalkyl; and

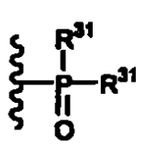
t is 0, 1 or 2.

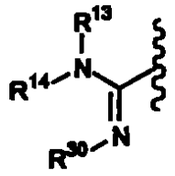
2. The compound of Claim 1 wherein B is selected from the group consisting of:

(1)

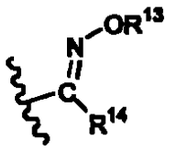


provided that R^3 for this group is selected from the group consisting of: $-C(O)NR^{13}R^{14}$,



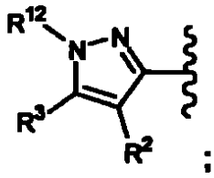


and



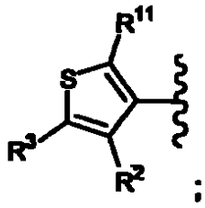
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(2)



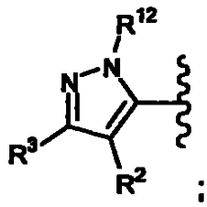
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(3)



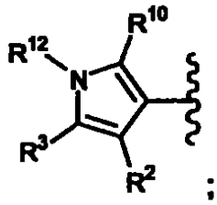
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(4)



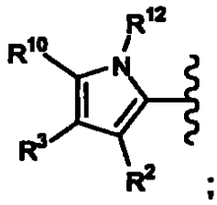
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(5)



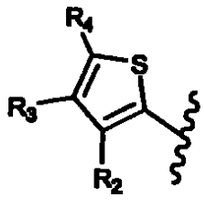
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(6)

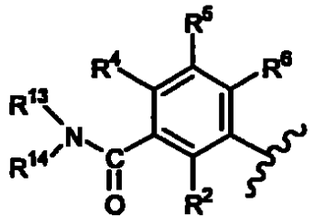


; and

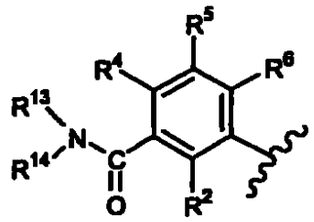
(7)



3. The compound of Claim 1 wherein B is:

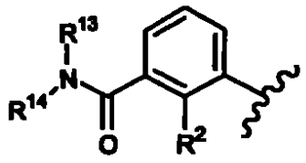


4. The compound of Claim 1 wherein B is:



R^2 is –OH, and R^{13} and R^{14} are each the same or different alkyl group.

5. The compound of Claim 1 wherein B is



6. The compound of Claim 5 wherein R^2 is –OH.

7. The compound of Claim 6 wherein R^{13} and R^{14} are the same or different alkyl group.

8. The compound of Claim 7 wherein R^{13} and R^{14} methyl.

9. A compound selected from the group consisting of compounds of the formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088.

10. The compound of Claim 9 selected from the group consisting of compounds of the formulas 1.0A and 3.0A.

11. The compound of Claim 9 selected from the group consisting of the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088.

12. The compound of any of Claims 1 to 8 wherein said compound is a calcium or sodium salt.

13. The compound of any of Claims 9 to 11 wherein said compound is a calcium or sodium salt.

14. A pharmaceutical composition comprising an effective amount of at least one compound of any of Claims 1 to 11 and a pharmaceutically acceptable carrier.

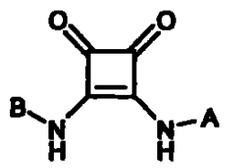
15. A pharmaceutical composition comprising an effective amount of a calcium salt or a sodium salt of at least one compound of any of Claims 1 to 11 and a pharmaceutically acceptable carrier

16. The use of at least one compound of formula IA for the manufacture of a medicament for treating a chemokine mediated disease,

said chemokine mediated disease being selected from the group consisting of: acute inflammatory pain, chronic inflammatory pain, acute neuropathic pain, chronic neuropathic pain, acute respiratory distress syndrome, delayed type hypersensitivity reaction, atherosclerosis, cerebral and cardiac ischemia, osteoarthritis, multiple sclerosis, restinosis, angiogenesis, osteoporosis, gingivitis, respiratory viruses, herpes viruses, hepatitis viruses, HIV, Kaposi's sarcoma associated virus, meningitis, cystic fibrosis, pre-term labor, cough, pruritis, multi-organ dysfunction, trauma, strains, sprains, contusions, psoriatic arthritis, herpes, encephalitis, CNS vasculitis, traumatic brain injury, CNS tumors, subarachnoid hemorrhage, post surgical trauma, interstitial pneumonitis, hypersensitivity, crystal induced arthritis, acute and chronic pancreatitis, acute alcoholic hepatitis, necrotizing enterocolitis, chronic sinusitis, angiogenic ocular disease, ocular inflammation, retinopathy of prematurity, diabetic retinopathy, macular degeneration with the wet type preferred and corneal neovascularization, polymyositis, vasculitis, acne, gastric and duodenal ulcers, celiac disease, esophagitis, glossitis, airflow obstruction, airway hyperresponsiveness, bronchiectasis, bronchiolitis, bronchiolitis obliterans, chronic bronchitis, cor pulmonae, cough, dyspnea, emphysema, hypercapnea, hyperinflation, hypoxemia, hyperoxia-induced inflammations, hypoxia, surgical lung volume reduction, pulmonary fibrosis, pulmonary hypertension, right ventricular hypertrophy, peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD), granulocytic ehrlichiosis, sarcoidosis, small

airway disease, ventilation-perfusion mismatching, wheeze, colds, gout, alcoholic liver disease, lupus, burn therapy, periodontitis, transplant reperfusion injury and early transplantation rejection, acute inflammation, chronic inflammation and rheumatoid arthritis, and

said compounds of formula IA being represented by the formula:

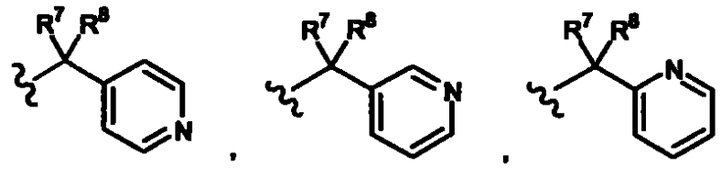


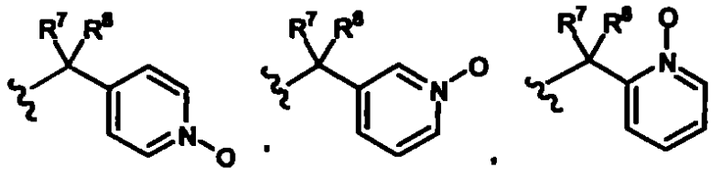
(IA)

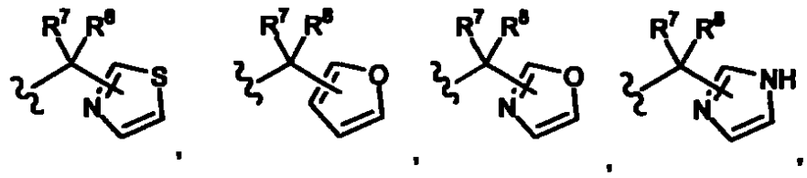
and the pharmaceutically acceptable salts and solvates thereof, wherein:

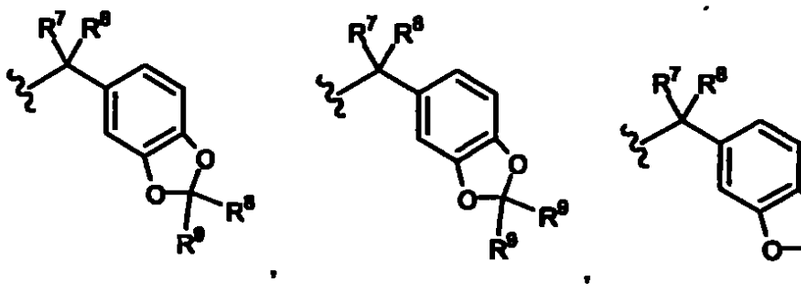
A is selected from the group consisting of:

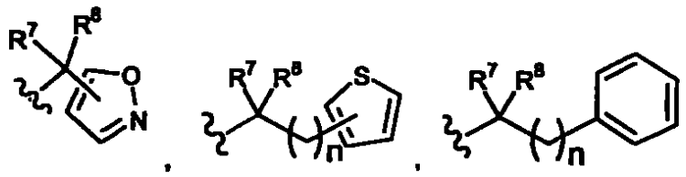
(1)

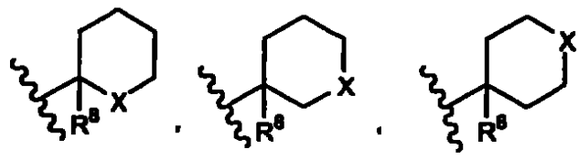


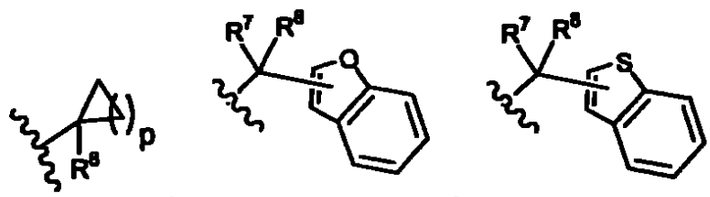


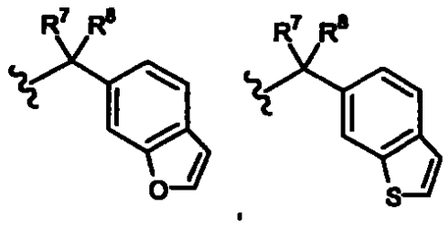


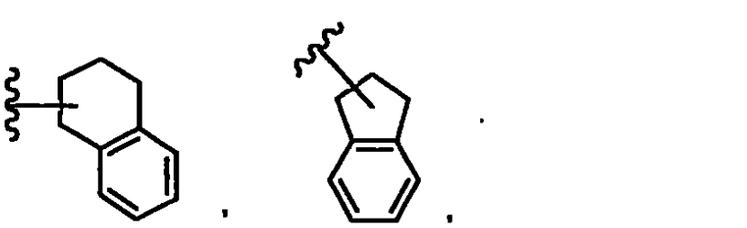


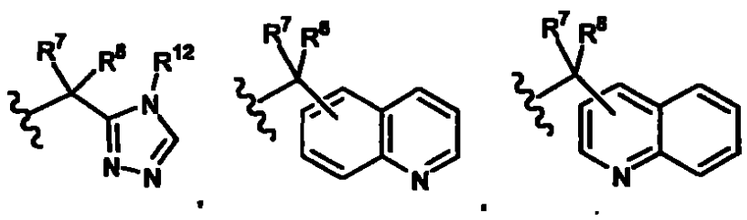


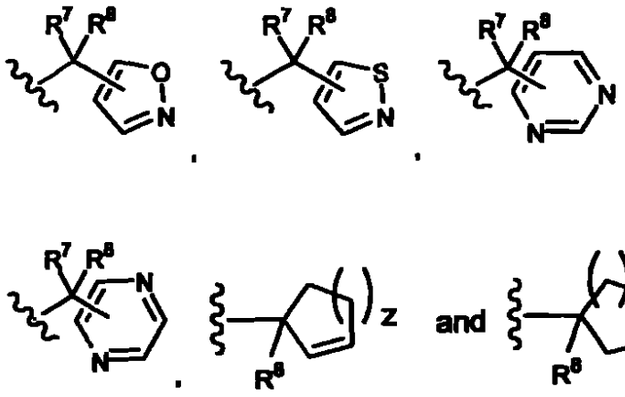




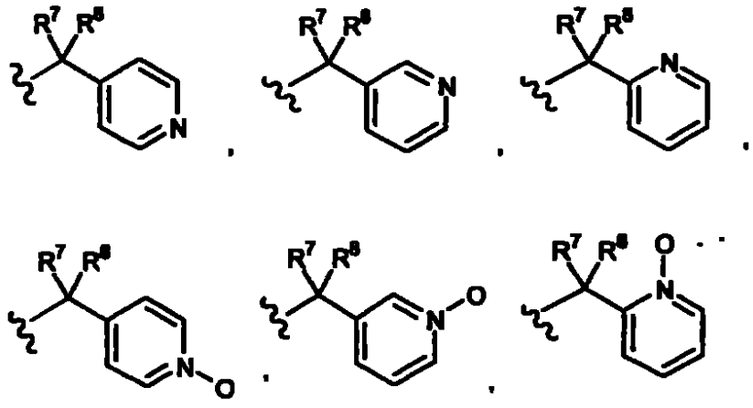


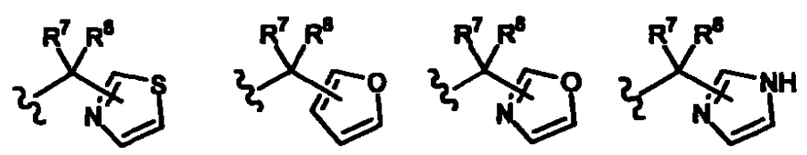


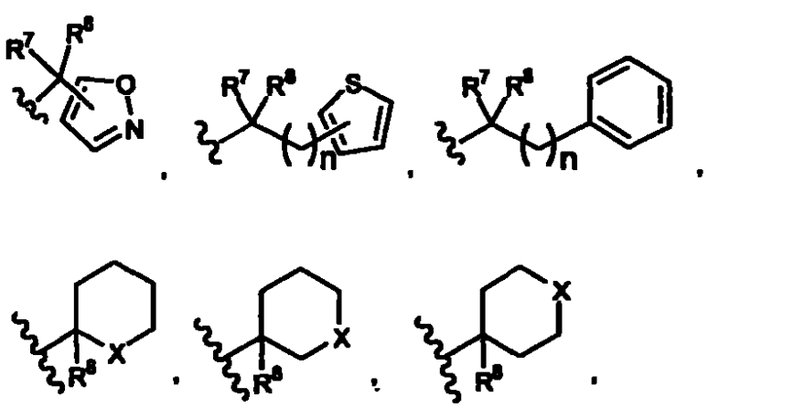


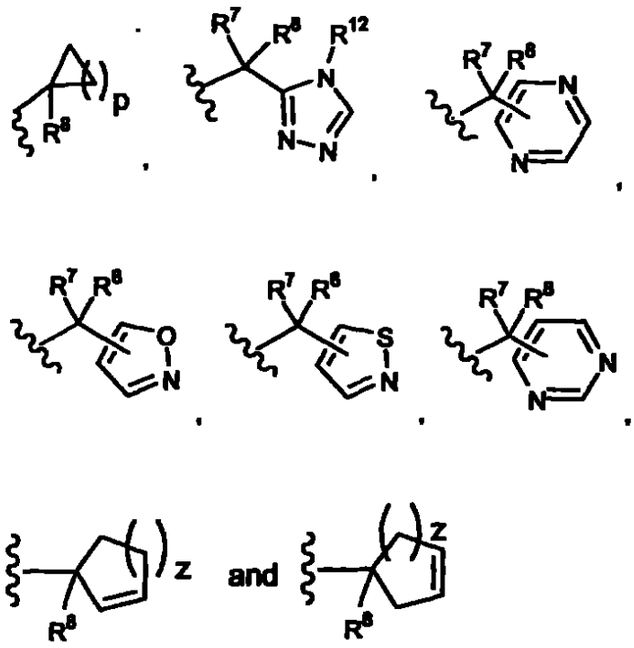


(2)



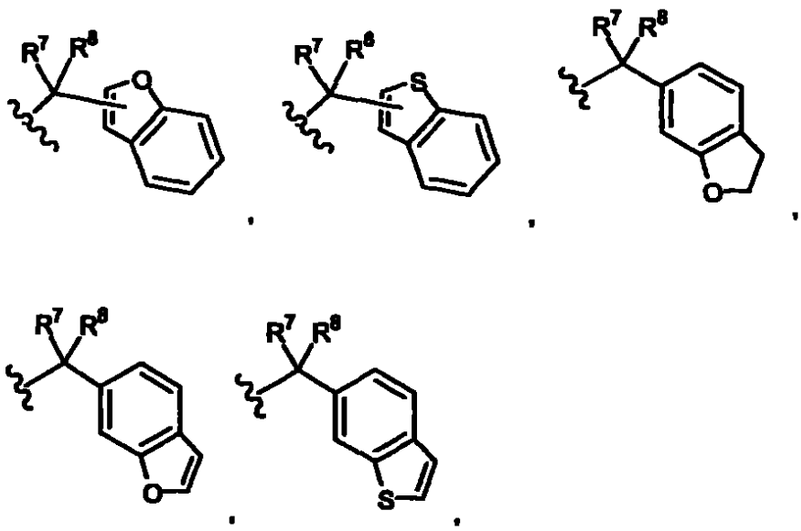


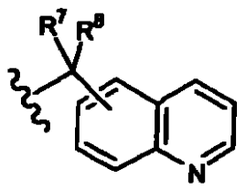
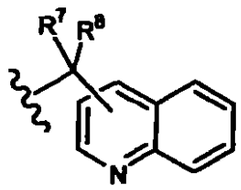


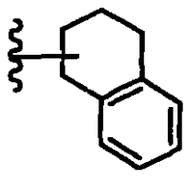


wherein the above rings of said A groups are substituted with 1 to 6 substituents each independently selected from the group consisting of: R^9 groups;

(3)

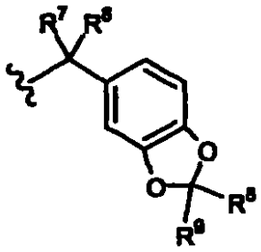
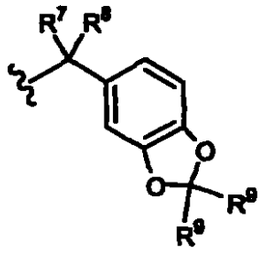



and

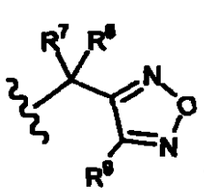
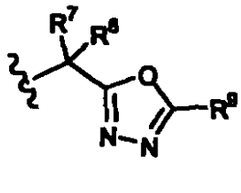
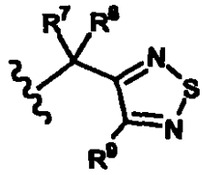

wherein one or both of the above rings of said A groups are substituted with 1 to 6 substituents each independently selected from the group consisting of: R^9 groups;

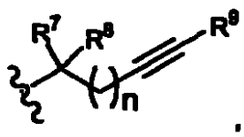
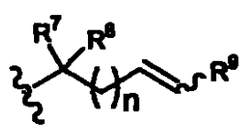
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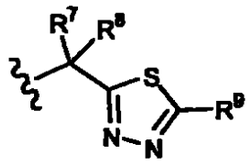
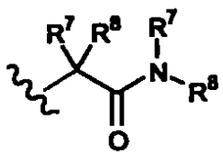

and


wherein the above phenyl rings of said A groups are substituted with 1 to 3 substituents each independently selected from the group consisting of: R^9 groups; and

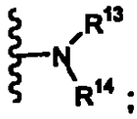
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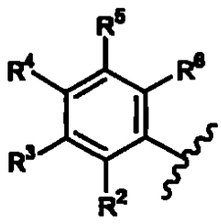
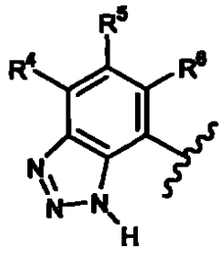
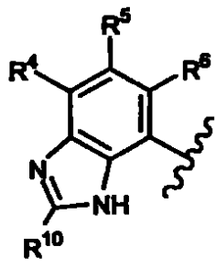



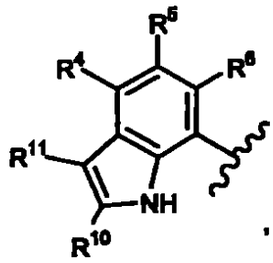
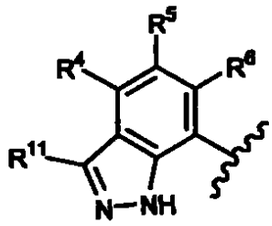
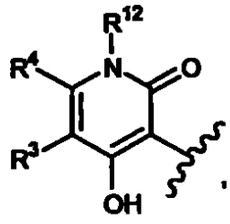



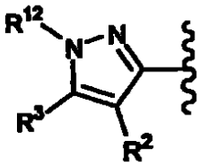
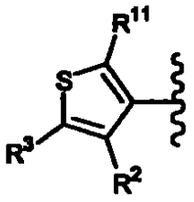
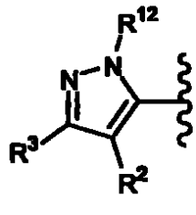
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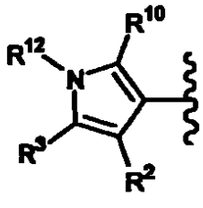
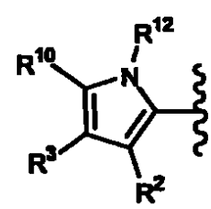
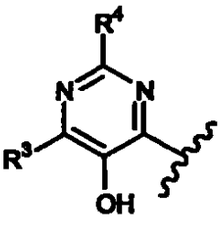

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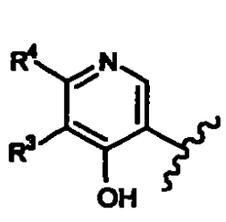
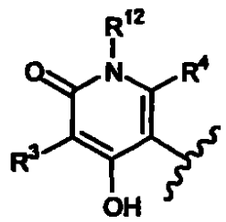
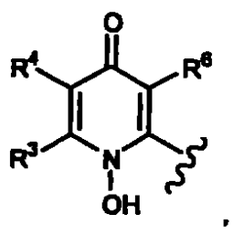
B is selected from the group consisting of:

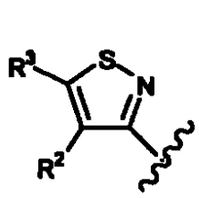
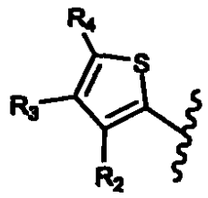
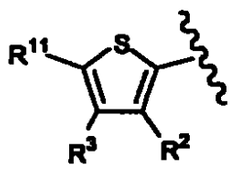






and

;

n is 0 to 6;

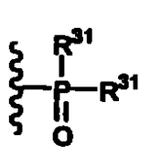
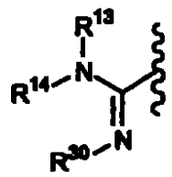
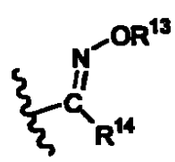
p is 1 to 5;

X is O, NH, or S;

Z is 1 to 3;

R^2 is selected from the group consisting of: hydrogen, OH, -C(O)OH, -SH, $-SO_2NR^{13}R^{14}$, $-NHC(O)R^{13}$, $-NHSO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, $-NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, $-C(O)NHOR^{13}$, $-C(O)NR^{13}OH$, $-S(O_2)OH$, $-OC(O)R^{13}$, an unsubstituted heterocyclic acidic functional group, and a substituted heterocyclic acidic functional group; wherein there are 1 to 6 substituents on said substituted heterocyclic acidic functional group each substituent being independently selected from the group consisting of: R^9 groups;

each R^3 and R^4 is independently selected from the group consisting of: hydrogen, cyano, halogen, alkyl, alkoxy, -OH, $-CF_3$, $-OCF_3$, $-NO_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NHR^{17}$, $-C(O)NR^{13}R^{14}$, $-SO_{(t)}NR^{13}R^{14}$, $-SO_{(t)}R^{13}$, $-C(O)NR^{13}OR^{14}$, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl,



and


wherein there are 1 to 6 substituents on said substituted aryl group and each substituent is independently selected from the group consisting of: R^9 groups; and wherein there are 1 to 6 substituents on said substituted heteroaryl group and each substituent is independently selected from the group consisting of: R^9 groups;

each R^5 and R^6 are the same or different and are independently selected from the group consisting of hydrogen, halogen, alkyl, alkoxy, $-CF_3$, $-OCF_3$, $-NO_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-SO_{(t)}NR^{13}R^{14}$, $-C(O)NR^{13}OR^{14}$, cyano, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl group; wherein there are 1 to 6 substituents on said substituted aryl group and each substituent is independently selected from the group consisting of: R^9 groups; and wherein there are 1 to 6 substituents on said substituted heteroaryl group and each substituent is independently selected from the group consisting of: R^9 groups;

each R^7 and R^8 is independently selected from the group consisting of: H, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkylalkyl, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, alkynyl, alkenyl, and cycloalkenyl; and wherein there are one or more substituents on said substituted R^7 and R^8 groups, wherein each substitutent is independently selected from the group consisting of:

a) halogen,
b) $-CF_3$,
c) $-COR^{13}$,
d) $-OR^{13}$,
e) $-NR^{13}R^{14}$,
f) $-NO_2$,
g) $-CN$,
h) $-SO_2OR^{13}$,
i) $-Si(alkyl)_3$, wherein each alkyl is independently selected,
j) $-Si(aryl)_3$, wherein each alkyl is independently selected,
k) $-(R^{13})_2R^{14}Si$, wherein each R^{13} is independently selected,
l) $-CO_2R^{13}$,
m) $-C(O)NR^{13}R^{14}$,
n) $-SO_2NR^{13}R^{14}$,

o) $-SO_2R^{13}$,

p) $-OC(O)R^{13}$,

q) $-OC(O)NR^{13}R^{14}$,

r) $-NR^{13}C(O)R^{14}$, and

s) $-NR^{13}CO_2R^{14}$;

R^{8a} is selected from the group consisting of: hydrogen, alkyl, cycloalkyl and cycloalkylalkyl;

each R^9 is independently selected from the group consisting of:

a) $-R^{13}$,

b) halogen,

c) $-CF_3$,

d) $-COR^{13}$,

e) $-OR^{13}$,

f) $-NR^{13}R^{14}$,

g) $-NO_2$,

h) $-CN$,

i) $-SO_2R^{13}$,

j) $-SO_2NR^{13}R^{14}$,

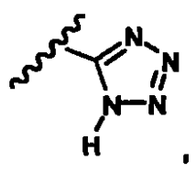
k) $-NR^{13}COR^{14}$,

l) $-CONR^{13}R^{14}$,

m) $-NR^{13}CO_2R^{14}$,

n) $-CO_2R^{13}$,

o)



,

p) alkyl substituted with one or more –OH groups,

q) alkyl substituted with one or more $-NR^{13}R^{14}$ group, and

r) $-N(R^{13})SO_2R^{14}$;

each R^{10} and R^{11} is independently selected from the group consisting of R^{13}, hydrogen, alkyl, halogen, $-CF_3$, $-OCF_3$, $-NR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, -OH, $-C(O)OR^{13}$,

-SH, -$SO_{(t)}NR^{13}R^{14}$, -SO_2R^{13}, -$NHC(O)R^{13}$, -$NHSO_2NR^{13}R^{14}$, -$NHSO_2R^{13}$, -$C(O)NR^{13}R^{14}$, -$C(O)NR^{13}OR^{14}$, -$OC(O)R^{13}$ and cyano;

R^{12} is selected from the group consisting of: hydrogen, -$C(O)OR^{13}$, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkylalkyl, and unsubstituted or substituted heteroarylalkyl group; wherein there are 1 to 6 substituents on the substituted R^{12} groups and each substituent is independently selected from the group consisting of: R^9 groups;

each R^{13} and R^{14} is independently selected from the group consisting of: H, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkylalkyl, unsubstituted or substituted heterocyclic, unsubstituted or substituted fluoroalkyl, and unsubstituted or substituted heterocycloalkylalkyl; wherein there are 1 to 6 substituents on said substituted R^{13} and R^{14} groups and each substituent is independently selected from the group consisting of: alkyl, -CF_3, -OH, alkoxy, aryl, arylalkyl, fluroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, -$N(R^{40})_2$, -$C(O)OR^{15}$, -$C(O)NR^{15}R^{16}$, -$S(O)_tNR^{15}R^{16}$, -$C(O)R^{15}$, -SO_2R^{15} provided that R^{15} is not H, halogen, and -$NHC(O)NR^{15}R^{16}$; or

R^{13} and R^{14} taken together with the nitrogen they are attached to in the groups -$C(O)NR^{13}R^{14}$ and -$SO_2NR^{13}R^{14}$ form an unsubstituted or substituted saturated heterocyclic ring, said ring optionally containing one additional heteroatom selected from the group consisting of: O, S and NR^{16}; wherein there are 1 to 3 substituents on the substituted cyclized R^{13} and R^{14} groups and each substituent is independently selected from the group consisting of: alkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, -$C(O)OR^{15}$, -$C(O)NR^{15}R^{16}$, -$SO_tNR^{15}R^{16}$, -$C(O)R^{15}$, -SO_2R^{15} provided that R^{15} is not H, -$NHC(O)NR^{15}R^{16}$, -$NHC(O)OR^{15}$, halogen, and a heterocycloalkenyl group,

each R^{15} and R^{16} is independently selected from the group consisting of: H, alkyl, aryl, arylalkyl, cycloalkyl and heteroaryl;

R^{17} is selected from the group consisting of: -SO_2alkyl, -SO_2aryl, -SO_2cycloalkyl, and -SO_2heteroaryl;

R^{18} is selected from the group consisting of: H, alkyl, aryl, heteroaryl, $-C(O)R^{19}$, $-SO_2R^{19}$ and $-C(O)NR^{19}R^{20}$;

each R^{19} and R^{20} is independently selected from the group consisting of: alkyl, aryl and heteroaryl;

R^{30} is selected from the group consisting of: alkyl, cycloalkyl, -CN, $-NO_2$, or $-SO_2R^{15}$ provided that R^{15} is not H;

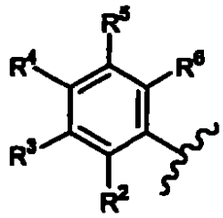
each R^{31} is independently selected from the group consisting of: unsubstituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl and unsubstituted or substituted cycloalkyl; wherein there are 1 to 6 substituents on said substituted R^{31} groups and each substituent is independently selected from the group consisting of: alkyl, halogen and $-CF_3$;

each R^{40} is independently selected from the group consisting of: H, alkyl and cycloalkyl; and

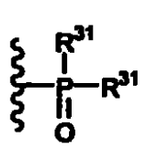
t is 0, 1 or 2.

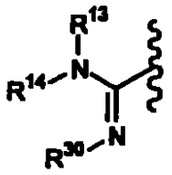
17. The use of Claim 16 wherein B is selected from the group consisting of:

(1)

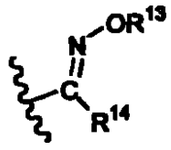


provided that R^3 for this group is selected from the group consisting of: $-C(O)NR^{13}R^{14}$,



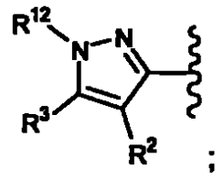


and



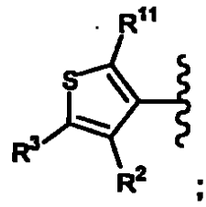
;

(2)



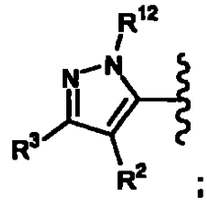
;

(3)



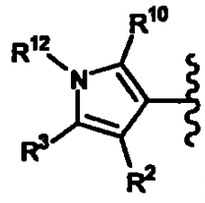
;

(4)



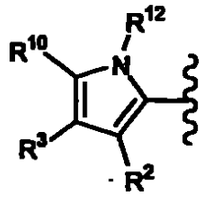
;

(5)



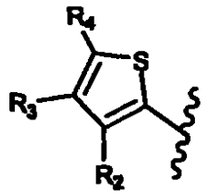
;

(6)

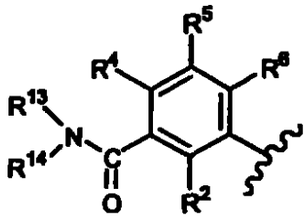


; and

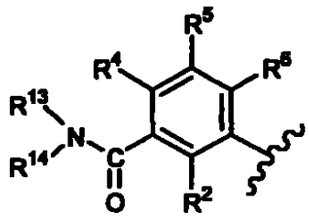
(7)



18. The use of Claim 16 wherein B is:

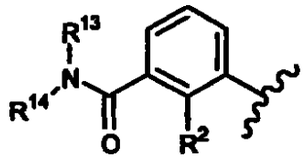


19. The use of Claim 16 wherein B is:



R^2 is –OH, and R^{13} and R^{14} are each the same or different alkyl group.

20. The use of Claim 16 wherein B is

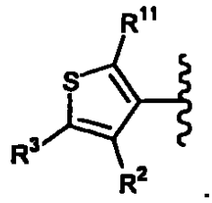


21. The use of Claim 20 wherein R^2 is –OH.

22. The use of Claim 21 wherein R^{13} and R^{14} are the same or different alkyl group.

23. The use of Claim 22 wherein R^{13} and R^{14} methyl.

24. The use of Claim 16 wherein B is



25. The use of Claim 24 wherein R^{11} is H.

26. The use of Claim 25 wherein R^2 is –OH.

27. The use of Claim 26 wherein R^3 is $-C(O)NR^{13}R^{14}$.

28. The use of Claim 27 wherein R^{13} and R^{14} are each independently selected from the group consisting of: alkyl, unsubstituted heteroaryl and substituted heteroaryl.

29. The use of Claim 24 wherein R^3 is $-S(O)_tNR^{13}R^{14}$.

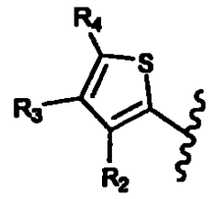
30. The use of Claim 29 wherein R^2 is –OH.

31. The use of Claim 30 wherein the R^{13} and R^{14} substituents are the same or different and are selected from the group consisting of: H and alkyl.

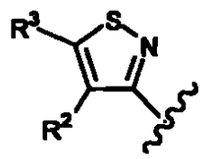
32. The use of Claim 31 wherein each R^{13} and R^{14} are independently selected from the group consisting of: H, methyl, ethyl, isopropyl and t-butyl.

33. The use of Claim 32 wherein R^{13} and R^{14} are ethyl.

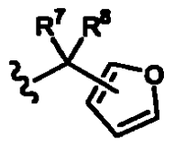
34. The use of Claim 16 wherein B is



35. The use of Claim 16 wherein B is

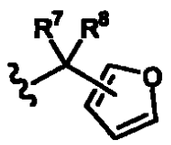


36. The use of any of Claims 16 to 35 wherein A is



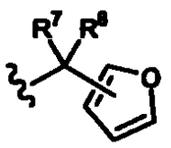
wherein the furan ring is unsubstituted or substituted.

37. The use of Claim 36 wherein A is



wherein the furan ring is substituted.

38. The use of Claim 37 wherein A is



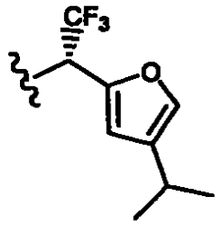
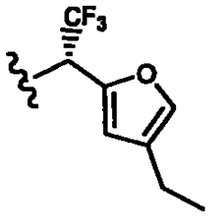
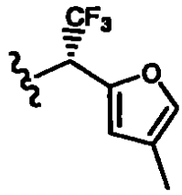
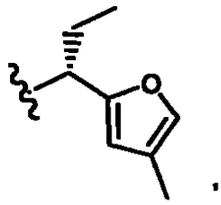
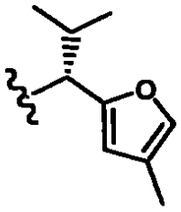
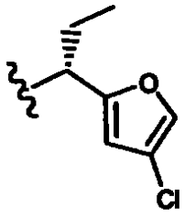
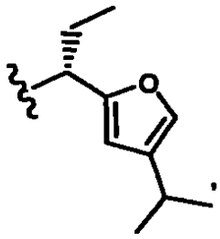
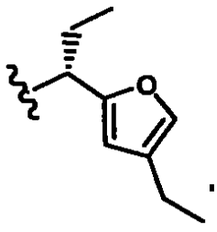
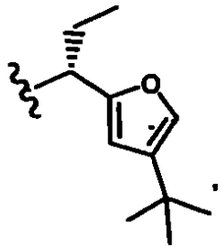
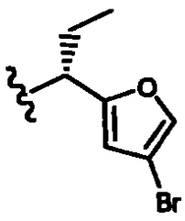
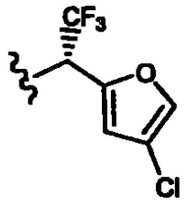
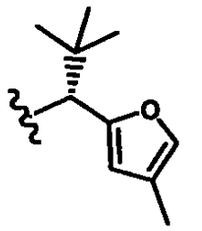
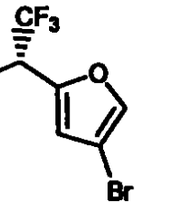
wherein the furan ring is substituted with at least one alkyl group.

39. The use of Claim 38 wherein R^7 and R^8 are independently selected from the group consisting of: H and alkyl.

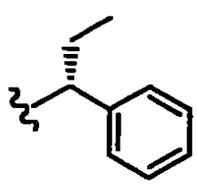
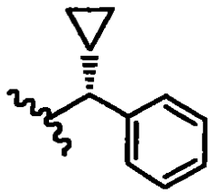
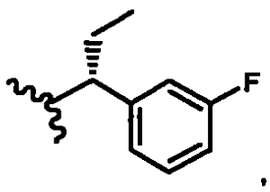
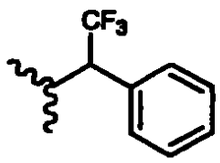
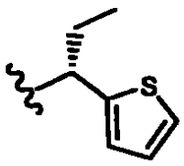
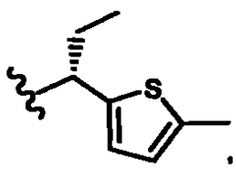
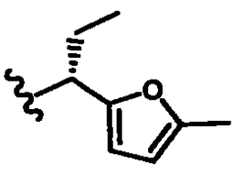
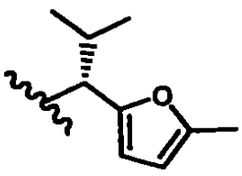
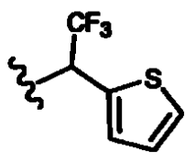
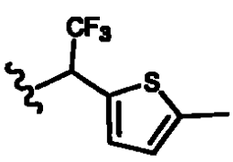
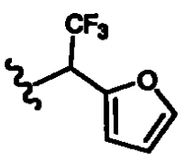
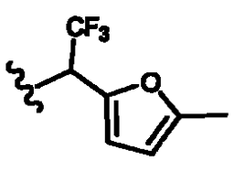
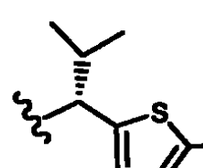
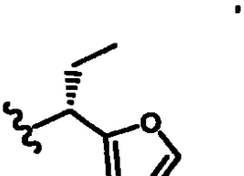
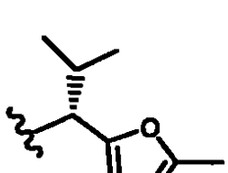
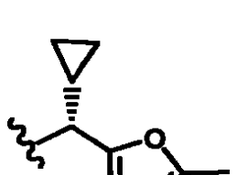
40. The use of Claim 39 wherein R^7 is H, and R^8 is alkyl.

41. The use of Claim 16 wherein

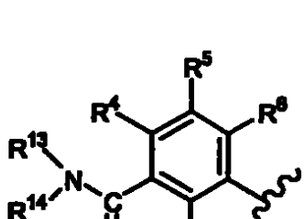
(1) A is selected from the group consisting of:

5
















and

; and

(2) B is:



wh rein:

R^2 is –OH;

R^4 is selected form the group consisting of: H, $-CH_3$ and $-CF_3$;

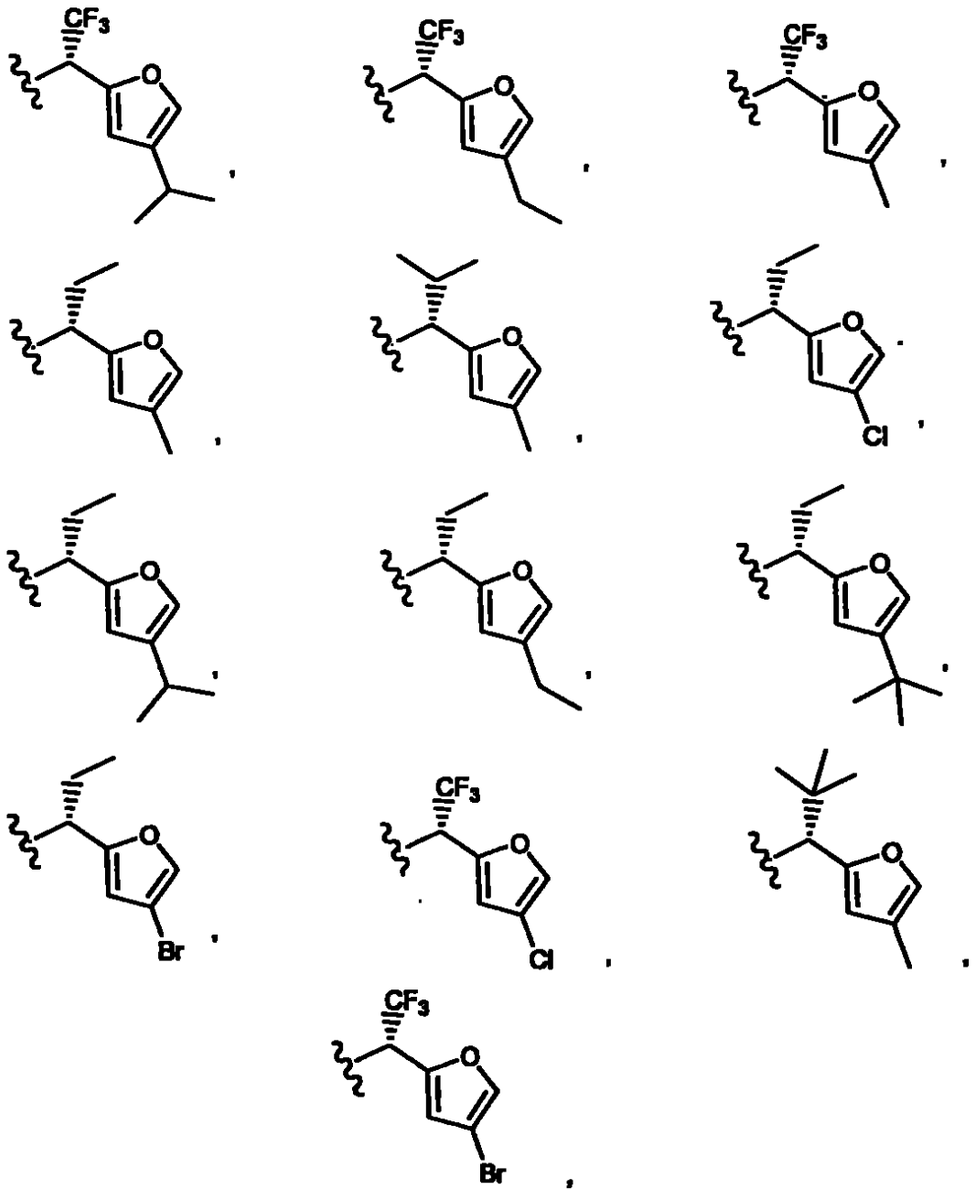
R^5 is selected from the group consisting of: H and cyano;

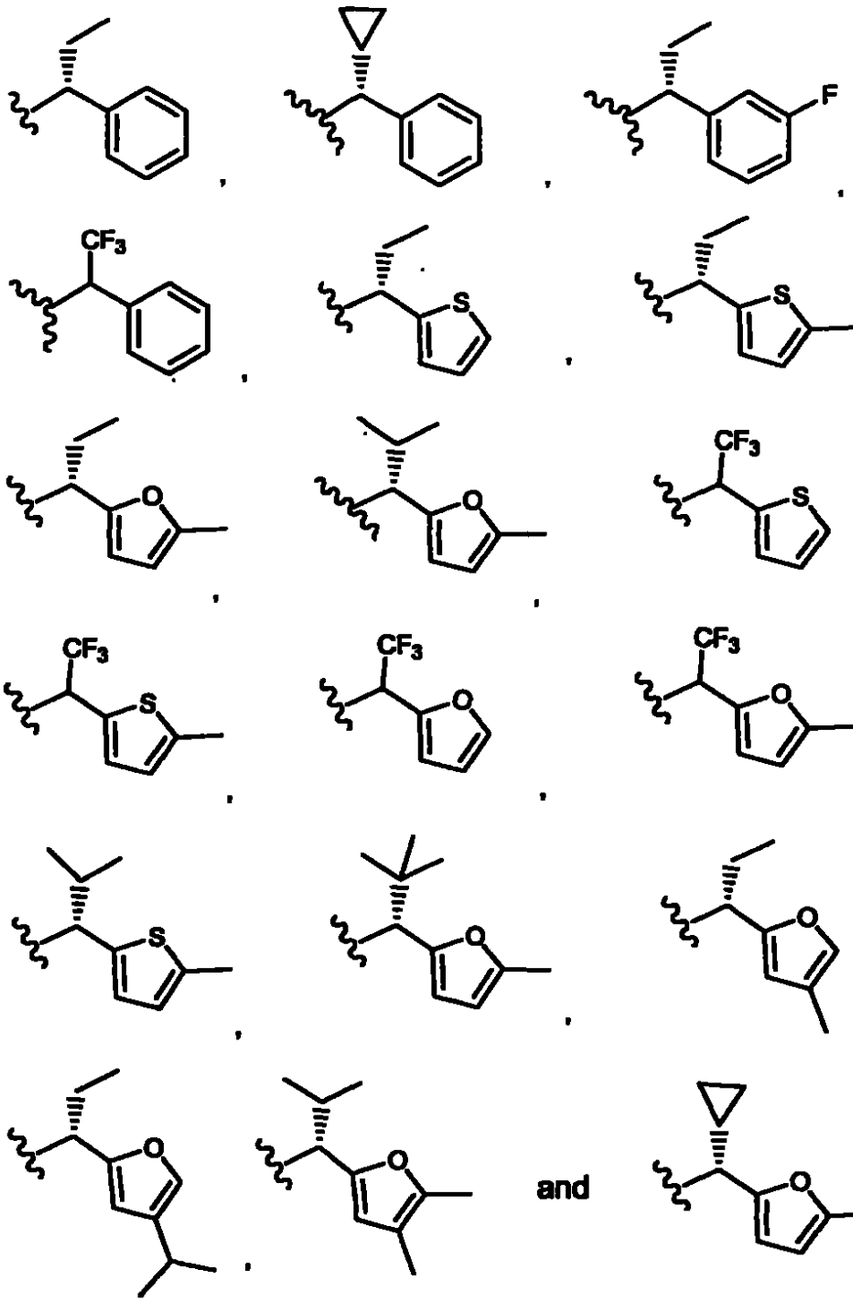
R^6 is selected from the group consisting of: H, $-CH_3$ and $-CF_3$;

R^{13} and R^{14} are methyl.

42. The use of Claim 16 wherein

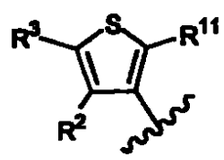
(1) A is selected from the group consisting of:





and ; and

(2) B is:



wherein:

R^2 is –OH;

R^3 is selected from the group consisting of: $-SO_2NR^{13}R^{14}$ and $-CONR^{13}R^{14}$;

R^{11} is H; and

each R^{13} and R^{14} are independently selected from the group consisting of: H, methyl, ethyl, isopropyl and t-butyl.

43. The use of Claim 42 wherein R^3 is $-SO_2NR^{13}R^{14}$.

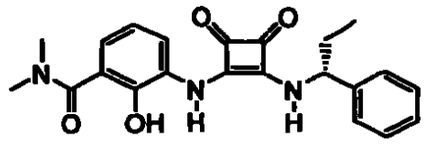
44. The use of Claim 43 wherein R^{13} and R^{14} are ethyl.

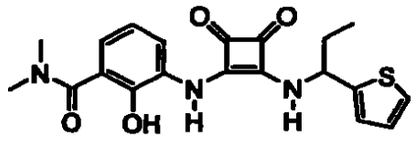
45. The use of Claim 16 wherein said compound is a calcium salt.

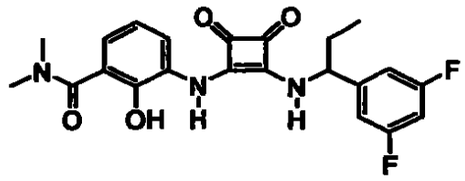
46. The use of Claim 16 wherein said compound is a sodium salt.

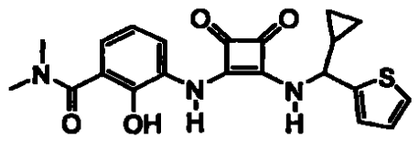
47. The use of Claim 16 wherein said disease is selected from the group consisting of: acute inflammatory pain, chronic inflammatory pain, acute neuropathic pain, and chronic neuropathic pain.

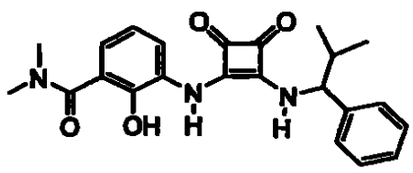
48. The use of Claim 16 wherein said compound is selected from the group consisting of:

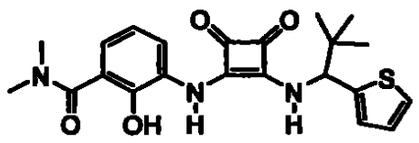


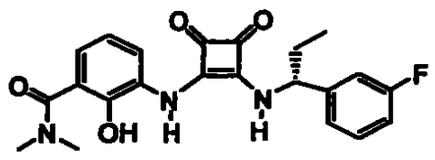


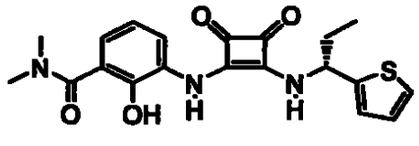


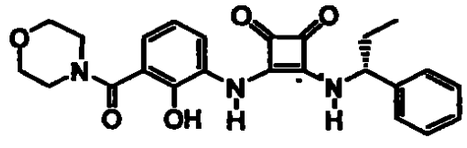


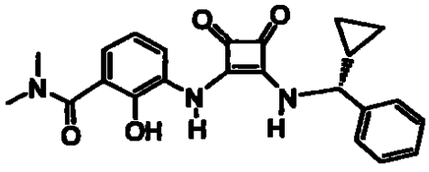


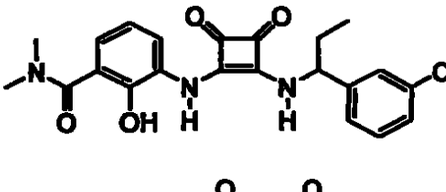


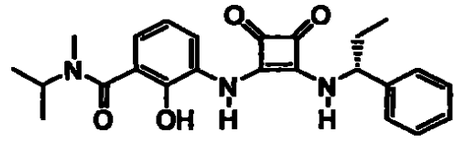


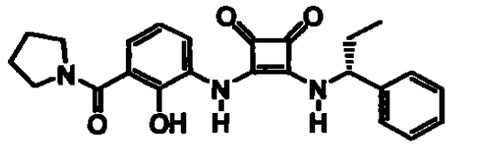


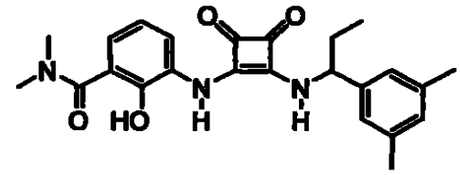


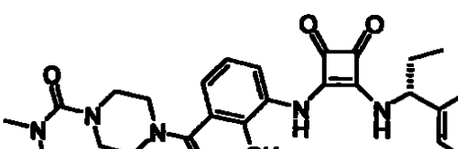


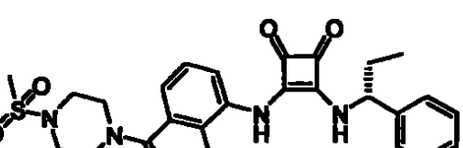


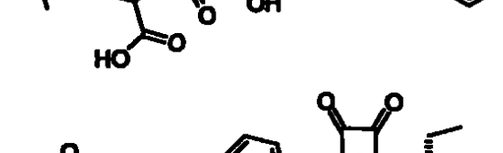


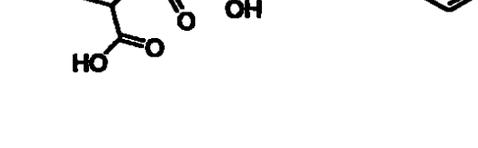


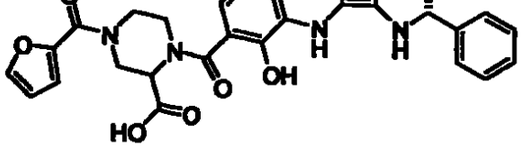


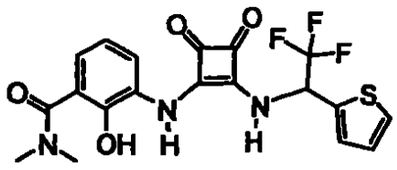


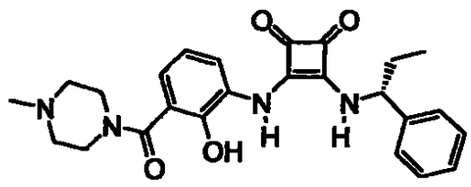


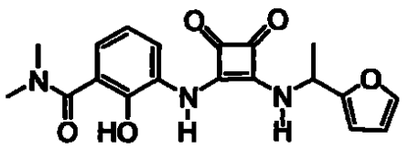


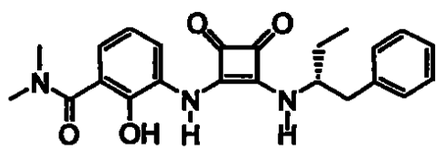


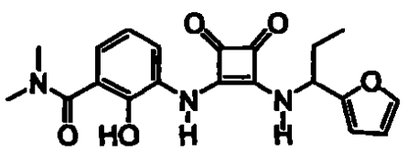


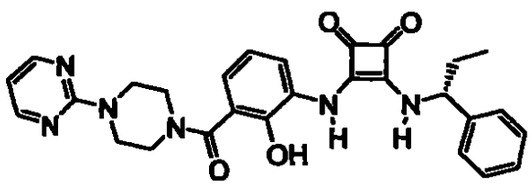


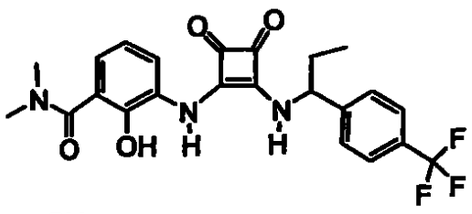


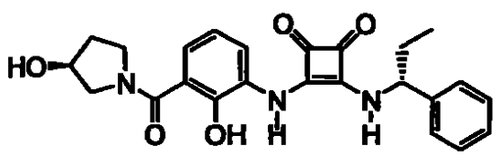


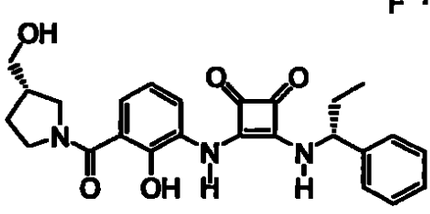


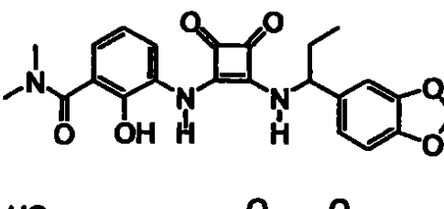


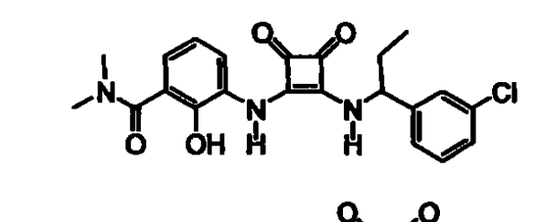


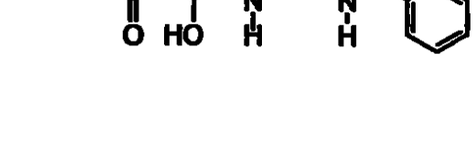


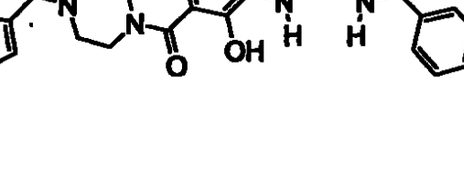


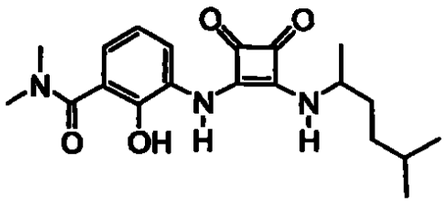


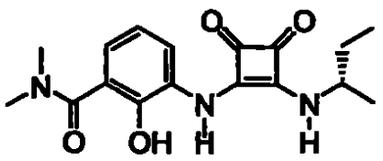


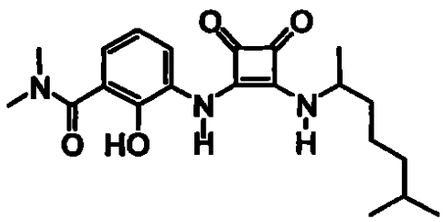


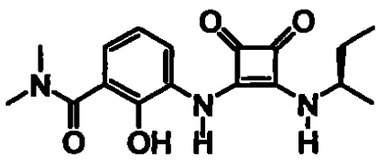


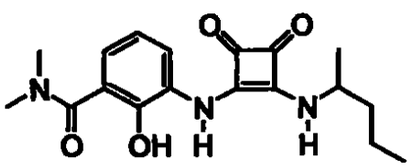


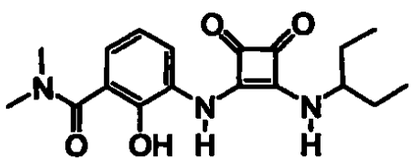


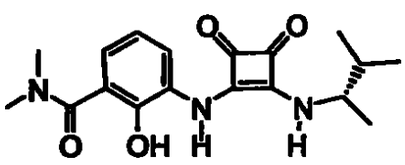


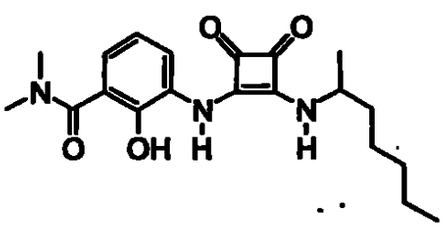


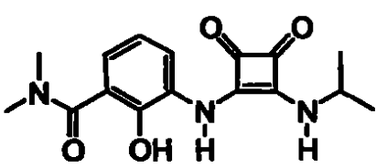


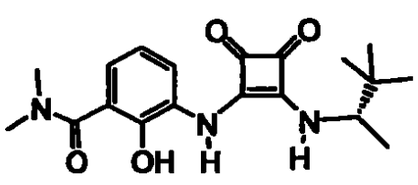


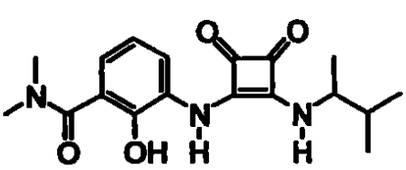


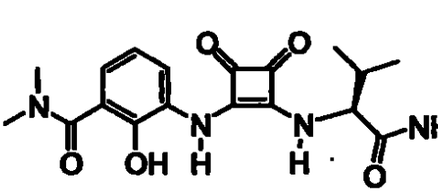


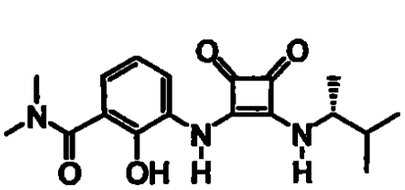


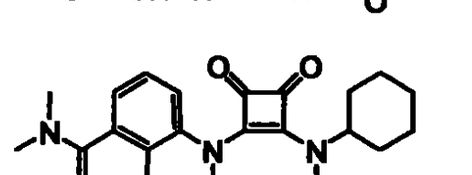


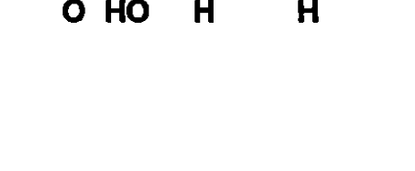


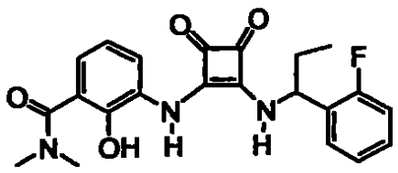


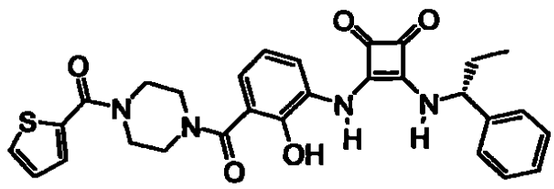


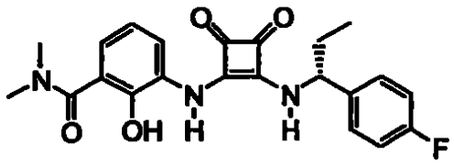


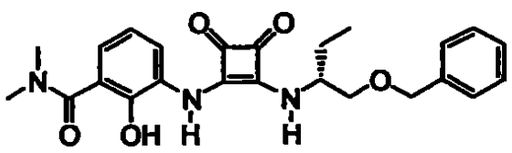


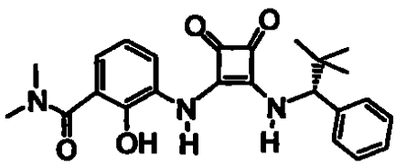


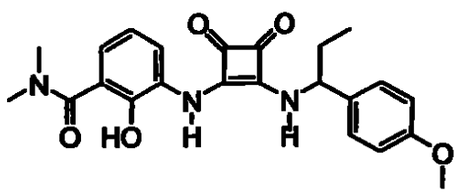


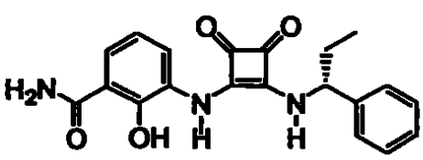


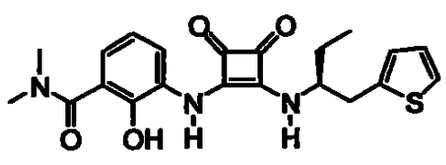


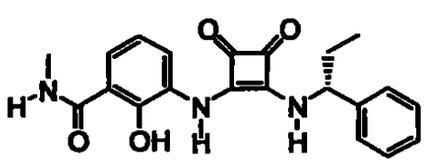


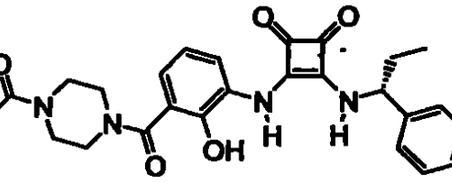


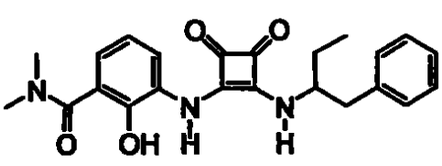


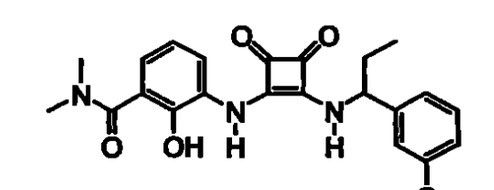


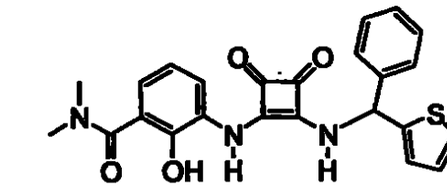


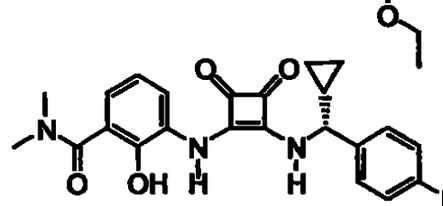


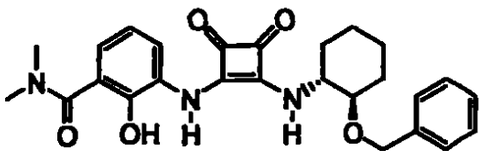


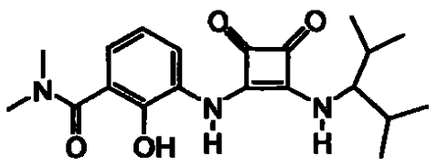


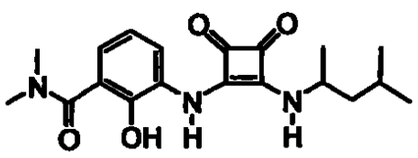


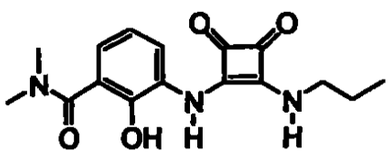


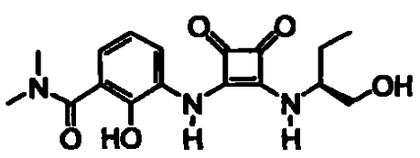


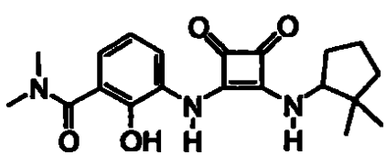


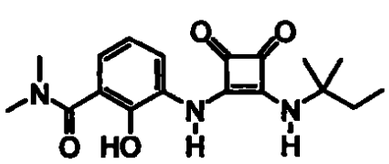


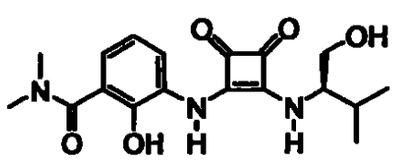


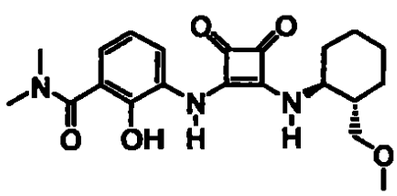


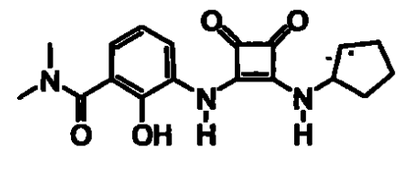


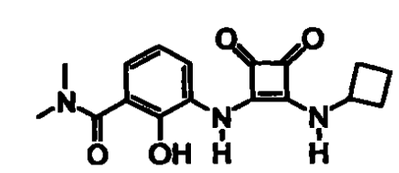


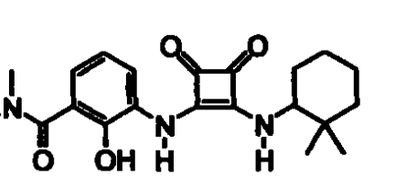


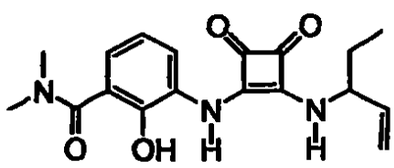


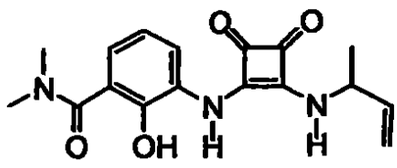


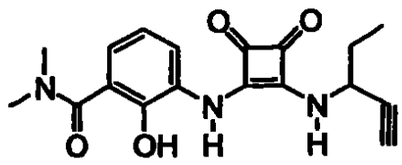


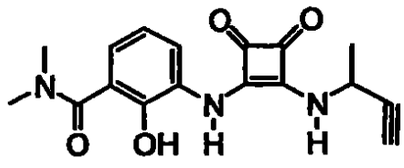


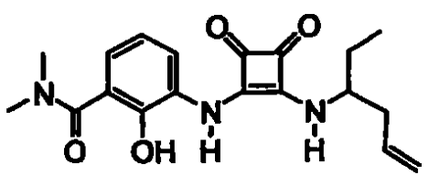


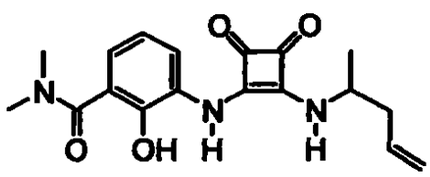


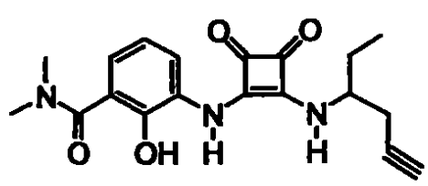


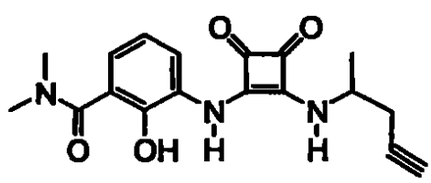


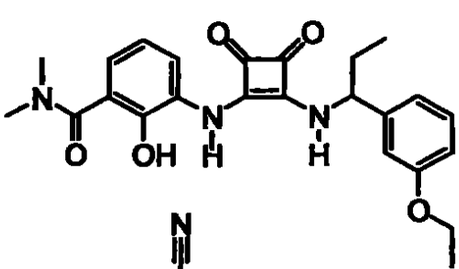


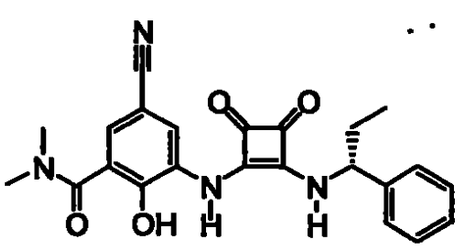


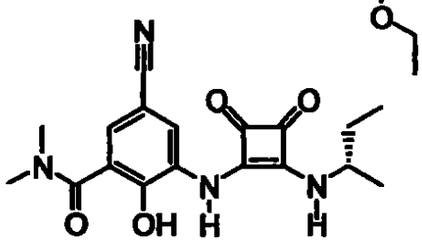


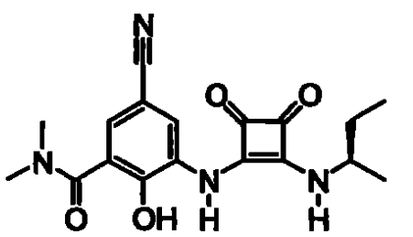


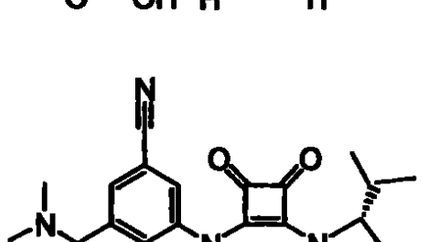


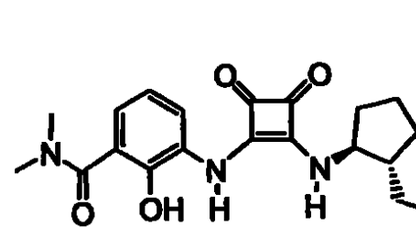


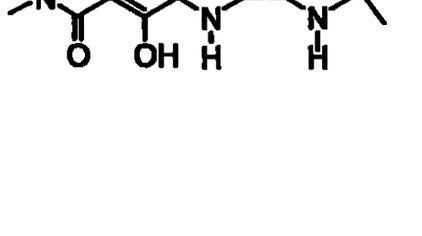


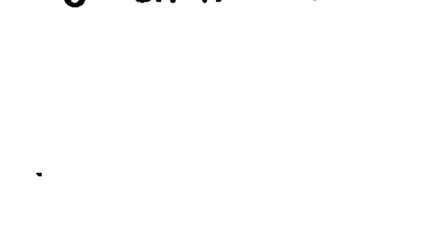


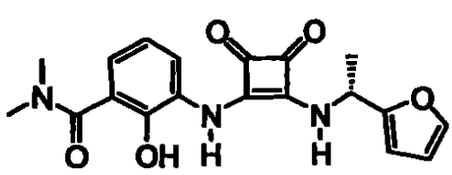


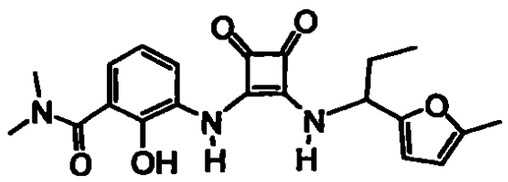


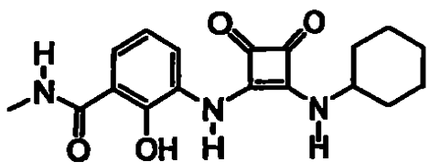


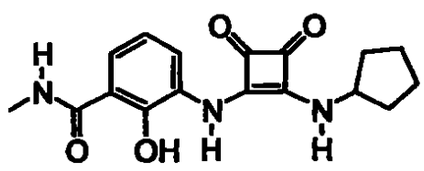


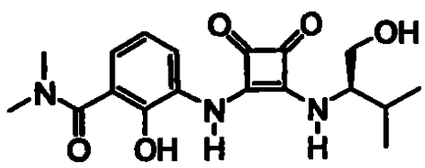


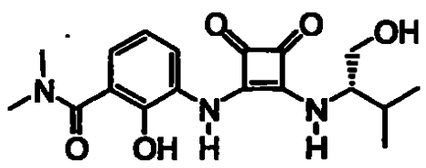


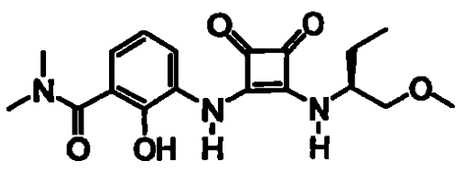


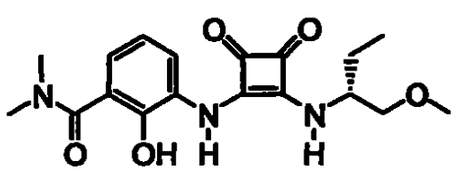


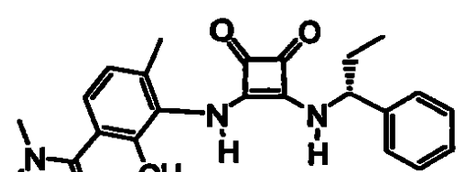


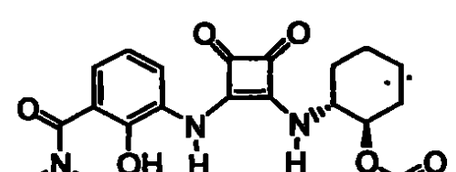


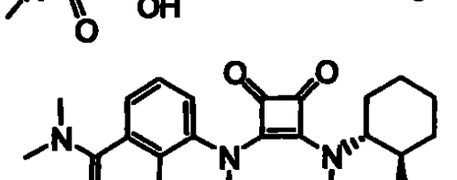


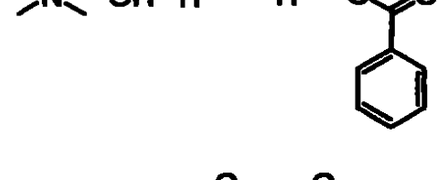


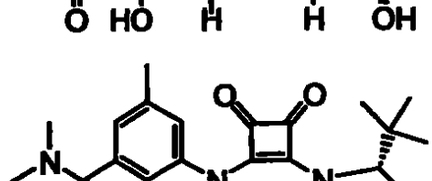


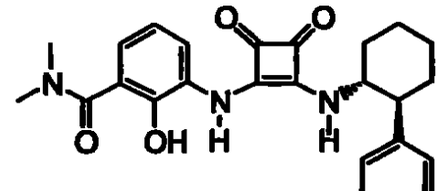


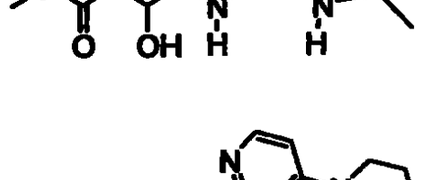




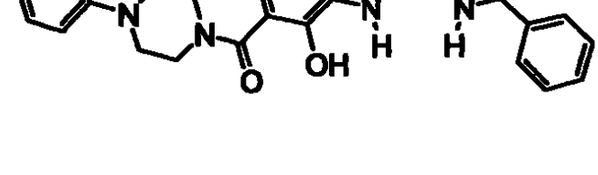


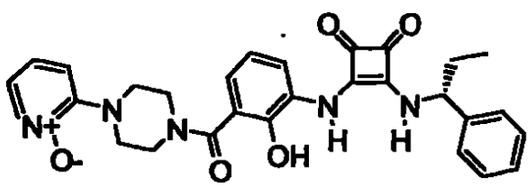


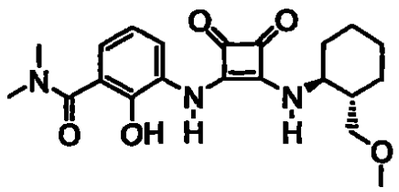


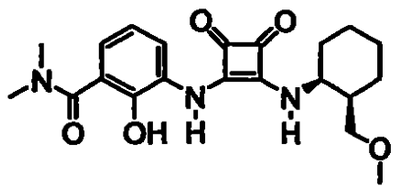


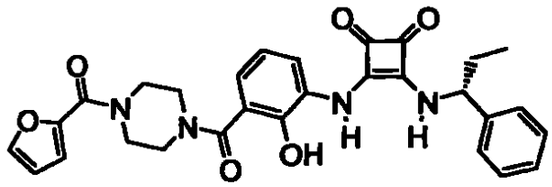


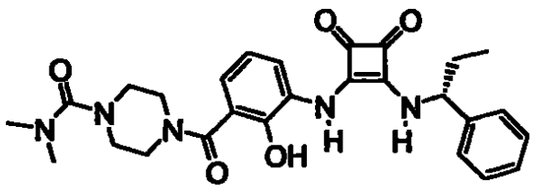


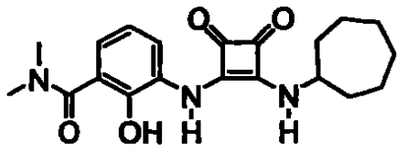


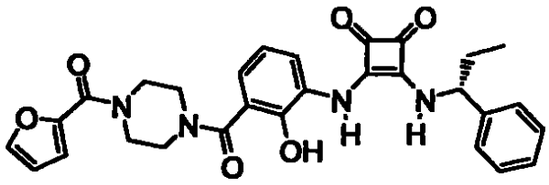


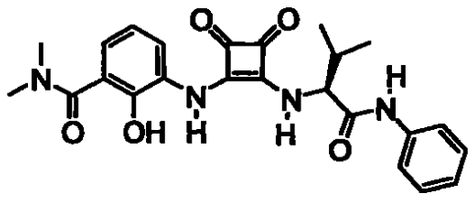


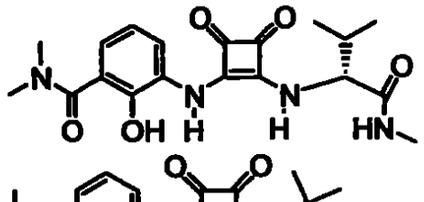


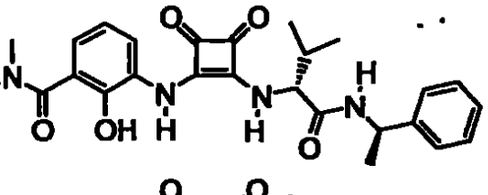


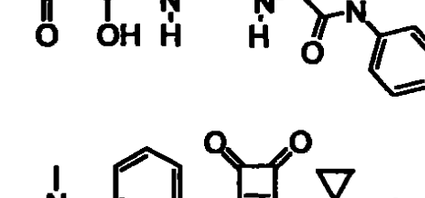


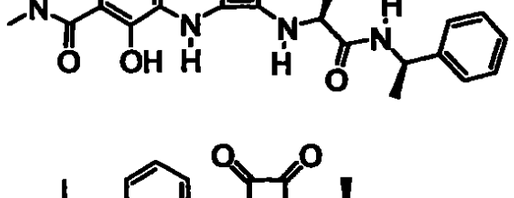


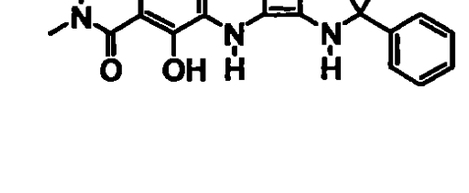


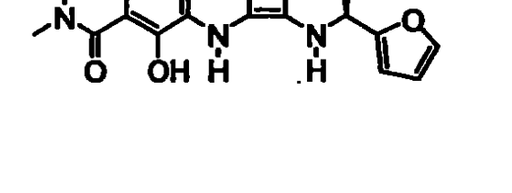


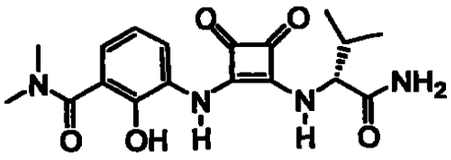


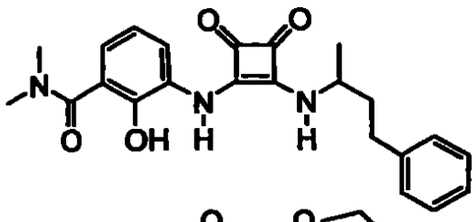


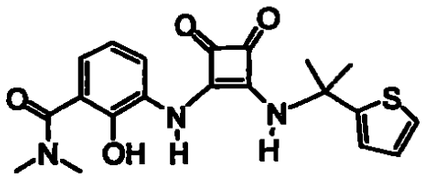


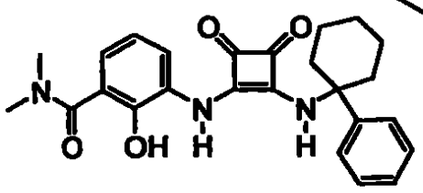


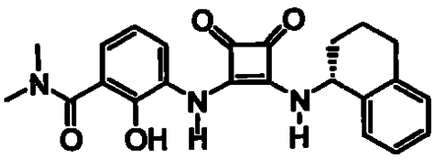


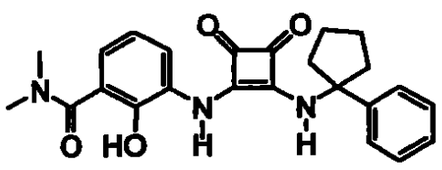


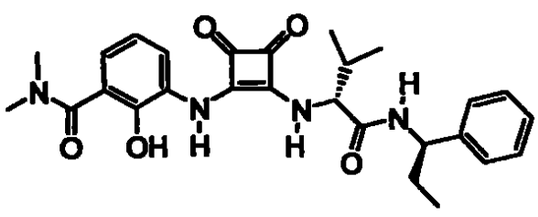


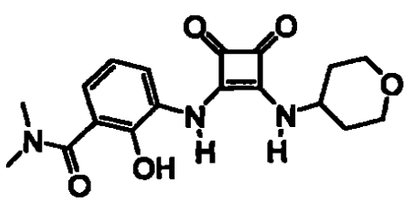


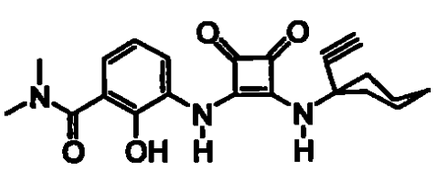


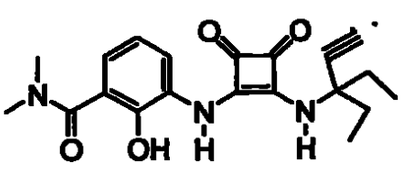


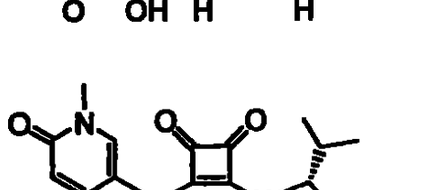


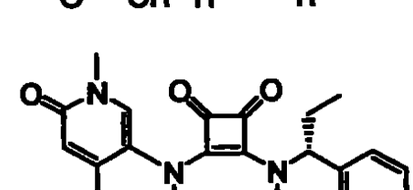


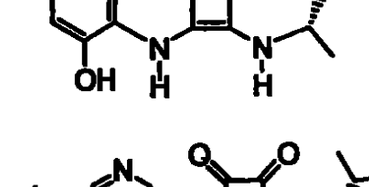


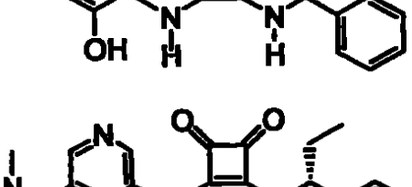


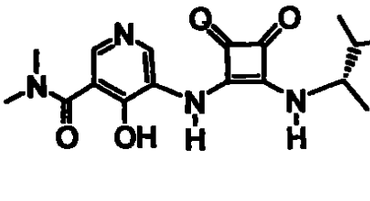


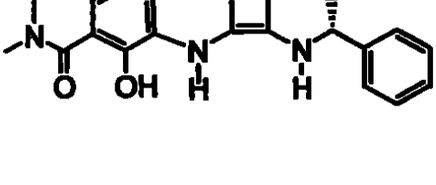


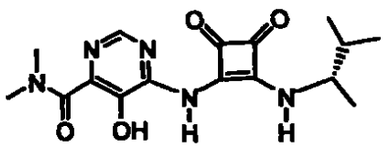


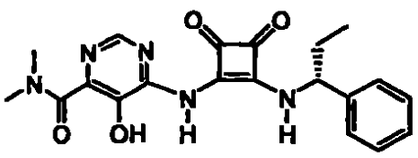


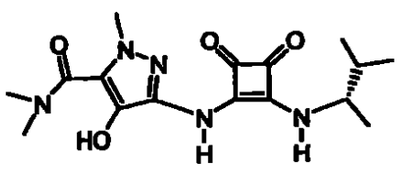


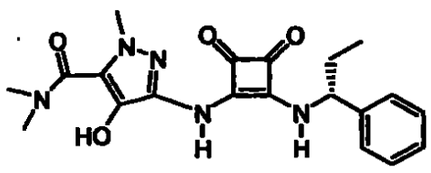


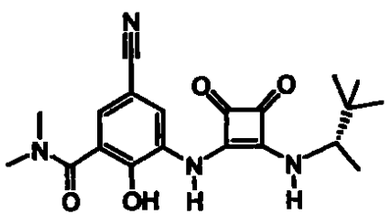


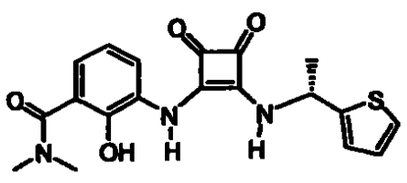


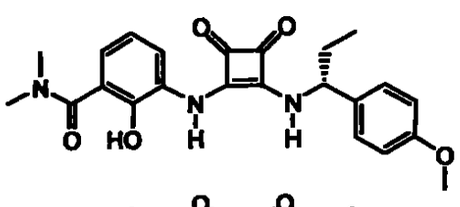


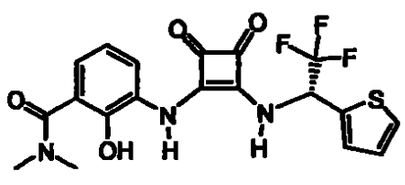


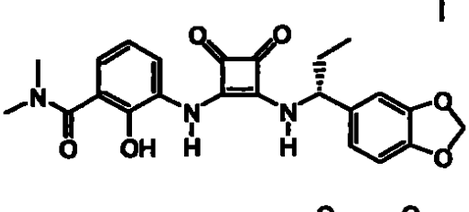


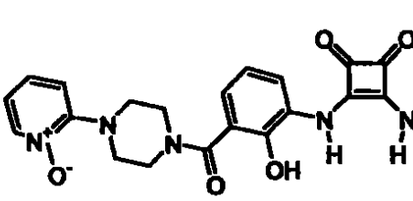


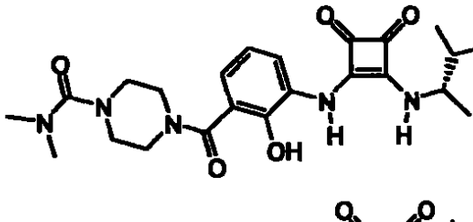


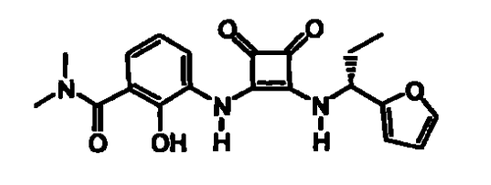


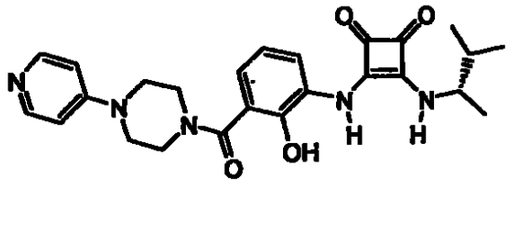


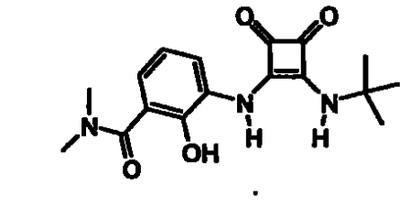


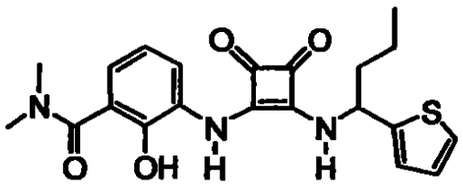


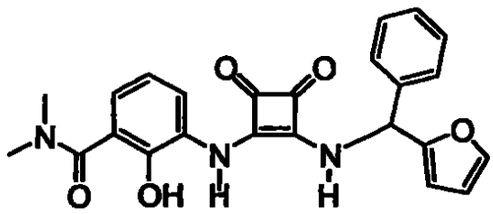


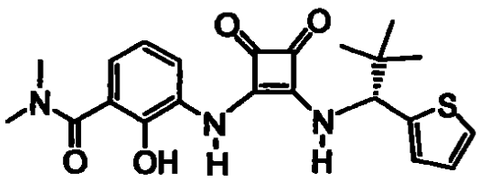


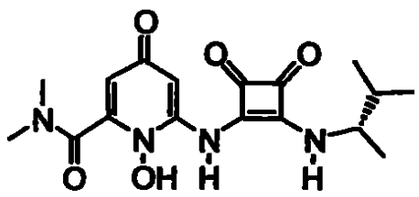


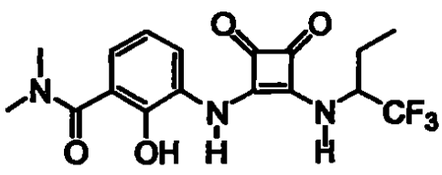


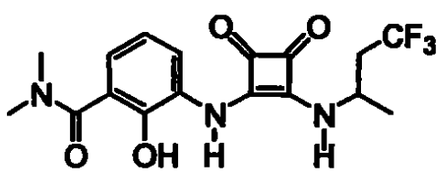


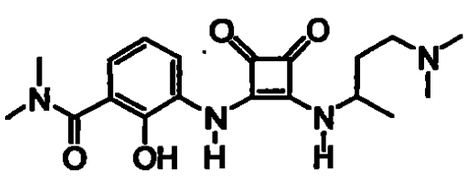


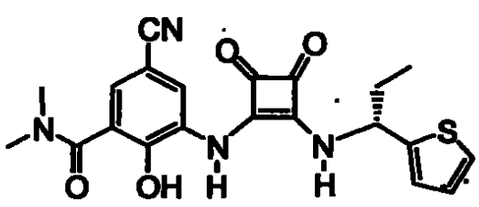


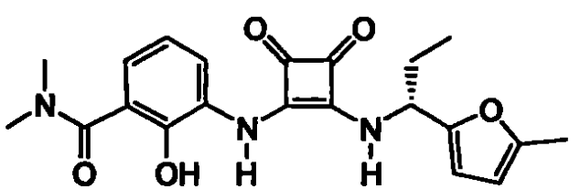


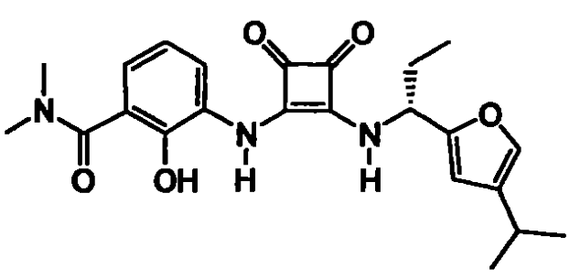


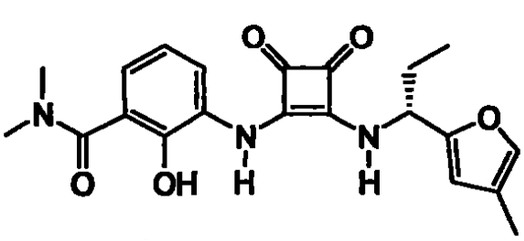


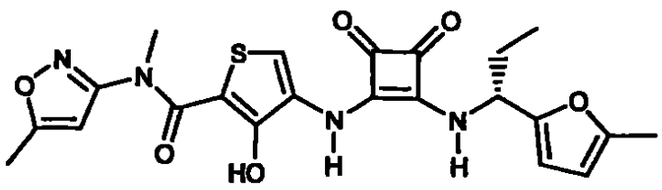


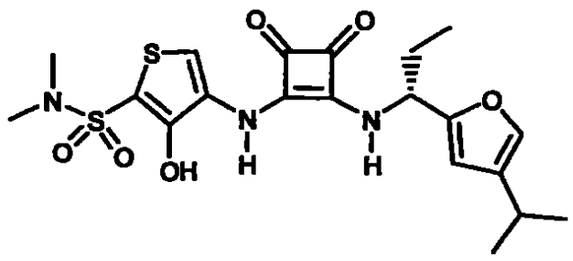




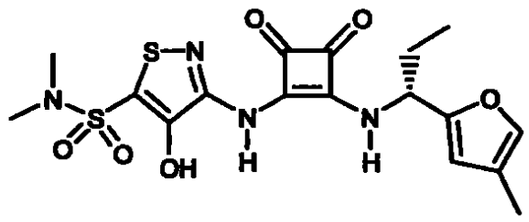






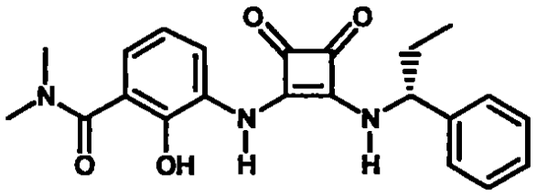


and



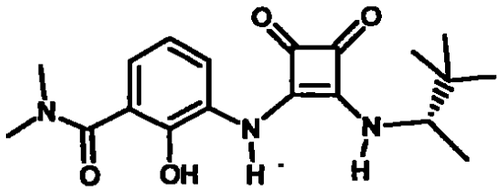
49. The use of Claim 48 wherein a calcium or sodium salt of the compounds is used.

50. The use of Claim 16 wherein said compound is:



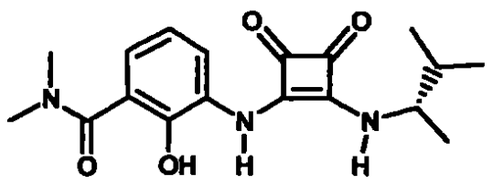
or a pharmaceutically acceptable salt or solvate thereof.

51. The use of Claim 16 wherein said compound is:



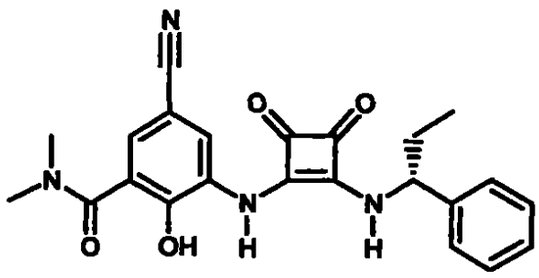
or a pharmaceutically acceptable salt or solvate thereof.

52. The use of Claim 16 wherein said compound is:



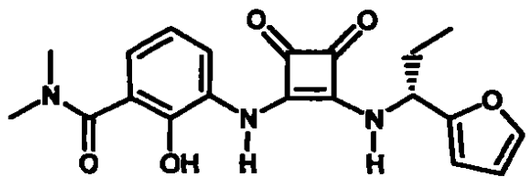
or a pharmaceutically acceptable salt or solvate thereof.

53. The use of Claim 16 wherein said compound is:



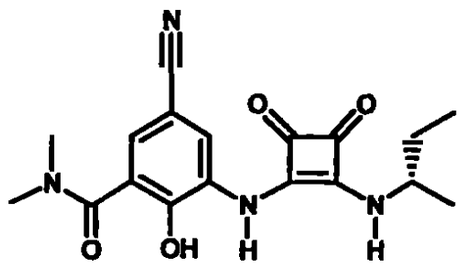
or a pharmaceutically acceptable salt or solvate thereof.

54. The use of Claim 16 wherein said compound is:



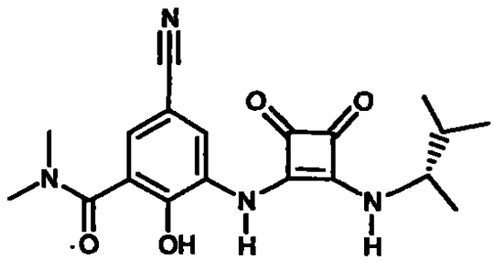
or a pharmaceutically acceptable salt or solvate thereof.

55. The use of Claim 16 wherein said compound is:



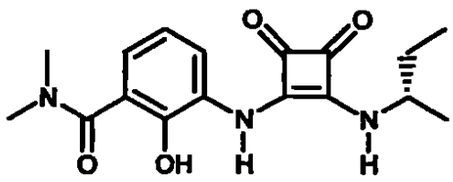
or a pharmaceutically acceptable salt or solvate thereof.

56. The use of Claim 16 wherein said compound is:



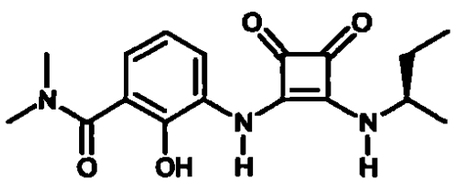
or a pharmaceutically acceptable salt or solvate thereof.

57. The use of Claim 16 wherein said compound is:



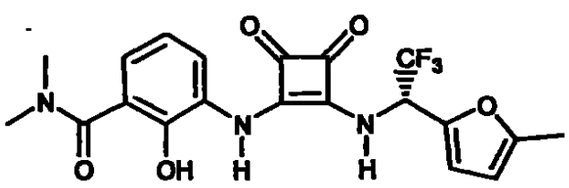
or a pharmaceutically acceptable salt or solvate thereof.

58. The use of Claim 16 wherein said compound is:



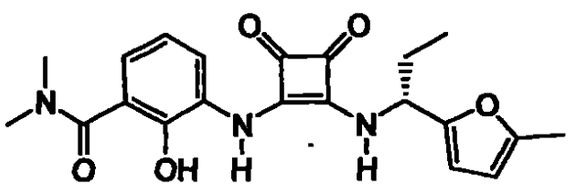
or a pharmaceutically acceptable salt or solvate thereof.

59. The use of Claim 16 wherein said compound is:



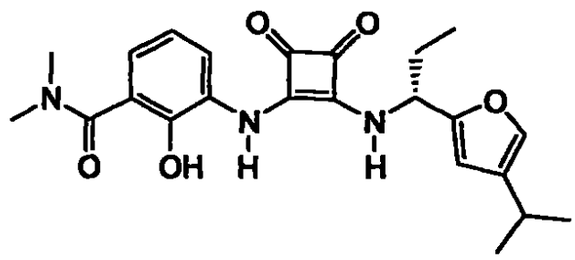
or a pharmaceutically acceptable salt or solvate thereof.

60. The use of Claim 16 wherein said compound is:



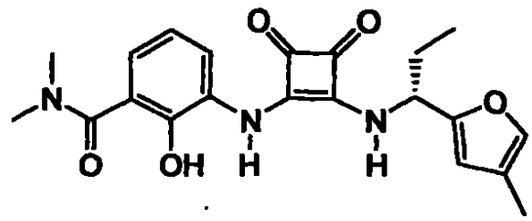
or a pharmaceutically acceptable salt or solvate thereof.

61. The use of Claim 16 wherein said compound is:



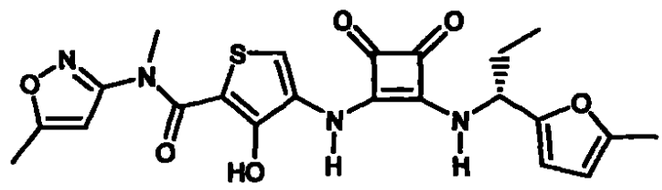
or a pharmaceutically acceptable salt or solvate thereof.

62. The use of Claim 16 wherein said compound is:



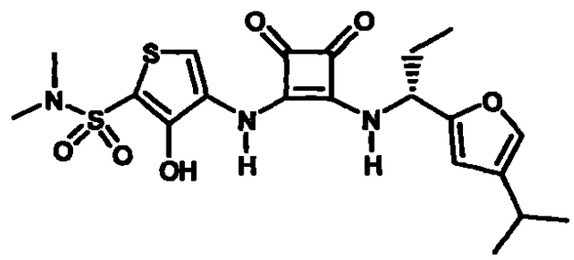
or a pharmaceutically acceptable salt or solvate thereof.

63. The use of Claim 16 wherein said compound is:



or a pharmaceutically acceptable salt or solvate thereof.

64. The use of Claim 16 wherein said compound is:



or a pharmaceutically acceptable salt or solvate thereof.

65. The use of anyone of Claims 50 to 64 wherein a calcium or sodium salt of said compound is used.

66. A use of at least one compound of any of Claims 1 to 13 for manufacturing a medicament for treating a chemokine-mediated disease, wherein the chemokine binds to a CXCR2 and/or CXCR1 receptor in a patient.

67. A use of at least one compound of any of Claims 1 to 13 for manufacturing a medicament for treating a chemokine-mediated disease, wherein the chemokine binds to a CXC receptor in a patient.

68. The use of Claim 66 wherein the chemokine mediated disease is selected from the group consisting of: chronic inflammation, acute inflammatory pain, chronic inflammatory pain, acute neuropathic pain, chronic neuropathic pain, psoriasis, atopic dermatitis, asthma, COPD, adult respiratory disease, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, stroke, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer's disease, graft vs. host reaction, allograft rejections, malaria, acute respiratory distress syndrome, delayed type hypersensitivity reaction, atherosclerosis, cerebral and cardiac ischemia, osteoarthritis, multiple sclerosis, restinosis, angiogenesis, osteoporosis, gingivitis, respiratory viruses, herpes viruses, hepatitis viruses, HIV, Kaposi's sarcoma associated virus, meningitis, cystic fibrosis, pre-term labor, cough, pruritis, multi-organ dysfunction, trauma, strains, sprains, contusions, psoriatic arthritis, herpes, encephalitis, CNS vasculitis, traumatic brain injury, CNS tumors, subarachnoid hemorrhage, post surgical trauma, interstitial pneumonitis, hypersensitivity, crystal induced arthritis, acute and chronic pancreatitis, acute alcoholic hepatitis, necrotizing enterocolitis, chronic sinusitis, angiogenic ocular disease, ocular inflammation, retinopathy of prematurity, diabetic retinopathy, macular degeneration with the wet type preferred and corneal neovascularization, polymyositis, vasculitis, acne, gastric and duodenal ulcers, celiac disease, esophagitis, glossitis, airflow obstruction, airway hyperresponsiveness, bronchiectasis, bronchiolitis, bronchiolitis obliterans, chronic bronchitis, cor pulmonae, cough, dyspnea, emphysema, hypercapnea, hyperinflation,

hypoxemia, hyperoxia-induced inflammations, hypoxia, surgical lung volume reduction, pulmonary fibrosis, pulmonary hypertension, right ventricular hypertrophy, peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD), granulocytic ehrlichiosis, sarcoidosis, small airway disease, ventilation-perfusion mismatching, wheeze, colds, gout, alcoholic liver disease, lupus, burn therapy, periodontitis, transplant reperfusion injury and early transplantation rejection, acute inflammation, and rheumatoid arthritis.

69. A use of at least one compound of any of Claims 1 to 13 for the manufacture of a medicament for treating cancer.

70. A use of at least one compound of any of Claims 1 to 13 for the manufacture of a medicament for treating cancer, the treatment comprising administering said medicament in combination with the administration of at least one anticancer agent.

71. The use of Claim 70 wherein said anticancer agent is selected from the group consisting of: alkylating agents, antimetabolites, natural products and their derivatives, hormones, anti-hormones, anti-angiogenic agents and steroids, and synthetics.

72. A use of at least one compound of any of Claims 1 to 13 for the manufacture of a medicament for inhibiting angiogenesis.

73. A use of at least one compound of any of Claims 1 to 13 for the manufacture of a medicament for inhibiting angiogenesis, the inhibition comprising administering said medicament in combination with the administration of at least one anti-angiogenesis compound.

74. A use of at least one compound of any of Claims 1 to 13 for the manufacture of a medicament for treating a disease selected from the group consisting of: gingivitis, respiratory viruses, herpes viruses, hepatitis viruses, HIV, kaposi's sarcoma associated virus and atherosclerosis.

75. The use of Claim 66 wherein the chemokine mediated disease is an angiogenic ocular disease.

76. The use of Claim 75 wherein said angiogenic ocular disease is selected from the group consisting of: ocular inflammation, retinopathy of prematurity, diabetic retinopathy, macular degeneration with the wet type preferred and corneal neovascularization.

77. The use of Claim 69 wherein the cancer treated is melanoma, gastric carcinoma, or non-small cell lung carcinoma.

78. The use of Claim 70 wherein the cancer treated is melanoma, gastric carcinoma, or non-small cell lung carcinoma.

79. The use of Claim 71, wherein the cancer treated is melanoma, gastric carcinoma, or non-small cell lung carcinoma.

80. A use of at least one compound of any of Claims 1 to 13 for the manufacture of a medicament for treating acute inflammatory pain.

81. A use of at least one compound of any of Claims 1 to 13 for the manufacture of a medicament for treating chronic inflammatory pain.

82. A use of at least one compound of any of Claims 1 to 13 for the manufacture of a medicament for treating acute neuropathic pain.

83. A use of at least one compound of any of Claims 1 to 13 for the manufacture of a medicament for treating chronic neuropathic pain.

84. A use of at least one compound of any of Claims 1 to 13 for the manufacture of a medicament for treating COPD.

85. The use of Claim 16 wherein said disease is acute inflammatory pain.

86. The use of Claim 16 wherein said disease is chronic inflammatory pain.

87. The use of Claim 16 wherein said disease acute neuropathic pain.

88. The use of Claim 16 wherein said disease is chronic neuropathic pain.

89. The use of Claim 16 wherein said disease is acute inflammation.

90. The use of Claim 16 wherein said disease is rheumatoid arthritis.

91. The use of any of Claims 48 to 64 wherein said disease is acute inflammation.

92. The use of any of Claims 48 to 64 wherein said disease is rheumatoid arthritis.

93. The use of Claim 91 wherein the medicament is manufactured from a calcium or sodium salt of the compound.

94. The use of Claim 92 wherein the medicament is manufactured from a calcium or sodium salt of the compound.

95. A compound selected from the group consisting of the final compounds of Examples 2006, 2010, 2015, 2029, 2034, 2035, 2038, 2039, 2047, 2050, 2074, 2079 and 2087.

96. The compound of Claim 95 wherein the compound is a calcium or sodium salt.

97. A pharmaceutical composition comprising an effective amount of at least one compound of any of Claims 95 to 96, and a pharmaceutically acceptable carrier.

98. A use of at least one compound of any of Claims 1 to 13, 95 and 96 for the manufacture of a medicament for the treatment of acute inflammation.

99. A use of at least one compound of any of Claims 1 to 13, 95 and 96 for the manufacture of a medicament for the treatment of rheumatoid arthritis.

100. A use of at least one compound of any of Claims 95 to 96 for the manufacture of a medicament for the treatment of COPD.

101. A use of at least one compound of any of Claims 95 to 96 for the manufacture of a medicament for the treatment of acute inflammatory pain.

102. A use of at least one compound of any of Claims 95 to 96 for the manufacture of a medicament for the treatment of chronic inflammatory pain.

103. A use of at least one compound of any of Claims 95 to 96 for the manufacture of a medicament for the treatment of acute neuropathic pain.

104. A use of at least one compound of any of Claims 95 to 96 for the manufacture of a medicament for the treatment of chronic neuropathic pain.

106. A use of at least one compound of any of Claims 1 to 13, 95 and 96 for the manufacture of a medicament for the treatment of chronic inflammation.

107. A use of at least one compound of any of Claims 16 and 48 to 64 for the manufacture of a medicament for the treatment of chronic inflammation.

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Memoria Descriptiva

de la

Patente de Invención

Sobre

"CICLOBUTEN-1,2-DIONAS 3,4-DI-SUSTITUIDAS COMO LIGANDOS DEL RECEPTOR DE QUIMIOCINA CXC"

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.

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CICLOBUTEN-1,2-DIONAS 3,4-DI-SUSTITUIDAS COMO LIGANDOS DEL RECEPTOR DE QUIMIOCINA CXC

Campo de la Invención

La presente invención se refiere a nuevos compuestos ciclobutendiona sustituidas, a composiciones farmacéuticas que contienen los compuestos, y al uso de los compuestos y formulaciones para tratar las enfermedades mediadas por quimiocina CXC.

Antecedentes de la Invención

Las quimiocinas son citocinas quimiotácticas que son liberadas por una amplia variedad de células para atraer los macrófagos, las células T, eosinófilos, basófilos, neutrófilos y células endoteliales a sitios de inflamación y desarrollo del tumor. Existen dos clases principales de quimiocinas, las Quimiocinas CXC y las Quimiocinas CC. La clasificación depende sí las dos primeras cisteínas están separadas por un solo aminoácido (Quimiocinas CXC) o son adyacentes (Quimiocinas CC). Las Quimiocinas CXC incluyen la interleucina-8 (IL-8), la proteína-1 activadora de neutrófilo (NAP-1). la proteína-2 activadora de neutrófilo (NAP-2), GROα, GROβ, GROγ. ENA-78.. GCP-2, IP-10, MIG y PF4. Las quimiocinas CC incluyen RANTES. MIP-1α. MIP-2β, proteína-1 quimiotáctica de monocitos (MPC-1). MCP-2. MCP-3 y eotaxina. Los miembros individuales de las familias de las quimiocinas son conocidos por estar unidos por al menos un receptor de quimiocina. con las Quimiocinas CXC generalmente unidas por los miembros de la clase de receptores CXCR. y las Quimiocinas CC por los miembros de la clase de receptores CCR. Por ejemplo, la IL-8 está unida por los receptores CXCR-1 y CXCR-2.

Dado que las Quimiocinas CXC promueven la acumulación y activación de

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los neutrófilos, estas quimiocinas han sido implicadas en un amplio rango de desórdenes crónicos y agudos incluyendo psoriasis y artritis reumatoidea. Baggiolini y Otros, FEBS Lett. 207, 97 (¡992); Miller y Otros, Crit. Rev. Immunol. 12, 17 (1992); Oppenheim y otros, Annu. Fev. Immunol. 9, 617 (1991); Seitz y Otros, J. Clin. Invest. 87, 463 (1991); Miller y Otros, Am. Rev. Respir. Dis. 146, 427 (1992); Donnely y Otros, Lancet 341. 643 (1993).

Las quimiocinas ELRCXC que incluyen IL-8, GROα, GROβ, GROγ, NAP-2, y ENA-78 (Strieter y Otros, 1995 JBC 270 p. 27348-57) también han sido implicadas en la inducción de la angiogénesis del tumor (nuevo desarrollo del vaso sanguíneo). Se cree que todas estas quimiocinas ejercen sus acciones uniéndose al receptor CXCR2 acoplado a la proteína G de 7 dominios de transmembrana (también conocido como IL-8RB), mientras la IL-8 también se une al CXCR1 (también conocido como IL-8RA). De este modo, la actividad angiogénica se debe a su unión y activación del CXCR2, y la posible CXCR1 para la IL-8, expresado en la superficie de las células endoteliales vasculares (ECs) en los vasos circundantes.

Muchos tipos diferentes de tumores han demostrado producir las quimiocinas ELRCXC y su producción ha sido correlacionada con un fenotipo más agresivo (Inoue y Otros 2000 Clin Cancer Res 6 p. 2104-2119) y un pobre diagnóstico (Yoneda y Otros 1998 J Nat Cancer Inst 90 p. 447-454). Las quimiocinas son factores quimiotácticos potentes y las quimiocinas ELRCXC han demostrado inducir la quimiotaxis EC. De este modo, estas quimiocinas inducen probablemente la quimiotaxis de las células endoteliales hacia su sitio de producción en el tumor. Este puede ser un paso crítico en la inducción de la angiogénesis por el tumor. Los inhibidores de CXCR2 o los inhibidores duales de CXCR2 y CXCR1 inhibirán la actividad angiogénica de las quimiocinas ELRXC y por lo tanto bloquearán el desarrollo del tumor. Esta actividad anti-tumoral ha sido

demostrada para los anticuerpos a la IL-8 (Arenberg y Otros 1996 J Clin Invest 97 p. 2792-2802), ENA-78 (Arenberg y Otros, 1998 J Clin Invest 102 p. 465-72). y GROα (Haghneghdar y Otros- J. Leukoc Biology 2000 67 p. 53-62).

Además, muchas células tumorales han demostrado expresar el CXCR2 y de este modo las células tumorales además pueden estimular su propio desarrollo cuando secretan las quimiocinas ELRCXC. De este modo, junto con la disminución de la angiogénesis, los inhibidores de CXCR2 pueden inhibir directamente el desarrollo de las células tumorales.

Por lo tanto, los receptores de Quimiocinas CXC representan objetivos promisorios para el desarrollo de nuevos agentes antiinflamatorios y anti-tumorales.

Aún persiste la necesidad de compuestos que sean capaces de modular la actividad en los receptores de Quimiocinas CXC. Por ejemplo, las condiciones asociadas con un incremento en la producción de IL-8 (la cual es responsable por la quimiotaxis del neutrófilo y los subconjuntos de células T en el sitio inflamatorio y desarrollo de tumores) se verían beneficiadas por los compuestos que son inhibidores de la unión del receptor de IL-8.

Breve Descripción de la Invención

La presente invención provee un método para tratar una enfermedad mediada por quimiocina en un paciente (por ejemplo, un mamífero, preferente-mente un ser humano) que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un compuesto (por ejemplo 1-3, y usualmente uno) de fórmula IA (o una sal o solvato farmacéuticamente aceptable del mismo), tal como se describe a continuación, dicha enfermedad mediada por quimiocina está seleccionada del grupo que consiste de: inflama-ciones crónicas, dolor inflamatorio agudo, dolor inflamatorio crónico, dolor neuropático

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agudo, dolor neuropático crónico, síndrome disneico agudo, reacción de hipersensibilidad del tipo retardada, aterosclerosis, isquemia cardíaca y cerebral. osteoartritis, esclerosis múltiple, restinosis, angiogénesis, osteoporosis, gingivitis, virus respiratorio, virus herpes, virus de la hepatitis, HIV, virus asociado con el sarcoma de Kaposi, meningitis, fibrosis cística, trabajo de pre-parto, tos, prurito, disfunción multiorgánica, trauma, torceduras, luxaciones, contusiones, artritis psoriática, herpes, encefalitis, vasculitis SNC, daño cerebral traumático, tumores en el SNC, hemorragia subaracnoidea, trauma pos quirúrgico, pneumonitis intersticial, hipersensibilidad, artritis inducida por cristal, pancreatitis aguda y crónica, hepatitis alcohólica aguda, enterocolitis necrotizante, sinusitis crónica, enfermedad ocular angiogénica, inflamación ocular, retinopatía del prematuro, retinopatía diabética, degeneración macular siendo el tipo húmedo preferido y neovacularización córneal, polimiositis, vasculitis, acné, úlceras gástricas y duodenales, enfermedad celíaca, esofagitis, glositis, obstrucción de vías respiratorias, hipersensibilidad de las vías respiratorias, bronquiectasis, bronquiolitis, bronquiolitis obliterans, bronquitis crónica, cor pulmonale, tos, dispnea, enfisema, hipercapnea, hiperinflación, hipoxemia, inflamaciones inducidas por hiperoxia, hipoxia, reducción de volumen del pulmón quirúrgica, fibrosis pulmonar, hipertensión pulmonar, hipertrofia ventricular derecha, peritonitis asociada con la diálisis peritoneal ambulatoria continua (CAPD), erliquiosis granulocítica, sacoidosis, enfermedad de la vía respiratoria menor, desequilibrio de ventilación-perfusión, respiración sibilante, resfríos, gota, enfermedad del hígado por alcohol, lupus, tratamiento de quemaduras, periodontitis, daño de reperfusión de transplante, rechazo de transplante prematuro, inflamación aguda y artritis reumatoide.

La presente invención provee un método para tratar el dolor inflamatorio agudo, el dolor inflamatorio crónico, el dolor neuropático agudo o el dolor

neuropático crónico en un paciente (por ejemplo un mamífero, preferentemente un ser humano) que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un compuesto (por ejemplo 1-3, y usualmente uno) de fórmula IA (o una sal o solvato farmacéuticamente aceptable del mismo), tal como se describe a continuación.

La presente invención provee un método para tratar una enfermedad mediada por la quimiocina en un paciente que necesita dicho tratamiento que comprenden administrar a dicho paciente una cantidad efectiva de al menos un (por ejemplo 1-3, usualmente 1) compuesto seleccionado del grupo que consiste de los compuestos de las fórmulas 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, o una sal o solvato farmacéuticamente aceptable de dichos compuestos.

La presente invención provee un método para tratar el dolor inflamatorio agudo, el dolor inflamatorio crónico, el dolor neuropático agudo o el dolor neuropático crónico en un paciente (por ejemplo un mamífero, preferentemente un ser humano) que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ejemplo 1-3, usualmente 1) compuesto seleccionado del grupo que consiste de los compuestos de las fórmulas 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, o una sal o solvato farmacéuticamente aceptable de dichos compuestos.

La presente invención, además provee un método para tratar el cáncer en un paciente que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ejemplo 1-3, usualmente 1) compuesto seleccionado del grupo que consiste de los compuestos de las fórmulas 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, o una sal o solvato

farmacéuticamente aceptable de dichos compuestos.

La presente invención, además provee un método para tratar el cáncer en un paciente que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ejemplo 1-3, usualmente 1) compuesto seleccionado del grupo que consiste de los compuestos de las fórmulas 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, o una sal o solvato farmacéuticamente aceptable de dichos compuestos, en forma concurrente o secuencial con: (a) un agente que afecta el microtúbulo, o (b) un agente antineoplásico, o (c) un agente anti-angiogénesis, o (d) un inhibidor de la quinasa receptor de VEGF, o (e) anticuerpos contra el receptor de VEGF, o (f) interferón, y/o g) radiación.

La presente invención, además provee un método para inhibir la angiogénesis en un paciente que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ejemplo 1-3, usualmente 1) compuesto seleccionado del grupo que consiste de los compuestos de las fórmulas 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, o una sal o solvato farmacéuticamente aceptable de dichos compuestos.

La presente invención, además provee un método para tratar la enfermedad ocular angiogénica (por ejemplo inflamación ocular, retinopatía del prematuro, retinopatía diabética, degeneración macular siendo preferido el tipo húmedo y neovascularización corneal), en un paciente que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ejemplo 1-3, usualmente 1) compuesto seleccionado del grupo que consiste de los compuestos de las fórmulas 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311,

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y 2001-2088, o una sal o solvato farmacéuticamente aceptable de dichos compuestos.

La presente invención, además provee un método para tratar una enfermedad seleccionada del grupo que consiste de: gingivitis, virus respiratorio, virus herpes, virus de la hepatitis, HIV, sarcoma de Kaposi asociado al virus y aterosclerosis, en un paciente que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ejemplo 1-3, usualmente 1) compuesto seleccionado del grupo que consiste de los compuestos de las fórmulas 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, o una sal o solvato farmacéuticamente aceptable de dichos compuestos.

La presente invención además provee nuevos compuestos seleccionados del grupo que consiste de los compuestos de las fórmulas 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088.

La presente invención además provee nuevos compuestos seleccionados del grupo que consiste de sales farmacéuticamente aceptables (por ejemplo sodio, o sales de calcio), o solvatos, de los compuestos de las fórmulas 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088.

La presente invención además provee una composición farmacéutica que comprende al menos un compuesto (por ejemplo 1-3, usualmente 1) seleccionado de los compuestos de las fórmulas 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, o una sal o solvato farmacéuticamente aceptable de dichos compuestos, y un portador farmacéuticamente aceptable.

La presente invención además provee un método para tratar una

enfermedad mediada por quimiocina en un paciente que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un compuesto (por ejemplo 1-3, usualmente 1) de la fórmula IB, tal como se describe a continuación.

La presente invención además provee un método para tratar cáncer en un paciente que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un compuesto (por ejemplo 1-3, usualmente 1) de la fórmula IB, tal como se describe a continuación.

La presente invención además provee un método para tratar cáncer en un paciente que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un compuesto (por ejemplo 1-3, usualmente 1) de la fórmula IB, tal como se describe a continuación, en forma concurrente o secuencial con: (a) un agente que afecta el microtúbulo, o (b) un agente antineoplásico, o (c) un agente anti-angiogénesis, o (d) un inhibidor de la quinasa receptor de VEGF, o (e) anticuerpos contra el receptor de VEGF, o (f) interferón, y/o g) radiación.

La presente invención además provee un método para inhibir la angiogénesis en un paciente que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un compuesto (por ejemplo 1-3, usualmente 1) de la fórmula IB, tal como se describe a continuación.

La presente invención además provee un método para tratar la enfermedad ocular angiogénica (por ejemplo, inflamación ocular, retinopatía del prematuro, retinopatía diabética, degeneración macular siendo preferido el tipo húmedo y neovascularización corneal), en un paciente que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un compuesto (por ejemplo 1-3, usualmente 1) de la fórmula IB, tal como se describe a continuación.

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La presente invención además provee un método para tratar una enfermedad seleccionada del grupo que consiste de: gingivitis, virus respiratorio, virus herpes, virus de la hepatitis, HIV, sarcoma de Kaposi asociado al virus y aterosclerosis, en un paciente que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un compuesto (por ejemplo 1-3, usualmente 1) de la fórmula IB, tal como se describe a continuación.

La presente invención además provee nuevos compuestos de fórmula IB, tal como se describe a continuación.

La presente invención además provee nuevos compuestos seleccionados del grupo que consiste de sales farmacéuticamente aceptables (por ejemplo, sales de sodio, o calcio), o solvatos, de los compuestos de fórmula IB, tal como se describe a continuación.

La presente invención además provee una composición farmacéutica que comprende al menos un compuesto (por ejemplo 1-3. usualmente 1) de fórmula IB, tal como se describe a continuación, y un portador farmacéuticamente aceptable.

Descripción Detallada de la Invención

Cuando una variable ocurre más de una vez en cualquier porción, su definición en cada ocurrencia es independiente de su definición en cada una de las otras ocurrencias. Además, las combinaciones de sustituyentes y/o variables son permisibles sólo si dichas combinaciones dan por resultado compuestos estables.

A menos que se indique lo contrario, las siguientes definiciones se aplican en la presente memoria descriptiva y en las reivindicaciones. Estas definiciones se aplican sin considerar sí un término se utiliza por sí mismo o en combinación con otros términos. Por ejemplo, la definición de "alquilo" también se aplica a la

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porción "alquilo" de "alcoxi".

"Paciente" incluye tanto al ser humano como a otros mamíferos, preferentemente el ser humano.

"Mamífero" incluye al ser humano, y preferentemente significa un ser humano.

"Alquilo" significa una cadena de hidrocarburo recta o ramificada que tiene de 1 a 20 átomos de carbono, preferentemente 1 a 12 átomos de carbono, más preferentemente de 1 a 6 átomos de carbono.

"Alcoxi" significa un grupo alquilo-O- en donde alquilo es tal como se definió anteriormente. Los ejemplos no limitativos de los grupos alcoxi incluyen; metoxi, etoxi, n-propoxi, iso-propoxi y n-butoxi. El enlace a la porción madre es a través del éter oxígeno.

"Alquenilo" significa un grupo hidrocarburo alifático recto o ramificado que tiene al menos un enlace doble carbono-carbono, y 2 a 10 átomos de carbono, preferentemente 2 a 12 átomos de carbono, y más preferentemente 2 a 6 átomos de carbono. Los ejemplos no limitativos de los grupos alquenilo incluyen: etenilo, propenilo, n-butenilo, 3-metilbut-2-enilo, n-pentenilo, octenilo y decenilo.

"Alquinilo" significa un grupo hidrocarburo alifático recto o ramificado que tiene al menos un enlace triple carbono-carbono, y 2 a 15 átomos de carbono, preferentemente 2 a 12 átomos de carbono, y más preferentemente 2 a 4 átomos de carbono. Los ejemplos no-limitantes de grupos alquinilo incluyen: etinilo, propinilo, 2-butinilo, 3-metilbutinilo, n-pentinilo, y decinilo.

"Arilo" significa un sistema de anillo monocíclico o multicíclico aromático, en donde al menos un anillo es aromático, que comprende aproximadamente 6 a aproximadamente 14 átomos de carbono, y preferentemente aproximadamente 6 a aproximadamente 10 átomos de carbono. Los ejemplos no limitantes de grupos arilo apropiado incluyen: fenilo, naftilo, indenilo, tetrahidronaftilo, indanilo,

antracenilo, y fluorenilo.

"Arilalquilo" significa un grupo arilo, tal como se definió anteriormente, unido a un grupo alquilo, tal como se definió anteriormente, en donde el grupo alquilo está unido a la porción madre. Los ejemplos no limitantes de grupos arilalquilo apropiados incluyen bencilo, fenetilo y naftelenilmetilo.

"Cicloalquilo" significa anillos carbocíclicos saturados que tienen de 3 a 10 átomos de carbono, preferentemente 5 a 10 átomos de carbono, y más preferentemente 5 a 7 átomos de carbono, y tienen uno a tres anillos. Los ejemplos no limitantes de grupos cicloalquilo incluyen: ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo, norbornilo, y adamantilo.

"Cicloalquilalquilo" significa un grupo cicloalquilo unido a la porción madre a través de un grupo alquilo. Los ejemplos no limitantes incluyen: ciclopropilmetilo y ciclohexilmetilo.

"Cicloalquenilo" significa un sistema de anillo mono o multicíclico no-aromático que comprende de 3 a 10 átomos de carbono, y preferentemente 5 a 10 átomos de carbono, y tiene al menos un enlace doble carbono-carbono. Los anillos cicloalquenilo preferidos tienen de 5 a 7 átomos de carbono. Los ejemplos no limitantes de los grupos cicloalquilo incluyen ciclopentenilo, ciclohexenilo, cicloheptenilo, y norbornenilo.

"Halo" significa los grupos flúor, cloro, bromo o yodo. Se prefieren flúor, cloro o bromo, y los más preferidos son flúor y cloro.

"Halógeno" significa flúor, cloro, bromo y yodo. Se prefieren flúor, cloro, o bromo y los más preferidos son flúor y cloro.

"Haloalquilo" significa un grupo alquilo tal como se definió anteriormente en donde uno o más átomos de hidrógeno en el alquilo es reemplazado por un grupo halo definido anteriormente.

"Heterociclilo" o "Heterocíclico" o "Heterocicloalquilo" significa un sistema

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de anillo monocíclico o multicíclico saturado no aromático (es decir, un anillo o sistema de anillo carbocíclico saturado) que comprende de 3 a 10 átomos de anillo (por ejemplo de 3 a 7 átomos de anillo), preferentemente de 5 a 10 átomos de anillo, en el cual uno o más de los átomos del sistema de anillo es un elemento diferente a carbono, por ejemplo nitrógeno, oxígeno o azufre, solo o en combinación. No hay átomos de oxígeno y/o azufre adyacentes presentes en el sistema de anillo. Los heterociclilos preferidos tienen de 5 a 6 átomos de anillo. El prefijo aza, oxa, o tia antes del nombre de raíz heterociclilo significa que al menos un átomo de nitrógeno, oxígeno o azufre, respectivamente está presente como un átomo de anillo. El átomo de nitrógeno o azufre del heterociclilo puede ser opcionalmente oxidado al correspondiente N-óxido, S-óxido, o S,S-dióxido. Los ejemplos no limitantes de los anillos heterociclilo monocíclico incluyen: piperidilo, pirrolidinilo, piperazinilo, morfolinilo, tiomorfolinilo, tiazolidinilo, 1,3-dioxolanilo, 1,4-dioxanilo, tetrahidrofuranilo, tetrahidrotiofenilo, y tetrahidrotiopiranilo.

El término grupo funcional ácido heterocíclico incluye los grupos tales como pirrol, imidazol, triazol, tetrazol y similares.

"Heteroarilo" significa un sistema de anillo monocíclico o multicíclico aromático que comprende de 5 a 14 átomos de anillo, preferentemente de 5 a 10 átomos de anillo, en el cual uno o más de los átomos de anillo es un elemento diferente a carbono, por ejemplo nitrógeno, oxígeno o azufre, solo o en combinación. Los heteroarilo preferidos contienen de 5 a 6 átomos de anillo. El prefijo aza, oxa, o tia antes del nombre de raíz heteroarilo significa que al menos un átomo de nitrógeno, oxígeno o azufre, respectivamente está presente como un átomo de anillo. Un átomo de nitrógeno de un heteroarilo puede estar opcionalmente oxidado al correspondiente N-óxido. Los ejemplos no limitantes de los heteroarilos incluyen: piridilo, pirazinilo, furanilo, tienilo, pirimidinilo, isoxazolilo, isotiazolilo, oxazolilo, tiazolilo, pirazolilo, furazanilo, pirrolilo, pirazolilo, triazolilo,

1,2,4-tiadiazolilo, pirazinilo, piridazinilo, quinoxalinilo, ftalazinilo, imidazo[1,2-a]piridinilo, imidazo[2,1-b]tiazolilo, benzofurazanilo, indolilo, azaindolilo, bencimidazolilo, benzotienilo, quinolinilo, imidazolilo, tienopiridilo, quinazolinilo, tienopirimidinilo, pirrolopiridilo, imidazopiridilo, isoquinolinilo, benzoazaindolilo, 1,2,4-triazinilo, y benzotiazolilo.

"Heteroarilalquilo" significa un grupo heteroarilo, tal como se de definió anteriormente, unido a un grupo alquilo, tal lo definido anteriormente, donde el enlace a la porción madre es a través del grupo alquilo.

Los N-óxidos pueden formar sobre un nitrógeno terciario presente en un sustituyente R, o sobre =N- en un sustituyente de anillo heteroarilo y están incluidos en los compuestos de fórmula I.

El término "pro-droga", tal como se utiliza en la presente, representa los compuestos que son rápidamente transformados *in vivo* al compuesto madre de la fórmula anterior, por ejemplo, por hidrólisis en sangre. Una descripción completa se provee en T. Higuchi & V. Stella, Prodrugs as Novel Delivery Systems, Vol. 14 del A.C.S. Symposium Series, y en Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, los cuales son incorporados a la presente como referencia.

Tal como se utiliza en la presente, el término "composición" abarca un producto que comprende los ingredientes especificados en las cantidades especificadas, como también cualquier producto que resulta, directa o indirectamente de la combinación de los ingredientes especificados en las cantidades especificadas.

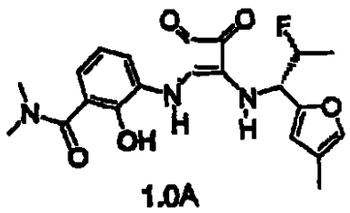
Tal como se lo utiliza en los métodos de la presente invención, "una cantidad efectiva" significa una cantidad terapéuticamente aceptable (es decir, esa cantidad que provee el efecto terapéutico deseado).

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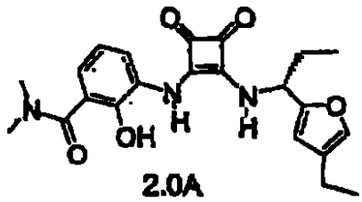
Además, tal como se utiliza en la presente, con referencia a las estructuras o fórmulas químicas, "Bn" representa bencilo, "Et" representa "etilo", "Me" representa metilo, y "Ph" representa fenilo.

Las realizaciones representativas de la presente invención se describen a continuación. Las realizaciones han sido numeradas a los fines de referencia a las mismas.

Compuestos de las fórmulas 1.0A, 2.0A, 3.0A, 4.0A, 5.0A y 6.0A son:

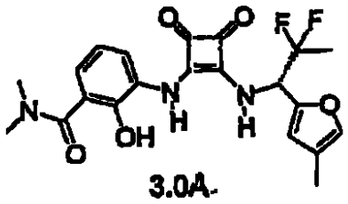


1.0A

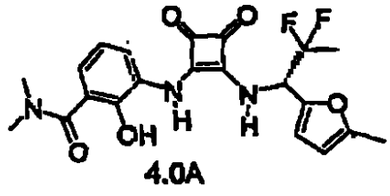


2.0A

(Ejemplo 360.110)

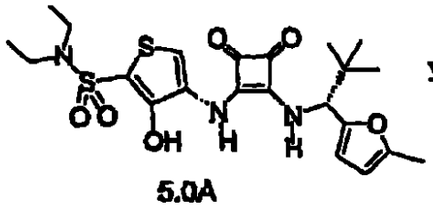


3.0A



4.0A

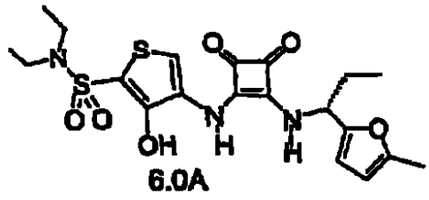
(Ejemplo 1207)



5.0A

(Ejemplo 2050)

y

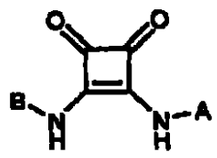


6.0A

(Ejemplo 2047)

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Para los métodos de tratamiento que utilizan los compuestos de fórmula IA, tal lo descripto anteriormente, dichos compuestos de fórmula IA son:



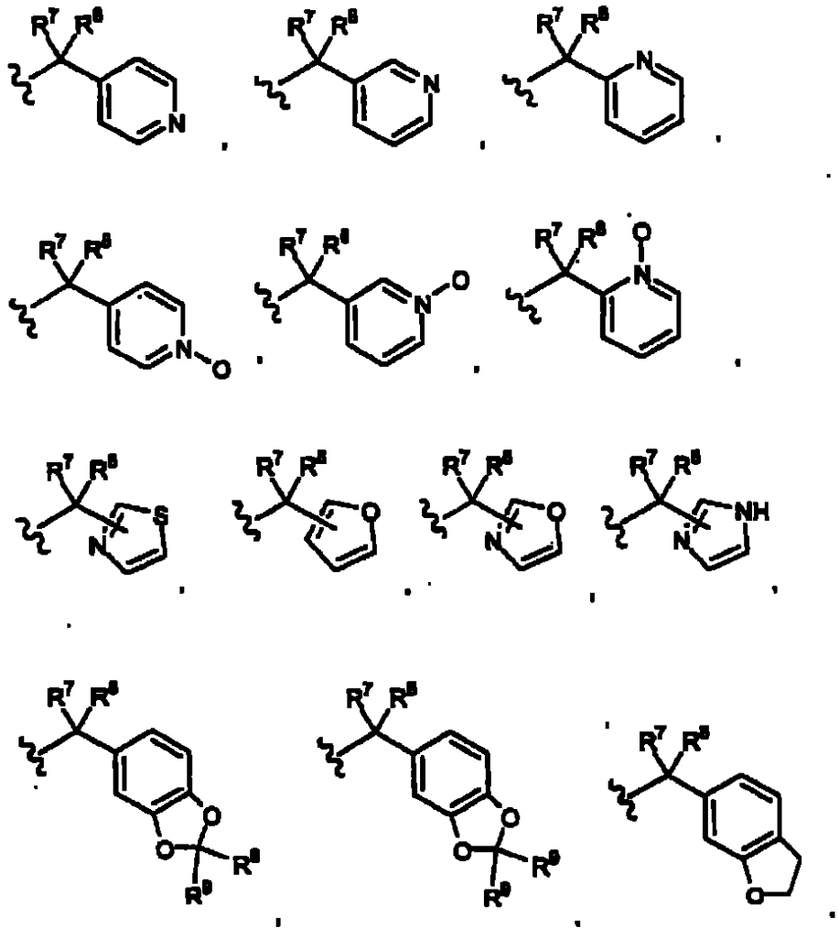
(IA)

y las sales farmacéuticamente aceptables (por ejemplo sal de sodio o calcio) y solvatos de los mismos, donde:

A está seleccionado del grupo que consiste de:

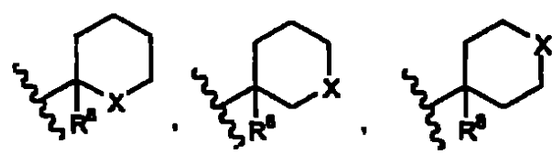
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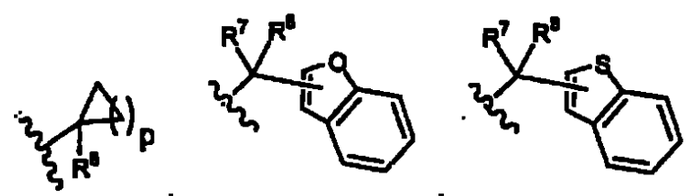
(1)

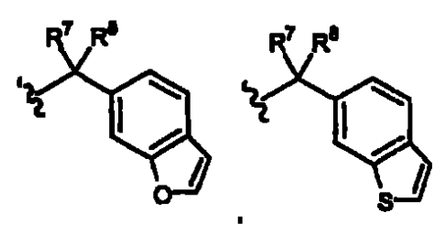


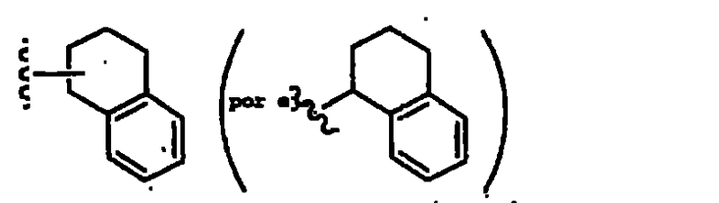
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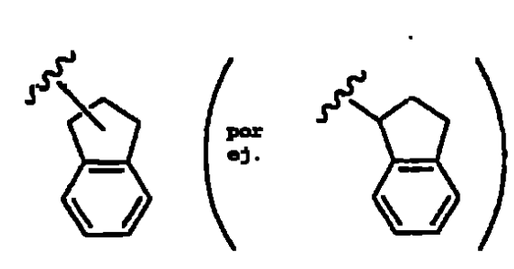




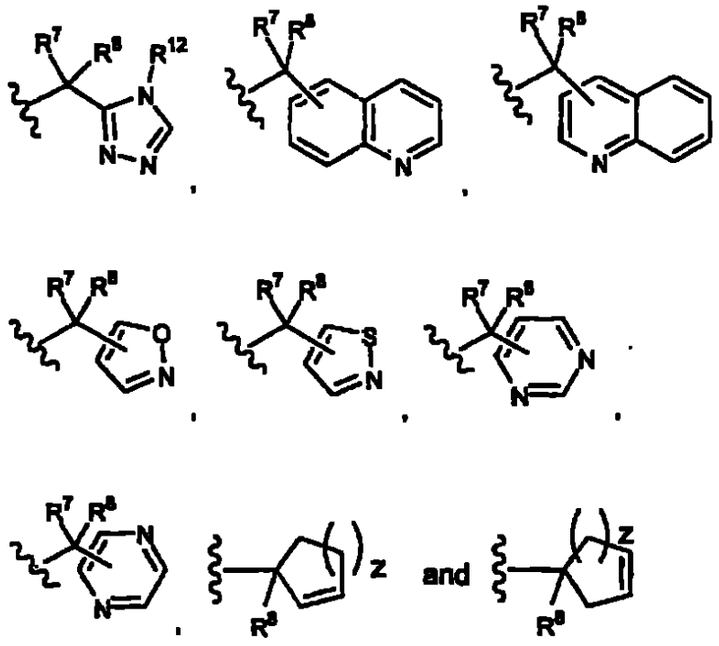




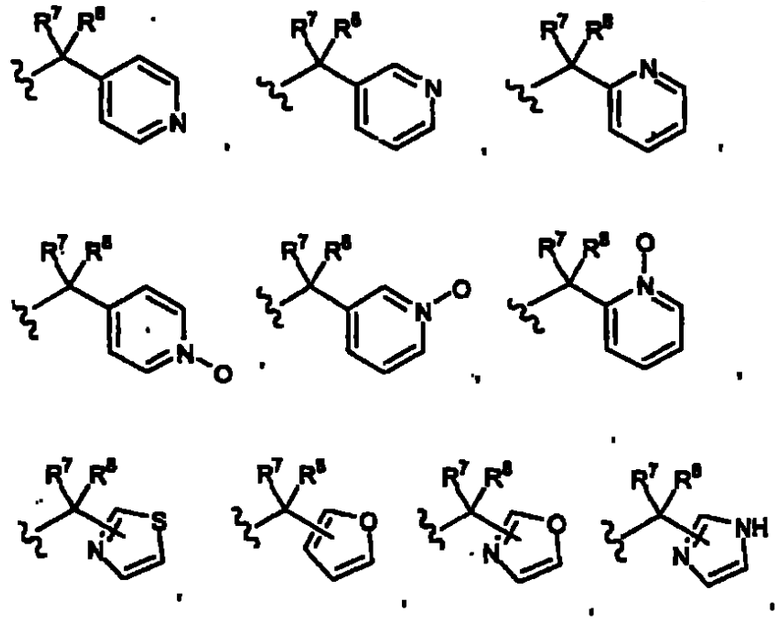




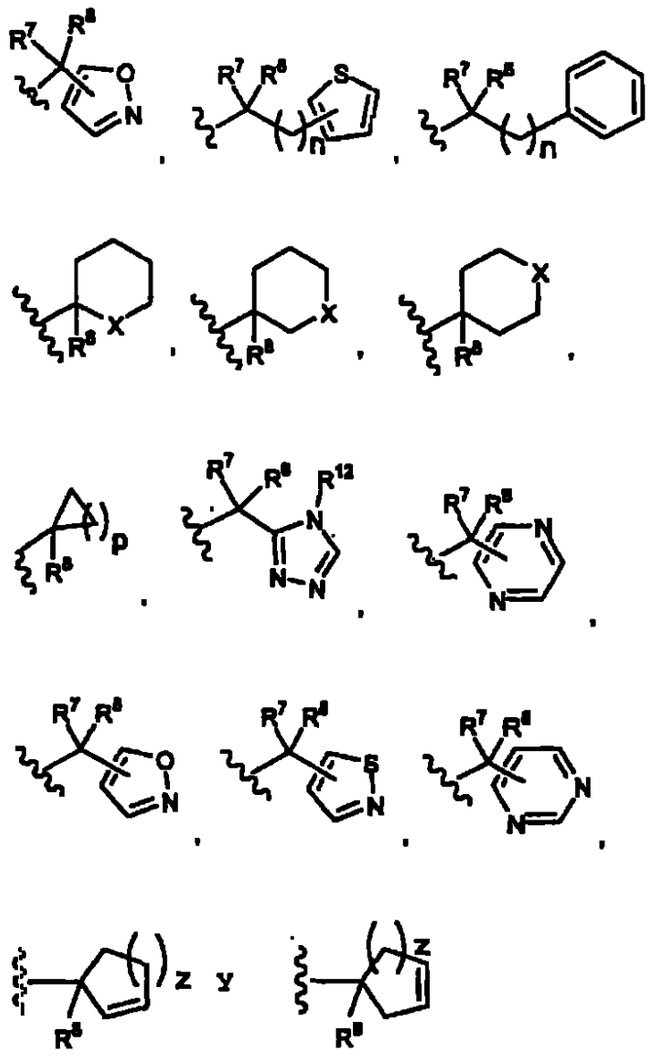
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(2)



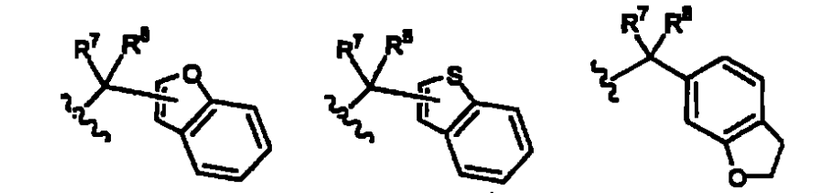
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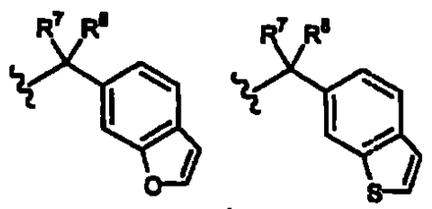


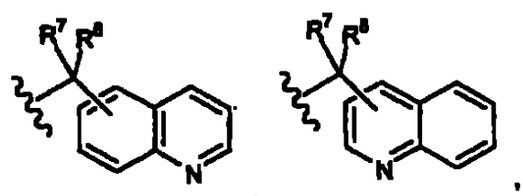
en donde los anillos anteriores de dichos grupos A están sustituidos con 1 a 6 sustituyentes cada uno independientemente seleccionado del grupo que consiste de: grupos R^6;

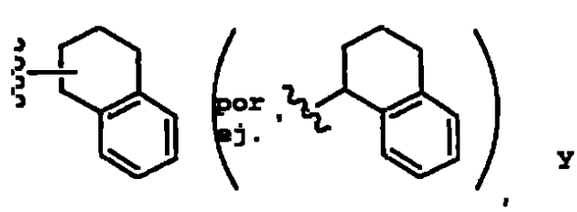
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(3)

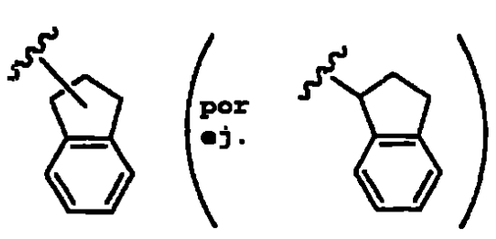








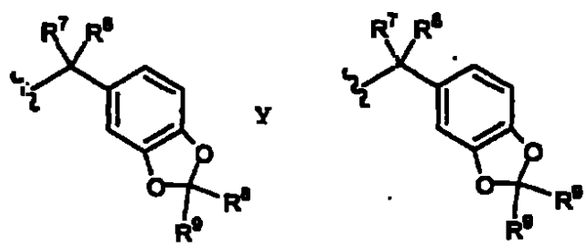
y



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en donde uno o ambos de los anillos anteriores de dichos grupos A están sustituidos con 1 a 6 sustituyentes cada uno independientemente seleccionado del grupo que consiste de: grupos R^9;

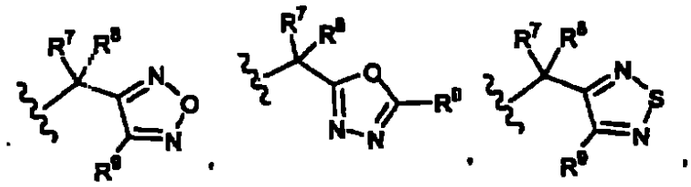
(4)

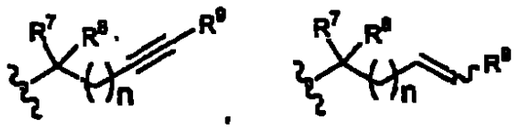


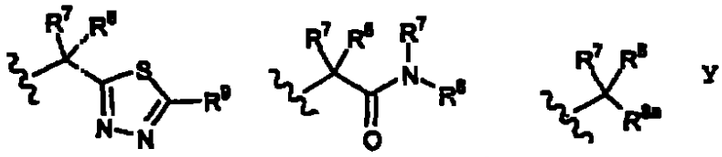
en donde los anillos fenilo anteriores de dichos grupos A están sustituidos con 1 a 3 sustituyentes cada uno independientemente seleccionado del grupo que consiste de: grupos R^9; y

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(5)

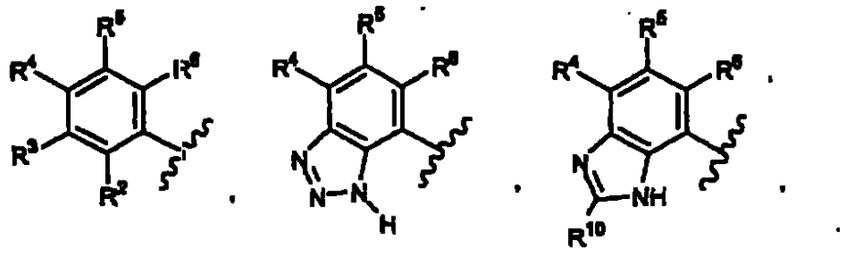


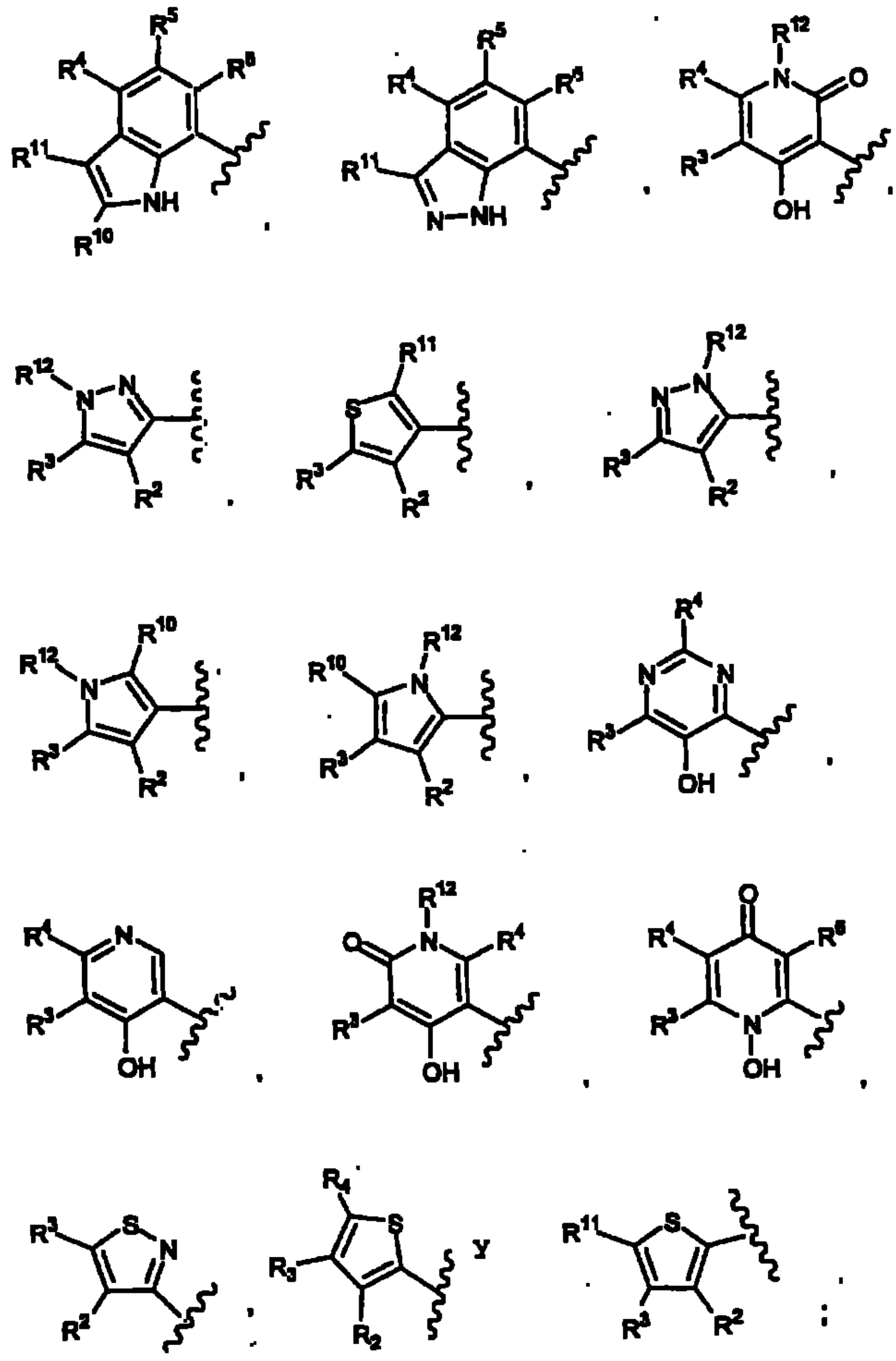






B está seleccionado del grupo que consiste de:





n es 0 a 6;

p es 1 a 5;

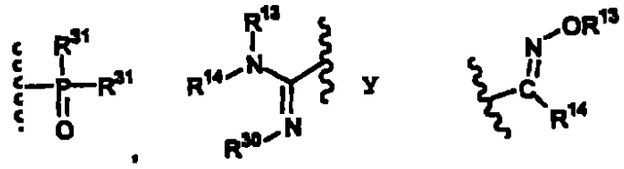
X es O, NH, o S;

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Z es 1 a 3;

R^2 está seleccionado del grupo que consiste de: hidrógeno, OH, -C(O)OH, -SH, $-SO_2NR^{13}R^{14}$, $-NHC(O)R^{13}$, $-NHSO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, $-NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, $-C(O)NHOR^{13}$, $-C(O)NR^{13}OH$, $-S(O_2)OH$, $-OC(OR^{13}$, un grupo funcional ácido heterocíclico no sustituido, y un grupo funcional ácido heterocíclico sustituido, en donde hay 1 a 6 sustituyentes sobre dicho grupo funcional ácido heterocíclico sustituido, cada sustituyente está independientemente seleccionado del grupo que consiste de: grupos R^9;

cada R^3 y R^4 es independientemente seleccionado del grupo que consiste de: hidrógeno, ciano, halógeno, alquilo, alcoxi, -OH, $-CF_3$, $-OCF_3$, $-NO_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NHR^{17}$, $-C(O)NR^{13}R^{14}$, $-SO_{(t)}NR^{13}R^{14}$, $-SO_{(t)}R^{13}$, $-C(O)NR^{13}OR^{14}$, arilo no sustituido o sustituido, heteroarilo no sustituido o sustituido,



donde hay 1 a 6 sustituyentes en dicho grupo arilo sustituido y cada sustituyente es independientemente seleccionado del grupo que consiste de: grupos R^9; y en donde hay 1 a 6 sustituyentes en dicho grupo heteroarilo sustituido y cada sustituyente es independientemente seleccionado del grupo que consiste de: grupos R^9;

cada R^5 y R^6 son iguales o diferentes y son independientemente seleccionados del grupo que consiste de hidrógeno, halógeno, alquilo, alcoxi, $-CF_3$, $-OCF_3$, $-NO_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-SO_{(t)}NR^{13}R^{14}$, $-C(O)NR^{13}OR^{14}$, ciano, arilo sustituido o no sustituido, y grupo heteroarilo no

sustituido o sustituido; donde hay 1 a 6 sustituyentes en dicho grupo arilo sustituido y cada sustituyente es independientemente seleccionado del grupo que consiste de: grupos R^9; y donde hay 1 a 6 sustituyentes en dicho grupo heteroarilo sustituido y cada sustituyentes es independientemente seleccionado del grupo que consiste de: grupos R^9;

cada R^7 y R^8 es independientemente seleccionado del grupo que consiste de. H, alquilo no sustituido o sustituido, arilo no sustituido o sustituido, heteroarilo no sustituido o sustituido, arilalquilo no sustituido o sustituido, heteroarilalquilo no sustituido o sustituido, cicloalquilo no sustituido o sustituido, cicloalquilalquilo no sustituido o sustituido, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, alquinilo, alquenilo, y cicloalquenilo; y donde hay uno o más sustituyentes (por ejemplo 1 a 6) en dichos grupos R^7 y R^8, donde cada sustituyente es independientemente seleccionado del grupo que consiste de:

a) halógeno,

b) $-CF_3$,

c) $-COR^{13}$,

d) $-OR^{13}$,

e) $-NR^{13}R^{14}$,

f) NO_2,

g) –CN,

h) $-SO_2OR^{13}$,

i) –Si(alquilo)$_3$, donde cada alquilo es independientemente seleccionado,

j) –Si(arilo)$_3$, donde cada alquilo es independientemente seleccionado,

k) $-(R^{13})_2R^{14}Si$, donde cada R^{13} es independientemente seleccionado,

l) $-CO_2R^{13}$,

m) $-C(O)NR^{13}R^{14}$,

n) $-SO_2NR^{13}R^{14}$,

o) $-SO_2R^{13}$,

p) $-OC(O)R^{13}$,

q) $-OC(O)NR^{13}R^{14}$,

r) $-NR^{13}C(O)R^{14}$, y

s) $-NR^{13}CO_2R^{14}$;

(fluoralquilo es un ejemplo no limitante de un grupo alquilo que está sustituido con halógeno);

R^{8a} es seleccionado del grupo que consiste de: hidrógeno, alquilo, ciclcoalquilo y cicloalquilalquilo;

cada R^8 es independientemente seleccionado del grupo que consiste de:

a) $-R^{13}$,

b) halógeno,

c) $-CF_3$,

d) $-COR^{13}$,

e) $-OR^{13}$,

f) $-NR^{13}R^{14}$,

g) $-NO_2$,

h) $-CN$,

i) $-SO_2R^{13}$,

j) $-SO_2NR^{13}R^{14}$,

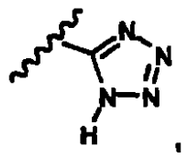
k) $-NR^{13}COR^{14}$,

l) $-CONR^{13}R^{14}$,

m) $-NR^{13}CO_2R^{14}$,

n) $-CO_2R^{13}$,

o)



p) alquilo sustituido con uno o más o más (por ejemplo uno) grupos –OH (por ejemplo, -$(CH_2)_qOH$, donde q es 1-6, usualmente 1 a 2, y preferentemente 1),

q) alquilo sustituido con uno o más (por ejemplo uno) grupo –$NR^{13}R^{14}$ (por ejemplo –$(CH_2)_qNR^{13}R^{14}$, donde q es 1-6, usualmente 1 a 2, y preferentemente 1), y

r) –$N(R^{13})SO_2R^{14}$ (por ejemplo R^{13} es H y R^{14} es alquilo, tal como metilo;

cada R^{10} y R^{11} es independientemente seleccionado a partir del grupo que consiste de R^{13}, hidrógeno, alquilo (por ejemplo C_1 a C_6, tal como metilo), halógeno, -CF_3, -OCF_3, -$NR^{13}R^{14}$, -$NR^{13}C(O)NR^{13}R^{14}$, -OH, -$C(O)OR^{13}$, -SH, -$SO_{(t)}NR^{13}R^{14}$, -SO_2R^{13}, -$NHC(O)R^{13}$, -$NHSO_2NR^{13}R^{14}$, -$NHSO_2R^{13}$, -$C(O)NR^{13}R^{14}$, -$C(O)NR^{13}OR^{14}$, -$OC(O)R^{13}$ y ciano;

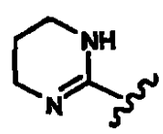
R^{12} es seleccionado del grupo que consiste de : hidrógeno, -$C(O)OR^{13}$, grupo arilo no sustituido o sustituido, heteroarilo no sustituido o sustituido, arilalquilo no sustituido o sustituido, cicloalquilo no sustituido o sustituido, alquilo no sustituido o sustituido, cicloalquilalquilo no sustituido o sustituido, y heteroarilalquilo no sustituido o sustituido; donde hay 1 a 6 sustituyentes en los grupos R^{12} sustituido y cada sustituyente es independientemente seleccionado del grupo que consiste de: grupos R^9;

cada R^{13} y R^{14} es independientemente seleccionado del grupo que consiste de: H, alquilo no sustituido o sustituido, arilo no sustituido o sustituido, heteroarilo no sustituido o sustituido, arilalquilo no sustituido o sustituido, heteroarilalquilo no sustituido o sustituido, cicloalquilo no sustituido o sustituido, cicloalquilalquilo no sustituido o sustituido, heterocíclico no sustituido o sustituido, fluoralquilo no

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sustituido o sustituido, heterocicloalquilalquilo no sustituido o sustituido (donde "heterocicloalquilo" significa heterocíclico); donde hay 1 a 6 sustituyentes en dichos grupos R^{13} y R^{14} sustituidos y cada sustituyente es independientemente seleccionado del grupo que consiste de: alquilo, $-CF_3$, -OH, alcoxi, arilo, arilalquilo, fluoralquilo, ciclcoalquilo, cicloalquilalquilo, heteroarilo, heteroarilalquilo, $-N(R^{40})_2$, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-S(O)_tNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ siempre que R^{15} no sea H, halógeno y $-NHC(O)NR^{15}R^{16}$; o

R^{13} y R^{14} tomados juntos con el nitrógeno al cual están unidos en los grupos $-C(O)NR^{13}R^{14}$ y $-SO_2NR^{13}R^{14}$ forman un anillo heterocíclico saturado no sustituido o sustituido (preferentemente un anillo heterocíclico de 3 a 7 miembros), dicho anillo opcionalmente contiene un heteroátomo adicional seleccionado del grupo que consiste de: O, S y NR^{18}; en donde hay 1 a 3 sustituyentes en los grupos R^{13} y R^{14} ciclados sustituidos (es decir hay 1 a 3 sustituyentes en el anillo formado cuando los grupos R^{13} y R^{14} son tomados juntos con el nitrógeno al cual están unidos) y cada sustituyente es independientemente seleccionado del grupo que consiste de: alquilo, arilo, hidroxi, hidroxialquilo, alcoxi, alcoxialquilo, arilalquilo, fluoralquilo, cicloalquilo, cicloalquilalquilo, heteroarilo, heteroarilalquilo, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-SO_tNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ siempre que R^{15} no sea H, $-NHC(O)NR^{15}R^{16}$, $NHC(O)OR^{15}$, halógeno, y un grupo heterocicloalquenilo (es decir un grupo heterocíclico que tiene al menos uno y preferentemente un enlace doble en un anillo, por ejemplo,



;

cada R^{15} y R^{16} es independientemente seleccionado a partir del grupo que

consiste de: H, alquilo, arilo, arilalquilo, cicloalquilo y heteroarilo;

R^{17} es seleccionado a partir del grupo que consiste de: -SO_2alquilo, -SO_2arilo, -SO_2cicloalquilo, y –SO_2heteroarilo;

R^{18} es seleccionado del grupo que consiste de: H, alquilo arilo, heteroarilo, -C(O)R^{19}, -SO_2R^{19} y –C(O)$NR^{19}R^{20}$;

cada R^{19} y R^{20} es independientemente seleccionado del grupo que consiste de: alquilo, arilo y heteroarilo;

R^{30} es seleccionado del grupo que consiste de: alquilo, cicloalquilo, -CN, -NO_2, o –SO_2R^{15} siempre que R^{15} no sea H;

cada R^{31} es independientemente seleccionado del grupo que consiste de: alquilo no sustituido o sustituido, arilo no sustituido o sustituido, heteroarilo no sustituido o sustituido y cicloalquilo no sustituido o sustituido, en donde hay 1 a 6 sustituyentes en dichos grupos R^{31} sustituidos y cada sustituyente es independientemente seleccionado del grupo que consiste de: alquilo, halógeno y –CF_3;

cada R^{40} es independientemente seleccionado del grupo que consiste de: H, alquilo y cicloalquilo; y

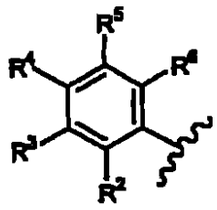
t es 0, 1 o 2.

Las realizaciones de los métodos de tratamiento que utilizan los compuestos de fórmula IA, tal lo descripto anteriormente se describen a continuación. Las realizaciones han sido numeradas a los fines de referencia al mismo.

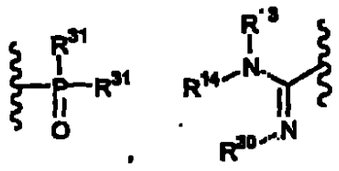
La realización 1 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es seleccionado del grupo que consiste de:

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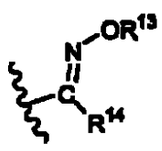
(1)



siempre que R^3 para este grupo sea seleccionado del grupo que consiste de: $-C(O)NR^{13}R^{14}$,

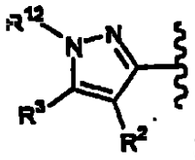


y



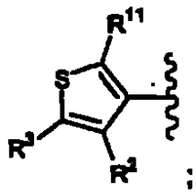
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(2)



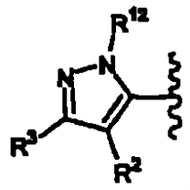
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(3)



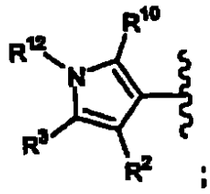
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(4)



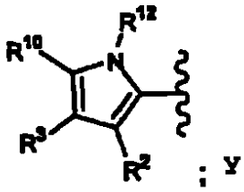
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(5)



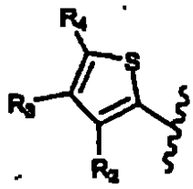
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(6)



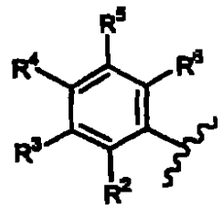
; y

(7)

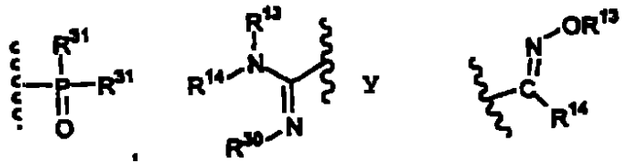


donde los sustituyentes son tal lo definido para los compuestos nuevos de fórmula IA.

La realización No.2 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es:

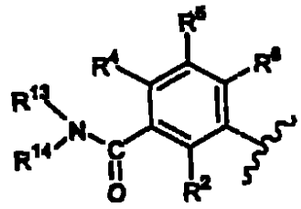


donde R^3 es seleccionado del grupo que consiste de: $-C(O)NR^{13}R^{14}$,



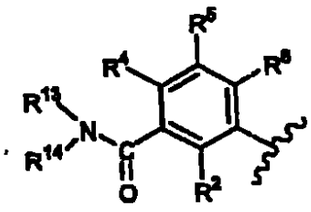
y todos los otros sustituyentes son tal lo definido en la fórmula IA.

La realización No. 3 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es:



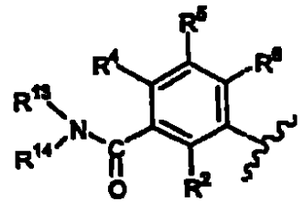
y todos los otros sustituyentes son tal lo definido en la fórmula IA.

La realización No. 4 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es:



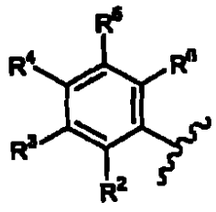
R^{13} y R^{14} son cada uno el mismo o diferente grupo alquilo, y todos los otros sustituyentes son tal lo definido en la fórmula IA.

La realización No. 5 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es:



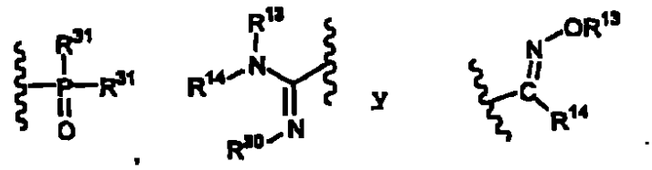
y (1) R^2 es –OH, y todos los otros sustituyentes son tal lo definido en la fórmula IA, o (2) R^2 es –OH, y R^{13} y R^{14} son cada uno el mismo o diferente grupo alquilo, y todos los otros sustituyentes son tal lo definido en la fórmula IA.

La realización No. 6 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es:



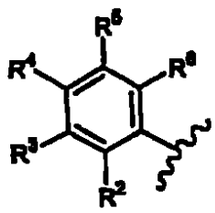
R^3 está seleccionado del grupo que consiste de:

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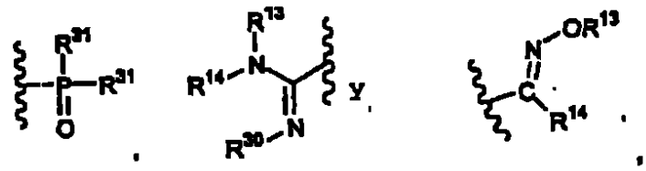


y todos los sustituyentes son tal lo definido en la fórmula IA.

La realización No. 7 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es:

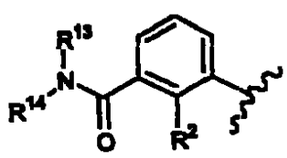


R^3 está seleccionado del grupo que consiste de:



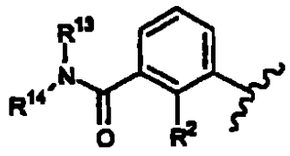
R^2 es –OH, y todos los otros sustituyentes son tal lo definido en la fórmula IA.

La realización No. 8 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es:



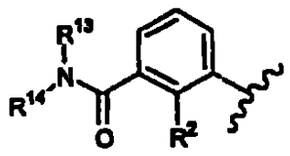
R^2, R^{13}, y R^{14} son tal lo definido para los compuestos de fórmula IA, y todos los sustituyentes son tal lo definido en la fórmula IA.

La realización No. 9 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es:



R^2 es –OH, R^{13} y R^{14} son tal lo definido para los compuestos de la fórmula y todos los otros sustituyentes son tal lo definido en la fórmula IA.

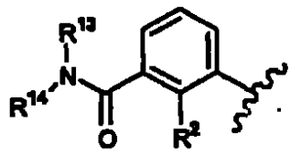
La realización No. 10 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es:



R^2 es tal lo definido para los compuestos de fórmula IA, R^{13} y R^{14} son el mismo o diferente grupo alquilo, y todas las otras áreas sustituyentes definidas para los compuestos de fórmula IA.

La realización No. 11 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es:

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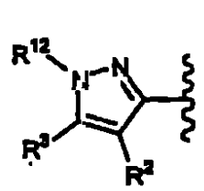
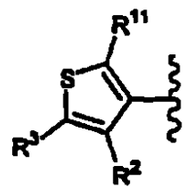
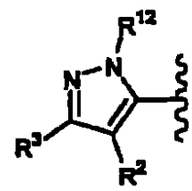
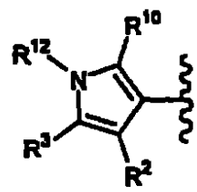
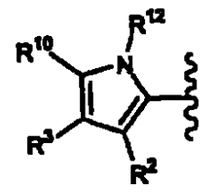
R^2 es –OH, R^{13} y R^{14} son el mismo o diferente grupo alquilo, y todas las otras áreas sustituyentes definidas para los compuestos de fórmula IA.

La realización No. 12 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es tal lo descripto en la Realización No. 6, R^4 es H, R^5 es H, R^6 es H, y todas las otras áreas sustituyentes definidas para los compuestos de fórmula IA.

La realización No. 13 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es tal lo descripto en la Realización No. 7, R^4 es H, R^5 es H, R^6 es H, y todas las otras áreas sustituyentes definidas para los compuestos de fórmula IA.

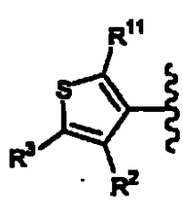
La realización No. 14 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es tal lo descripto en las realizaciones Nos. 4, 5, 8 y 9 salvo que R^{13} y R^{14} son cada uno metilo, y todos los otros sustituyentes son tal lo definido en la fórmula IA.

La realización No. 15 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es seleccionado del grupo que consiste de:





y


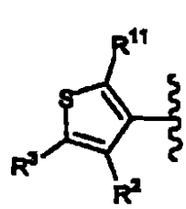
donde los sustituyentes son tal lo definido en la fórmula IA.

La realización No. 16 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es



donde los sustituyentes son tal lo definido en la fórmula IA.

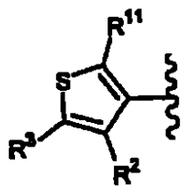
La realización No. 17 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es



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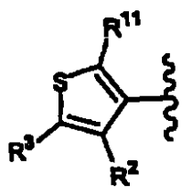
R^{11} es H, y todos los otros sustituyentes son tal lo definido en la fórmula IA.

La realización No. 18 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es:



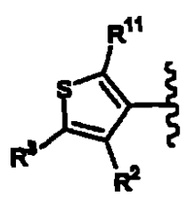
R^2 es –OH, y todos los otros sustituyentes son tal lo definido en la fórmula IA.

La realización No. 19 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es



R^3 es $-C(O)NR^{13}R^{14}$, y todos los otros sustituyentes son tal lo definido en la fórmula IA.

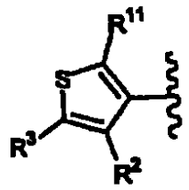
La realización No. 20 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es



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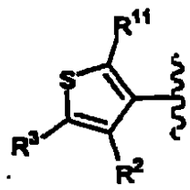
R^3 es $-S(O)_tNR^{13}R^{14}$ (por ejemplo t es 2), y todos los otros sustituyentes son tal lo definido en la fórmula IA.

La realización No. 21 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es



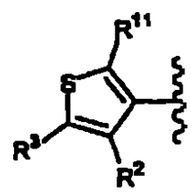
R^2 es –OH, R^3 es $-C(O)NR^{13}R^{14}$, y todos los otros sustituyentes son tal lo definido en la fórmula IA.

La realización No. 22 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es



R^2 es –OH, y R^3 es $-S(O)_tNR^{13}R^{14}$ (por ejemplo t es 2), y todos los otros sustituyentes son tal lo definido en la fórmula IA.

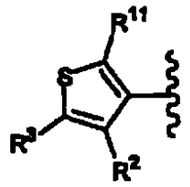
La realización No. 23 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es



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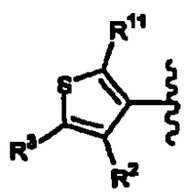
R^2 es –OH, R^3 es $-C(O)NR^{13}R^{14}$, R^{11} es H, y todos los otros sustituyentes son tal lo definido en la fórmula IA.

La realización No. 24 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es



R^3 es $-S(O)_tNR^{13}R^{14}$ (por ejemplo t es 2), cada R^{13} y R^{14} son iguales o diferentes y están seleccionados del grupo que consiste de: H y alquilo (por ejemplo metilo, etilo, isopropilo, y t-butilo). En esta realización, cada R^{13} y R^{14} son seleccionados en general del grupo que consiste de: H y etilo, y preferentemente R^{13} y R^{14} son etilo, y todos los otros sustituyentes son tal lo definido en la fórmula IA.

La realización No. 25 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es

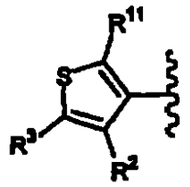


R^3 es $-S(O)_tNR^{13}R^{14}$ (por ejemplo t es 2), R^{11} es H, y cada R^{13} y R^{14} son iguales o diferentes y están seleccionados del grupo que consiste de: H y alquilo

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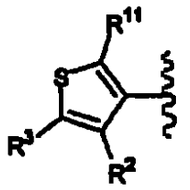
(por ejemplo metilo, etilo, isopropilo, y t-butilo). En esta realización, cada R^{13} y R^{14} son seleccionados en general del grupo .que consiste de: H y etilo, y preferentemente R^{13} y R^{14} son etilo, y todos los sustituyentes son tal lo definido en la fórmula IA.

La realización No. 26 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es



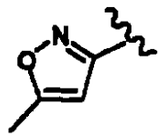
R^2 es –OH, y R^3 es $-S(O)_tNR^{13}R^{14}$ (por ejemplo t es 2), R^{11} es H, y todos los otros sustituyentes son tal lo definido en la fórmula IA.

La realización No. 27 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es

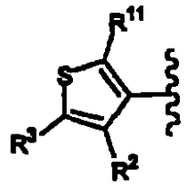


R^2 es –OH, R^3 es $-C(O)NR^{13}R^{14}$, R^{11} es H, y R^{13} y R^{14} son independientemente seleccionados del grupo que consiste de: alquilo, heteroarilo no sustituido y heteroarilo sustituido, y todos los otros sustituyentes son tal lo definido en la fórmula IA. En general, uno de R^{13} o R^{14} es alquilo (por ejemplo metilo). Un ejemplo de un grupo heteroarilo sustituido es

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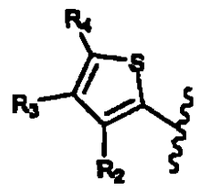


La realización No. 28 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es



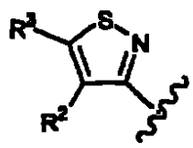
R^2 es –OH, y R^3 es $-S(O)_tNR^{13}R^{14}$ (por ejemplo t es 2), R^{11} es H, y cada R^{13} y R^{14} son iguales y diferentes y están seleccionados del grupo que consiste de: H y alquilo (por ejemplo, metilo, etilo, isopropilo y t-butilo), y todos los otros sustituyentes son tal lo definido en la fórmula IA. En esta realización, cada R^{13} y R^{14} son en general seleccionados del grupo que consiste de: H y etilo, y preferentemente R^{13} y R^{14} son etilo.

La realización No. 29 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es



y todos los sustituyentes son tal lo definido en la fórmula IA.

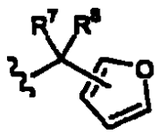
La realización No. 30 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es



y todos los sustituyentes son tal lo definido en la fórmula IA.

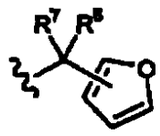
La realización No. 31 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es tal lo descripto en cualquiera de las realizaciones 1 a 30, y A es tal lo descripto en cualquiera de las realizaciones Nos. 39 – 44 descriptas a continuación.

La realización No. 32 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es tal lo descripto en cualquiera de las realizaciones 1 a 30, y A es



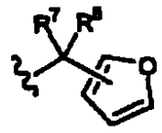
en donde el anillo de furano es no sustituido o sustituido tal lo descripto en la definición de A para la fórmula IA, y todos los otros sustituyentes son tal lo definido en la fórmula IA

La realización No. 33 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es tal lo descripto en cualquiera de las realizaciones 1 a 30, y A es



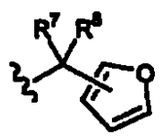
en donde el anillo de furano es sustituido y todos los otros sustituyentes son tal lo definido en la fórmula IA.

La realización No. 34 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es tal lo descripto en cualquiera de las realizaciones 1 a 30, y A es



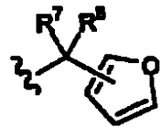
en donde el anillo de furano es sustituido con al menos un (por ejemplo 1 a 3, o 1 a 2) grupo alquilo y todos los otros sustituyentes son tal lo definido en la fórmula IA.

La realización No. 35 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es tal lo descripto en cualquiera de las realizaciones 1 a 30, y A es



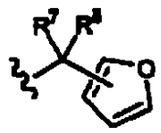
en donde el anillo de furano es sustituido con un grupo alquilo y todos los sustituyentes son tal lo definido en la fórmula IA.

La realización No. 36 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es tal lo descripto en cualquiera de las realizaciones 1 a 30, y A es



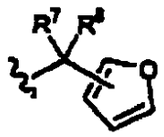
en donde el anillo de furano es sustituido con un grupo alquilo C_1 a C_3 (por ejemplo metilo o isopropilo), y todos los otros sustituyentes son tal lo definido en la fórmula IA.

La realización No. 37 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es tal lo descripto en cualquiera de las realizaciones 1 a 30, y A es



tal lo definido en cualquiera de las realizaciones Nos. 32 a 36, salvo que R^7 y R^8 son iguales o diferentes y cada uno es seleccionado del grupo que consiste de: H y alquilo.

La realización No. 38 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es tal lo descripto en cualquiera de las realizaciones 1 a 30, y A es

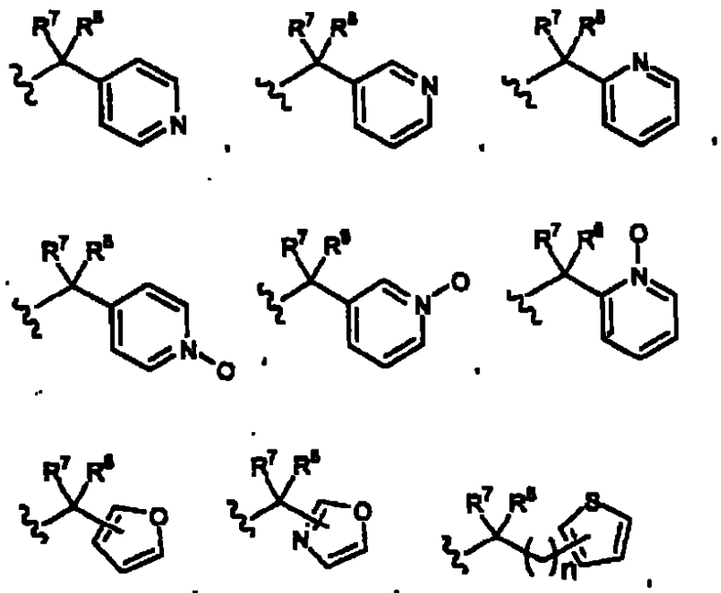


tal lo definido en cualquiera de las realizaciones Nos. 32 a 36, salvo que R^7 es H, y R^8 es alquilo (por ejemplo etilo o t-butilo).

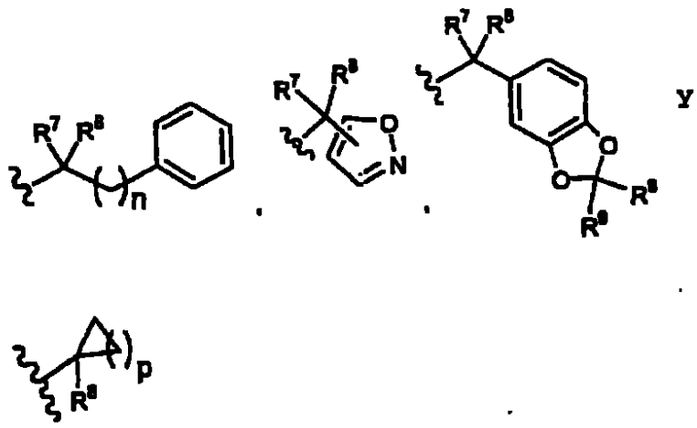
La realización No. 39 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde

(1) el sustituyente A en la fórmula IA es seleccionado preferentemente del grupo que consiste de:

(a)



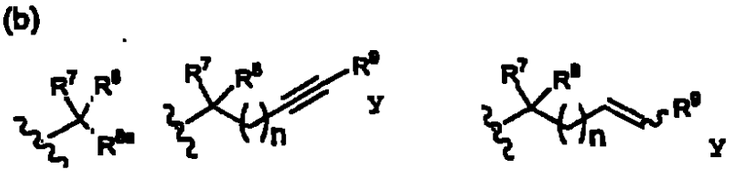
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en donde los anillos anteriores son no sustituidos o sustituidos, tal lo descripto para la fórmula IA:

y

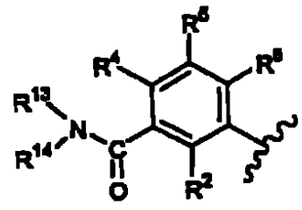
(b)

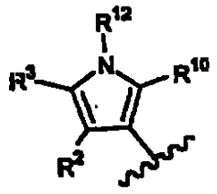


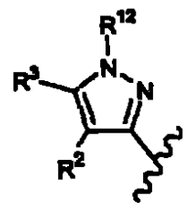
en donde en (a) y (b) anteriores: cada R^7 y R^8 es seleccionado independientemente del grupo que consiste de: H, alquilo no sustituido o sustituido, arilo no sustituido o sustituido, heteroarilo no sustituido o sustituido, arilalquilo no sustituido o sustituido, heteroarilalquilo no sustituido o sustituido, cicloalquilo no sustituido o sustituido, cicloalquilalquilo no sustituido o sustituido, -CO_2R^{13}, -$CONR^{13}R^{14}$, fluoralquilo, alquinilo, alquenilo, y cicloalquenilo, en donde dichos sustituyentes en dichos grupos R^7 y R^8 sustituidos son seleccionados del grupo que consiste de: a) ciano, b) –CO_2R^{13}, c) –$C(O)NR^{13}R^{14}$, d) –$SO_2NR^{13}R^{14}$, e) –NO_2, f) –CF_3, g) –OR^{13}, h) –$NR^{13}R^{14}$, i) –$OC(O)R^{13}$, j) –$OC(O)NR^{13}R^{14}$, y k) halógeno; y R^{8a} y R^9 son tal lo definido en la fórmula IA; y

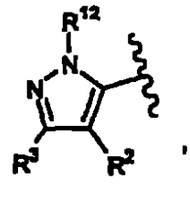
(2) el sustituyente B en la fórmula IA es preferentemente seleccionado del

grupo que consiste de:

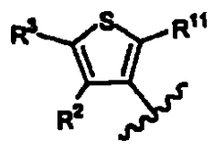








y

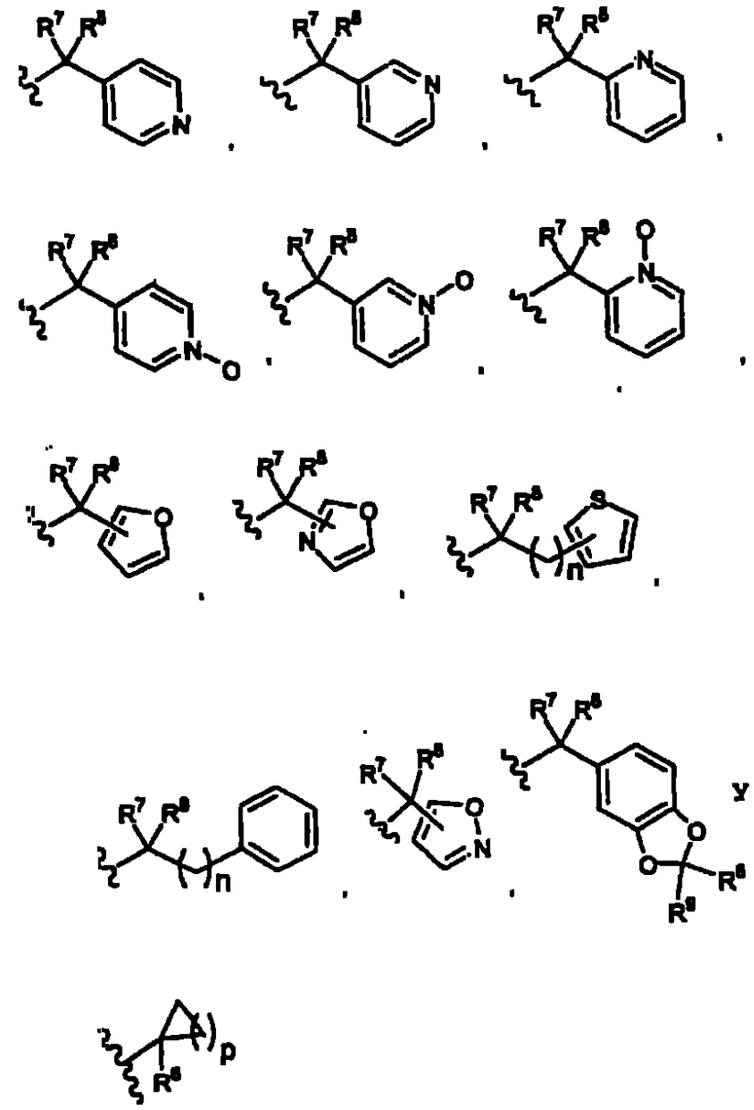


en donde R^2 a R^6 y R^{10} a R^{14} son tal lo definido anteriormente para los nuevos compuestos de la fórmula IA.

La realización No. 40 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde

(1) el sustituyente A en la fórmula IA es seleccionado preferentemente del grupo que consiste de:

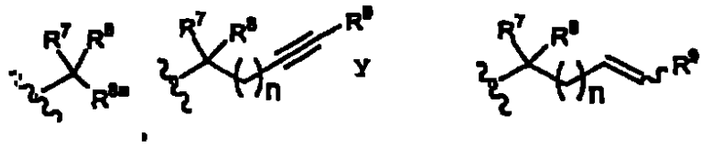
(a)



en donde los anillos anteriores son no sustituidos, o los anillos anteriores son sustituidos con 1 a 3 sustituyentes seleccionados del grupo que consiste de: halógeno, alquilo, cicloalquilo, $-CF_3$, ciano, $-OCH_3$, y $-NO_2$; cada R^7 y R^8 es seleccionado independientemente del grupo que consiste de: H, alquilo (por

ejemplo, metilo, etilo, t-butilo, e isopropilo), fluoralquilo (tal como, $-CF_3$ y $-CF_2CH_3$), cicloalquilo (por ejemplo ciclopropilo, y ciclohexilo), y cicloalquilalquilo (por ejemplo, ciclopropilmetilo); y R^9 es seleccionado del grupo que consiste de: H, halógeno, alquilo, cicloalquilo, $-CF_3$, ciano, $-OCH_3$, y $-NO_2$; y

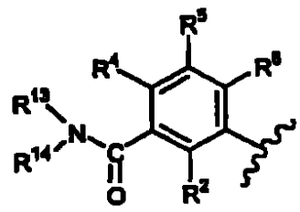
(b)

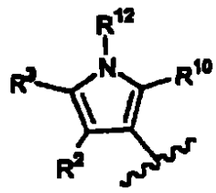


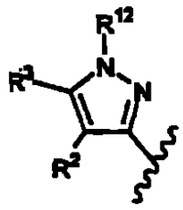
en donde cada R^7 y R^8 es independientemente seleccionado del grupo que consiste de: H, alquilo (por ejemplo metilo, etilo, t-butilo, e isopropilo), fluoralquilo (tal como, $-CF_3$ y $-CF_2CH_3$), cicloalquilo (por ejemplo, ciclopropilo, y ciclohexilo), y cicloalquilalquilo (por ejemplo, ciclopropilmetilo); en donde R^{8a} es tal lo definido en la fórmula IA, y en donde R^9 es seleccionado del grupo que consiste de: H, halógeno, alquilo, cicloalquilo, $-CF_3$, ciano, $-OCH_3$, y $-NO_2$; cada R^7 y R^8 es seleccionado independientemente del grupo que consiste de: H, alquilo (por ejemplo metilo, etilo, t-butilo, e isopropilo), fluoralquilo (tal como, $-CF_3$ y $-CF_2CH_3$), cicloalquilo (por ejemplo, ciclopropilo, y ciclohexilo), y cicloalquilalquilo (por ejemplo, ciclopropilmetilo); y

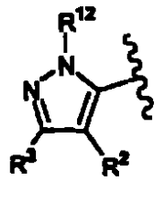
(2) el sustituyente B en la fórmula IA es seleccionado más preferentemente del grupo que consiste de:

189
190

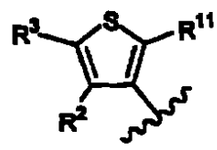








y



en donde

R^2 es seleccionado del grupo que consiste de: H, OH, -NHC(O)R^{13} y –$NHSO_2R^{13}$;

R^3 es seleccionado del grupo que consiste de: -$SO_2NR^{13}R^{14}$, -NO_2, ciano, -$C(O)NR^{13}R^{14}$, -SO_2R^{13}, y –$C(O)OR^{13}$;

R^4 es seleccionado del grupo que consiste de: H, -NO_2, ciano, -CH_3, halógeno, y –CF_3;

R^5 es seleccionado del grupo que consiste de: H, -CF_3, -NO_2,halógeno y ciano;

R^6 es seleccionado del grupo que consiste de: H, alquilo, y -CF_3;

cada R^{10} y R^{11} es independientemente seleccionado del grupo que consiste de: R^{13}, hidrógeno, halógeno, -CF_3, -$NR^{13}R^{14}$, $NR^{13}C(O)NR^{13}R^{14}$, -$C(O)OR^{13}$, -SH, -$SO_{(t)}NR^{13}R^{14}$, -SO_2R^{13}, -NHC(O)R^{13}, -$NHSO_2NR^{13}R^{14}$, -$NHSO_2R^{13}$, -$C(O)NR^{13}R^{14}$,

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$-C(O)NR^{13}OR^{14}$, $-OC(O)R^{13}$, $-COR^{13}$, y ciano;

cada R^{13} y R^{14} es seleccionado independientemente del grupo que consiste de: H, metilo, etilo, isopropilo y t-butilo; o

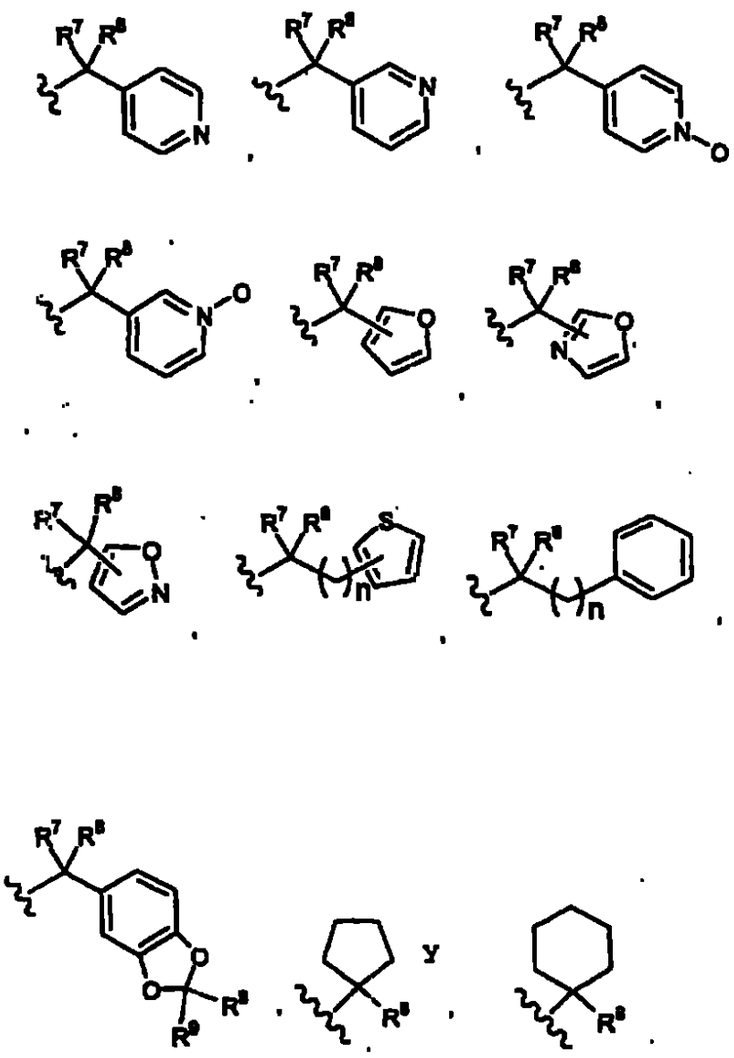
R^{13} y R^{14} cuando se toman juntos con el nitrógeno al cual están unidos en los grupos $-C(O)NR^{13}R^{14}$ y $-SO_2NR^{13}R^{14}$ forman un anillo heterocíclico saturado no sustituido o sustituido (preferentemente un anillo de 3 a 7 miembros) que tiene opcionalmente un heteroátomo adicional seleccionado del grupo que consiste de: O, S o NR^{18}; en donde R^{18} es seleccionado del grupo que consiste de: H, alquilo, arilo, heteroarilo, $-C(O)R^{19}$, $-SO_2R^{19}$ y $-C(O)NR^{19}R^{20}$, donde cada R^{19} y R^{20} es seleccionado independientemente del grupo que consiste de: alquilo, arilo y heteroarilo; en donde hay 1 a 3 sustituyentes en los grupos R^{13}y R^{14} ciclados sustituidos (es decir los sustituyentes en el anillo formado cuando R^{13} y R^{14} son tomados juntos con el nitrógeno al cual están unidos) y cada sustituyente es independientemente seleccionado del grupo que consiste de: alquilo, arilo, hidroxi, hidroxialquilo, alcoxi, alcoxialquilo, arilalquilo, fluoralquilo, cicloalquilo, cicloalquil alquilo, heteroarilo, heteroarilalquilo, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-SO_tNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$, $-SO_2R^{15}$ siempre que R^{15} no sea H, $-NHC(O)NR^{15}R^{16}$ y halógeno; y en donde cada R^{15} y R^{16} es seleccionado independientemente del grupo que consiste de: H, alquilo, arilo, arilalquilo, cicloalquilo y heteroarilo.

La realización No. 41 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde

El sustituyente A en la fórmula IA es aún seleccionado más preferentemente del grupo que consiste de:

191
192

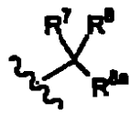
(a)



en donde los anillos anteriores son no sustituidos, o los anillos anteriores son sustituidos con 1 a 3 sustituyentes seleccionados independientemente del grupo que consiste de: H, F, Cl, Br, alquilo, cicloalquilo, y $-CF_3$; R^7 es seleccionado del grupo que consiste de: H, fluoralquilo, alquilo, y cicloalquilo; R^8 es seleccionado del grupo que consiste de: H, alquilo, $-CF_2CH_3$ y $-CF_3$; y R^9 es seleccionado del grupo que consiste de: H, F, Cl, Br, alquilo o $-CF_3$; y

198
193

(b)

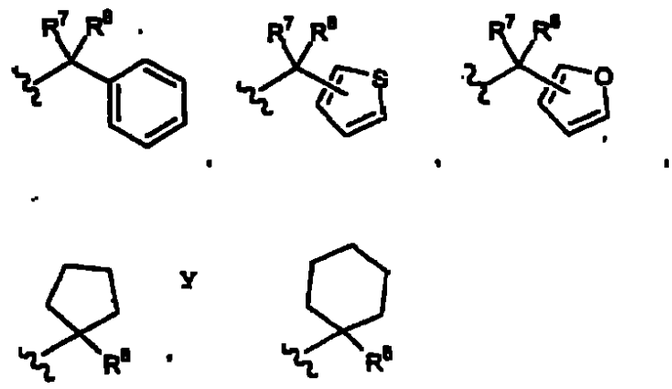


en donde R^7 es seleccionado del grupo que consiste de: H, fluoralquilo, alquilo y cicloalquilo; R^8 es seleccionado del grupo que consiste de: H, alquilo, CF_2CH_3 y $-CF_3$; y R^{8a} es tal lo definido para la fórmula IA.

La realización No. 42 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde:

(1) el sustituyente A en la fórmula IA es aún seleccionado más preferentemente del grupo que consiste de:

(a)



y

en donde los anillos anteriores son no sustituidos, o los anillos anteriores son sustituidos con 1 a 3 sustituyentes seleccionados independientemente del grupo que consiste de: H, F, Cl, Br, alquilo, cicloalquilo, y $-CF_3$; R^7 es seleccionado del grupo que consiste de: H, $-CF_3$, $-CF_2CH_3$, metilo, etilo, isopropilo, ciclopropilo y t-butilo; y R^8 es H; y

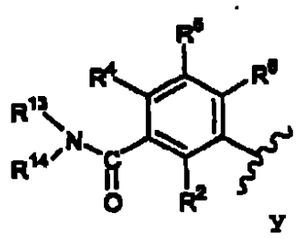
193
194

(b)

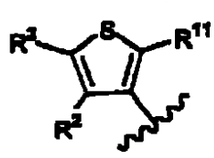


en donde R^7 es seleccionado del grupo que consiste de: H, $-CF_3$, $-CF_2CH_3$, metilo, etilo, isopropilo, ciclopropilo, y t-butilo; y R^8 es H; y R^{8a} es tal lo definido para la fórmula IA

(2) el sustituyente B en la fórmula IA es preferentemente seleccionado del grupo que consiste de:



y



en donde:

R^2 es seleccionado del grupo que consiste de: H, OH, $-NHC(O)R^{13}$ y $-NHSO_2R^{13}$;

R^3 es seleccionado del grupo que consiste de: $-C(O)NR^{13}R^{14}$, $-SO_2NR^{13}R^{14}$, $-NO_2$, ciano, $-SO_2R^{13}$, y $-C(O)OR^{13}$;

R^4 es seleccionado del grupo que consiste de: H, $-NO_2$, ciano, $-CH_3$, o $-CF_3$;

R^5 es seleccionado del grupo que consiste de: H, $-CF_3$, $-NO_2$,halógeno y ciano; y

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R^6 es seleccionado del grupo que consiste de: H, alquilo y $-CF_3$;

R^{11} es seleccionado del grupo que consiste de: H, halógeno y alquilo; y

cada R^{13} y R^{14} es seleccionado independientemente del grupo que consiste de: H, metilo, etilo, isopropilo, y t-butilo; o

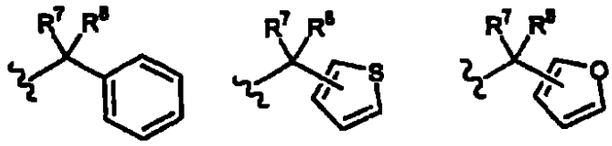
R^{13} y R^{14} cuando se toman juntos con el nitrógeno al cual están unidos en los grupos $-C(O)NR^{13}R^{14}$ y $-SO_2NR^{13}R^{14}$ forman un anillo heterocíclico saturado no sustituido o sustituido (preferentemente un anillo de 3 a 7 miembros) que opcionalmente tiene un heteroátomo adicional seleccionado a partir de O, S o NR^{18} en donde R^{18} es seleccionado a partir de H, alquilo, arilo, heteroarilo, $-C(O)R^{19}$, $-SO_2R^{19}$ y $-C(O)NR^{19}R^{20}$, en donde cada R^{19} y R^{20} es seleccionado independientemente de alquilo, arilo y heteroarilo, en donde hay 1 a 3 sustituyentes en los grupos R^{13} y R^{14} ciclado sustituido (es decir en el anillo formado cuando R^{13} y R^{14} son tomados juntos con el nitrógeno al cual está unido) y cada sustituyente es independientemente seleccionado del grupo que consiste de: alquilo, arilo, hidroxi, hidroxialquilo, alcoxi, alcoxialquilo, arilalquilo, fluoralquilo, cicloalquilo, cicloalquilalquilo, heteroarilo, heteroarilalquilo, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ siempre que R^{15} no sea H, $-NHC(O)NR^{15}R^{16}$ y halógeno; y donde cada R^{15} y R^{16} es independientemente seleccionado del grupo que consiste de: H, alquilo, arilo, arilalquilo, cicloalquilo y heteroarilo.

La realización No. 43 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde:

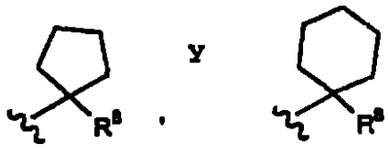
(1) el sustituyente A en la fórmula IA es aún seleccionado más preferentemente del grupo que consiste de:

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196

(a)



y



en donde los anillos anteriores están no sustituidos, o los anillos anteriores están sustituidos con 1 a 3 sustituyentes seleccionados independientemente del grupo que consiste de: F, Cl, Br, alquilo, cicloalquilo, y $-CF_3$; R^7 es seleccionado del grupo que consiste de: H, $-CF_3$, $-CF_2CH_3$, metilo, etilo, isopropilo, ciclopropilo y t-butilo; y R^8 es H;

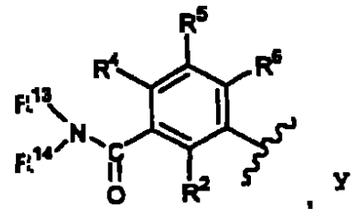
(b)

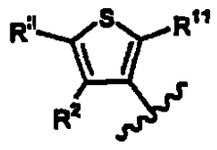


en donde R^7 es seleccionado del grupo que consiste de: H, $-CF_3$, $-CF_2CH_3$, metilo, etilo, isopropilo, ciclopropilo, y t-butilo; y R^8 es H; y R^{8a} es tal lo definido para la fórmula IA;

(2) el sustituyente B en la fórmula IA es aún más preferentemente seleccionado del grupo que consiste de:

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en donde:

R^2 es seleccionado del grupo que consiste de: H, OH, $-NHC(O)R^{13}$ y $-NHSO_2R^{13}$;

R^3 es seleccionado del grupo que consiste de: $-C(O)NR^{13}R^{14}$, $-SO_2NR^{13}R^{14}$, $-NO_2$, ciano, y $-SO_2R^{13}$;

R^4 es seleccionado del grupo que consiste de: H, $-NO_2$, ciano, $-CH_3$, o $-CF_3$;

R^5 es seleccionado del grupo que consiste de: H, $-CF_3$, $-NO_2$,halógeno y ciano; y

R^6 es seleccionado del grupo que consiste de: H, alquilo y $-CF_3$;

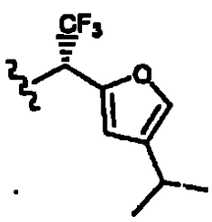
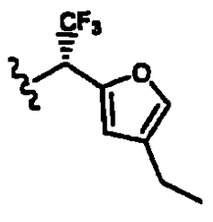
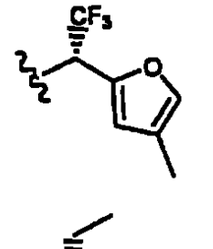
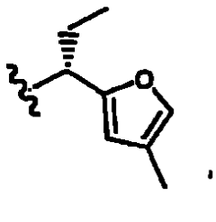
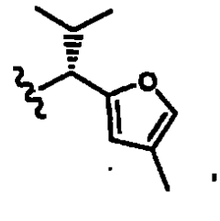
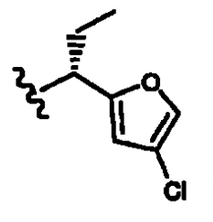
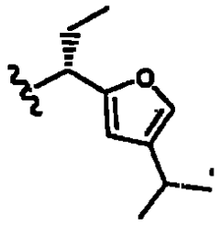
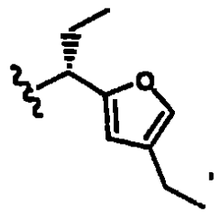
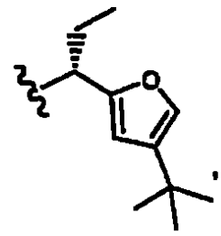
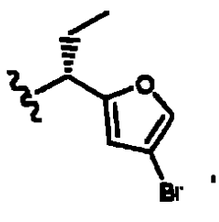
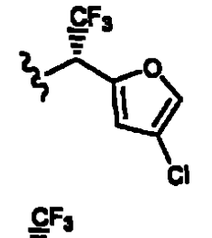
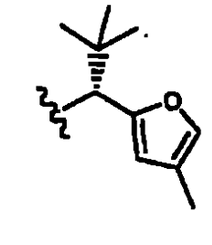
R^{11} es seleccionado del grupo que consiste de: H, halógeno y alquilo; y

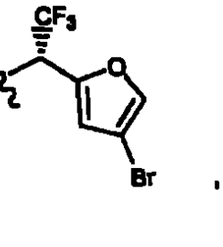
cada R^{13} y R^{14} es seleccionado independientemente del grupo que consiste de: metilo y etilo.

La realización No. 44 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde:

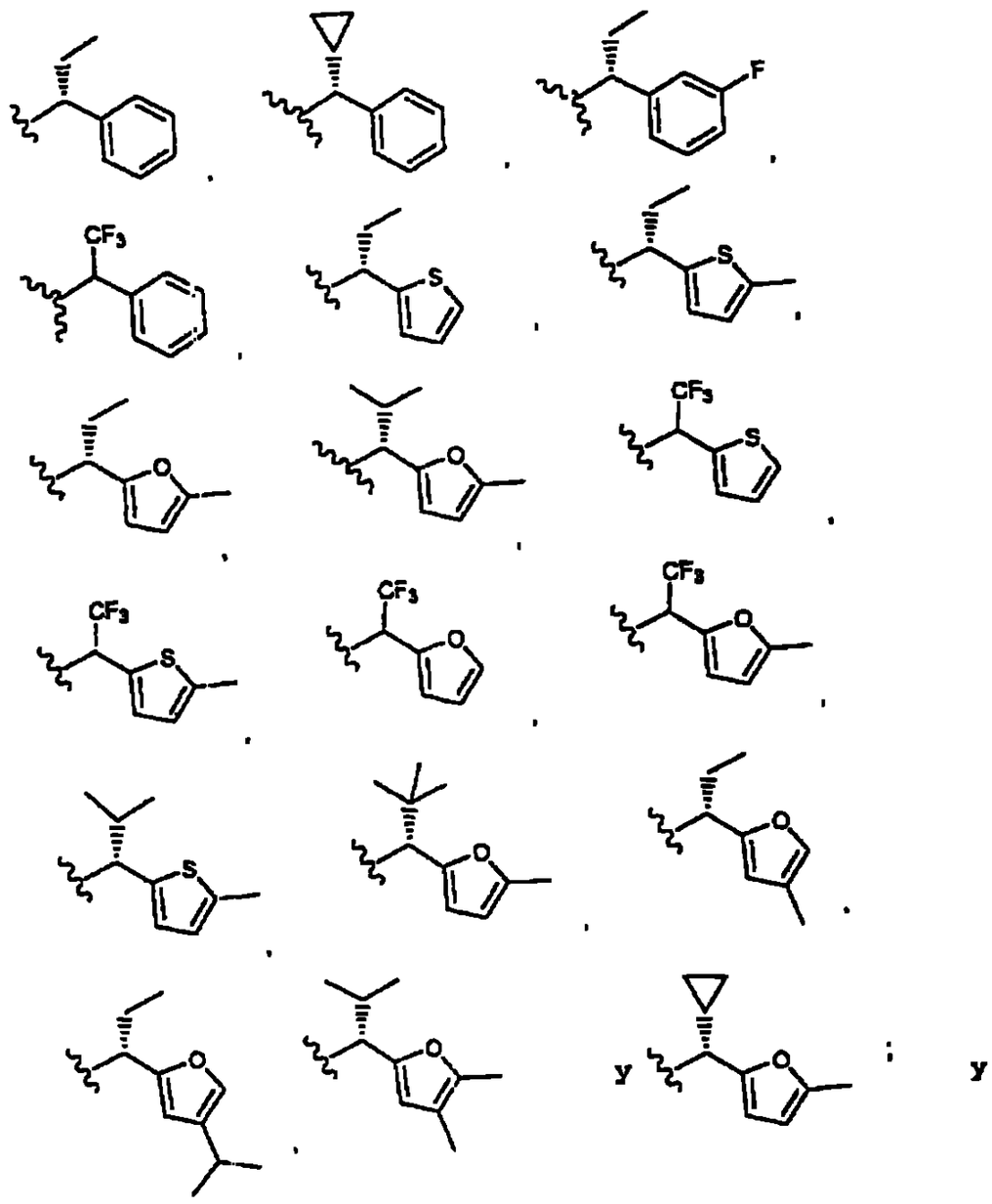
(1) el sustituyente A en la fórmula IA es seleccionado más preferentemente del grupo que consiste de:

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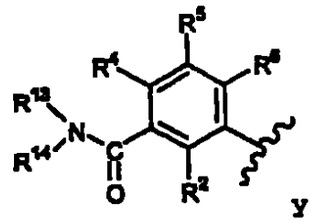



198
199

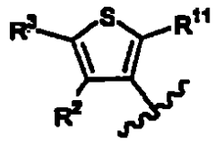


(2) el sustituyente B en la fórmula IA es seleccionado más preferentemente del grupo que consiste de:

199
200



y



en donde:

R^2 es –OH;

R^3 es seleccionado del grupo que consiste de: $-SO_2NR^{13}R^{14}$ y $–CONR^{13}R^{14}$;

R^4 es seleccionado del grupo que consiste de: H, $-CH_3$ y $-CF_3$;

R^5 es seleccionado del grupo que consiste de: H y ciano;

R^6 es seleccionado del grupo que consiste de: H, $-CH_3$ y $-CF_3$;

R^{11} es H; y

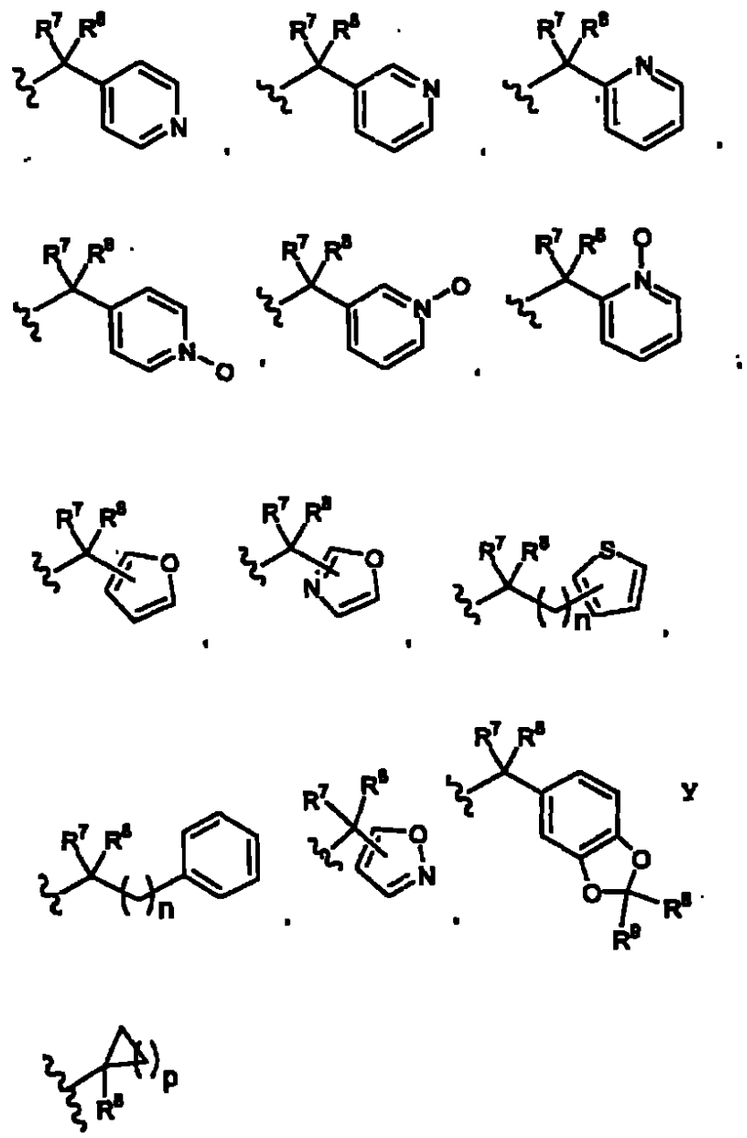
R^{13} y R^{14} son metilo.

La realización No. 45 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde:

(1) el sustituyente A en la fórmula IA es seleccionado del grupo que consiste de:

200
201

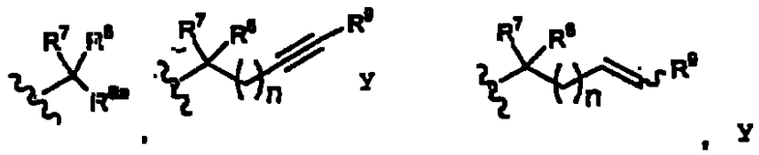
(a)



en donde los anillos anteriores son no sustituidos o sustituidos, tal lo descripto para la fórmula IA: y

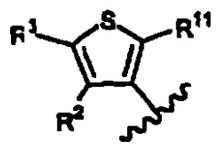
201
202

(b)



en donde en (a) y (b) anteriores: cada R^7 y R^8 es independientemente seleccionado del grupo que consiste de: H, alquilo no sustituido o sustituido, arilo no sustituido o sustituido, heteroarilo no sustituido o sustituido, arilalquilo no sustituido o sustituido, heteroarilalquilo no sustituido o sustituido, cicloalquilo no sustituido o sustituido, cicloalquilalquilo no sustituido o sustituido, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, fluoralquilo, alquinilo, alquenilo, y cicloalquenilo, en donde dichos sustituyentes en dichos grupos R^7 y R^8 sustituidos son seleccionados del grupo que consiste de: a) ciano, b) $-CO_2R^{13}$, c) $-C(O)NR^{13}R^{14}$, d) $-SO_2NR^{13}R^{14}$, e) $-NO_2$, f) $-CF_3$, g) $-OR^{13}$, h) $-NR^{13}R^{14}$. i) $-OC(O)R^{13}$, j) $-OC(O)NR^{13}R^{14}$, y k) halógeno; y R^{8a} y R^9 son tal lo definido en la fórmula IA; y

(2) el sustituyente B en la fórmula IA es:



en donde R^2, R^3 y R^{11} son tal lo definido anteriormente para los nuevos compuestos de fórmula IA.

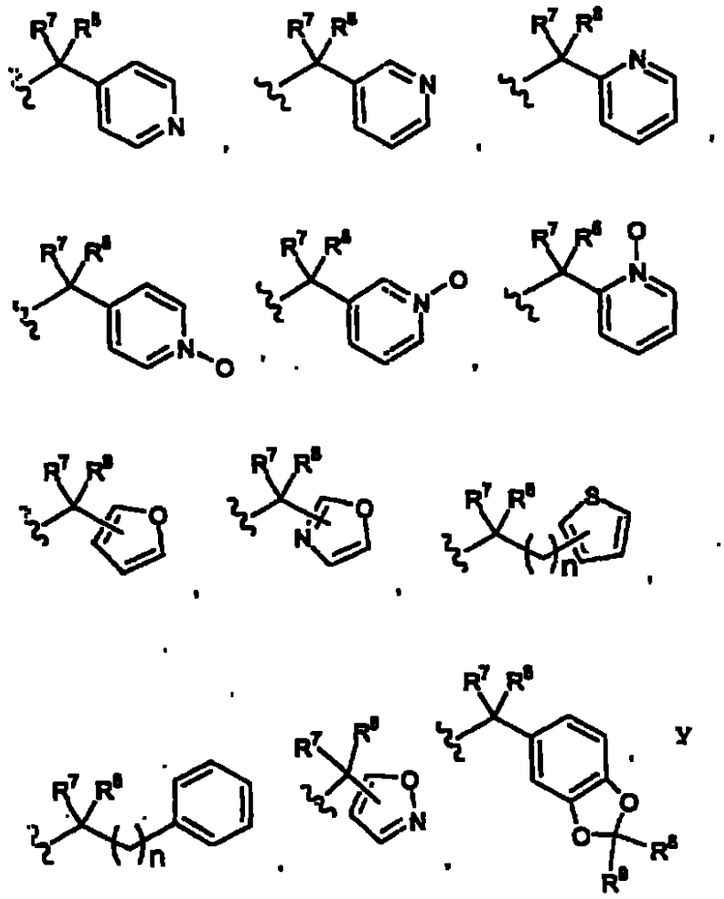
La realización No. 46 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde:

(1) el sustituyente A en la fórmula IA es seleccionado del grupo que

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203

consiste de:

(a)

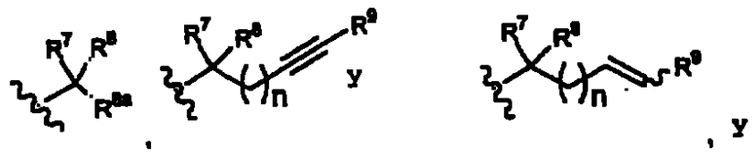


en donde los anillos anteriores son no sustituidos o sustituidos, tal lo descripto para la fórmula IA:

y

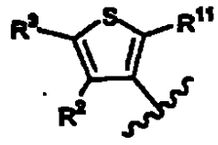
203
204

(b)



en donde en (a) y (b) anterior: cada R^7 y R^8 es seleccionado independientemente del grupo que consiste de: H, alquilo no sustituido o sustituido, arilo no sustituido o sustituido, heteroarilo no sustituido o sustituido, arilalquilo no sustituido o sustituido, heteroarilalquilo no sustituido o sustituido, cicloalquilo no sustituido o sustituido, cicloalquilalquilo no sustituido o sustituido, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, fluoralquilo, alquinilo, alquenilo, y cicloalquenilo, en donde dichos sustituyentes en dichos grupos R^7 y R^8 sustituidos son seleccionados del grupo que consiste de: a) ciano, b) $-CO_2R^{13}$, c) $-C(O)NR^{13}R^{14}$, d) $-SO_2NR^{13}R^{14}$, e) $-NO_2$, f) $-CF_3$, g) $-OR^{13}$, h) $-NR^{13}R^{14}$. i) $-OC(O)R^{13}$, j) $-OC(O)NR^{13}R^{14}$, y k) halógeno; y R^{8a} y R^9 son tal lo definido en la fórmula IA; y

(2) el sustituyente B en la fórmula IA es:



R^2 es seleccionado del grupo que consiste de: H, OH, $-NHC(O)R^{13}$ y $-NHSO_2R^{13}$;

R^3 es seleccionado del grupo que consiste de: $-SO_2NR^{13}R^{14}$, $-NO_2$, ciano, $-C(O)NR^{13}R^{14}$, $-SO_2R^{13}$, y $-C(O)OR^{13}$;

R^{11} es seleccionado del grupo que consiste de: R^{13}, hidrógeno, halógeno, $-CF_3$, $-NR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, -OH, $-C(O)OR^{13}$, -SH, $-SO_{(t)}NR^{13}R^{14}$, $-SO_2R^{13}$,

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205

-$NHC(O)R^{13}$, -$NHSO_2NR^{13}R^{14}$, -$NHSO_2R^{13}$, -$C(O)NR^{13}R^{14}$, -$C(O)NR^{13}OR^{14}$, -$OC(O)R^{13}$, -COR^{13}, -OR^{13}, y ciano;

cada R^{13} y R^{14} es seleccionado independientemente del grupo que consiste de: H, metilo, etilo, isopropilo, y t-butilo; o

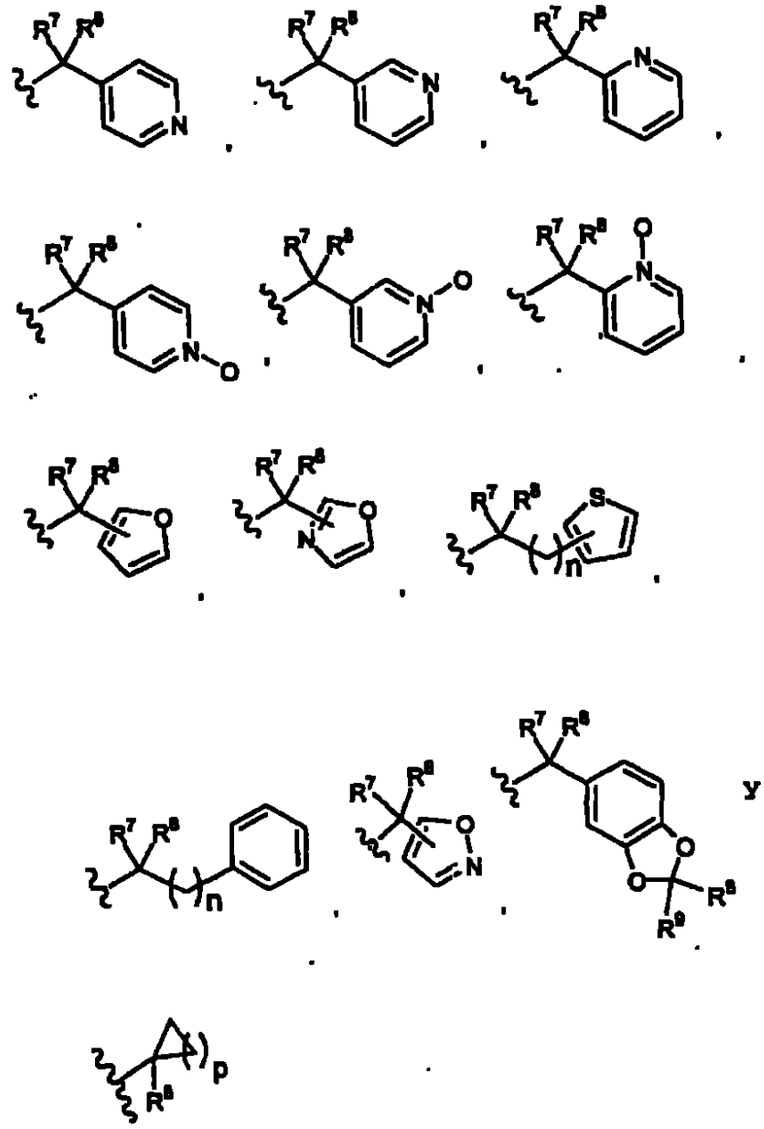
R^{13} y R^{14} cuando se toman juntos con el nitrógeno al cual están unido en los grupos –$C(O)NR^{13}R^{14}$ y –SO_2 $NR^{13}R^{14}$, forman un anillo heterocíclico no sustituido o sustituido (preferentemente un anillo de 3 a 7 miembros) que tiene opcionalmente un heteroátomo adicional seleccionado del grupo que consiste de: O, S, o NR^{18}; en donde R^{18} es seleccionado del grupo que consiste de: H, alquilo, arilo, heteroarilo, -$C(O)R^{19}$, -SO_2R^{19} y –$C(O)NR^{19}R^{20}$, donde cada R^{19} y R^{20} es seleccionado independientemente del grupo que consiste de: alquilo, arilo y heteroarilo; en donde hay 1 a 3 sustituyentes en los grupos R^{13}y R^{14} ciclados sustituidos (es decir los sustituyentes en el anillo formado cuando R^{13} y R^{14} son tomados juntos con el nitrógeno al cual están unidos) y cada sustituyente es independientemente seleccionado del grupo que consiste de: alquilo, arilo, hidroxi, hidroxialquilo, alcoxi, alcoxialquilo, arilalquilo, fluoralquilo, cicloalquilo, cicloalquil alquilo, heteroarilo, heteroarilalquilo, amino, -$C(O)OR^{15}$, -$C(O)NR^{15}R^{16}$, -$SO_2NR^{15}R^{16}$, -$C(O)R^{15}$, -SO_2R^{15}, siempre que R^{15} no sea H, -$NHC(O)NR^{15}R^{16}$ y halógeno; y en donde cada R^{15} y R^{16} es seleccionado independientemente del grupo que consiste de: H, alquilo, arilo, arilalquilo, cicloalquilo y heteroarilo.

La realización No. 47 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde:

(1) el sustituyente A en la fórmula IA es seleccionado del grupo que consiste de:

205
206

(a)

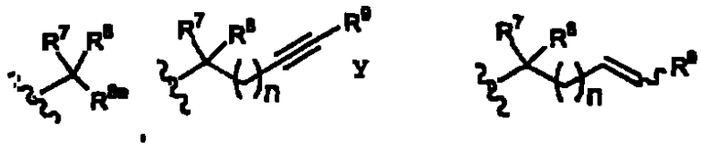


en donde los anillos anteriores son no sustituidos, o los anillos anteriores son sustituidos con 1 a 3 sustituyentes seleccionados independientemente del grupo que consiste de: halógeno, alquilo, cicloalquilo, $-CF_3$, ciano, $-OCH_3$, y $-NO_2$; cada R^7 y R^8 es seleccionado independientemente del grupo que consiste de: H, alquilo (por ejemplo, metilo, etilo, t-butilo, e isopropilo), fluoralquilo (tal como, $-CF_3$

206
207

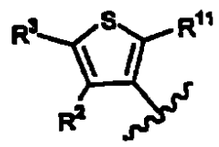
y $-CF_2CH_3$), cicloalquilo (por ejemplo ciclopropilo, y ciclohexilo), y cicloalquilalquilo (por ejemplo, ciclopropilmetilo); y R^9 es seleccionado del grupo que consiste de: H, halógeno, alquilo, cicloalquilo, $-CF_3$, ciano, $-OCH_3$, y $-NO_2$; y

(b)



en donde cada R^7 y R^8 es independientemente seleccionado del grupo que consiste de: H, alquilo (por ejemplo metilo, etilo, t-butilo, e isopropilo), fluoralquilo (tal como, $-CF_3$ y $-CF_2CH_3$), cicloalquilo (por ejemplo, ciclopropilo, y ciclohexilo), y cicloalquilalquilo (por ejemplo, ciclopropilmetilo); en donde R^{8a} es tal lo definido en la fórmula IA, y en donde R^9 es seleccionado del grupo que consiste de: H, halógeno, alquilo, cicloalquilo, $-CF_3$, ciano, $-OCH_3$, y $-NO_2$; cada R^7 y R^8 es seleccionado independientemente del grupo que consiste de: H, alquilo (por ejemplo metilo, etilo, t-butilo, e isopropilo), fluoralquilo (tal como, $-CF_3$ y $-CF_2CH_3$), cicloalquilo (por ejemplo, ciclopropilo, y ciclohexilo), y cicloalquilalquilo (por ejemplo, ciclopropilmetilo); y

(2) el sustituyente B en la fórmula IA es:



en donde

R^2 es seleccionado del grupo que consiste de: H, OH, $-NHC(O)R^{13}$ y $-NHSO_2R^{13}$;

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208

R^3 es $-SO_2NR^{13}R^{14}$;

R^{11} es seleccionado del grupo que consiste de: R^{13}, hidrógeno, halógeno, $-CF_3$, $-NR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, -OH, $-C(O)OR^{13}$, -SH, $-SO_{(t)}NR^{13}R^{14}$, $-SO_2R^{13}$, $-NHC(O)R^{13}$, $-NHSO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, $-C(O)NR^{13}R^{14}$, $-C(O)NR^{13}OR^{14}$, $-OC(O)R^{13}$, $-COR^{13}$, $-OR^{13}$, y ciano;

cada R^{13} y R^{14} es seleccionado independientemente del grupo que consiste de: H, metilo, etilo, isopropilo, y t-butilo; o

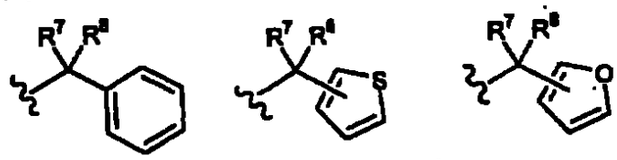
R^{13} y R^{14} cuando se toman juntos con el nitrógeno al cual están unido en los grupos $-C(O)NR^{13}R^{14}$ forman un anillo heterocíclico no sustituido o sustituido (preferentemente un anillo de 3 a 7 miembros) que tiene opcionalmente un heteroátomo adicional seleccionado del grupo que consiste de: O, S, o NR^{18}; en donde R^{18} es seleccionado del grupo que consiste de: H, alquilo, arilo, heteroarilo, $-C(O)R^{19}$, $-SO_2R^{19}$ y $-C(O)NR^{19}R^{20}$, donde cada R^{19} y R^{20} es seleccionado independientemente del grupo que consiste de: alquilo, arilo y heteroarilo; en donde hay 1 a 3 sustituyentes en los grupos R^{13}y R^{14} ciclados sustituidos (es decir los sustituyentes en el anillo formado cuando R^{13} y R^{14} son tomados juntos con el nitrógeno al cual están unidos) y cada sustituyente es independientemente seleccionado del grupo que consiste de: alquilo, arilo, hidroxi, hidroxialquilo, alcoxi, alcoxialquilo, arilalquilo, fluoralquilo, cicloalquilo, cicloalquilalquilo, heteroarilo, heteroarilalquilo, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-SO_tNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$, siempre que R^{15} no sea H, $-NHC(O)NR^{15}R^{16}$ y halógeno; y en donde cada R^{15} y R^{16} es seleccionado independientemente del grupo que consiste de: H, alquilo, arilo, arilalquilo, cicloalquilo y heteroarilo.

La realización No. 48 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde:

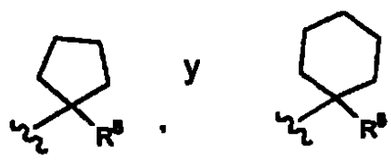
(1) el sustituyente A en la fórmula IA es seleccionado del grupo que consiste de:

208
209

(a)



y



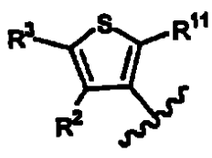
en donde los anillos anteriores son no sustituidos, o los anillos anteriores son sustituidos con 1 a 3 sustituyentes seleccionados independientemente del grupo que consiste de: H, F, Cl, Br, alquilo, cicloalquilo, y $-CF_3$; R^7 es seleccionado del grupo que consiste de: H, $-CF_3$, $-CF_2CH_3$, metilo, etilo, isopropilo, ciclopropilo y t-butilo; y R^8 es H; y

(b)



en donde R^7 es seleccionado del grupo que consiste de: H, $-CF_3$, $-CF_2CH_3$, metilo, etilo, isopropilo, ciclopropilo, y t-butilo; y R^8 es H; y R^{8a} es tal lo definido para la fórmula IA

(2) el sustituyente B en la fórmula IA es:



en donde:

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R^2 es seleccionado del grupo que consiste de: H, OH, -NHC(O)R^{13} y –$NHSO_2R^{13}$;

R^3 es seleccionado del grupo que consiste de: -C(O)$NR^{13}R^{14}$, -$SO_2NR^{13}R^{14}$, -NO_2, ciano, -SO_2R^{13}, y -C(O)OR^{13};

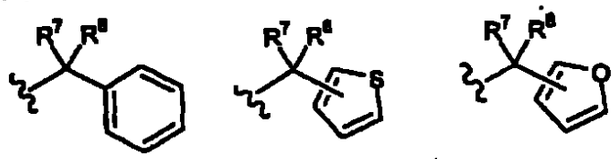
R^{11} es seleccionado independientemente del grupo que consiste de: H, halógeno y alquilo; y

cada R^{13} y R^{14} es independientemente seleccionado del grupo que consiste de: H, metilo, etilo, isopropilo y t-butilo.

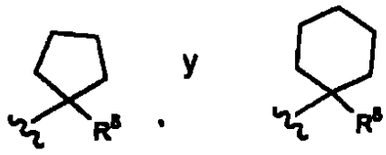
La realización No. 49 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde:

(1) el sustituyente A en la fórmula IA es seleccionado del grupo que consiste de:

(a)



y



en donde los anillos anteriores son no sustituidos, o los anillos anteriores son sustituidos con 1 a 3 sustituyentes seleccionados independientemente del grupo que consiste de: F, Cl, Bı, alquilo, cicloalquilo, y -CF_3; R^7 es seleccionado del grupo que consiste de: H, -CF_3, -CF_2CH_3, metilo, etilo, isopropilo, ciclopropilo y t-butilo; y R^8 es H; y

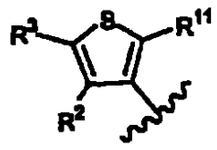
210
211

(b)



en donde R^7 es seleccionado del grupo que consiste de: H, $-CF_3$, $-CF_2CH_3$, metilo, etilo, isopropilo, ciclopropilo, y t-butilo; y R^8 es H; y R^{8a} es tal lo definido para la fórmula IA

(2) el sustituyente B en la fórmula IA es:



en donde:

R^2 es seleccionado del grupo que consiste de: H, OH, $-NHC(O)R^{13}$ y $-NHSO_2R^{13}$ (*preferentemente* –OH);

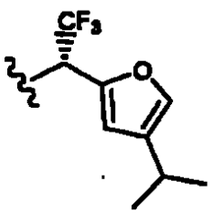
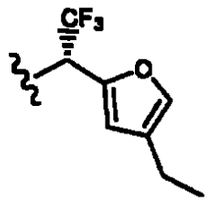
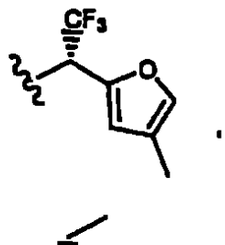
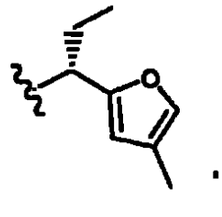
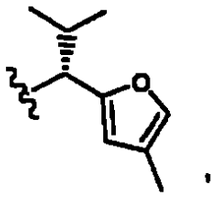
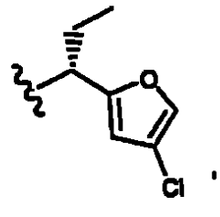
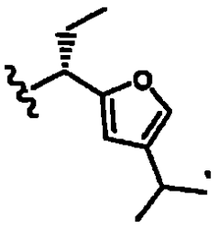
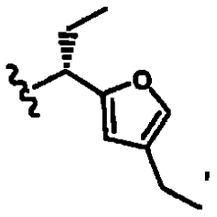
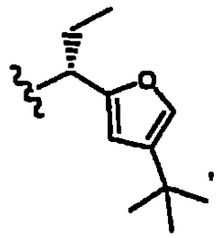
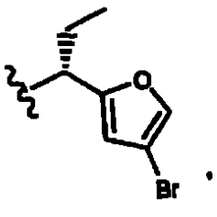
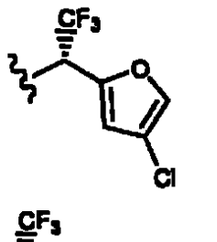
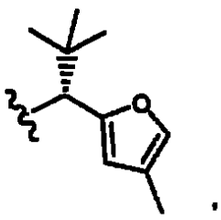
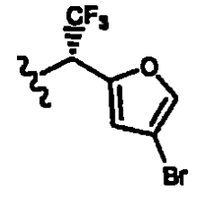
R^3 es $-SO_2NR^{13}R^{14}$;

R^{11} es seleccionado independientemente del grupo que consiste de: H, halógeno y alquilo (preferentemente H); y

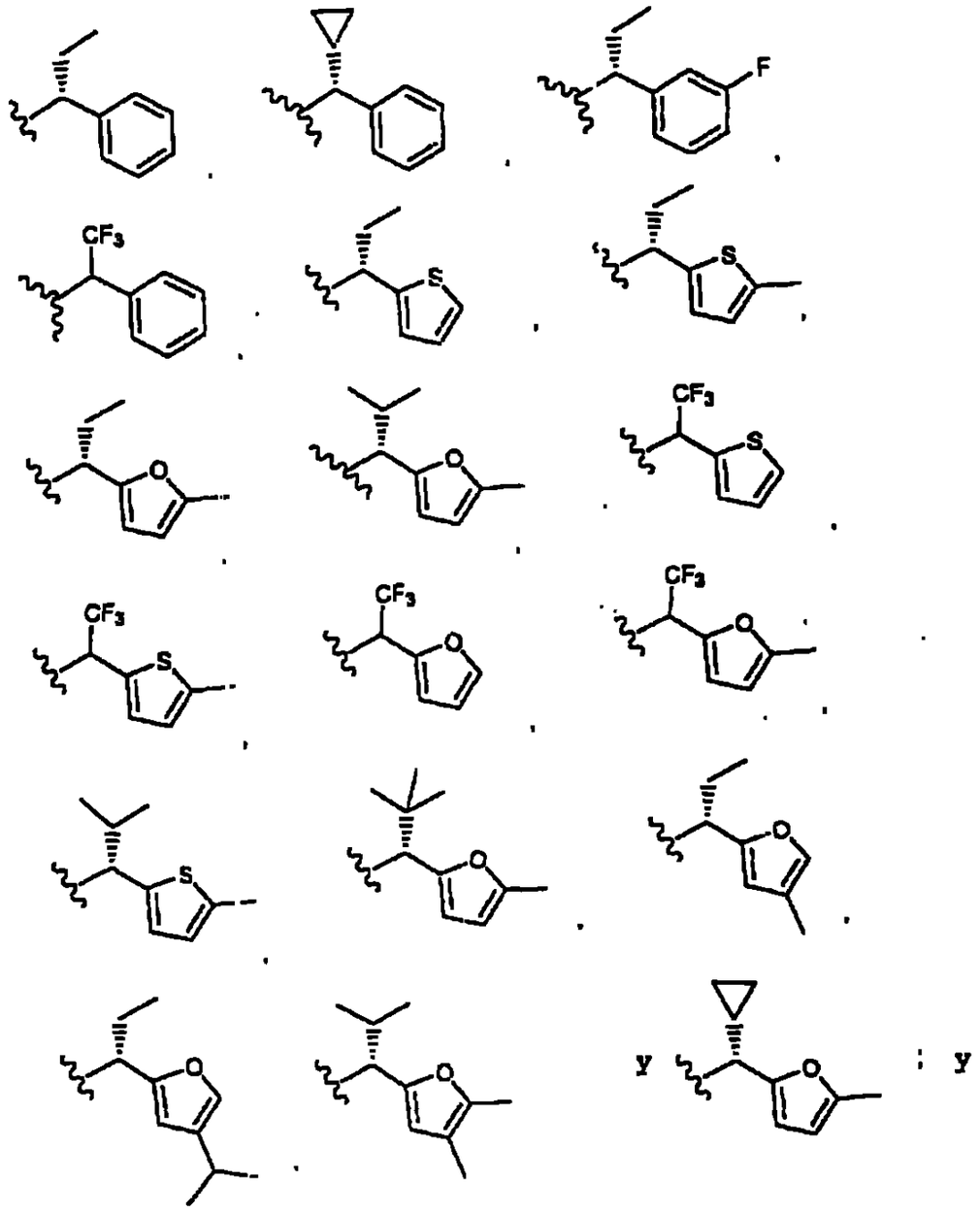
cada R^{13} y R^{14} es independientemente seleccionado del grupo que consiste de: H y etilo, preferentemente R^{13} y R^{14} son etilo.

La realización No. 50 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde:

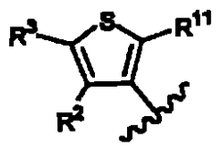
(1) el sustituyente A en la fórmula IA es seleccionado del grupo que consiste de:

212
213



2) el sustituyente B en la fórmula IA es:



en donde:

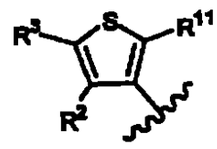
R^2 es –OH;

R^3 es: $-SO_2 NR^{13}R^{14}$;

R^{11} es H; y

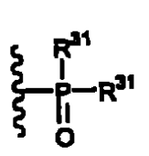
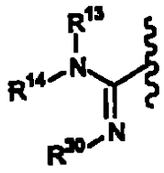
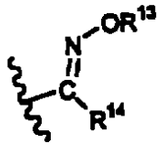
R^{13} y R^{14} son etilo.

La realización No. 51 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es seleccionado del grupo que consiste de:

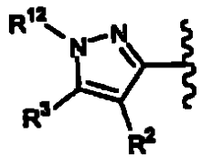


siempre que R^3 para este grupo es seleccionado del grupo que consiste de: $-C(O)NR^{13}R^{14}$,

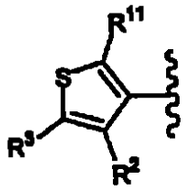
214
215



y

;

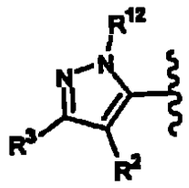
(2)


;

(3)

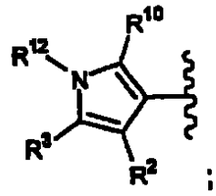

;

(4)


;

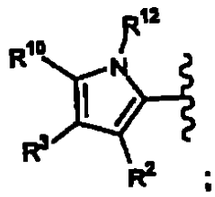
215
216

(5)



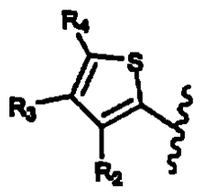
;

(6)



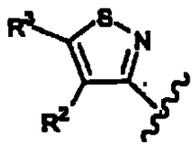
;

(7)



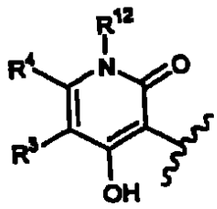
;

(8)



;

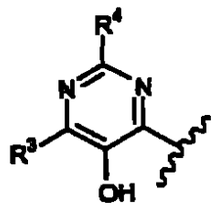
(9)



;

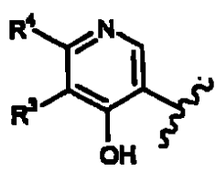
216
219

(10)



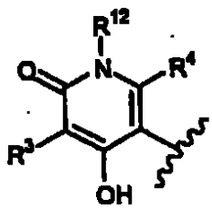
;

(11)



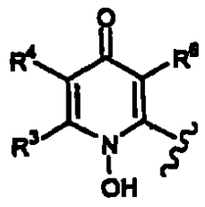
;

(12)



; y

(13)



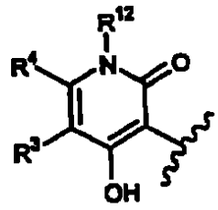
;

en donde todos los sustituyentes son tal lo definido para la fórmula IA.

La realización No. 52 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es seleccionado del grupo que consiste de:

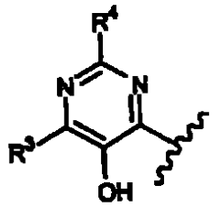
217
218

(1)



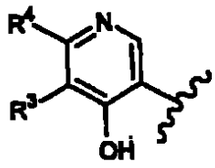
;

(2)



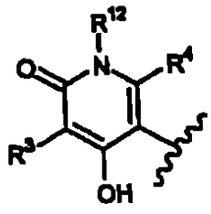
;

(3)



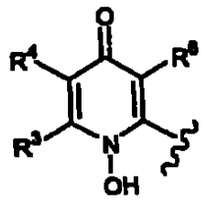
;

(4)



; y

(5)

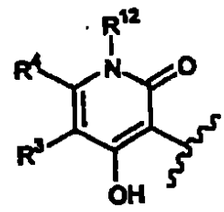


;

218
219

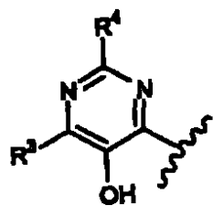
en donde todos los sustituyentes son tal lo definido para la fórmula IA.

La realización No. 53 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es:



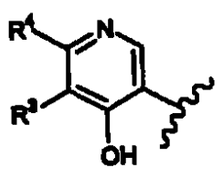
en donde todos los sustituyentes son tal lo definido en la fórmula IA.

La realización No. 54 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es:



en donde todos los sustituyentes son tal lo definido en la fórmula IA.

La realización No. 55 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es:

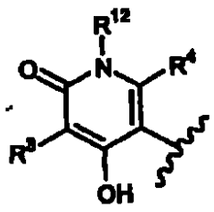


;

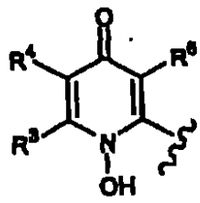
en donde todos los sustituyentes son tal lo definido en la fórmula IA.

219
270

La realización No. 56 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es:

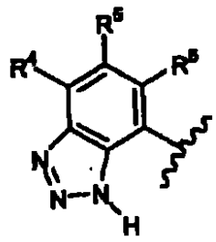


La realización No. 57 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es:



en donde todos los sustituyentes son tal lo definido en la fórmula IA.

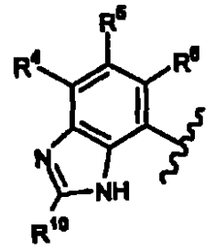
La realización No. 58 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es:



en donde todos los sustituyentes son tal lo definido en la fórmula IA.

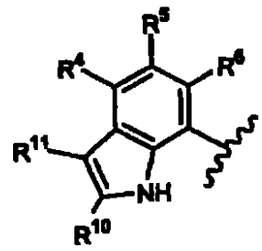
La realización No. 59 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es:

220
221



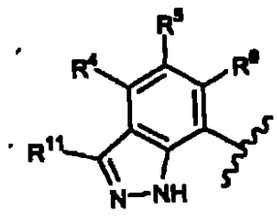
en donde todos los sustituyentes son tal lo definido en la fórmula IA.

La realización No. 60 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es:



en donde todos los sustituyentes son tal lo definido en la fórmula IA.

La realización No. 61 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es:

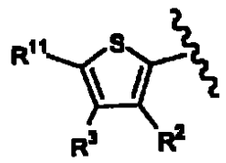


en donde todos los sustituyentes son tal lo definido en la fórmula IA.

La realización No. 62 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es seleccionado del grupo que consiste

224
222

de:



en donde todos los sustituyentes son tal lo definido en la fórmula IA.

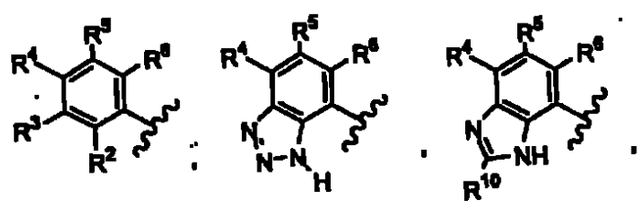
La realización No. 63 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es descripta en cualquiera de las realizaciones Nos. 51 a 62 y A es tal lo descripto en cualquiera de las realizaciones Nos. 32-44.

La realización No. 64 está dirigida a cualquiera de las realizaciones Nos. 1 a 63 en donde el compuesto de fórmula IA es una sal farmacéuticamente aceptable.

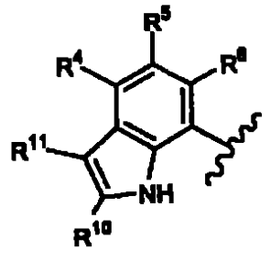
La realización No. 65 está dirigida a cualquiera de las realizaciones Nos. 1 a 63 en donde el compuesto de fórmula IA es una sal de sodio.

La realización No. 66 está dirigida a cualquiera de las realizaciones Nos. 1 a 63 en donde el compuesto de fórmula IA es una sal de calcio.

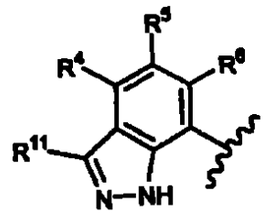
La realización No. 67 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es seleccionado del grupo que consiste de:



222
223

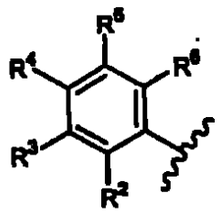


y



en donde todos los sustituyentes son tal lo definido en la fórmula IA.

La realización No. 68 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde B es seleccionado del grupo que consiste de:



en donde:

R^2, R^4, R^5 y R^6 son tal lo definido para la fórmula IA; y

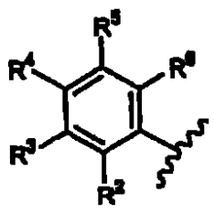
R^3 es seleccionado del grupo que consiste de: hidrógeno, ciano, halógeno, alquilo, alcoxi, -OH, $-CF_3$, $-OCF_3$, $-NO_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NHR^{17}$, - - $SO_{(t)}NR^{13}R^{14}$, $-SO_{(t)}R^{13}$, $-C(O)NR^{13}OR^{14}$, arilo no sustituido o sustituido, heteroarilo no sustituido o sustituido, en donde hay 1 a 6 sustituyentes en dicho grupo arilo sustituido y cada sustituyente es independientemente seleccionado del grupo que consiste de: grupos R^9; y en donde hay 1 a 6 sustituyentes en dicho grupo heteroarilo sustituido y cada sustituyente es independientemente seleccionado del grupo que consiste de: grupos R^9;

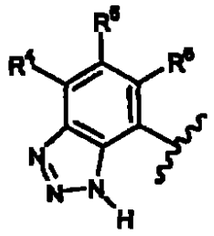
La realización No. 69 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde:

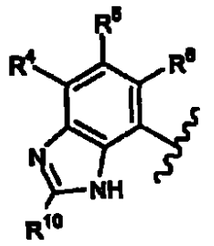
223
224

(1) el sustituyente A es tal lo definido en la realización No. 39; y

(2) el sustituyente B en la fórmula IA es preferentemente seleccionado del grupo que consiste de:

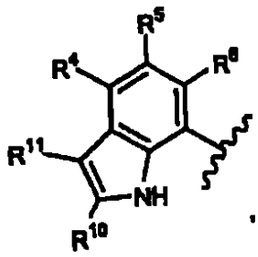
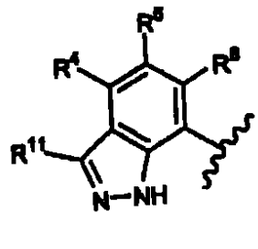
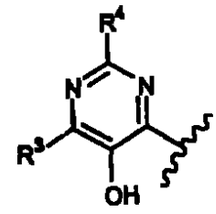
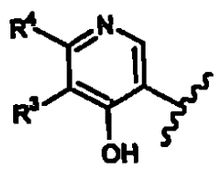
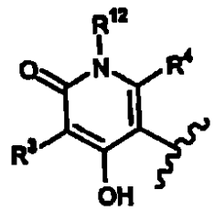
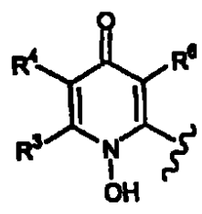
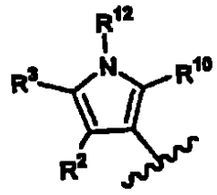
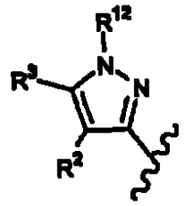
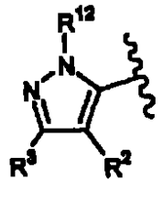
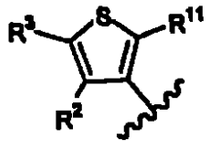


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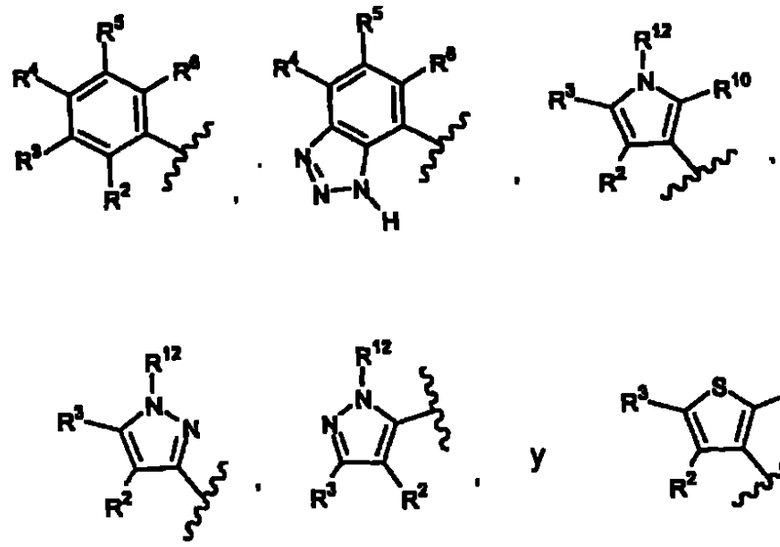
en donde R^2 a R^6 y R^{10} a R^{14} son tal lo definido para la fórmula IA.

La realización No. 70 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde:

(1) el sustituyente A es tal lo definido en la realización No. 40; y

(2) el sustituyente B en la fórmula IA es más preferentemente seleccionado del grupo que consiste de:

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en donde:

R^2 es seleccionado del grupo que consiste de: H, OH, -NHC(O)R^{13} y –$NHSO_2R^{13}$;

R^3 es seleccionado del grupo que consiste de: -$SO_2NR^{13}R^{14}$, -NO_2, ciano, -$C(O)NR^{13}R^{14}$, -SO_2R^{13}, y –$C(O)OR^{13}$;

R^4 es seleccionado del grupo que consiste de: H, -NO_2, ciano, -CH_3, halógeno, y –CF_3;

R^5 es seleccionado del grupo que consiste de: H, -CF_3, -NO_2,halógeno y ciano;

R^6 es seleccionado del grupo que consiste de: H, alquilo, y -CF_3;

cada R^{10} y R^{11} es independientemente seleccionado del grupo que consiste de: hidrógeno, halógeno, -CF_3, -$NR^{13}R^{14}$, $NR^{13}C(O)NR^{13}R^{14}$, -$C(O)OR^{13}$, -SH, -$SO_{(t)}NR^{13}R^{14}$, -SO_2R^{13}, -$NHC(O)R^{13}$, -$NHSO_2NR^{13}R^{14}$, -$NHSO_2R^{13}$, -$C(O)NR^{13}R^{14}$, -$C(O)NR^{13}OR^{14}$, -$OC(O)R^{13}$, -COR^{13}, y ciano;

cada R^{13} y R^{14} es seleccionado independientemente del grupo que consiste de: H, metilo, etilo, isopropilo y t-butilo; o

R^{13} y R^{14} cuando se toman juntos con el nitrógeno al cual están unidos en

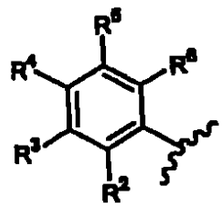
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los grupos $-NR^{13}R^{14}$ $-C(O)NR^{13}R^{14}$, $-SO_2NR^{13}R^{14}$, $-OC(O)NR^{13}R^{14}$, $CONR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, $SO_tNR^{13}R^{14}$, $-NHSO_2NR^{13}R^{14}$ forman un anillo heterocíclico saturado no sustituido o sustituido (preferentemente un anillo de 3 a 7 miembros) que tiene opcionalmente un heteroátomo adicional seleccionado del grupo que consiste de: O, S o NR^{18}; en donde R^{18} es seleccionado del grupo que consiste de: H, alquilo, arilo, heteroarilo, $-C(O)R^{19}$, $-SO_2R^{19}$ y $-C(O)NR^{19}R^{20}$, donde cada R^{19} y R^{20} es seleccionado independientemente del grupo que consiste de: alquilo, arilo y heteroarilo; en donde hay 1 a 3 sustituyentes en los grupos R^{13} y R^{14} ciclados sustituidos (es decir los sustituyentes en el anillo formado cuando R^{13} y R^{14} son tomados juntos con el nitrógeno al cual están unidos) y cada sustituyente es independientemente seleccionado del grupo que consiste de: alquilo, arilo, hidroxi, hidroxialquilo, alcoxi, alcoxialquilo, arilalquilo, fluoralquilo, cicloalquilo, cicloalquilalquilo, heteroarilo, heteroarilalquilo, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-SO_tNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$, $-SO_2R^{15}$ siempre que R^{15} no sea H, $-NHC(O)NR^{15}R^{16}$ y halógeno; y en donde cada R^{15} y R^{16} es seleccionado independientemente del grupo que consiste de: H, alquilo, arilo, arilalquilo, cicloalquilo y heteroarilo.

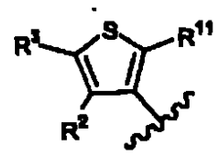
La realización No. 71 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde:

(1) el sustituyente A es tal lo definido en la realización No. 42, y

(2) el sustituyente en la fórmula IA es preferentemente seleccionado del grupo que consiste de:



y



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en donde:

R^2 es seleccionado del grupo que consiste de: H, OH, -NHC(O)R^{13} y –$NHSO_2R^{13}$;

R^3 es seleccionado del grupo que consiste de: -C(O)$NR^{13}R^{14}$, -$SO_2NR^{13}R^{14}$, -NO_2, ciano, -SO_2R^{13}, y –C(O)OR^{13};

R^4 es seleccionado del grupo que consiste de: H, -NO_2, ciano, -CH_3, o –CF_3;

R^5 es seleccionado del grupo que consiste de: H, -CF_3, -NO_2,halógeno y ciano;

R^6 es seleccionado del grupo que consiste de: H, alquilo, y -CF_3;

R^{11} es seleccionado del grupo que consiste de: H, halógeno y alquilo, y

cada R^{13} y R^{14} es seleccionado independientemente del grupo que consiste de: H, metilo, etilo, isopropilo y t-butilo; o

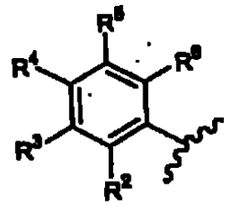
R^{13} y R^{14} cuando se toman juntos con el nitrógeno al cual están unidos en los grupos –$NR^{13}R^{14}$ –C(O)$NR^{13}R^{14}$, –$SO_2NR^{13}R^{14}$, -OC(O)$NR^{13}R^{14}$, -CONR^{13}R^{14}, -NR^{13}C(O)$NR^{13}R^{14}$, $SO_tNR^{13}R^{14}$, -$NHSO_2NR^{13}R^{14}$ forman un anillo heterocíclico saturado no sustituido o sustituido (preferentemente un anillo de 3 a 7 miembros) que tiene opcionalmente un heteroátomo adicional seleccionado del grupo que consiste de: O, S o NR^{18}; en donde R^{18} es seleccionado del grupo que consiste de: H, alquilo, arilo, heteroarilo, -C(O)R^{19}, -SO_2R^{19} y –C(O)$NR^{19}R^{20}$, donde cada R^{19} y R^{20} es seleccionado independientemente del grupo que consiste de: alquilo, arilo y heteroarilo; en donde hay 1 a 3 sustituyentes en los grupos R^{13}y R^{14} ciclados sustituidos (es decir los sustituyentes en el anillo formado cuando R^{13} y R^{14} son tomados juntos con el nitrógeno al cual están unidos) y cada sustituyente es independientemente seleccionado del grupo que consiste de: alquilo, arilo, hidroxi, hidroxialquilo, alcoxi, alcoxialquilo, arilalquilo, fluoralquilo, cicloalquilo, cicloalquilalquilo, heteroarilo, heteroarilalquilo, amino, -C(O)OR^{15}, -C(O)$NR^{15}R^{16}$, -

$SO_tNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$, $-SO_2R^{15}$ siempre que R^{15} no sea H, $-NHC(O)NR^{15}R^{16}$ y halógeno; y en donde cada R^{15} y R^{16} es seleccionado independientemente del grupo que consiste de: H, alquilo, arilo, arilalquilo, cicloalquilo y heteroarilo.

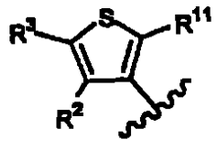
La realización No. 72 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde:

(1) el sustituyente A es tal lo definido en la realización No. 43; y

(2) el sustituyente B en la fórmula IA es preferentemente seleccionado del grupo que consiste de:



y



en donde:

R^2 es seleccionado del grupo que consiste de: H, OH, $-NHC(O)R^{13}$ y $-NHSO_2R^{13}$;

R^3 es seleccionado del grupo que consiste de: $-C(O)NR^{13}R^{14}$, $-SO_2NR^{13}R^{14}$, $-NO_2$, ciano, y $-SO_2R^{13}$;

R^4 es seleccionado del grupo que consiste de: H, $-NO_2$, ciano, $-CH_3$, o $-CF_3$;

R^5 es seleccionado del grupo que consiste de: H, $-CF_3$, $-NO_2$, halógeno y ciano;

R^6 es seleccionado del grupo que consiste de: H, alquilo, y $-CF_3$;

R^{11} es seleccionado del grupo que consiste de: H, halógeno y alquilo, y

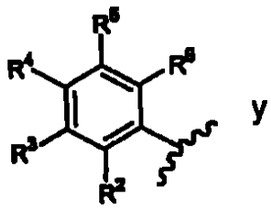
cada R^{13} y R^{14} es seleccionado independientemente del grupo que consiste de: metilo y etilo.

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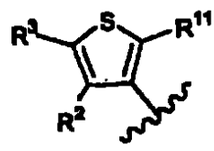
La realización No. 73 está dirigida a los métodos de tratamiento que utilizan los compuestos de fórmula IA donde:

(1) el sustituyente A es tal lo definido en al realización No. 44; y

(2) el sustituyente B en la fórmula IA es preferentemente seleccionado del grupo que consiste de:



y



en donde:

R^2 es –OH;

R^3 es seleccionado del grupo que consiste de: $-SO_2NR^{13}R^{14}$ y $-CONR^{13}R^{14}$;

R^4 es seleccionado del grupo que consiste de: H, $-CH_3$ y $-CF_3$;

R^5 es seleccionado del grupo que consiste de: H y ciano;

R^6 es seleccionado del grupo que consiste de: H, $-CH_3$ y $-CF_3$;

R^{11} es H; y

R^{13} y R^{14} son metilo.

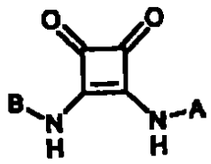
La realización No. 74 está dirigida a cualquiera de las realizaciones Nos. 67 a 73 en donde el compuesto de fórmula IA es una sal farmacéuticamente aceptable.

La realización No. 75 está dirigida a cualquiera de las realizaciones Nos. 67 a 73 en donde el compuesto de fórmula IA es una sal de sodio.

La realización No. 76 está dirigida a cualquiera de las realizaciones Nos. 67 a 73 en donde el compuesto de fórmula IA es una sal de calcio.

La presente invención también está dirigida a nuevos compuestos de fórmula IB:

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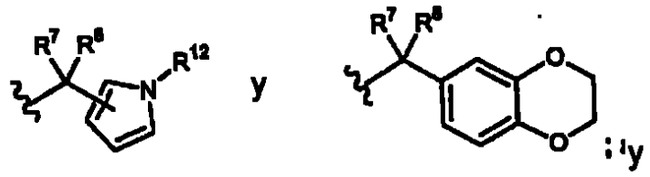


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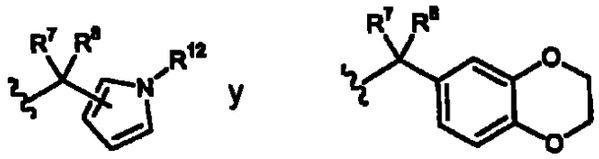
y las sales farmacéuticamente aceptables (por ejemplo, sal de sodio o calcio) y solvatos de los mismos, en donde:

A es seleccionado del grupo que consiste de:

(1)



(2)



en donde dichos anillos de dichos grupos A están sustituidos con 1 a 6 sustituyentes cada uno independientemente seleccionado del grupo que consiste de: grupos R^9; y

Los sustituyentes B, R^7, R^8, R^9 y R^{12} son tal lo definido para la fórmula IA:

De este modo, para los compuestos de fórmula IB, los sustituyentes B, R^*, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{30}, R^{31}, R^{40}, q, y t son tal lo definido en la fórmula IA:

En otras realizaciones de los compuestos de fórmula IB, el sustituyente B es tal lo definido en cualquiera de la realizaciones 1 a 30 descriptas

anteriormente.

En otras realizaciones de los compuestos de fórmula IB, el sustituyente B es tal lo definido en cualquiera de la realizaciones 51 a 62 descriptas anteriormente

En otras realizaciones de los compuestos de fórmula IB, el sustituyente B es tal lo definido en cualquiera de la realizaciones 67 a 73 descriptas anteriormente.

Otra realización de la presente invención está dirigida a una composición farmacéutica que comprende al menos un (por ejemplo uno) compuesto de fórmula IB y un portador farmacéuticamente aceptable.

Otra realización de la presente invención está dirigida a las sales de calcio de los compuestos de fórmula IB.

Otra realización de la presente invención está dirigida a las sales de sodio de los compuestos de fórmula IB.

Otra realización de la presente invención está dirigida a una composición farmacéutica que comprende al menos una (por ejemplo una) sal de sodio de un compuesto de fórmula IB y un portador farmacéuticamente aceptable.

Otra realización de la presente invención está dirigida a una composición farmacéutica que comprende al menos una (por ejemplo una) sal de calcio de un compuesto de fórmula IB y un portador farmacéuticamente aceptable.

Las enfermedades mediadas por quimiocina, que son tratadas mediante la administración de al menos un (por ejemplo, uno) compuesto seleccionado del grupo que consiste de las fórmulas 1.0A, 3.0A y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, o una sal o solvato farmacéuticamente aceptable de dichos compuestos, incluyen: inflamación crónica, dolor inflamatorio agudo, dolor inflamatorio crónico, dolor neuropático agudo, dolor neuropático crónico, psoriasis, dermatitis atópica, asma, COPD (enfermedad de

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obstrucción pulmonar crónica), enfermedad respiratoria del adulto, enfermedad del intestino inflamatoria, enfermedad de Crohn, colitis ulcerativa, choque séptico, choque endotóxico, sepsia gram negativa, síndrome del choque tóxico, apoplejía, daño por reperfusión cardíaca y renal, glomerulonefritis, trombosis, enfermedad de Alzheimer, reacción injerto vs. huésped, rechazos aloinjertos, malaria, síndrome disneico agudo, reacción de hipersensibilidad del tipo retardada, aterosclerosis, isquemia cardíaca y cerebral, osteoartritis, esclerosis múltiple, restinosis, angiogénesis, osteoporosis, gingivitis, virus respiratorio, virus herpes, virus de la hepatitis, HIV, virus asociado con el sarcoma de Kaposi, meningitis, fibrosis cística, trabajo de pre-parto, tos, prurito, disfunción multiorgánica, trauma, torceduras, luxaciones, contusiones, artritis psoriática, herpes, encefalitis, vasculitis SNC, daño cerebral traumático, tumores en el SNC, hemorragia subaracnoidea, trauma pos quirúrgico, pneumonitis intersticial, hipersensibilidad, artritis inducida por cristal, pancreatitis aguda y crónica, hepatitis alcohólica aguda, enterocolitis necrotizante, sinusitis crónica, enfermedad ocular angiogénica, inflamación ocular, retinopatía del prematuro, retinopatía diabética, degeneración macular siendo el tipo húmedo preferido y neovacularización córneal, polimiositis, vasculitis, acné, úlceras gástricas y duodenales, enfermedad celíaca, esofagitis, glositis, obstrucción de vías respiratorias, hipersensibilidad de las vías respiratorias, bronquiectasis, bronquiolitis, bronquiolitis obliterans, bronquitis crónica, cor pulmonale, tos, dispnea, enfisema, hipercapnea, hiperinflación, hipoxemia, inflamaciones inducidas por hiperoxia, hipoxia, reducción de volumen del pulmón quirúrgica, fibrosis pulmonar, hipertensión pulmonar, hipertrofia ventricular derecha, peritonitis asociada con la diálisis peritoneal ambulatoria continua (CAPD), erliquiosis granulocítica, sacoidosis, enfermedad de la vía respiratoria menor, desequilibrio de ventilación-perfusión, respiración sibilante, resfríos, gota, enfermedad del hígado por alcohol, lupus,

tratamiento de quemaduras, periodontitis, daño de reperfusión de transplante, rechazo de transplante temprano, inflamación aguda y artritis reumatoide.

Las enfermedades mediadas por quimiocina, que son tratadas mediante la administración de al menos un (por ejemplo uno) compuesto de fórmula IB incluyen: inflamación crónica, dolor inflamatorio agudo, dolor inflamatorio crónico, dolor neuropático agudo, dolor neuropático crónico, psoriasis, dermatitis atópica, asma, COPD (enfermedad de obstrucción pulmonar crónica), enfermedad respiratoria del adulto, artritis, enfermedad del intestino inflamatoria, enfermedad de Crohn, colitis ulcerativa, choque séptico, choque endotóxico, sepsia gram negativa, síndrome del choque tóxico, apoplejía, daño por reperfusión cardíaca y renal, glomerulonefritis, trombosis, enfermedad de Alzheimer, reacción injerto vs. huésped, rechazos aloinjertos, malaria, síndrome disneico agudo, reacción de hipersensibilidad del tipo retardada, aterosclerosis, isquemia cardíaca y cerebral, osteoartritis, esclerosis múltiple, restinosis, angiogénesis, osteoporosis, gingivitis, virus respiratorio, virus herpes, virus de la hepatitis, HIV, virus asociado con el sarcoma de Kaposi, meningitis, fibrosis cística, trabajo de pre-parto, tos, prurito, disfunción multiorgánica, trauma, torceduras, luxaciones, contusiones, artritis psoriática, herpes, encefalitis, vasculitis SNC, daño cerebral traumático, tumores en el SNC, hemorragia subaracnoidea, trauma pos quirúrgico, pneumonitis intersticial, hipersensibilidad, artritis inducida por cristal, pancreatitis aguda y crónica, hepatitis alcohólica aguda, enterocolitis necrotizante, sinusitis crónica, enfermedad ocular angiogénica, inflamación ocular, retinopatía del prematuro, retinopatía diabética, degeneración macular siendo el tipo húmedo preferido y neovacularización córneal, polimiositis, vasculitis, acné, úlceras gástricas y duodenales, enfermedad celíaca, esofagitis, glositis, obstrucción de vías respiratorias, hipersensibilidad de las vías respiratorias, bronquiectasis, bronquiolitis, bronquiolitis obliterans, bronquitis crónica, cor pulmonale, tos,

dispnea, enfisema, hipercapnea, hiperinflación, hipoxemia, inflamaciones inducidas por hiperoxia, hipoxia, reducción de volumen del pulmón quirúrgica, fibrosis pulmonar, hipertensión pulmonar, hipertrofia ventricular derecha, peritonitis asociada con la diálisis peritoneal ambulatoria continua (CAPD), erliquiosis granulocítica, sacoidosis, enfermedad de la vía respiratoria menor, desequilibrio de ventilación-perfusión, respiración sibilante, resfríos, gota, enfermedad del hígado por alcohol, lupus, tratamiento de quemaduras, periodontitis, daño de reperfusión de transplante, rechazo de transplante temprano, inflamación aguda y artritis reumatoide.

Otra realización de la presente invención está dirigida a un método para tratar dolor inflamatorio agudo en un paciente (por ejemplo, un mamífero, preferentemente un ser humano) que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ejemplo 1 – 3, y usualmente uno) compuesto de fórmula IA (o una sal o solvato farmacéuticamente aceptable del mismo).

Otra realización de la presente invención está dirigida a un método para tratar dolor inflamatorio crónico en un paciente (por ejemplo, un mamífero, preferentemente un ser humano) que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ejemplo 1 – 3, y usualmente uno) compuesto de fórmula IA (o una sal o solvato farmacéuticamente aceptable del mismo).

Otra realización de la presente invención está dirigida a un método para tratar dolor neuropático agudo en un paciente (por ejemplo, un mamífero, preferentemente un ser humano) que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ejemplo 1 – 3, usualmente uno) compuesto de fórmula IA (o una sal o solvato farmacéuticamente aceptable del mismo).

Otra realización de la presente invención está dirigida a un método para tratar dolor neuropático crónico en un paciente (por ejemplo, un mamífero, preferentemente un ser humano) que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ejemplo 1 – 3, usualmente uno) compuesto de fórmula IA (o una sal o solvato farmacéuticamente aceptable del mismo).

Otra realización de la presente invención está dirigida a un método para tratar dolor inflamatorio agudo en un paciente (por ejemplo, un mamífero, preferentemente un ser humano) que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ejemplo 1) compuesto seleccionado del grupo que consiste de compuestos de las fórmulas 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, (o una sal o solvato farmacéuticamente aceptable de dichos compuestos).

Otra realización de la presente invención está dirigida a un método para tratar dolor inflamatorio crónico en un paciente (por ejemplo, un mamífero, preferentemente un ser humano) que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ejemplo 1) compuesto seleccionado del grupo que consiste de compuestos de las fórmulas 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, (o una sal o solvato farmacéuticamente aceptable de dichos compuestos).

Otra realización de la presente invención está dirigida a un método para tratar dolor neuropático agudo en un paciente (por ejemplo, un mamífero, preferentemente un ser humano) que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ejemplo 1) compuesto seleccionado del grupo que consiste de compuestos de las fórmulas

1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, (o una sal o solvato farmacéuticamente aceptable de dichos compuestos).

Otra realización de la presente invención está dirigida a un método para tratar dolor neuropático crónico en un paciente (por ejemplo, un mamífero, preferentemente un ser humano) que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ejemplo 1) compuesto seleccionado del grupo que consiste de compuestos de las fórmulas 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, (o una sal o solvato farmacéuticamente aceptable de dichos compuestos).

Otra realización de la presente invención está dirigida a un método para tratar COPD (enfermedad de obstrucción pulmonar crónica), en un paciente (por ejemplo, un mamífero, preferentemente un ser humano) que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ejemplo 1) compuesto seleccionado del grupo que consiste de compuestos de las fórmulas 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, (o una sal o solvato farmacéuticamente aceptable de dichos compuestos).

Otra realización de la presente invención está dirigida a un método para tratar dolor inflamatorio agudo en un paciente (por ejemplo, un mamífero, preferentemente un ser humano) que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ejemplo 1 – 3, usualmente uno) compuesto de fórmula IB (o una sal o solvato farmacéuticamente aceptable del mismo).

Otra realización de la presente invención está dirigida a un método para tratar dolor inflamatorio crónico en un paciente (por ejemplo, un mamífero,

preferentemente un ser humano) que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ejemplo 1 – 3, usualmente uno) compuesto de fórmula IB (o una sal o solvato farmacéuticamente aceptable del mismo).

Otra realización de la presente invención está dirigida a un método para tratar dolor neuropático agudo en un paciente (por ejemplo, un mamífero, preferentemente un ser humano) que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ejemplo 1 – 3, usualmente uno) compuesto de fórmula IB (o una sal o solvato farmacéuticamente aceptable del mismo).

Otra realización de la presente invención está dirigida a un método para tratar dolor neuropático crónico en un paciente (por ejemplo, un mamífero, preferentemente un ser humano) que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ejemplo 1 – 3, usualmente uno) compuesto de fórmula IB (o una sal o solvato farmacéuticamente aceptable del mismo).

Otra realización de la presente invención está dirigida a un método para tratar COPD (enfermedad de obstrucción pulmonar crónica), en un paciente (por ejemplo, un mamífero, preferentemente un ser humano) que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ejemplo 1 – 3, usualmente uno) compuesto de fórmula IB (o una sal o solvato farmacéuticamente aceptable del mismo).

Otra realización de la presente invención está dirigida a un método para tratar cáncer en un paciente (por ejemplo, un mamífero, preferentemente un ser humano) que necesita dicho tratamiento que comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ejemplo 1) compuesto seleccionado del grupo que consiste de compuestos de las fórmulas 1.0A, 3.0A, y

los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, (o una sal o solvato farmacéuticamente aceptable de dichos compuestos), y (b) un agente que afecta el microtúbulo , o un agente antineoplásico, o un agente anti-angiogénesis, o un inhibidor de la quinasa receptor de VEGF, o anticuerpos contra el receptor de VEGF, o interferón, y/o c) radiación.

En otras realizaciones dirigidas al tratamiento del cáncer, al menos un (por ejemplo uno) compuesto seleccionado del grupo que consiste de compuestos de las fórmulas 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, (o una sal o solvato farmacéuticamente aceptable de dichos compuestos), es administrado en combinación con agentes antineoplásicos (por ejemplo uno o más, tal como uno, tal como uno o dos), seleccionados del grupo que consiste de: gemcitabine, paclitaxel (Taxol®), 5-fluoruracilo (5-FU), ciclofosfamida (Cytoxan®), temozolomida, taxotere y Vincristine.

En otra realización la presente invención provee un método para el tratamiento de cáncer en un paciente (por ejemplo, un mamífero, preferentemente un ser humano) que necesita dicho tratamiento que comprende administrar, en forma concurrente o secuencial, una cantidad efectiva de (a) al menos un (por ejemplo 1) compuesto seleccionado del grupo que consiste de compuestos de las fórmulas 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, (o una sal o solvato farmacéuticamente aceptable de dichos compuestos), y (b) un agente que afecta el microtúbulo (por ej., paclitaxel).

Una realización de la presente invención está dirigida a un método para tratar cáncer en un paciente (por ejemplo, un mamífero, preferentemente un ser humano) que necesita dicho tratamiento que comprende administrar a dicho

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paciente, en forma concurrente o secuencial, una cantidad terapéuticamente efectiva de (a) al menos un (por ejemplo 1 – 3, y usualmente uno) compuesto de fórmula IB (o una sal o solvato farmacéuticamente aceptable de los mismos), y (b) un agente que afecta el microtúbulo o un agente antineoplásico o agente anti-angiogénesis o inhibidor de quinasa receptor de VEGF o anticuerpos contra el receptor de VEGF o interferón, y/o c) radiación.

En otras realizaciones dirigidas al tratamiento de cáncer, al menos un (por ejemplo 1-3, y usualmente uno) compuesto de fórmula IB (o una sal o solvato farmacéuticamente aceptable del mismo), es administrado en combinación con agentes antineoplásicos (por ejemplo uno o más, tal como uno, tal como uno o dos), seleccionados del grupo que consiste de: gemcitabine, paclitaxel (Taxol®), 5-fluoruracilo (5-FU), ciclofosfamida (Cytoxan®), temozolomida, taxotere y Vincristine.

En otra realización la presente invención provee un método para el tratamiento de cáncer en un paciente (por ejemplo, un mamífero, tal como un ser humano) que necesita dicho tratamiento que comprende administrar, en forma concurrente o secuencial, una cantidad efectiva de (a) al menos un (por ejemplo 1-3, y usualmente uno) compuesto de fórmula IB (o una sal o solvato farmacéuticamente aceptable del mismo), y (b) un agente que afecta el microtúbulo (por ejemplo, paclitaxel).

Otra realización de la presente invención está dirigida a un método para tratar melanoma, carcinoma gástrico, y cáncer de pulmón de células no-pequeñas en un paciente que necesita dicho tratamiento, el cual comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ejemplo uno) compuesto de fórmula IB (o una sal o solvato farmacéuticamente aceptable de dicho compuesto).

Otra realización de la presente invención está dirigida a un método para

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tratar melanoma, carcinoma gástrico, y cáncer de pulmón de células no-pequeñas en un paciente que necesita dicho tratamiento, el cual comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ejemplo uno) compuesto de fórmula IB (o una sal o solvato farmacéuticamente aceptable de dicho compuesto), en combinación con la administración de al menos un agente anticancerígeno.

Otra realización de la presente invención está dirigida a un método para tratar melanoma, carcinoma gástrico, y cáncer de pulmón de células no-pequeñas en un paciente que necesita dicho tratamiento, el cual comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ejemplo uno) compuesto de fórmula IB (o una sal o solvato farmacéuticamente aceptable de dicho compuesto), en combinación con la administración de al menos un agente anticancerígeno, en donde dicho agente anticancerígeno es seleccionado del grupo que consiste de: agentes alquilantes, antimetabolitos, productos naturales, y sus derivados, hormonas, anti-hormonas, agentes anti-angiogénicos y esteroides, y sintéticos.

Otra realización de la presente invención está dirigida a un método para tratar melanoma, carcinoma gástrico, y cáncer de pulmón de células no-pequeñas en un paciente que necesita dicho tratamiento, el cual comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ejemplo uno) compuesto seleccionado del grupo que consiste de los compuestos de las fórmulas 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, (o una sal o solvato farmacéuticamente aceptable de dichos compuestos).

Otra realización de la presente invención está dirigida a un método para tratar melanoma, carcinoma gástrico, y cáncer de pulmón de células no-pequeñas en un paciente que necesita dicho tratamiento, el cual comprende administrar a

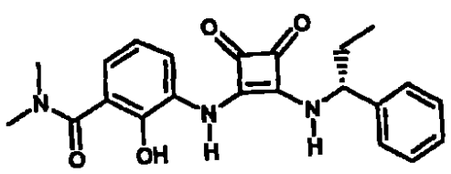
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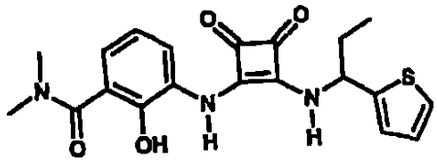
dicho paciente una cantidad efectiva de al menos un (por ejemplo uno) compuesto seleccionado del grupo que consiste de los compuestos de las fórmulas 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, (o una sal o solvato farmacéuticamente aceptable de dichos compuestos), en combinación con la administración de al menos un agente anticancerígeno.

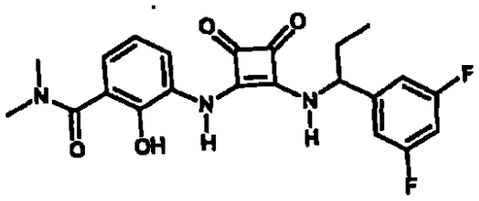
Otra realización de la presente invención está dirigida a un método para tratar melanoma, carcinoma gástrico, y cáncer de pulmón de células no-pequeñas en un paciente que necesita dicho tratamiento, el cual comprende administrar a dicho paciente una cantidad efectiva de al menos un (por ejemplo uno) compuesto seleccionado del grupo que consiste de los compuestos de las fórmulas 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, (o una sal o solvato farmacéuticamente aceptable de dichos compuestos), en combinación con la administración de al menos un agente anticancerígeno, en donde dicho agente anticancerígeno es seleccionado del grupo que consiste de: agentes alquilantes, antimetabolitos, productos naturales, y sus derivados, hormonas, anti-hormonas, agentes anti-angiogénicos y esteroides, y sintéticos.

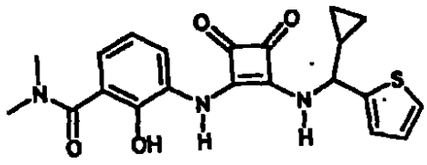
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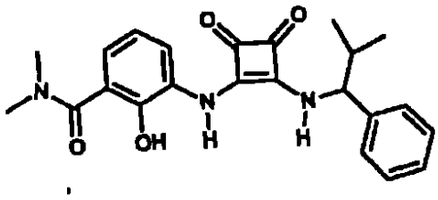
Los compuestos representativos utilizados para tratar las enfermedades mediadas por quimiocina incluyen pero sin limitarse a:

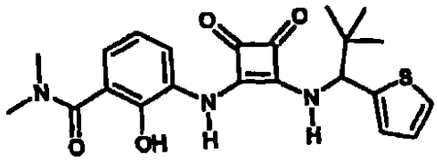


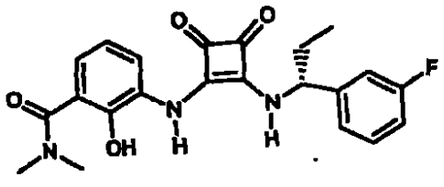


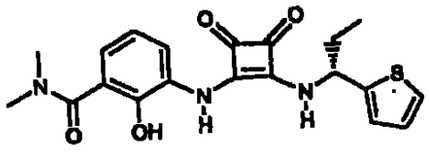


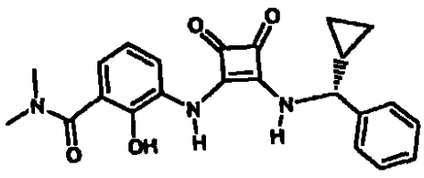


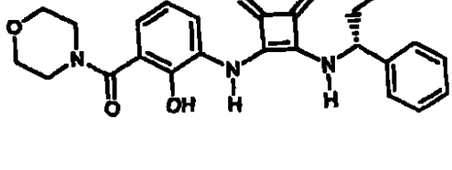




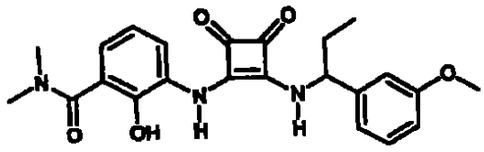


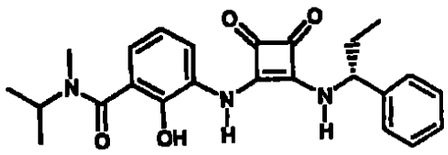


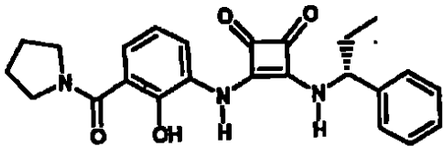


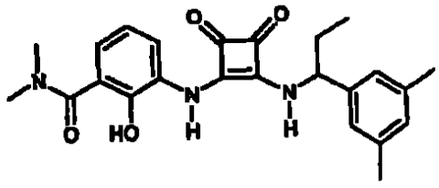


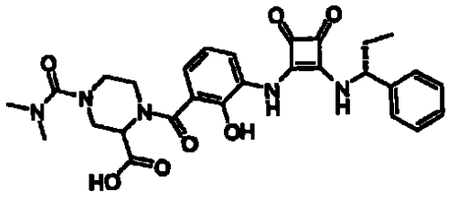
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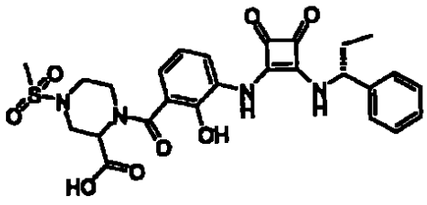


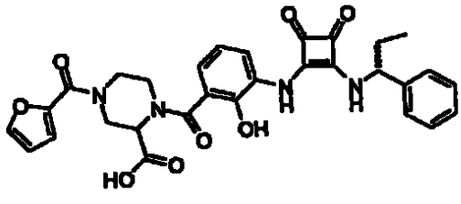




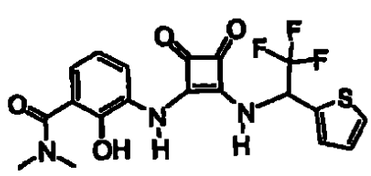


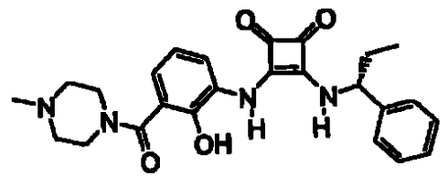


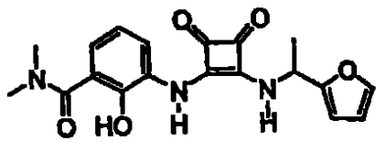


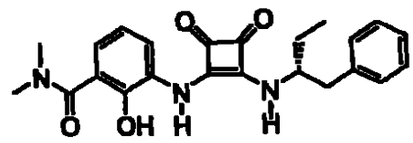


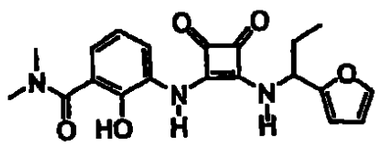
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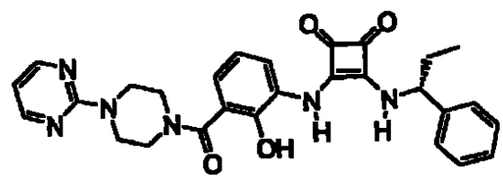


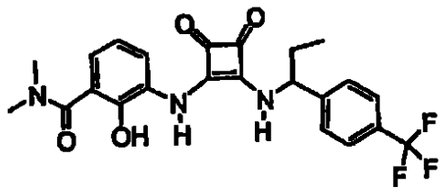


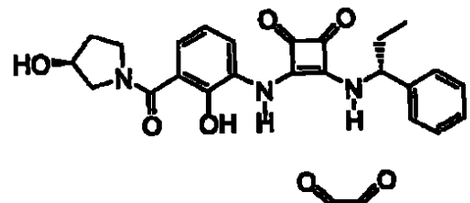




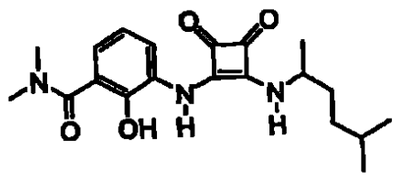


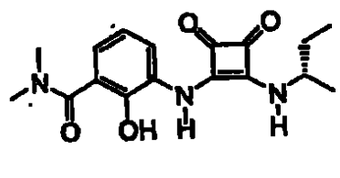


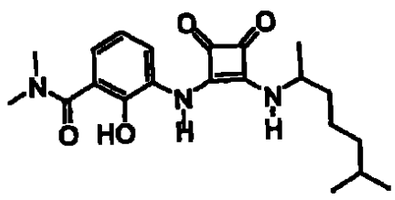


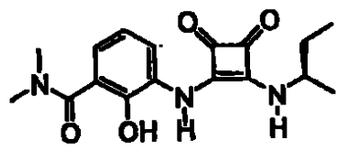


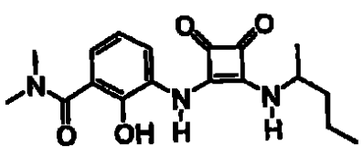
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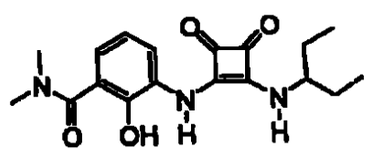


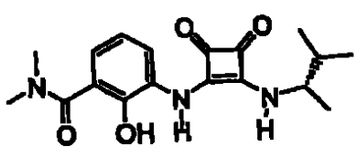


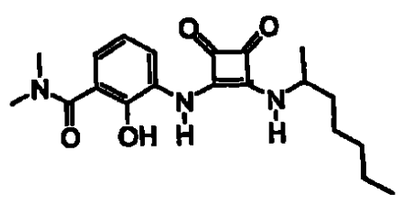


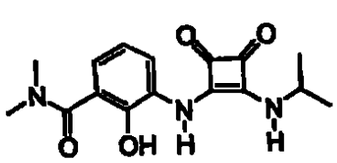


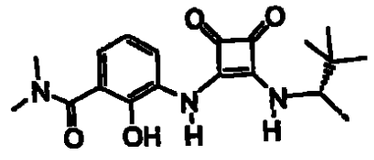


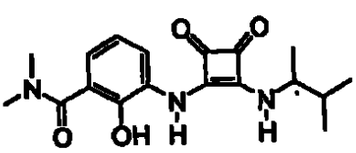


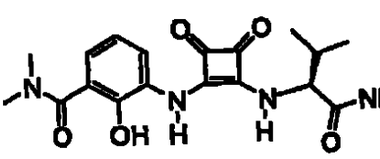


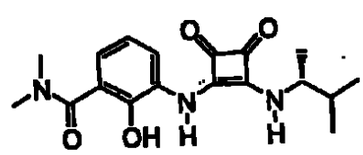


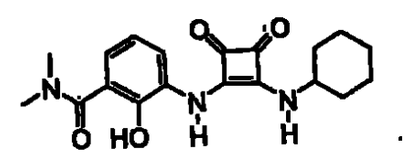


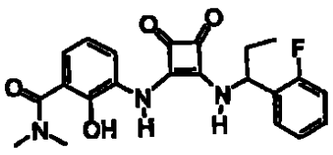


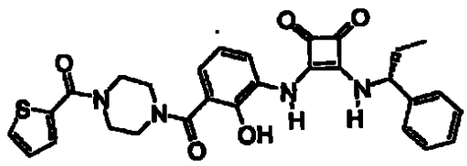


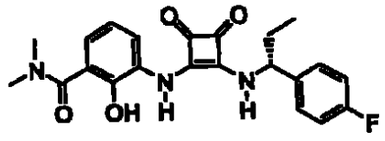


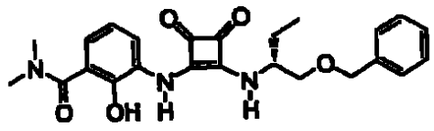


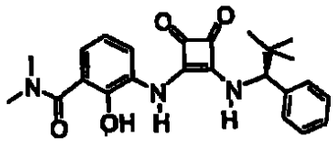


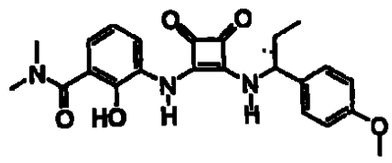


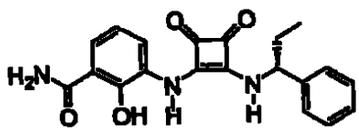


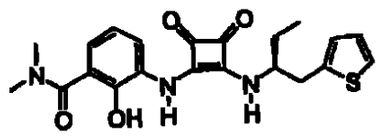


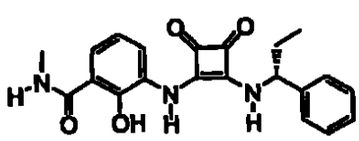


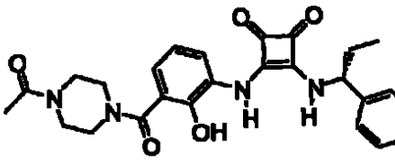


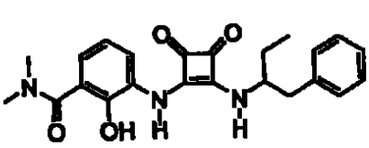


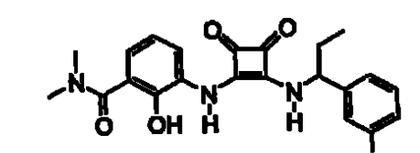


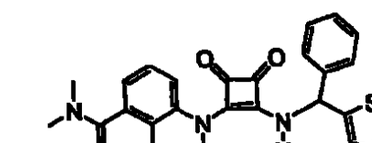


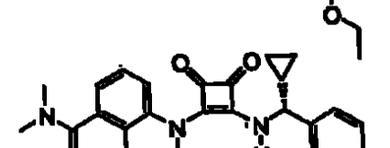


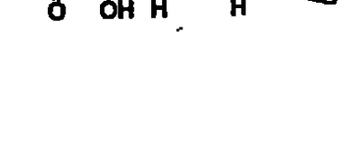


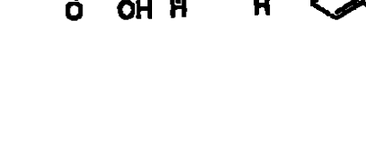




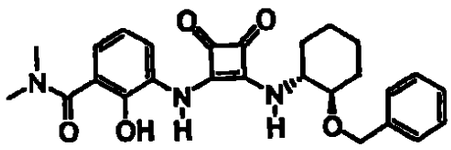


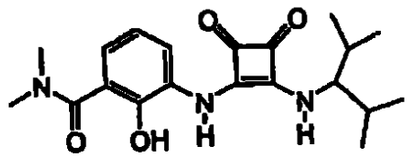


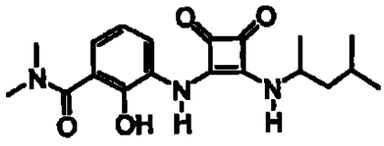


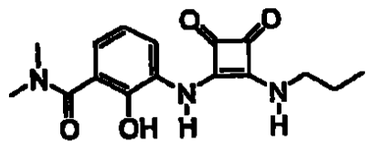


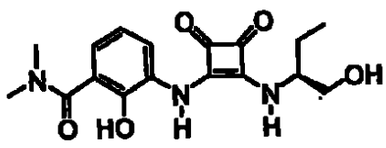
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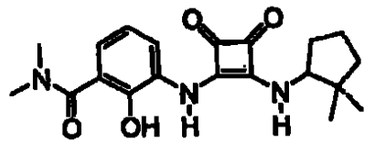


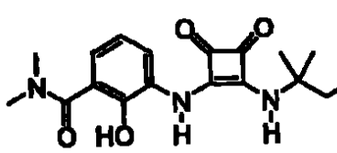


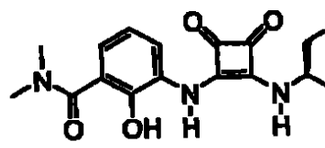


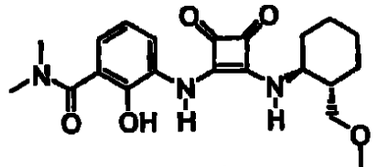


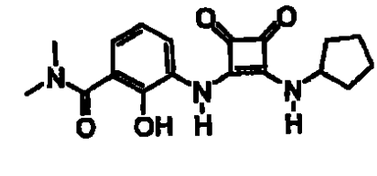


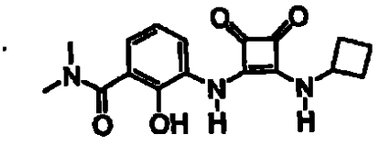


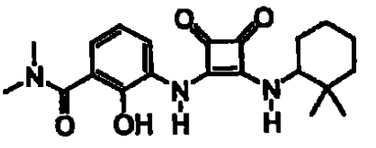




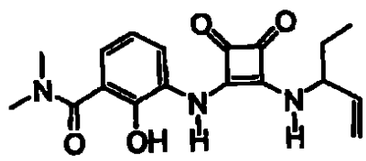


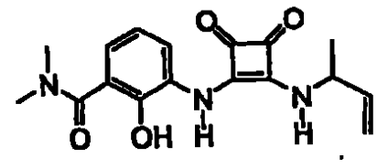


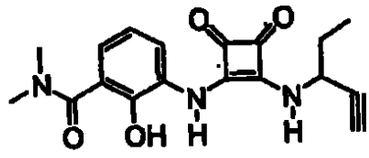


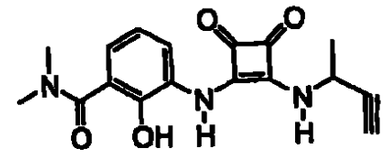


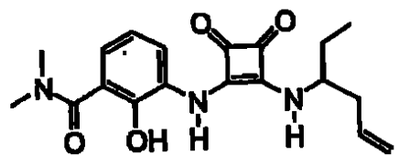
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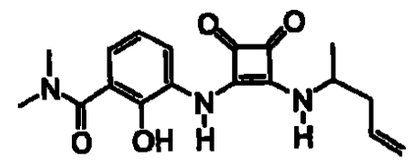


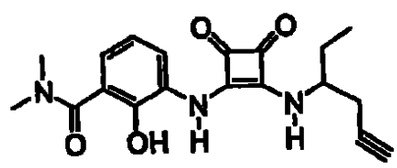


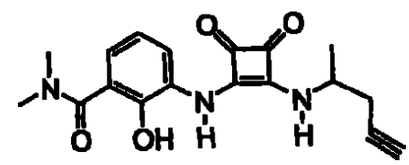


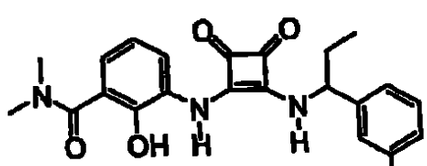


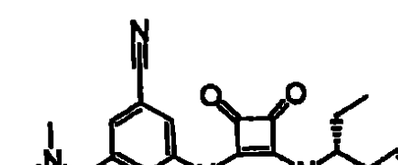


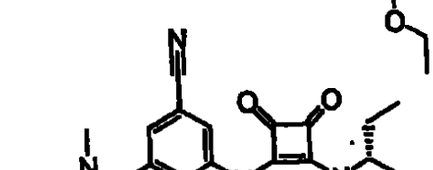


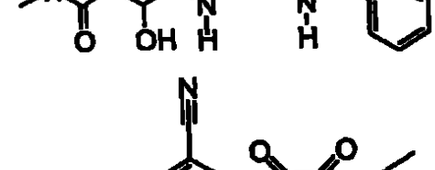


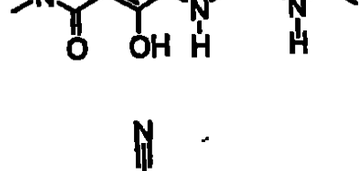


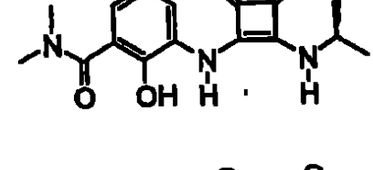


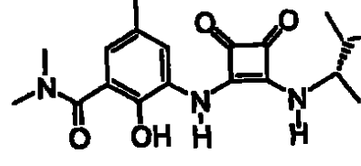


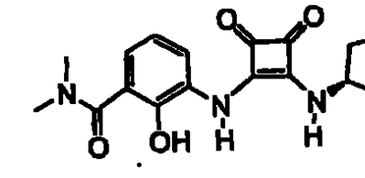




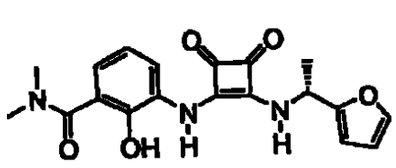


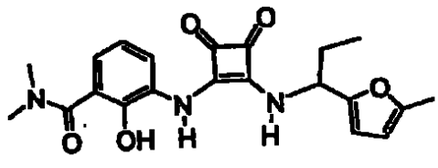


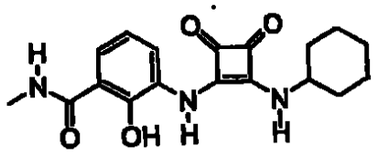


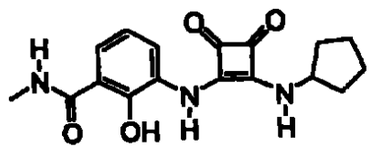


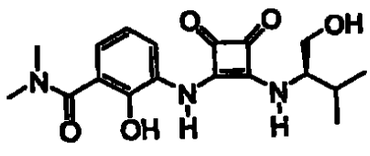
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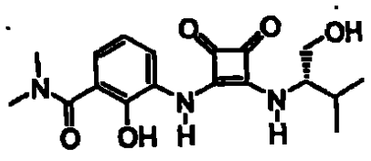


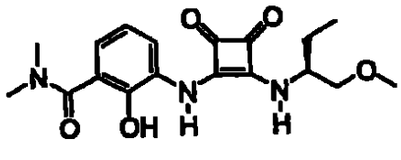


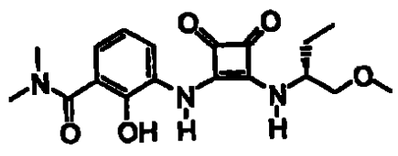


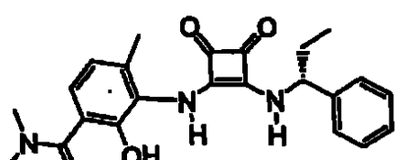


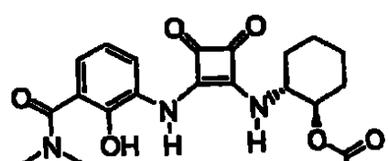


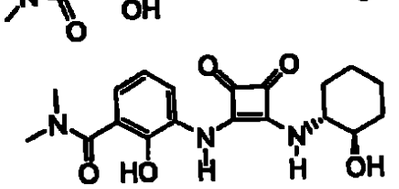


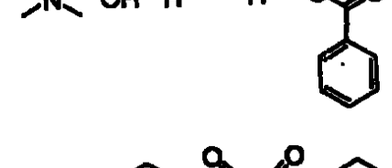


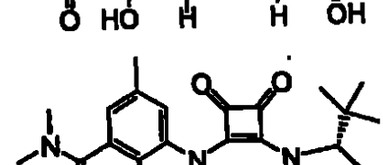


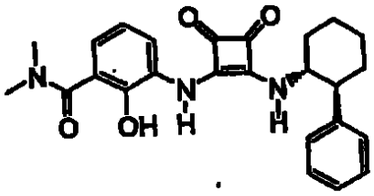


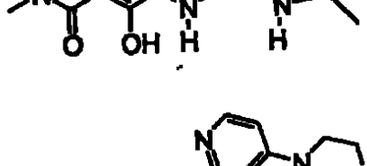


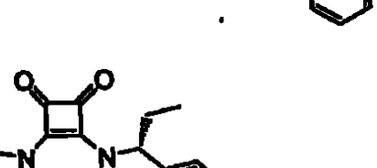


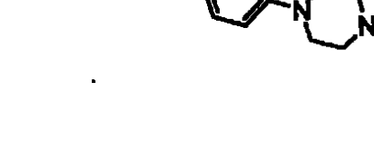


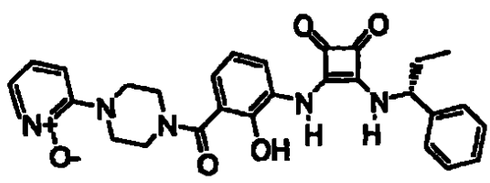


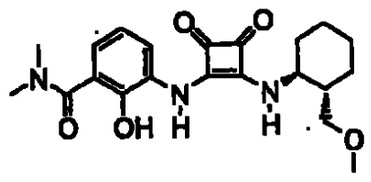


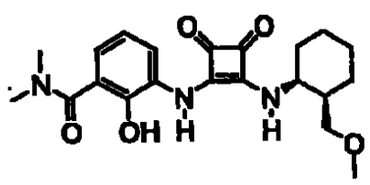


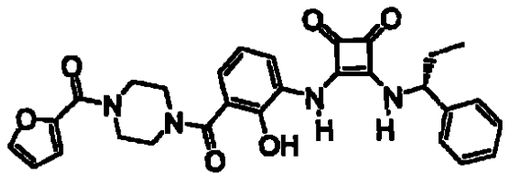


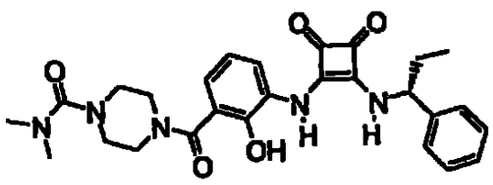


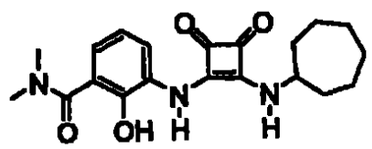


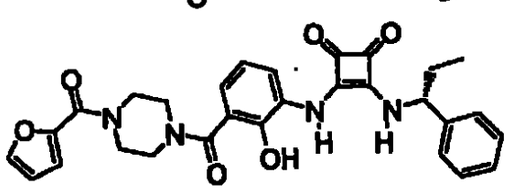


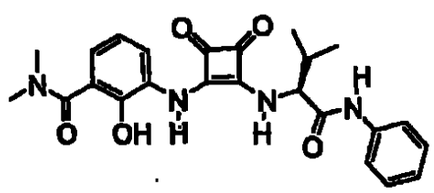


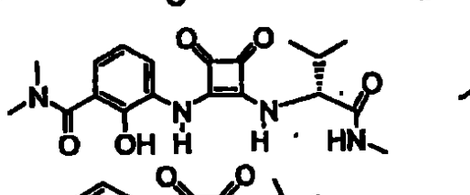


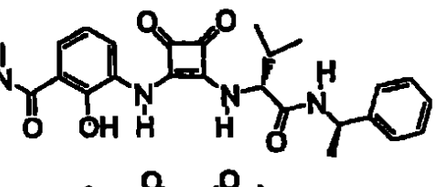


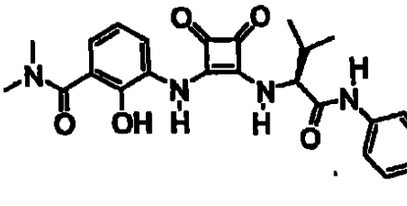


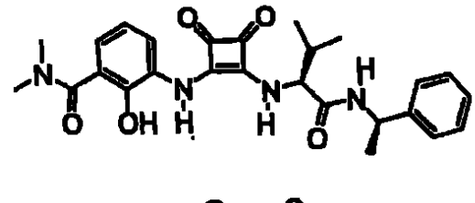


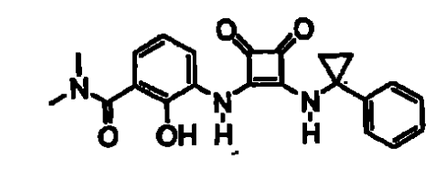


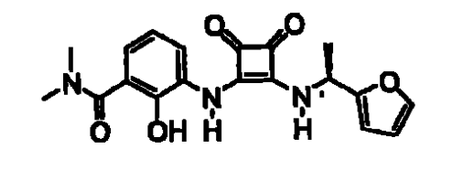




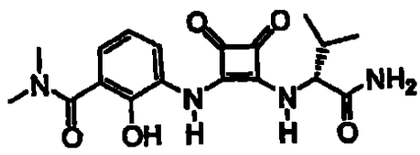


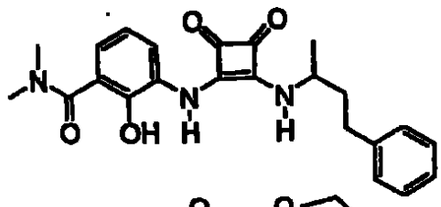


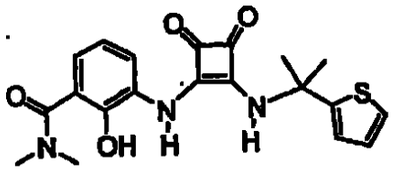


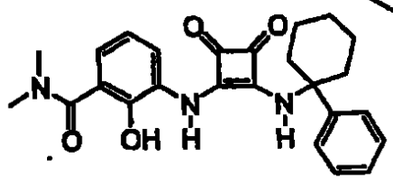


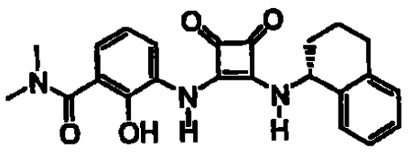
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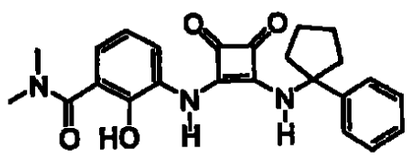


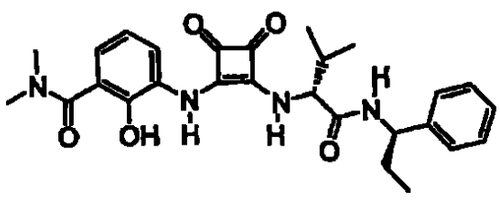


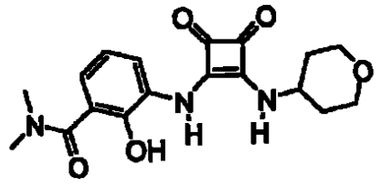


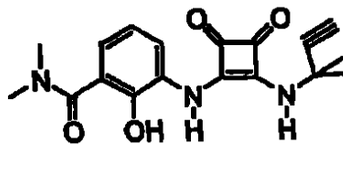


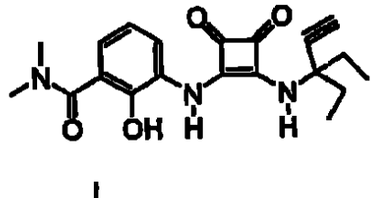


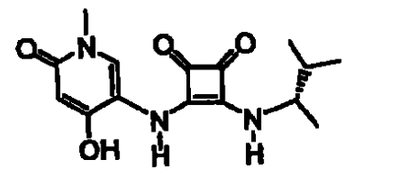


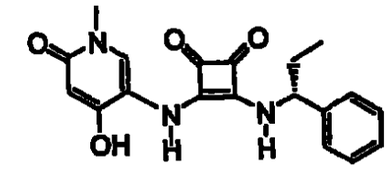


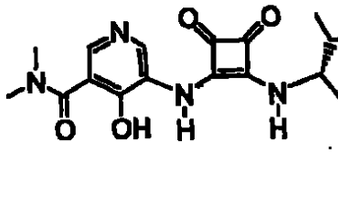


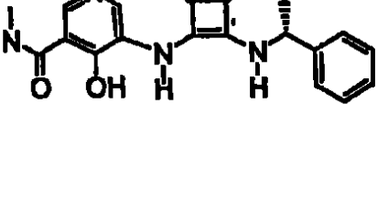




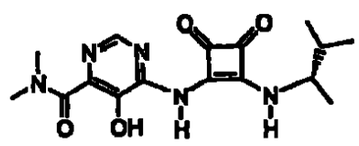


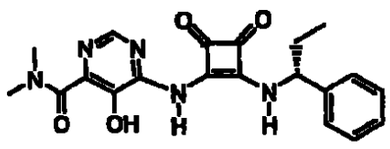


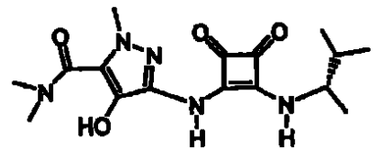


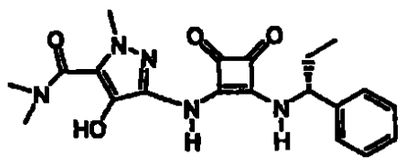


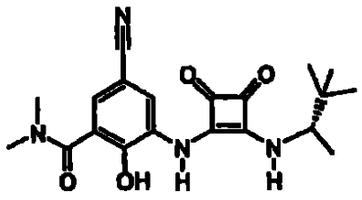
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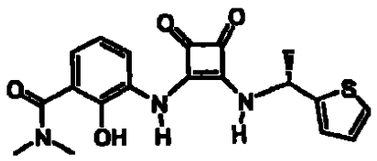


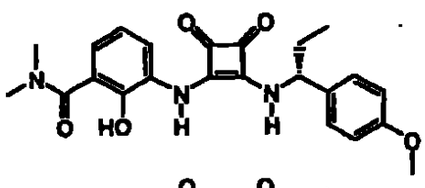


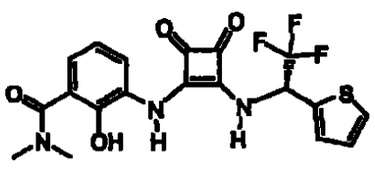


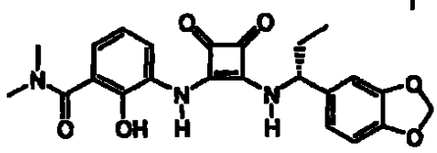


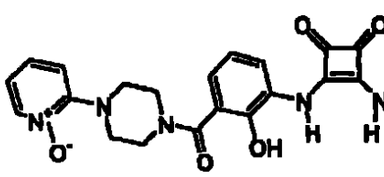


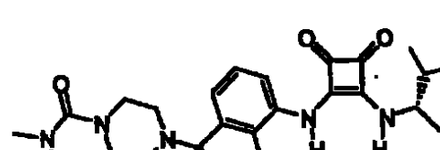


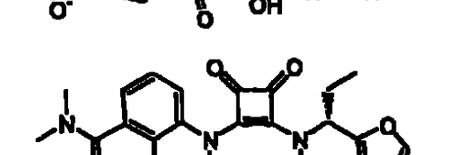


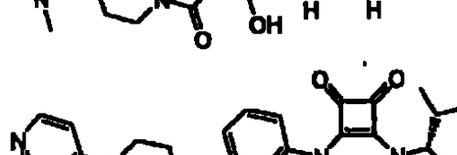


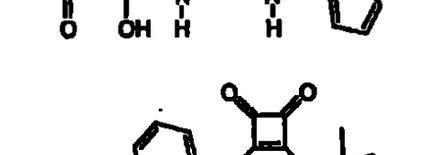


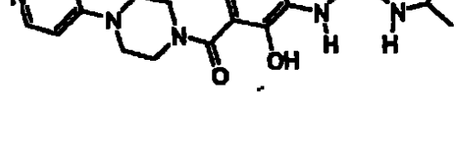


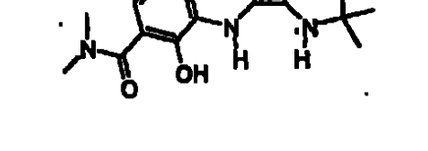




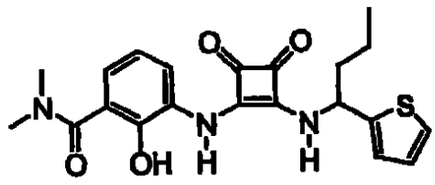


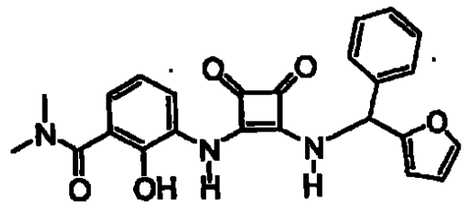


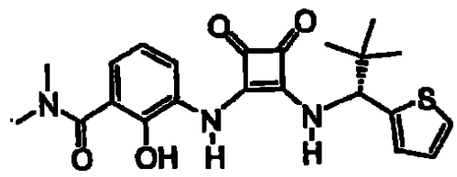


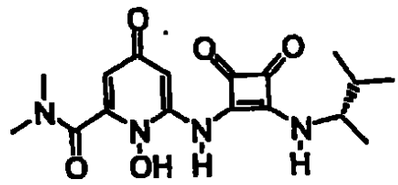


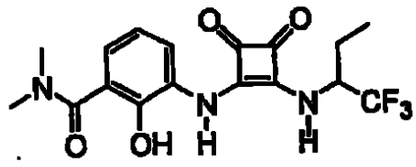
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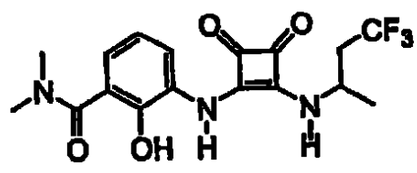


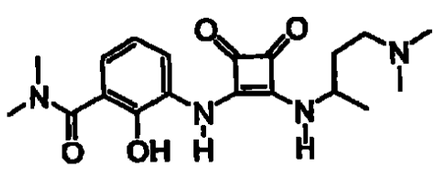


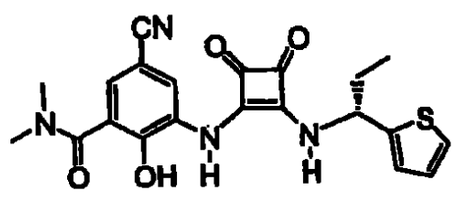


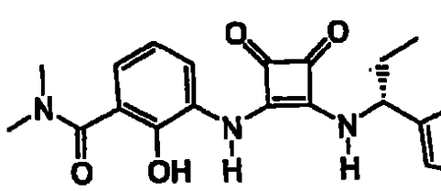




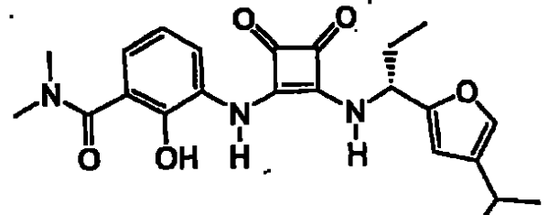


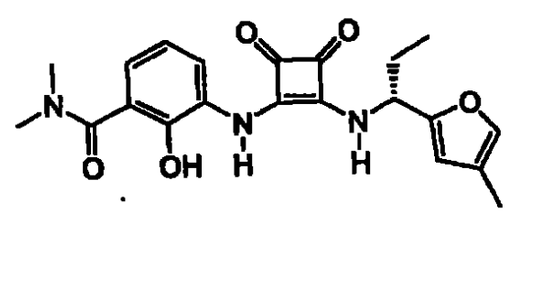


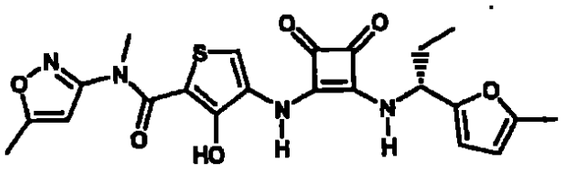


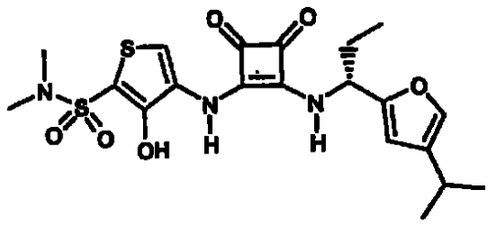


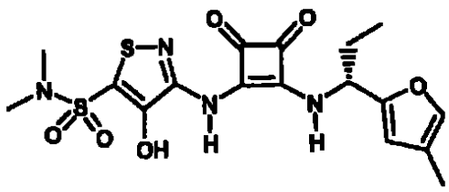


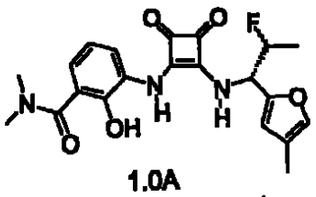




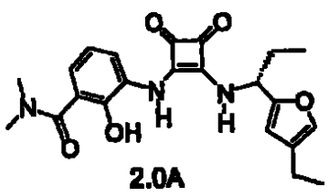




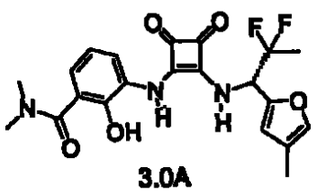




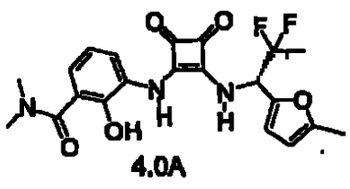
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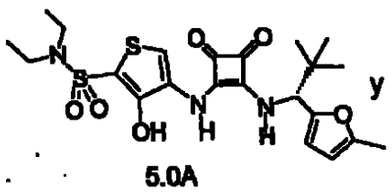
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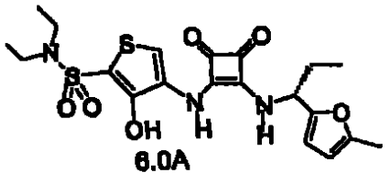
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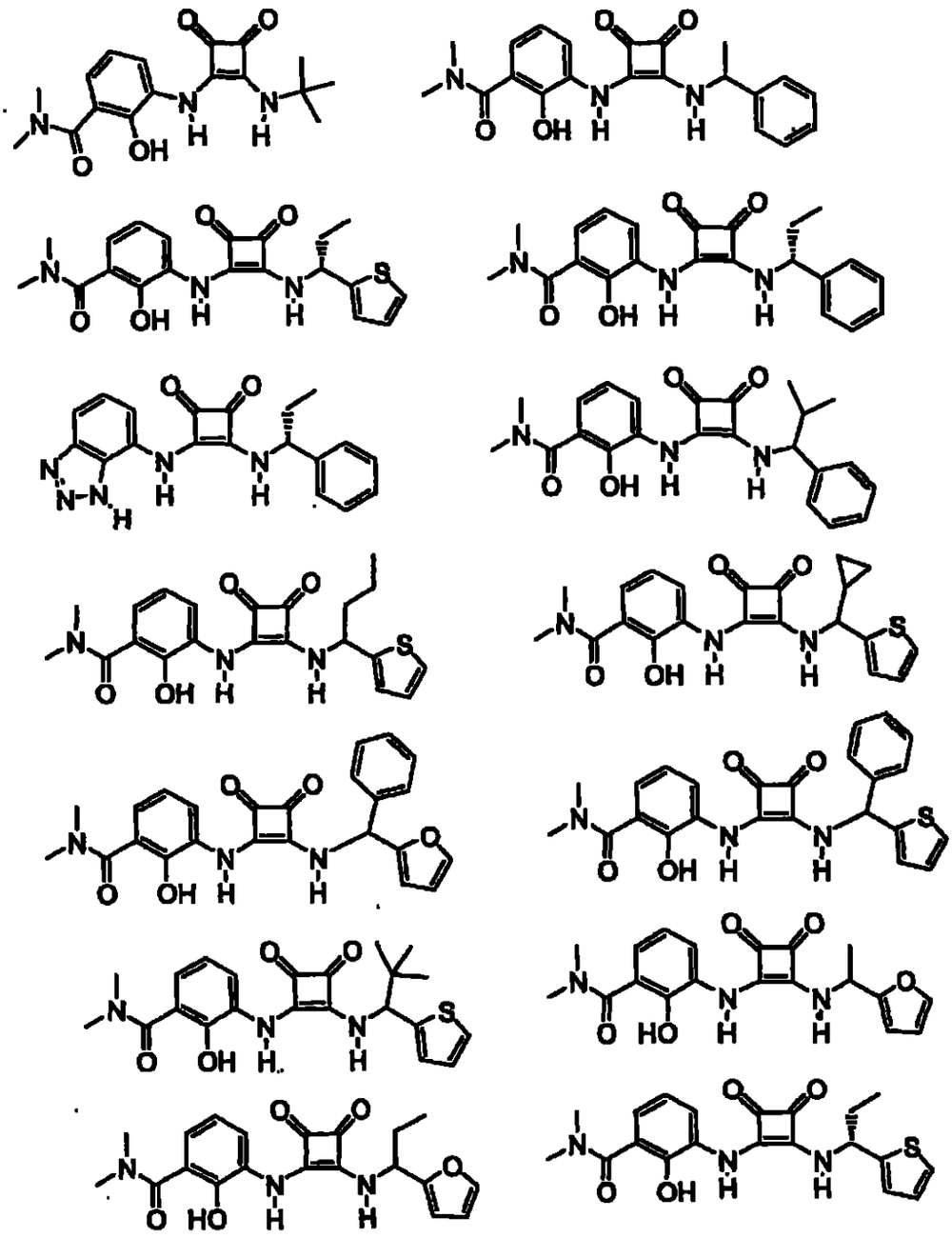
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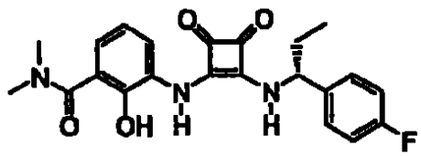
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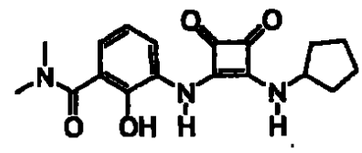
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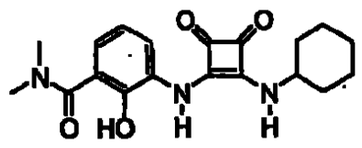
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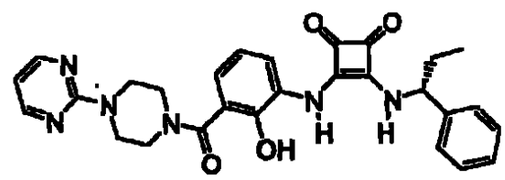


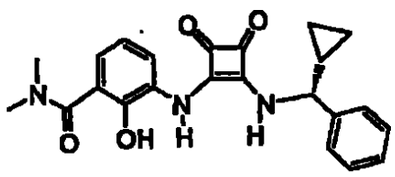
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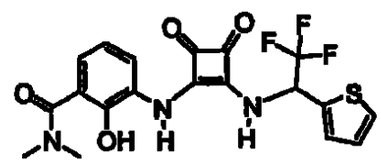


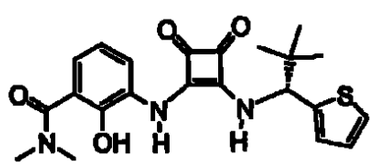


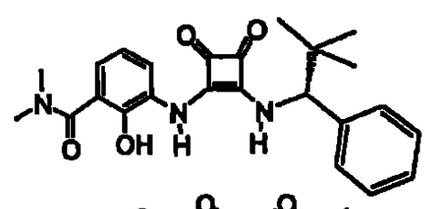


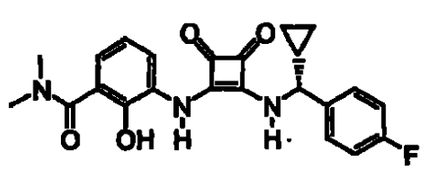


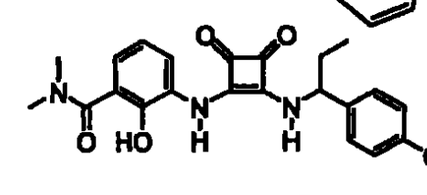


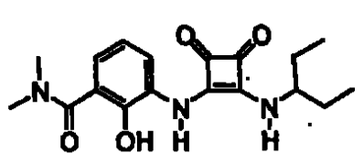


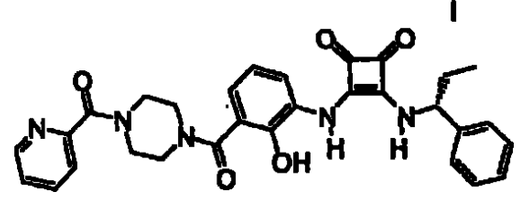


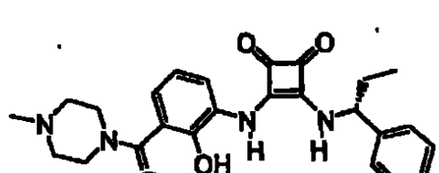


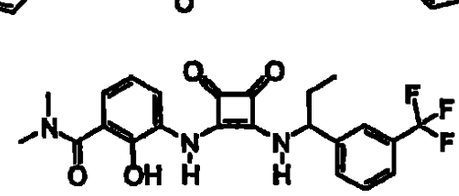


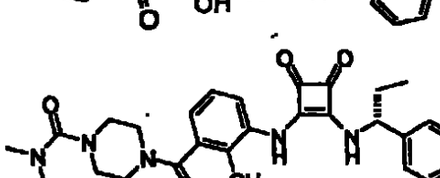


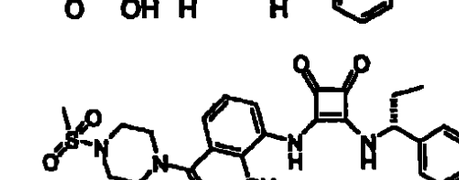


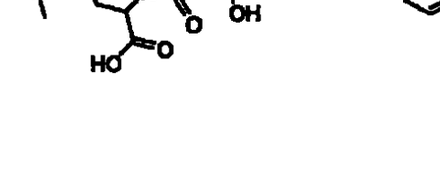


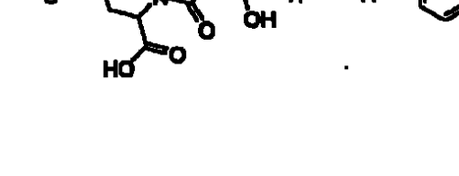




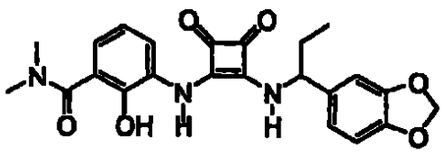


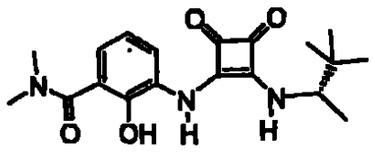


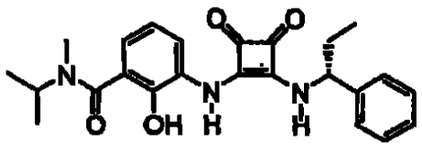


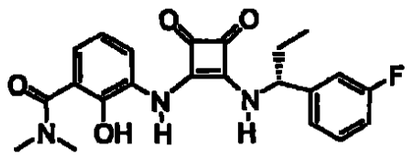


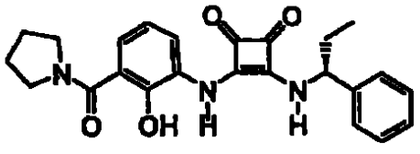
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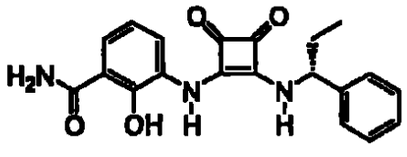


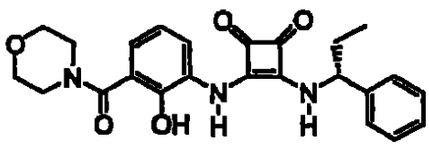


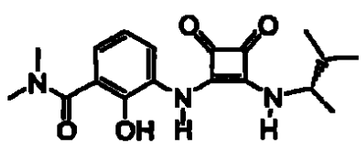


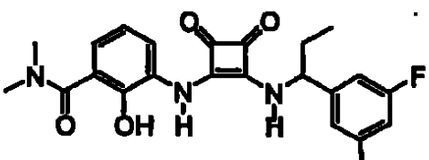


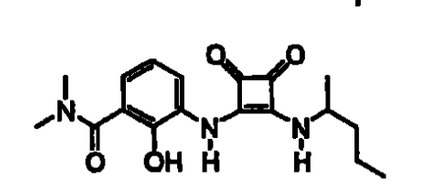


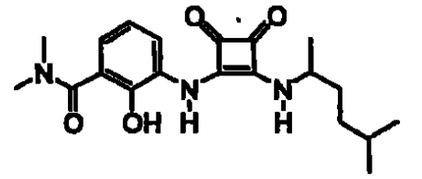


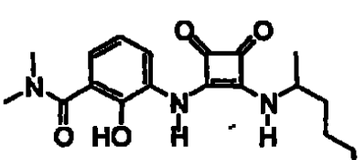


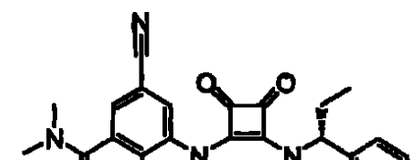




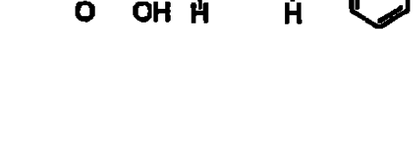




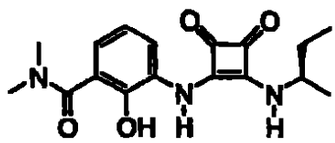


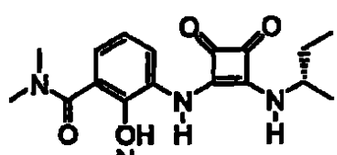


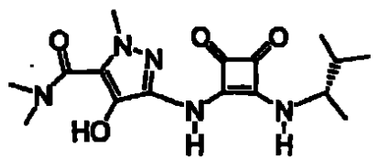


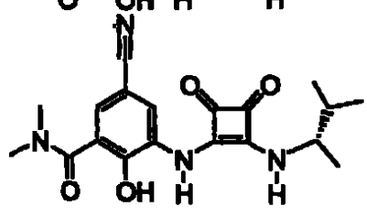


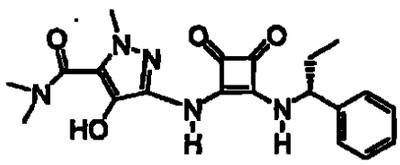
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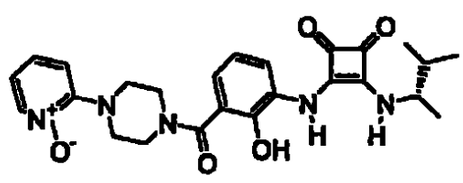


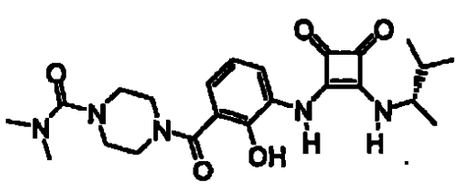


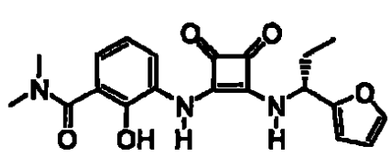


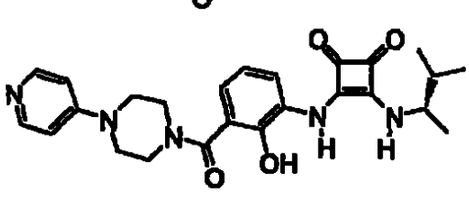


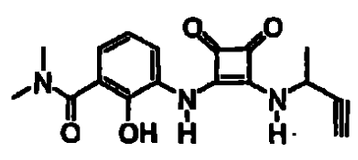


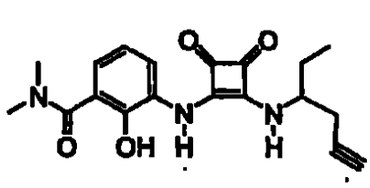


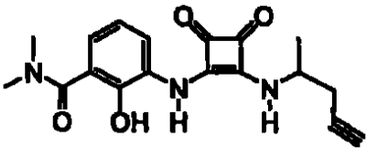


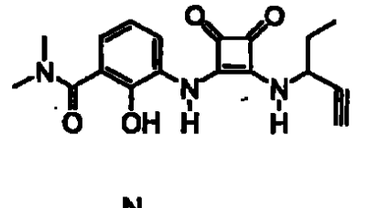


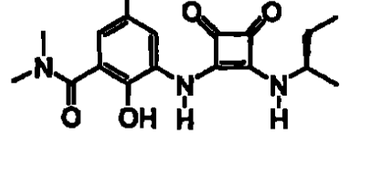


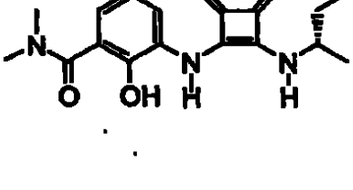


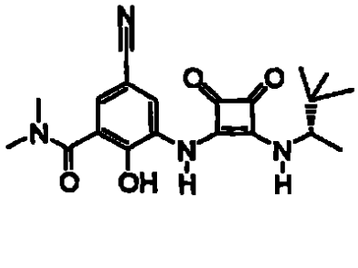


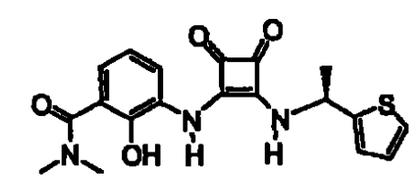


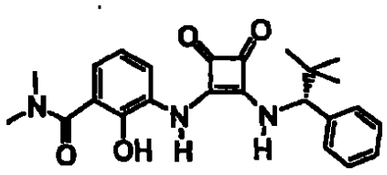


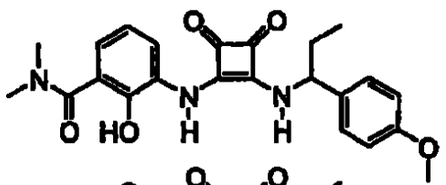


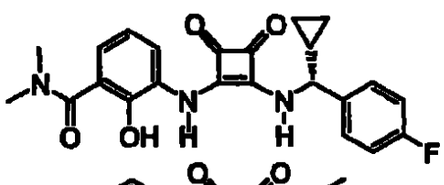


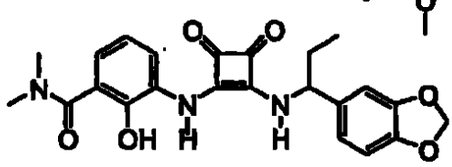


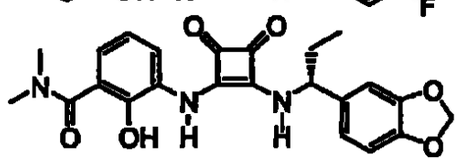


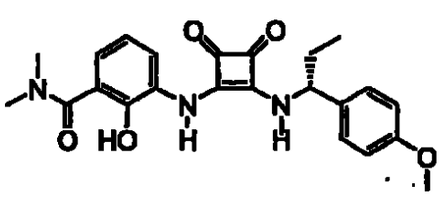


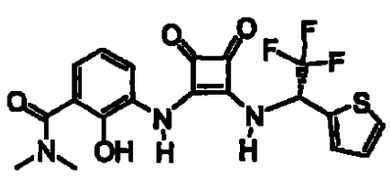


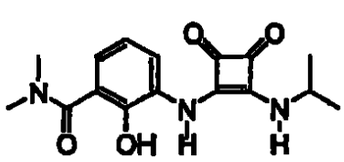


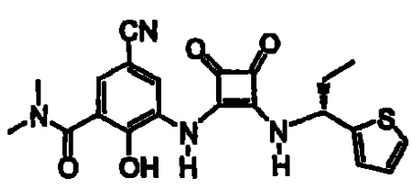


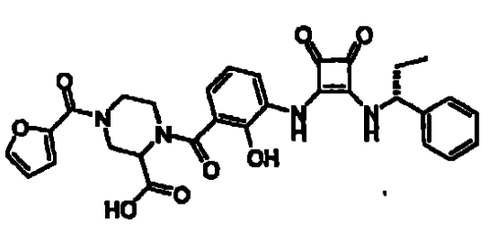


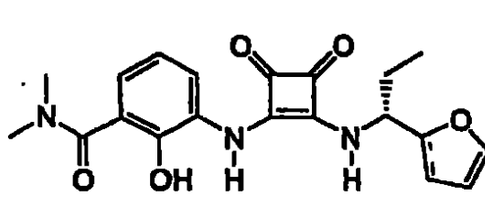


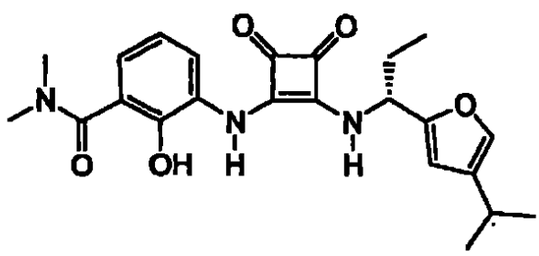


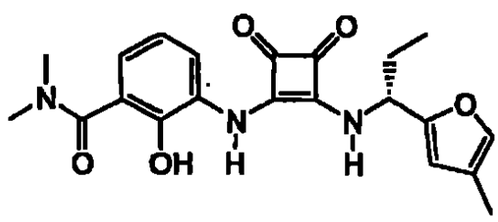


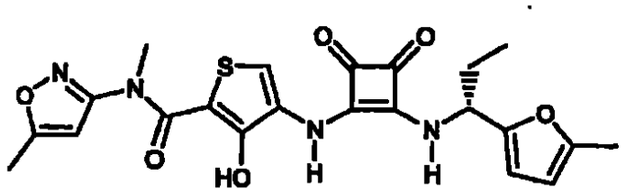


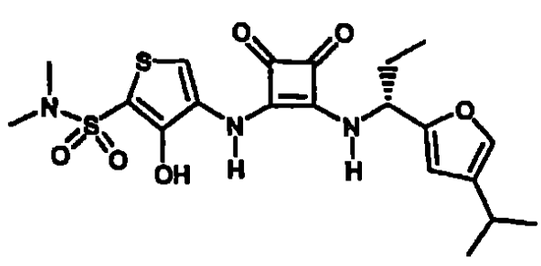


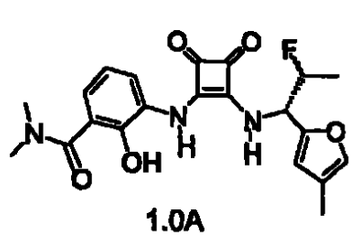




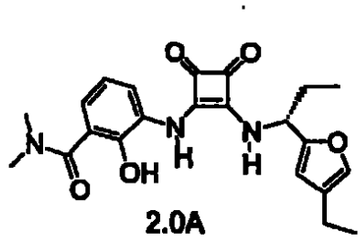






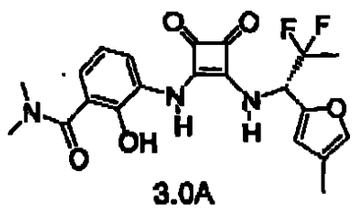


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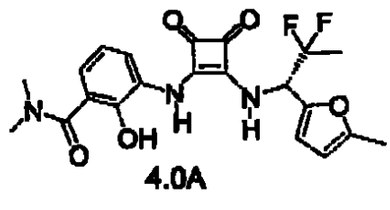


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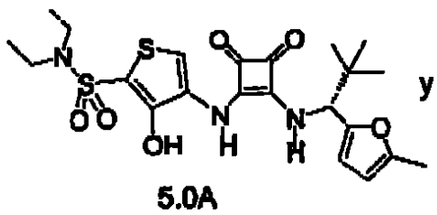
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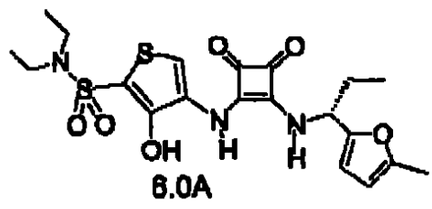


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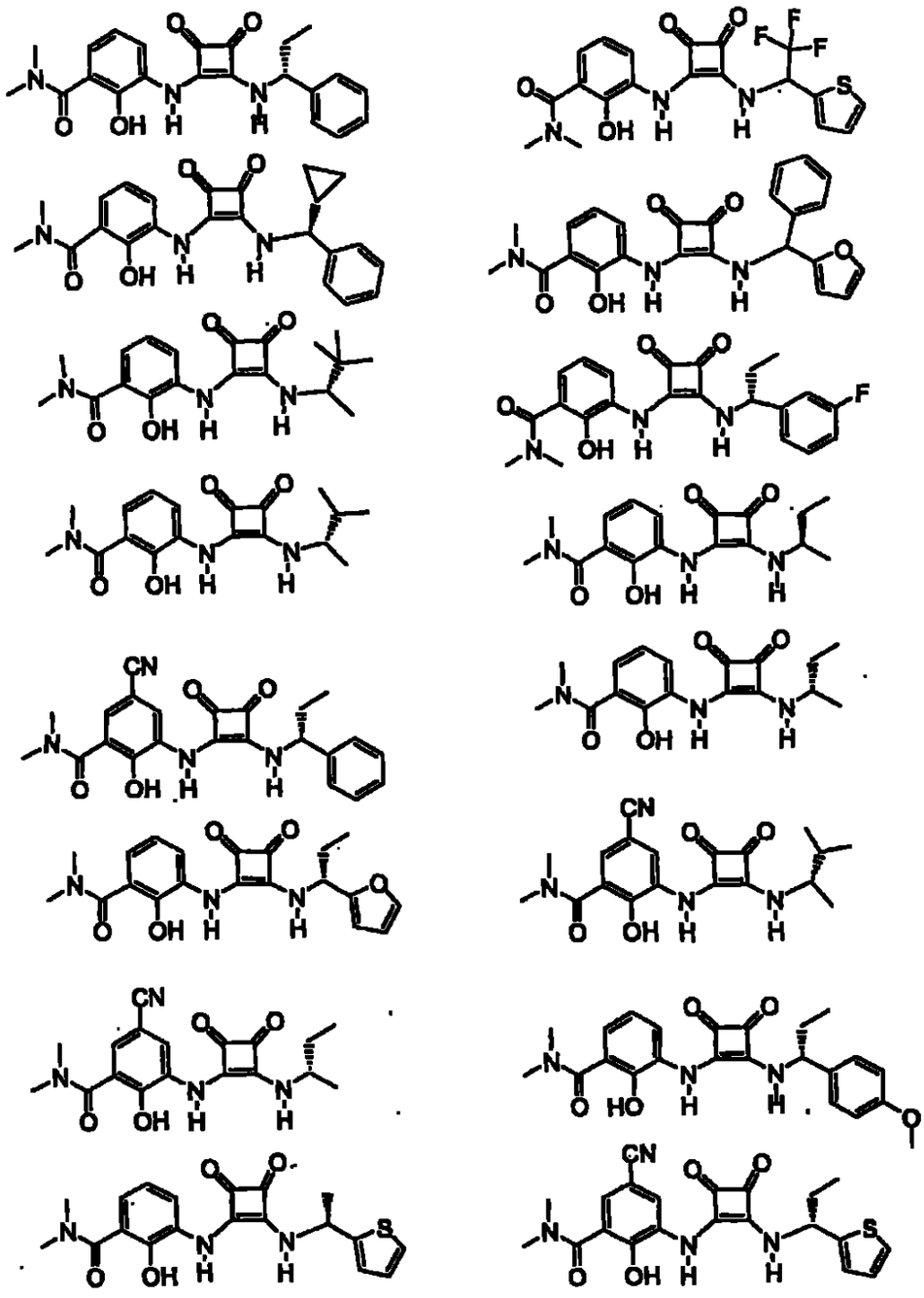
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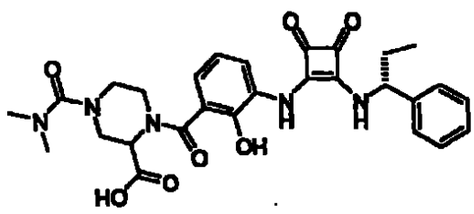
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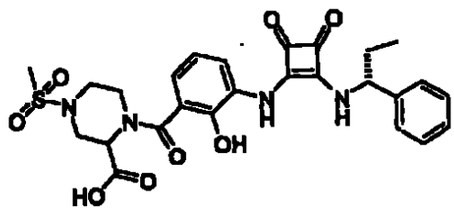


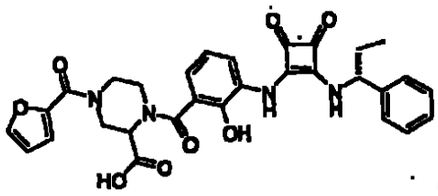
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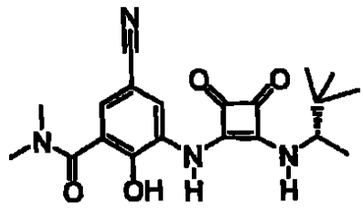
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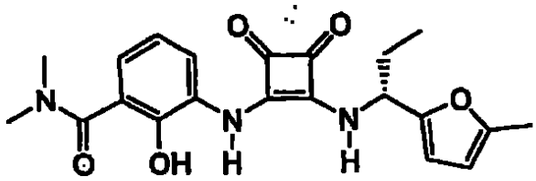


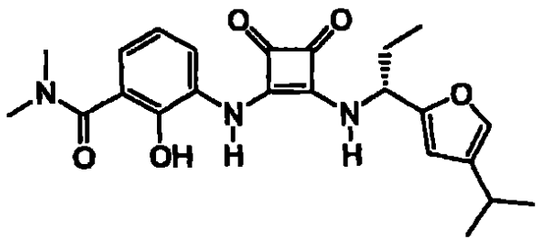


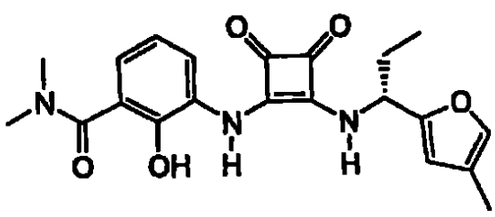


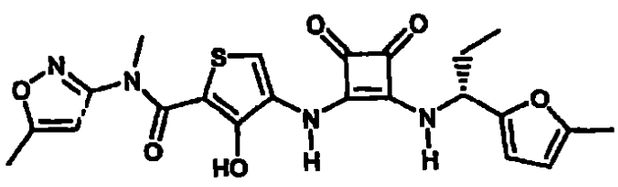


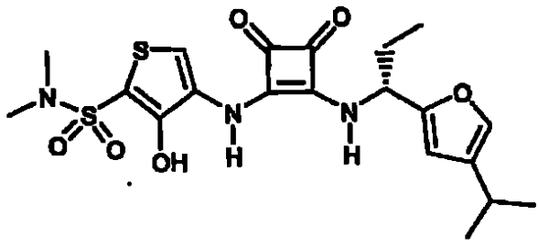


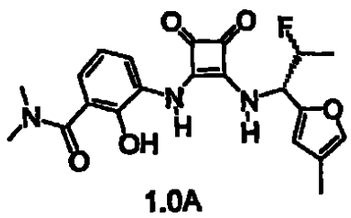




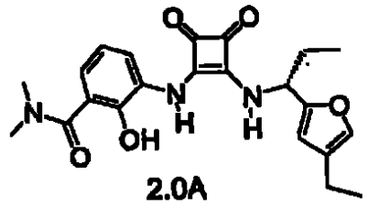




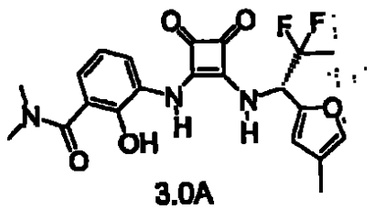




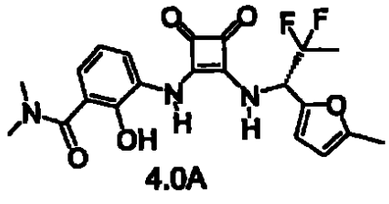
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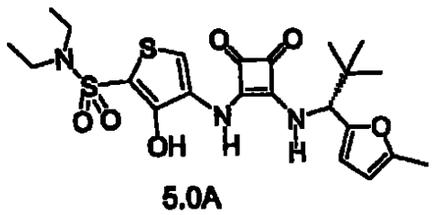
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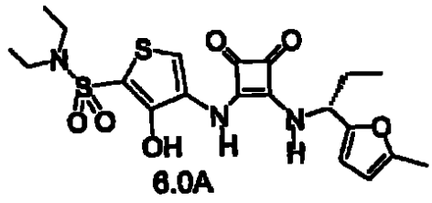


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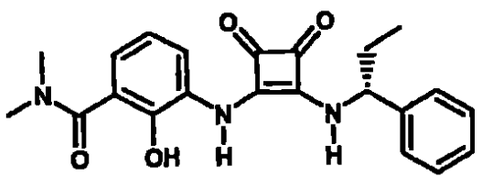
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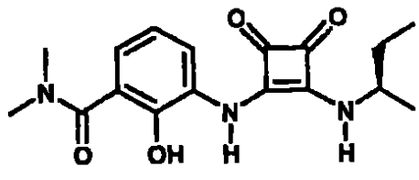


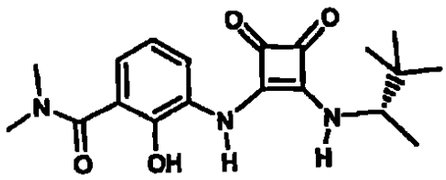
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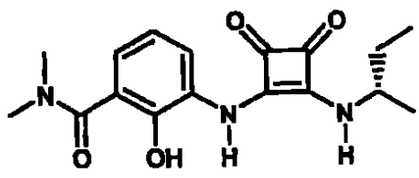
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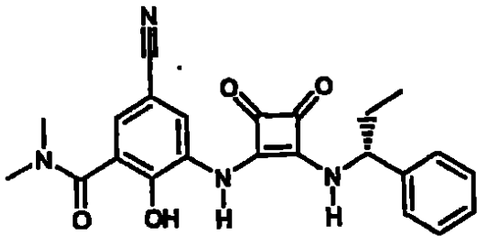
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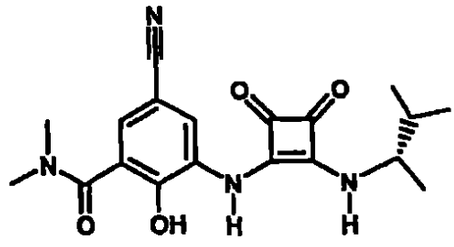


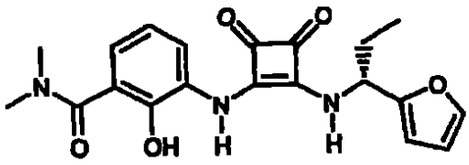


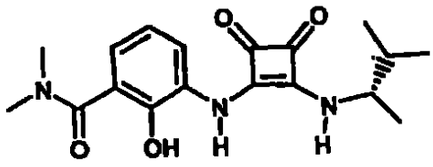


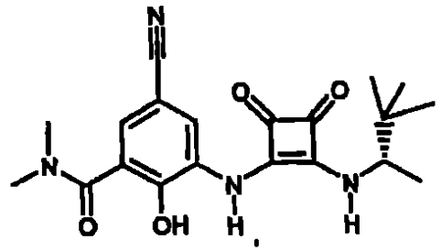


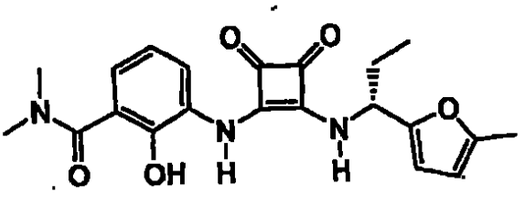


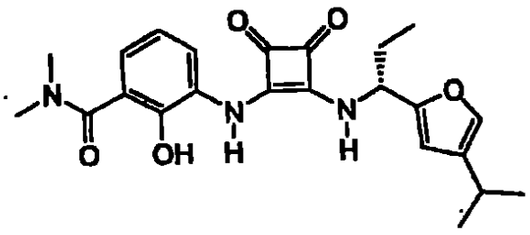


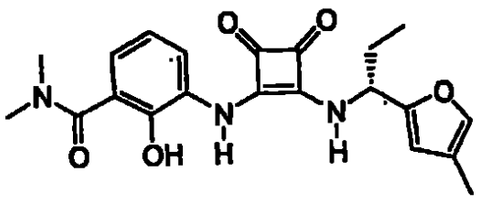


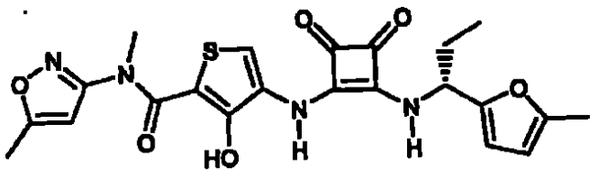


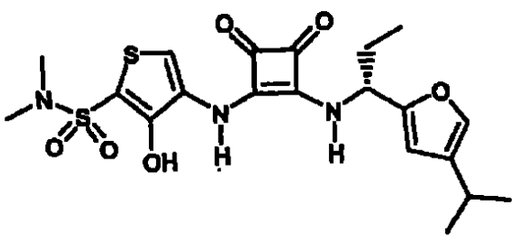


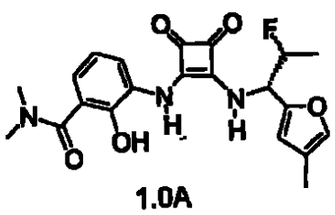




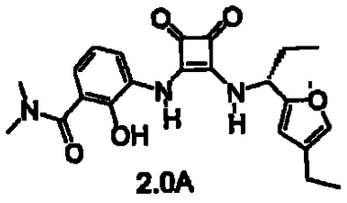




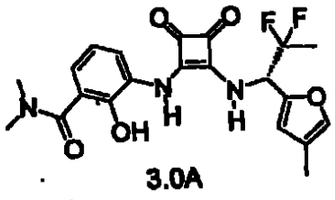




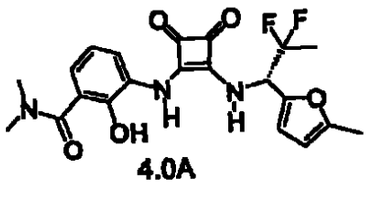
1.0A



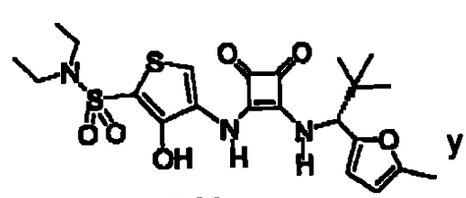
2.0A



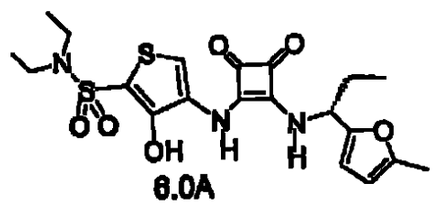
3.0A



4.0A



5.0A y



6.0A

Ciertos compuestos de la invención pueden existir en diferentes formas estereoisoméricas (por ejemplo, enantiómeros, diastereoisómeros y atropisómeros). La invención contempla todos estos estereoisómeros tanto en forma pura como mezcla, incluyendo las mezclas racémicas. Los isómeros pueden ser preparados utilizando métodos convencionales.

La presente invención además incluye Prodrogas de los compuestos de la presente invención.

Ciertos compuestos serán ácidos en naturaleza, por ejemplo aquellos compuestos que poseen un grupo carboxilo o fenólico hidroxilo. Estos compuestos pueden formar sales farmacéuticamente aceptables. Los ejemplos de dichas sales pueden incluir sales de sodio, potasio, calcio, aluminio, oro o plata. También se contemplan las sales formadas con aminas farmacéuticamente aceptables tales como amonio, alquilaminas, hidroxialquilaminas, N-metilglucamina y similares.

Ciertos compuestos básicos también forman sales farmacéuticamente aceptables por ejemplo sales de adición de ácido. Por ejemplo, los átomos pirido-nitrógeno pueden formar sales con ácido fuerte, mientras que los compuestos que tienen sustituyentes básicos tales como los grupos amino también forman sales con ácidos más débiles. Los ejemplos de ácidos adecuados para la formación de sal son clorhídrico, sulfúrico, fosfórico, acético, cítrico, oxálico, malónico, salicílico, malico, fumárico, succinico, ascórbico, maleico, metansulfónico y otros ácidos

minerales y carboxílicos bien conocidos por los expertos en la técnica. Las sales son preparadas poniendo en contacto la forma de base libre con una cantidad suficiente del ácido deseado para producir una sal en la forma convencional. Las formas de base libre pueden ser regeneradas tratando la sal con una solución de base diluida adecuada tal como NaOH acuoso diluido, carbonato de potasio, amonio y bicarbonato de sodio. Las formas de base libre difieren de sus respectivas formas de sal de algún modo en ciertas propiedades físicas, tales como solubilidad en solventes polares, pero las sales de ácido y básicas son por el contrario equivalentes a sus respectivas formas de base libre respectivas a los fines de la invención.

Todas las mencionadas sales de ácido y básicas tienen la intención de ser sales farmacéuticamente aceptables dentro del alcance de la invención y todas las sales de ácido y básicas son consideradas equivalentes a las formas libres de los compuestos correspondientes a los fines de la invención.

Los compuestos de la invención pueden existir en formas solvatadas y no solvatadas, incluyendo las formas hidratadas. En general, las formas solvatadas, con los solventes farmacéuticamente aceptables tales como agua, etanol y similares, son equivalentes a las formas no solvatadas a los fines de la invención.

En una realización del tratamiento de cáncer, un compuesto seleccionado del grupo que consiste de compuestos de las fórmulas IB, 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, (o una sal o solvato farmacéuticamente aceptable de dichos compuestos) es administrado en combinación con uno de los siguientes agentes neoplásicos: gemcitab ne, paclitaxel (Taxol®), 5-fluoruracilo (5-FU), ciclofosfamida (Cytoxan®), temozolomida, taxotere o Vincristine.

En otra realización la presente invención provee un método para tratar el cáncer, que comprende administrar, en forma concurrente o secuencial, una

cantidad efectiva de (a) un compuesto seleccionado del grupo que consiste de los compuestos de las fórmulas 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, (o una sal o solvato farmacéuticamente aceptable de dichos compuestos), y un agente que afecta el microtúbulo, por ejemplo paclitaxel.

En otra realización la presente invención provee un método que comprende administrar a un paciente que lo necesita, en forma concurrente o secuencial, una cantidad terapéuticamente efectiva de (a) un compuesto seleccionado del grupo que consiste de los compuestos de las fórmulas 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, (o una sal o solvato farmacéuticamente aceptable de dichos compuestos), y (b) un agente antineoplásico, un agente que afecta el microtúbulo o un agente anti-angiogénesis.

Para preparar las composiciones farmacéuticas a partir de los compuestos descriptos por la presente invención, los portadores inertes farmacéuticamente aceptables pueden ser sólidos o líquidos. Las preparaciones en forma sólida incluyen, polvos, comprimidos, gránulos dispersables, cápsulas, sellos y supositorios. Los polvos y los comprimidos pueden estar compuestos de aproximadamente 5 a aproximadamente 95 por ciento de ingrediente activo. Los portadores sólidos adecuados son conocidos en la técnica, por ejemplo, carbonato de magnesio, estearato de magnesio, talco, azúcar o lactosa. Los comprimidos, polvos, sellos y cápsulas pueden ser utilizados como formas de dosificación sólidas apropiadas para la administración oral. Los ejemplos de portadores farmacéuticamente aceptables y métodos de fabricación para las diversas composiciones se pueden hallar en A. Gennaro (ed.), *Remmington's Pharmaceutical Sciences,* 18ª Edición, (1990), Mack Publishing Co., Easton, Pensilvania.

Las preparaciones en forma líquida incluyen soluciones, suspensiones y emulsiones. Como ejemplo se pueden mencionar las soluciones acuosas o acuosa-propilen glicol para inyección parenteral o la adición de endulzantes y opacantes para soluciones orales, suspensiones y emulsiones. Las preparaciones en forma líquida también pueden incluir soluciones para administración intranasal.

Las preparaciones en aerosol adecuadas para inhalación pueden incluir soluciones y sólidos en forma de polvo, las cuales pueden estar en combinación con un portador farmacéuticamente aceptable, tal como un gas inerte comprimido, por ejemplo, nitrógeno.

También se incluyen las preparaciones en forma sólida las cuales van a ser convertidas, en breve antes de su uso, a preparaciones en forma líquida para administración oral o parenteral. Dichas formas líquidas incluyen soluciones, suspensiones y emulsiones.

Los compuestos de la invención también pueden ser administrables en forma transdérmica. La composición transdérmica puede tomar la forma de cremas, lociones, aerosoles y/o emulsiones y pueden ser incluidas en un parche transdérmico del tipo matriz o reservorio como ya que son convencionales en la técnica para esta finalidad.

Preferentemente el compuesto es administrado en forma oral.

Preferentemente, la composición farmacéutica está en forma de dosis unitaria. En dicha forma, la preparación es subdividida en dosis unitarias de tamaño adecuado que contienen cantidades apropiadas del componente activo, por ejemplo, una cantidad efectiva para lograr el fin deseado.

La cantidad de compuesto activo en una dosis unitaria de preparación puede ser variada o ajustada desde aproximadamente 0,01 mg a aproximadamente 1000 mg, preferentemente desde aproximadamente 0,01 mg a aproximadamente 750 mg, más preferentemente desde aproximadamente 0,01

mg a aproximadamente 500 mg, y más preferentemente desde aproximadamente 0,01 mg a aproximadamente 250 mg, de acuerdo con la aplicación en particular.

La dosis real empleada puede ser variada dependiendo de los requerimientos del paciente y la severidad de la enfermedad a ser tratada. La determinación del régimen de dosificación adecuada para una situación en particular está dentro de la capacidad de la técnica. Por conveniencia, la dosificación total puede ser dividida y administrada en porciones durante el día según se requiera.

La cantidad y frecuencia de la administración de los compuestos de la invención y/o las sales farmacéuticamente aceptables de los mismos será regulada de acuerdo con el criterio del médico interviniente tomando en cuenta factores tales como la edad, el estado y la estructura del paciente como también la severidad de los síntomas que se tratan. Un régimen de dosificación diario recomendado típico para administración oral puede variar desde aproximadamente 0,04 mg/día a aproximadamente 400 mg/día, en dos a cuatro dosis divididas.

Las clases de compuestos que pueden ser utilizados como agente quimioterapéutico (agente antineoplásico) incluyen, agentes alquilantes, antimetabolitos, productos naturales y sus derivados, hormonas y esteroides, y sintéticos. Ejemplos de compuestos dentro de estas clases se aportan a continuación.

Agentes alquilantes (incluyendo mostazas de nitrógeno, derivados de etilenimina, sulfonatos de alquilo, nitrosoureas y triazenos): Mostaza de Uracilo, Clormetina, Ciclofosfamida (Cytoxan®), Ifosfamida, Melfalan, Clorambucilo, Pipobroman, Trietilen-melamina, Trietilentiofosforamina, Busulfan, Carmustine, Lomustine, Stretozocin, Dacarbazine y Temozolomida.

Antimetabolitos (incluyendo antagonistas del ácido folico, análogos de

pirimidina, análogos de purina, e inhibidores de adenosina deaminasa): Metotrexato, 5-Fluoruracilo, Floxuridina, Citarabina, 6-Mercaptopurina, 6-Tioguanina, Fludarabin fosfato, Pentostatina, y Gemcitabina.

Productos Naturales y sus derivados (incluyendo vinca alcaloides, antibióticos antitumorales, enzimas, linfocinas y epipodofillotoxinas): Vinblastine, Vincristine, Vindesine, Bleomicin, Dactinomicin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Paclitaxel (paclitaxel está comercialmente disponible como Taxol® y se describe en más detalle a continuación en la sección titulada "Agentes que Afectan al Microtúbulo"), Mitramicin, Deoxico-formicin, Mitomicin-C, L-Asparginasa, Interferones (especialmente IFN-a), Etoposide, y Teniposide.

Hormonas y Esteroides (incluyendo análogos sintéticos): 17α-etinilestradiol, Dietilstilbestrol, Testosterona, Prednisona, Fluoximesterona, Dromostanolona propionato, Testolactona, Megestrolacetato, Tamoxifen, Metilprednisolona, Metil-testosterona, Prenisolona, Triamcinolona, Clorotrianiseno, Hidroxiprogesterona, Aminoglutetimida, Estramustine, Medroxiprogesteronacetato, Leuprolide, Flutamida, Toeremifeno, Zoladex.

Sintéticos (incluyendo complejos orgánicos tales como complejos de coordinación de platino): Cisplatin, Carboplatin, Hidroxiurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Leamisol., y Hexametilmelamina.

Los métodos para la administración segura y efectiva de la mayoría de estos agentes quimioterapéuticos son conocidos por los expertos en la técnica. Además, su administración se describe en la literatura estándar. Por ejemplo, la administración de muchos de los agentes quimioterapéuticos se describe en "Physicians Desk Reference" (PDR), por ejemplo edición 2002 (Medical Economics Company, Montvale, NJ 07645-1742, EE.UU.); la descripción de la cual se incorpora a la presente como referencia.

Tal como se utiliza en la presente, un agente que afecta el microtúbulo es

un compuesto que interfiere con la mitosis celular, es decir, tiene un efecto anti-mitótico, afectando la formación y/o acción del microtúbulo. Dichos agentes pueden ser, por ejemplo, agentes estabilizantes del microtúbulo o agentes rompen la formación del microtúbulo.

Los agentes que afectan el microtúbulo útiles en la invención son bien conocidos por los expertos en la técnica e incluyen, pero sin limitarse a alocolchicine (NSC 406042), Halocondrin B (NSC 609395), colchicine (NSC 757), derivados de colchicine (por ejemplo NSC 33410), dolastatin 10 (NSC 376128), maytansine (NSC 153858), rizoxin (NSC 332598)k paclitaxel (Taxol , NSC 125973), derivados de Taxol® (por ejemplo derivados (por ejemplo NSC 608832) tiocolchicine (NSC 361792), cisteína tritilo (NSC 83265), vinblastine sulfato (NSC 49842), sulfato de vincristine (NSC 67574), epotilone A, epotilone, y discodermolide (Ver Servicios, (1996) *Science*, 274:209) estramustine, nocodazol, MAP4, y similares. Ejemplos de dichos agentes también se describen en la literatura científica y de patente, ver por ejemplo, Bulinski (1997), *J. Cell Sci.* 110:3055-3064; Panda (1997) *Proc. Natl. Acad. Sci.* USA 94:10560:10546; Muhlradt (1998) Cancer Res. 57:3344-3346; Nicolaou (1997) *Nature* 387:268-272; Vasquez (1997) *Mol. Biol. Cell.* 8:973-985; Panda (1996) *J. Biol. Chem.* 271:29807-29812.

Los agentes particularmente preferidos son los compuestos con actividad similar a la del paclitaxel. Estos incluyen, pero sin limitarse al paclitaxel y los derivados de paclitaxel (compuestos similares al paclitaxel) y análogos. El paclitaxel y sus derivados están comercialmente disponibles. Además, los métodos para fabricar paclitaxel y los derivados de paclitaxel y los análogos son bien conocidos por los expertos en la técnica (ver por ejemplo las Patentes Estadounidenses Nos: 5.569.729; 5.565.478; 5.530.020; 5.527.924; 5.508.447; 5.489.589; 5.488.116, 5.484.809; 5.478.854; 5.478.736; 4.475.120; 5.468.769;

5.461.169; 5.440.057; 5.422.364; 5.411.984; 4.405.972; y 5.296.506).

Más específicamente, el término "paclitaxel" tal como se utiliza en la presente se refiere a la droga comercialmente disponible como Taxol® (NSC número: 125973). Taxol® inhibe la replicación de la célula eucariótica intensificando la polimerización de las porciones de tubulina en manojos de microtúbulo estabilizados que son incapaces de reorganizar las estructuras adecuadas para la mitosis. De las muchas drogas quimioterapéuticas disponibles, paclitaxel ha generado interés debido a su eficacia en ensayos clínicos contra tumores refractarios a la droga, incluyendo tumores de varios y glándula mamaria (Hawkins (1992) *Oncology,* 6: 17-23, Horwitz (1992) *Trends Pharmacol. Sci.* 13: 134-146, Rowinsky (1990) *J. Natl. Canc. Inst.* 82: 1247-1259).

Los agentes que afectan el microtúbulo adicionales pueden ser evaluados utilizando uno de los muchos ensayos conocidos en la técnica, por ejemplo un ensayo semiautomatizado que mide la actividad polimerizante tubulina de los análogos de paclitaxel en combinación con un ensayo celular para medir el potencial de estos compuestos para bloquear las células en la mitosis (ver Lopes (1997) *Cancer Chemother. Pharmcol.* 41:37-47).

En general, la actividad de un compuesto de ensayo está determinada por el contacto de una célula con ese compuesto y por la determinación de sí se ha roto o no el ciclo celular, en particular, a través de la inhibición de un evento mitótico. Dicha inhibición puede ser mediada por la ruptura del aparato mitótico, por ejemplo, la ruptura de la formación de la espiga. Las células en las cuales se interrumpe la mitosis puede estar caracterizada por la morfología alterada (por ejemplo compactación del microtúbulo, cantidad de cromosoma incrementada, etc.) .

Los compuestos con una posible actividad de polimerización de tubulina pueden ser cribados *in vitro.* En una realización preferida, los compuestos son

cribados contra las células WR21 cultivadas (derivadas de la línea de ratones 69-2 wap-ras) para la inhibición de la proliferación y/o para la morfología celular alterada, en particular la compactación del microtúbulo. El cribado *in vivo* de los compuestos de ensayo positivo puede realizarse entonces utilizando ratones inmunológicamente deficientes que soportan las células tumorales WR21. Los protocolos detallados para el cribado se describen por Porter (1995) *Lab. Amin.Sci.* 45(2): 145-150.

Otros métodos para el cribado de compuestos para la actividad deseada son bien conocidos en la técnica. Típicamente dichos ensayos involucran los ensayos para la inhibición del ensamblado y/o desarme del microtúbulo. Los ensayos para el ensamblado del microtúbulo se describen, por ejemplo, en Gaskin y Otros (1974) *J. Molec. Biol.*, 89: 737-75. La patente estadounidense No. 5.569.720 también provee ensayos *in vitro e in vivo* para los compuestos con actividad similar al paclitaxel.

Los métodos para la administración segura y efectiva de los agentes que afectan el microtúbulo son conocidos por los expertos en la técnica. Además, su administración se describe en la literatura estándar. Por ejemplo, la administración de muchos de los agentes quimioterapéuticos se describe en "Physicians Desk Reference" (PDR), por ejemplo edición 2002 (Medical Economics Company, Montvale, NJ 07645-1742, EE.UU.); la descripción de la cual se incorpora a la presente como referencia.

La cantidad y frecuencia de la administración de los compuestos de los compuestos de las fórmulas IA, IB, 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, (o una sal o solvato farmacéuticamente aceptable de dichos compuestos) y los agentes quimioterapéuticos y/o terapia de radiación será regulada de acuerdo con el criterio del médico interviniente tomando en cuenta factores tales como la edad,

el estado y la estructura del paciente como también la severidad de los síntomas que se tratan. Un régimen de dosificación de los compuestos de las fórmulas IA, IB, 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, (o una sal o solvato farmacéuticamente aceptable de dichos compuestos) puede ser la administración oral de aproximadamente 10 mg a 2000 mg/día preferentemente 10 a 1000 mg/día, más preferentemente 50 a 600 mg/días, en dos a cuatro (preferentemente dos) dosis divididas, para bloquear el desarrollo del tumor. La terapia intermitente (por ejemplo una de tres semanas o tres de cuatro semanas) puede ser utilizada.

El agente quimioterapéutico y/o la terapia de radiación puede ser administrada de acuerdo con los protocolos terapéuticos bien conocidos en la técnica. Será evidente para los expertos en la técnica que la administración del agente quimioterapéutico y/o la terapia de radiación puede ser variada de acuerdo con la enfermedad a ser tratada y los efectos conocidos del agente quimioterapéutico y/o terapia de radiación sobre esa enfermedad. Además, de acuerdo con el conocimiento del clínico idóneo, los protocolos terapéuticos (por ejemplo, cantidad de dosis y tiempos de administración) pueden ser variados en vista de los efectos observados de los agentes terapéuticos administrados (es decir, agente antineoplásico o radiación) en el paciente, y en vista de las respuestas observadas de la enfermedad a los agentes terapéuticos administrados.

Las realizaciones de la presente invención están dirigidas a métodos de tratamiento en donde los compuestos de las fórmulas IB, 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, (o una sal o solvato farmacéuticamente aceptable de dichos compuestos) son administrados en forma concurrente o secuencial con un

agente quimioterapéutico y/o radiación. De este modo, no es necesario que, por ejemplo, el agente quimioterapéutico y dichos compuestos, o la radiación y dichos compuestos, deban ser administrados simultáneamente o esencialmente en forma simultánea. La ventaja de una administración simultánea o esencialmente simultánea está bien dentro del la determinación del médico idóneo.

Además, en general, los compuestos de las fórmulas IB, 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, (o una sal o solvato farmacéuticamente aceptable de dichos compuestos), y el agente quimioterapéutico, no deben ser administrados en la misma composición farmacéutica, y puede, debido a diferentes características físicas y químicas, tener que ser administrados por diferentes rutas. Por ejemplo, los compuestos de las fórmulas IB, 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, (o una sal o solvato farmacéuticamente aceptable de dichos compuestos) pueden ser administrados en forma oral para generar y mantener buenos niveles de sangre de los mismos, mientras el agente quimioterapéutico puede ser administrado en forma intravenosa. La determinación del modo de administración y la conveniencia de administración, donde sea posible, en la misma composición farmacéutica, está bien dentro del conocimiento del médico idóneo. La administración inicial puede ser hecha de acuerdo con los protocolos establecidos conocidos en la técnica, y luego, en base a los efectos observados, la dosis, el modo de administración y los tiempos de administración pueden ser modificados por el médico idóneo.

La elección particular de un compuesto de las fórmulas IB, 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, (o una sal o solvato farmacéuticamente aceptable de dichos compuestos) y el agente quimioterapéutico y/o radicación dependerá del

diagnóstico de los médicos intervinientes y su criterio respecto del estado del paciente y el protocolo de tratamiento apropiado.

Los compuestos de las fórmulas IB, 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, (o una sal o solvato farmacéuticamente aceptable de dichos compuestos), y el agente quimioterapéutico y/o radiación pueden ser administrados en forma concurrente (por ejemplo, en forma simultánea, esencialmente en forma simultánea o dentro del mismo protocolo de tratamiento) o en forma secuencial, dependiendo de la naturaleza de la enfermedad proliferativa, el estado del paciente, y la elección real del agente quimioterapéutico y/o radiación a ser administrado en conjunto (es decir, dentro de un solo protocolo de tratamiento) con los compuestos IB, 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, (o una sal o solvato farmacéuticamente aceptable de dichos compuestos).

Si los compuestos de las fórmulas IB, 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, (o una sal o solvato farmacéuticamente aceptable de dichos compuestos), y el agente quimioterapéutico y/o radiación no son administrados en forma simultánea o esencialmente simultánea, luego la orden inicial de administración de los compuestos de las fórmulas IB, 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, (o una sal o solvato farmacéuticamente aceptable de dichos compuestos), y el agente quimioterapéutico y/o radiación, no pueden ser importantes. De este modo, los compuestos de fórmulas IB, 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, (o una sal o solvato farmacéuticamente aceptable de dichos compuestos) pueden ser administrados primero, seguido de la

administración del agente quimioterapéutico y/o radiación: o el agente quimioterapéutico y/o radiación pueden ser administrados primero seguido de la administración de los compuestos de las fórmulas IB, 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, (o una sal o solvato farmacéuticamente aceptable de dichos compuestos). Esta administración alternativa puede ser repetida durante un solo protocolo de tratamiento. La determinación de la orden de administración, y la cantidad de repeticiones de administración de cada agente terapéutico durante un protocolo de tratamiento, está bien dentro del conocimiento del médico idóneo después de la evaluación de la enfermedad que se está tratando y el estado del paciente.

Por ejemplo, el agente quimioterapéutico y/o radiación puede ser administrado primero, especialmente si es un agente citotóxico, y luego el tratamiento continuó con la administración de los compuestos de las fórmulas IB, 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, (o una sal o solvato farmacéuticamente aceptable de dichos compuestos) seguido, donde se considere ventajoso, de la administración del agente terapéutico y/o radiación, y así hasta que se complete el protocolo de tratamiento.

De este modo, de acuerdo con la experiencia y el conocimiento, el médico interviniente puede modificar cada protocolo para la administración de un componente (agente terapéutico – es decir, los compuestos de las fórmulas IB, 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088, (o una sal o solvato farmacéuticamente aceptable de dichos compuestos), el agente quimioterapéutico o radiación) del tratamiento de acuerdo con las necesidades del paciente individual a medida que el tratamiento avanza.

El médico interviniente, al juzgar si el tratamiento es efectivo a la dosis administrada, considerará el bienestar general del paciente como también señales más definidas tales como alivio de los síntomas relacionados con la enfermedad, inhibición del desarrollo del tumor, contracción real del tumor, o inhibición de la metástasis. El tamaño del tumor puede ser medido mediante métodos estándar tales como estudios radiológicos, por ejemplo, CAT o scan MRI, y mediciones sucesivas pueden ser utilizadas para juzgar si el desarrollo del tumor ha sido o no retardado o aún revertido. El alivio de los síntomas relacionados con la enfermedad tal como el dolor, y la mejora en el estado general también puede ser utilizado para juzgar la efectividad del tratamiento.

Ejemplos Biológicos

Los compuestos de la presente invención son útiles en el tratamiento de las enfermedades y trastornos mediados por la quimiocina CXC. Esta utilidad se manifiesta en su capacidad de inhibir la quimiocina IL-8 y GRO-α tal lo demostrado por los siguientes ensayos *in vitro*.

Ensayos de Unión del Receptor:

Ensayo CXCR1 SPA

Para cada pocillo de una placa de 96 pocillos, una mezcla de reacción de 10 µg de membranas sobreexpresantes hCXCR1-CHO (Biosignal) y 200 µg/pocillo de perlas WGA-SPA (Amersham) en 100 µl se preparó en un buffer de ensayo de CXCR1 (25 mM HEPES, pH 7,8, 2 mM de $CaCl_2$, 1 mM $MgCl_2$, 125 mM de NaCl, 0,1% de BSA) (Sigma). Un stock de 0,4 nM de ligando, [125]-IL-8 (NEN) se preparó en el buffer de ensayo de CXCR1. Las soluciones stock 20X de los compuestos de ensayo se prepararon en DMSO (Sigma). Una solución stock 6X de IL-8 (R&D) se preparó en un buffer de ensayo de CXCR2. Las soluciones

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anteriores se agregaron a una placa de ensayo de 96 pocillos (PerkinElmer) de la siguiente forma: 10 µl de compuesto de ensayo o DMSO, 40 µl de buffer de ensayo de CXCR1 o stock de IL-8, 100 µl de mezcla de reacción, 50 µl de stock de ligando (Final[Ligando] = 0,1 nM). Las placas de ensayo se agitaron durante 5 minutos en el agitador de placa, luego se incubaron durante 8 horas antes de determinarse el cpm/pocillo en el contador Microbeta Trilus (PerkinElmer). El porcentaje de inhibición de la unión total de NSB (250 nM IL-8) se determinó para los valores IC50. Los compuestos de la presente invención tuvieron un IC_{50} de <20 µM. Los compuestos más preferidos tuvieron un Ki dentro del rango de 3 nM a 1120 nM.

Ensayo de CXCR2 SPA

Para cada pocillo de una placa de 96 pocillos, una mezcla de reacción de 4 µg de membranas sobreexpresantes de hCXCR2-CHO (Biosignal) y 200 µg/pocillo de perlas de WGA-SPA (Amersham) en 100 µl se preparó en un buffer de ensayo de CXCR2 (25 mM HEPES, pH 7,4, 2mM de $CaCl_2$, 1 mM de $MgCl_2$). Un stock de 0,4 nM de ligando, [125]-IL-8 (NEN), se preparó en el buffer de ensayo de CXCR2. Las soluciones stock 20X de los compuestos de ensayo se prepararon en DMSO (Sigma). Una solución stock 6X de GRO-α (R&D) se preparó en un buffer de ensayo de CXCR2. Las soluciones anteriores se agregaron a una placa de ensayo de 96 pocillos (PerkinElmer o Corning) de la siguiente manera: 10 µl de compuesto de ensayo o DMSO, 40 µl de buffer de ensayo de CXCR2 o stock GRO-α, 100 µl de mezcla de reacción, 50 µl de stock de ligando (Final [Ligando] = 0,1 nM). Cuando las soluciones 40 X stock de los compuestos de ensayo en DMSO se prepararon, entonces se utilizó el protocolo anterior salvo que se hizo en lugar de 5 µl del compuesto de ensayo o DMSO y 45 µl de buffer de ensayo de CXCR2. Las placas de ensayo se agitaron durante 5

minutos en un agitador de placa, luego se incubó durante 2 a 8 horas antes de determinarse el cpm/pocillo en el contador Microbeta Trilux (PerkinElmer). Se determinó el porcentaje de inhibición de la unión total menos la unión no específica (250 nM de Gro-α o 50 µM de antagonista) y se calcularon los valores IC50. Los compuestos de la presente invención tenían un IC_{50} de <5 µM. Los compuestos más preferidos tenían un Ki dentro del rango de 0,8 nM a 40 nM. El compuesto del ejemplo 360.31 tenía un Ki de 3 nM.

Ensayo de Fluorescencia de Calcio (FLIPR)

Las células HEK 293 transfectadas de manera estable con hCXCR2 y Gα/q se colocaron en placas a 10.000 células por pocillo en una placa Poli-D-Lisina Negro/Transparente (Becton Dickinson) y se incubaron 48 horas en 5% de CO_2, a 37ºC. Los cultivos luego se incubaron con 4 mM de fluo-4, AM (Sondas Moleculares) en Buffer de Carga de Tinte (1% FBS, HBSS w. Ca & Mg, 20 mM HEPES (Cellgro), 2,5 mM Probenicid (Sigma) durante 1 hora. Los cultivos se lavaron con buffer de lavado (HBSS w Ca, & Mg, 20 mM HEPEs, Probenicid (2,5 mM)) tres veces, luego se agregó 100 µl/pocillo de buffer de lavado.

Durante la incubación, los compuestos se prepararon como stocks 4X en 0,4% de DMSO (Sigma) y buffer de lavado y se agregó a sus respectivos pocillos en la primera placa de adición. Las concentraciones de IL-8 o GRO-α (Sistemas R&D) se prepararon 4X en buffer de lavado + 0,1% de BSA y se agregaron a sus respectivos pocillos en una segunda placa de adición.

La placa de cultivo y ambas placas de adición se colocaron en el sistema de imagen FLIPR para determinar el cambio en la fluorescencia del calcio al agregar el compuesto y luego el ligando. En breve, 50 µl de soluciones del compuesto o la solución en DMSO se agregaron a los pocillos respectivos y se midió el cambio de la fluorescencia de calcio mediante el FLIPR durante 1 minuto.

Al cabo de una incubación de 3 minutos dentro del instrumento, se agregó 50 µl de ligando y se midió el cambio en la fluorescencia del calcio mediante el instrumento de FLIPR durante 1 minuto. El área bajo cada curva de estimulación se determinó y se utilizaron los valores para determinar el porcentaje de estimulación por compuesto (agonista) y el porcentaje de inhibición de la respuesta de Calcio Total al ligando (0,3 nM IL-8 o GRO-α) para los valores IC50 de los compuestos de ensayo.

Ensayos de Quimiotaxis para 293-CXCR2

Se estableció un ensayo de quimiotaxis utilizando insertos Fluorblok (Falcon) para las células 293-CXCR2 (células HEK-283 que sobreexpresan el CXCR2 humano). El protocolo estándar utilizado al presente es el siguiente:

1. Se revistieron insertos con colágeno IV (2 µg/ml) durante 2 horas a 37ºC.
2. El colágeno se eliminó y los insertos se dejaron secar al aire durante la noche.
3. Las células se rotularon con 10 uM de AM calceína (Sondas Moleculares) durante 2 horas. El rotulado se llevó a cabo en medios completos con 2% de FBS.
4. Las diluciones del compuesto se realizaron en medios mínimos (0,1 % de BSA) y se colocaron dentro del inserto el cual está posicionado dentro del recipiente de una placa de 24 pocillos. Dentro del recipiente está IL-8 a una concentración de 0,25 nM en medios mínimos. Las células se lavaron y se suspendieron nuevamente en medios mínimos y se colocaron dentro del inserto a una concentración de 50.000 células por inserto.
5. La placa se incubó durante 2 horas y los insertos se eliminaron y se

colocaron en una nueva placa de 24 recipientes. La fluorescencia se detectó a una excitación = 485 nM y una emisión = 530 nM.

Ensayos de Citotoxicidad

Un ensayo de toxicidad para los compuestos de CXCR2 se llevó a cabo en células 293-CXCR2. Las concentraciones de los compuestos se ensayaron por toxicidad a concentraciones elevadas para determinar si pueden ser utilizadas para una posterior evaluación de ensayos de enlace y en base a células.

El protocolo es el siguiente:

1. Las células 93-CXCR2 se colocaron en placas durante la noche a una concentración de 5000 células por pocillo en medios completos.

2. Las diluciones del compuesto se llevaron a cabo en medios mínimos de 0,1% de BSA. Los medios completos se vertieron y se agregaron las diluciones del compuesto. Las placas se incubaron durante 4, 24 y 48 horas. Las células se rotularon con 10 uM de AM calceína durante 15 minutos para determinar la viabilidad celular. El método de detección es el mismo que el anterior.

Ensayo de Agar Blando

10.000 SKMEL-5 células/pocillo son colocados en una mezcla de 1,2% de agar y medios completos con varias diluciones de compuesto. La concentración final de agar es 0,6%. Al cabo de 21 días las colonias de células viables se tiñeron con una solución de MTT (1 mg/ml en PBS). Las placas luego se examinaron para determinar la cantidad y el tamaño de la colonia. Se determinó IC_{50} comparando el área total vs. la concentración del compuesto.

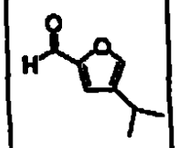
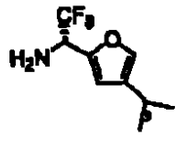
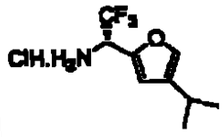
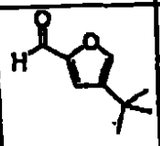
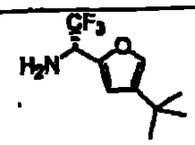
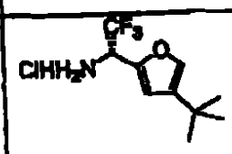
Los compuestos de las fórmulas IA, IB, 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088 pueden ser producidos mediante procesos descriptos en WO 02/083624 publicado el 24 de octubre de 2002, y mediante las preparaciones y los ejemplos a continuación.

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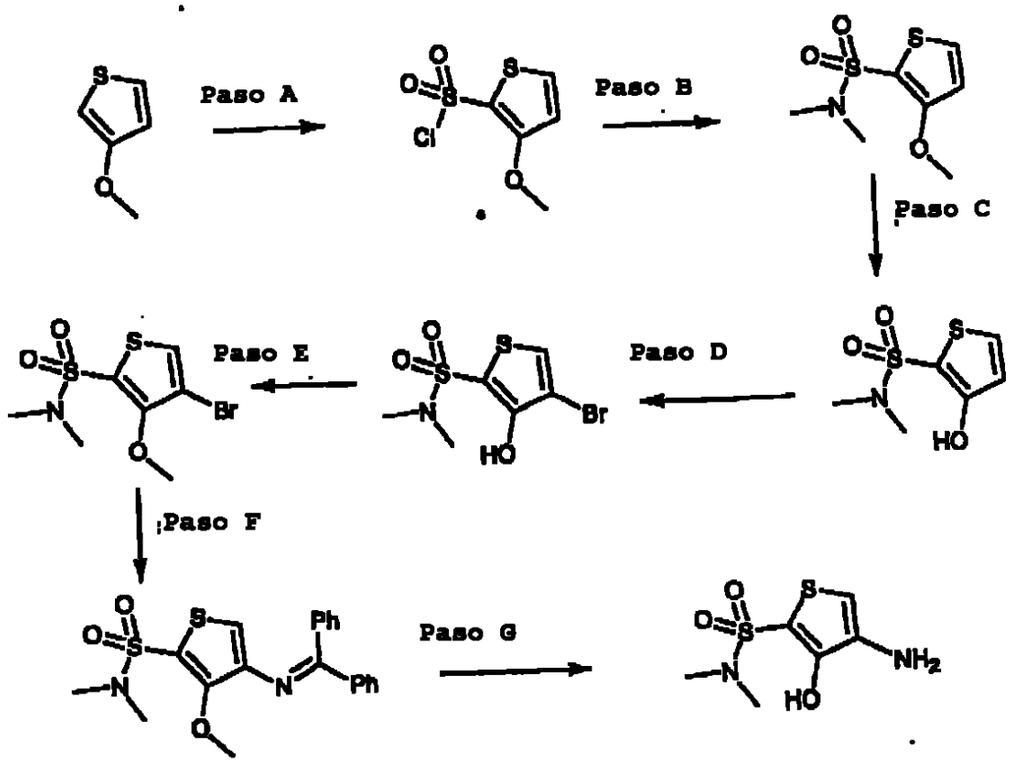
La invención descripta en la presente se ejemplifica mediante las siguientes preparaciones y ejemplos que no deben ser considerados para limitar el alcance de la revelación. Las vías mecánicas alternativas y las estructuras análogas puede ser evidentes para los expertos en la técnica.

EJEMPLOS PREPARATIVOS 13, 17A - 13.17B

Siguiendo el procedimiento establecido en el Ejemplo Preparativo 13.13 del documento WO 02/83624 publicado el 24 de octubre de 2002 pero utilizando los aldehidos preparados o disponibles comercialmente, se obtuvieron los productos amino ópticamente puros de la Tabla siguiente. El número "34.8" en la columna "Aldehido" se refiere al Ejemplo de Preparación 34.8 en el documento WO 02/083624.

Prep Ej.	Aldehido	Amina	Producto	Rendimiento (%)
13.17A	34.8 			38%
13.17B				31%

EJEMPLO DE PREPARACIÓN 13.29



Paso A

A una solución de 3-metoxitiofeno (3 g) en diclorometano (175 ml) a –78ºC se agregó ácido clorosulfónico (8,5 ml) en gotas. La mezcla se agitó durante 15 min. a –78ºC y 1,5 hora a temperatura ambiente. A continuación, la mezcla se vertió cuidadosamente en hielo partido, y se extrajo con diclorometano. Los extractos se lavaron con salmuera, se secaron en sulfato de magnesio, se filtraron a través de una almohadilla de gel de sílice de 1 pulgada. El filtrado se concentró a vacío, para dar el compuesto deseado (4,2 g).

Paso B

El producto del Paso A anterior (4,5 g) se disolvió en diclorometano (140 ml) y se agregó con trietilamina (8,8 ml) seguido de dietil amina en THF (2M, 21 ml). La mezcla resultante se agitó a temperatura ambiente durante la noche. La

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mezcla se lavó con salmuera y se saturó con bicarbonato (ac) y salmuera nuevamente, se secó en sulfato de sodio, se filtró a través de una almohadilla de gel de sílice de 1 pulgada. El filtrado se concentró a vacío para dar el compuesto deseado (4,4 g).

Paso C

El producto del Paso B anterior (4,3 g) se disolvió en diclorometano (125 ml) y se enfrió en un baño a –78ºC. Se agregó una solución de tribromuro bórico (1,0 M en diclorometano, 24,3 ml). La mezcla se agitó durante 4 horas mientras se incrementaba la temperatura lentamente de –78ºC a 10ºC. Se agregó H_2O, se separaron las dos capas, y la capa acuosa se extrajo con diclorometano. La capa orgánica combinada y los extractos se lavaron con salmuera, se secaron en sulfato de magnesio, se filtraron, y se concentraron a vacío para dar 3,96 g del compuesto hidroxi deseado.

Paso D

El producto del Paso C anterior (3,96 g) se disolvió en 125 ml de diclorometano, y se agregó con carbonato de potasio (6,6 g) seguido de bromo (2 ml). La mezcla se agitó durante 5 horas a temperatura ambiente, se templó con 100 ml de H_2O. La mezcla acuosa se ajustó a pH ~ 5 utilizando una solución acuosa de cloruro de hidrógeno 0,5 N, y se extrajo con diclorometano. Los extractos se lavaron con un 10% de solución acuosa de $Na_2S_2O_3$ y salmuera, se secó en sulfato de sodio, y se filtró a través de una almohadilla de celite. El filtrado se concentró a vacío para dar 4,2 g del compuesto bromo deseado.

Paso E

El producto del Paso D (4,2 g) se disolvió en 100 ml de acetona y se agregó carbonato de potasio (10 g) seguido por yodometano (9 ml). La mezcla se calentó a reflujo y continuó durante 3,5 horas. Después de enfriar a temperatura ambiente, la mezcla se filtró a través de una almohadilla de celite. El filtrado se concentró a vacío hasta un residuo de color marrón oscuro, el cual se purificó mediante cromatografía de columna flash eluyendo con diclorometano-hexanos (1:1, v/v) para dar 2,7 g del producto deseado.

Paso F

El producto del paso E (2,7 g) se convirtió al compuesto imina deseado (3 g), siguiendo el procedimiento similar al del Ejemplo de Preparación 13.19 Paso D.

Paso G

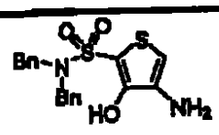
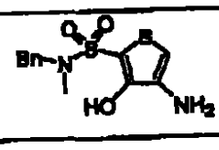
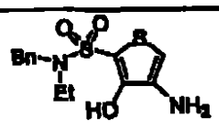
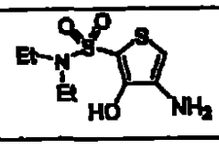
El producto imina del paso F (3 g) se disolvió en 80 ml de diclorometano y se enfrió en un baño a –78ºC. Una solución de tribromuro bórico (1,0 M en diclorometano, 9,2 ml) se agregó en gotas. La mezcla se agitó durante 4,25 horas desde –78ºC hasta 5ºC. Se agregó H_2O (50 ml), y las capas se separaron. La capa acuosa se extrajo con diclorometano. La capa orgánica y los extractos se combinaron, se lavaron con salmuera, y se concentraron hasta un residuo aceitoso. El residuo se disolvió en 80 ml de metanol, se agitó con acetato de sodio (1,5g) y clorhidrato de hidroxiamina (0,95 g) a temperatura ambiente durante 2 horas. La mezcla se vertió en una mezcla acuosa de hidróxido de sodio (1,0 M ac., 50 ml) y éter (100 ml). Las dos capas se separaron. La capa acuosa se lavó con éter tres veces. Los lavados de éter combinados se extrajeron nuevamente con H_2O una vez. Las capas acuosas se combinaron, se lavaron una vez con diclorometano, se ajustaron a pH ~ 6 utilizando 3.0 M y 0,5 M de soluciones

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acuosas de cloruro de hidrógeno y se extrajeron con diclorometano. Los extractos orgánicos se combinaron, se lavaron con salmuera, se secaron en sulfato de sodio, y se concentraron a vacío para dar 1,2 del compuesto amino deseado.

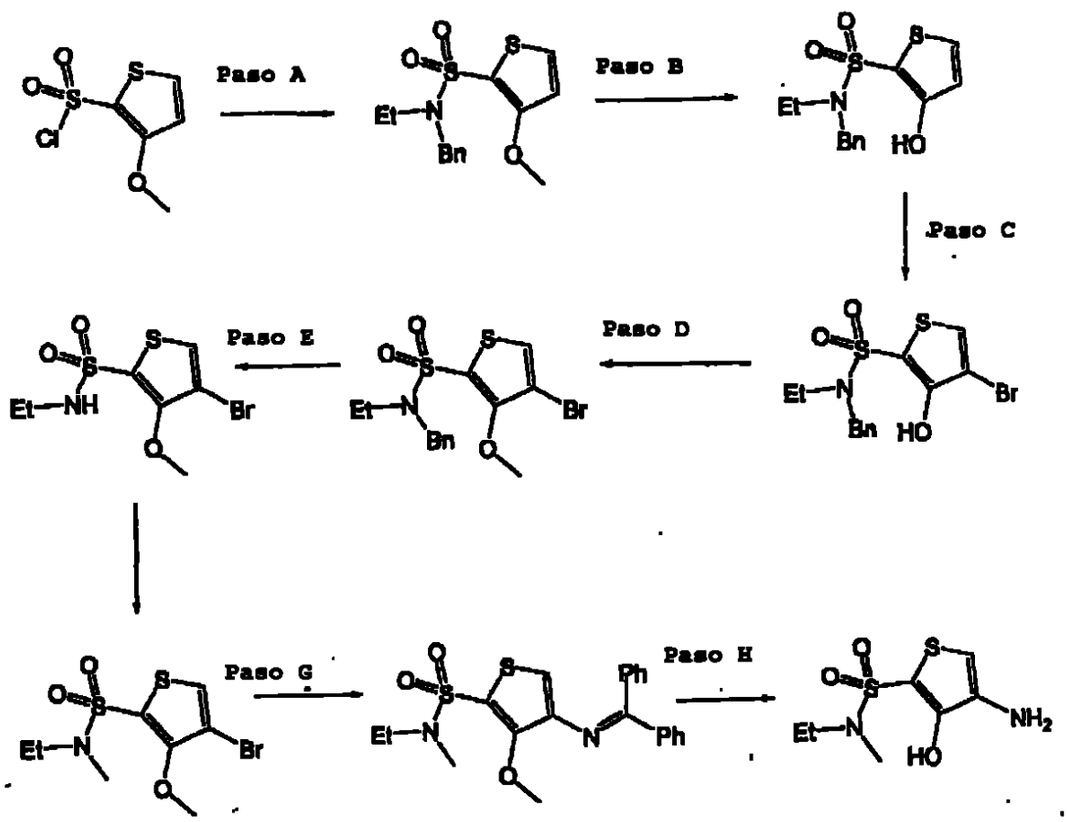
EJEMPLOS PREPARATIVOS 13.30 – 13.32

Siguiendo los procedimientos establecidos en el Ejemplo de Preparación 13.29, pero utilizando las aminas comercialmente disponibles, se obtuvieron los productos hidroxi-amino-tiofeno de la siguiente Tabla.

Ej. Prep	Amina	Producto	Rendim. (%) MH^+
13.30	Bn_2NH		10% 375.1
13.31	MeBnNH		14% 299.0
13.32	EtBnNH		22%
13.32A	$(Et)_2NH$		25%

EJEMPLO DE PREPARACIÓN 13.33

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Paso A

2-clorosulfonil-3-metoxi-tiofeno (4,0 g, 18,8 mmol), el producto del Paso A del Ejemplo de Preparación 13.29, se convirtió a 3-metoxi-2-etilbencilsulfonil-tiofeno (5,5 g, 94%, MH^+ = 312.1) utilizando etilbencilamina, siguiendo el procedimiento establecido en el Ejemplo de Preparación 13.29, Paso B.

Paso B

El producto del Paso A anterior (5,5 g, 17,70 mmol) se demetiló siguiendo el procedimiento establecido en el Ejemplo de Preparación 13.29, Paso C. Se obtuvo el producto de alcohol en 4,55 g (87%, MH^+ = 298.0).

Paso C

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El producto del Paso B anterior (4,55 g, 15,30 mmol) se brominó utilizando el procedimiento establecido en el Ejemplo de Preparación 13.29 Paso D. El correspondiente bromuro se obtuvo en 4,85 g (84%).

Paso D

El bromo-alcohol del Paso C anterior (4,84 g, 12,86 mmol) se metiló utilizando el procedimiento establecido en el Ejemplo de Preparación 13.29 Paso E. El producto se obtuvo en 4,82 g (96%).

Paso E

El producto del Paso D anterior (4,82 g, 12,36 mmol) se agitó con ácido sulfúrico concentrado (5 ml) a temperatura ambiente durante 3 horas. Se agregó agua helada a la mezcla seguido de CH_2Cl_2 (50 ml). La mezcla acuosa se ajustó a pH ~ 6 utilizando una solución acuosa de NaOH 1,0 M. Las capas se separaron. La capa acuosa se extrajo con CH_2Cl_2 (50 ml x 3). Las capas orgánicas combinadas se lavaron con salmuera, se secaron en Na_2SO_4, y se concentraron hasta un aceite de color marrón oscuro, el cual se purificó mediante cromatografía de columna flash, eluyendo con CH_2Cl_2-hexanos (1:1, v/v). La eliminación de los solventes dio 3,03 g (82%) del producto debencilado (M^+ = 300.0, M+2 = 302.0).

Paso F

El producto del Paso E (1,34 g, 4,45 mmol) se metiló utilizando el procedimiento establecido en el Ejemplo de Preparación 13.29, Paso E. El producto deseado se obtuvo en 1,36 g (97%, M^+ = 314.1, M+2 = 316.0).

Paso G

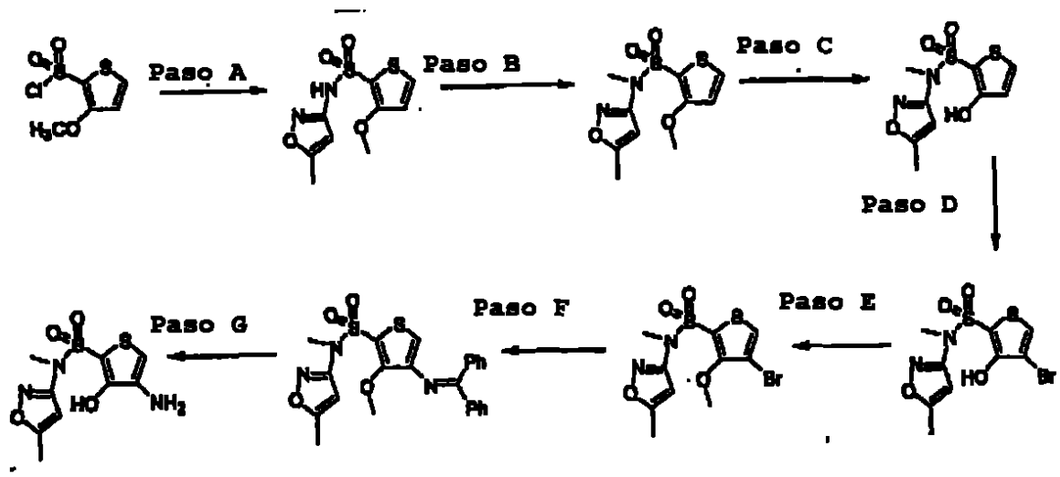
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294

El producto del Paso F (1,36 g, 4,33 mmol) se convirtió al producto imina (1,06 g, 55%, MH^+ = 415.1) utilizando el procedimiento establecido en el Ejemplo de Preparación 13.29, Paso F.

Paso H

El producto imina del Paso G (1,06 g, 2,56 mmol) se convirtió al compuesto hidroxi-amino tiofeno deseado (0,26 g, 43%) utilizando el procedimiento establecido en el Ejemplo de Preparación 13.29, Paso G.

EJEMPLO DE PREPARACIÓN 13.34



Paso A

2-clorosulfonil-3-metoxi-tiofeno (3,8 g, 17,87 mmol), el producto del Paso A del Ejemplo de Preparación 13.29, se disolvió en 100 ml de CH_2Cl_2 y 20 ml de piridina. Se agregó 3-amino-5-metil-isoxazol (3,5 g, 35,68 mmol). La Mezcla se agitó durante 20 horas a temperatura ambiente, se diluyó con 100 ml de CH_2Cl_2, y se lavó con una solución acuosa de HCl 0,5 N (50 ml x 2), H_2O (50 ml), y

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salmuera (50 ml). La solución orgánica se secó con Na_2SO_4, y se concentró a vacío hasta un aceite de color marrón.

Este aceite se disolvió en 100 ml de CH_2Cl_2, se lavó nuevamente con una solución acuosa de HCl 0,5 M (30 ml x 3) y salmuera. Una vez seco en Na_2SO_4, la solución orgánica se concentró a vacío hasta un sólido de color amarillo, 4,48 g (91%, MH^+ = 275.0) del producto deseado.

Paso B

El producto del Paso A anterior (4,48 g, 16,33 mmol) se disolvió en acetona (100 ml), se agregó con carbonato de potasio (5,63 g, 40,80 mmol) y yodometano (10,1 ml, 163,84 mmol). La mezcla se agitó a temperatura ambiente durante 1,5 hora, se diluyó con 100 ml de hexanos y 50 ml de CH2Cl2, y se filtró a través de una almohadilla de gel de sílice de 1 pulgada, enjuagando con CH_2Cl_2. El filtrado se concentró a presión reducida para dar 4,23 g (90%, MH^+ = 289.0) del producto deseado en forma de un sólido de color amarillo claro.

Paso C

A una suspensión agitada de hidruro de sodio (130 mg, 95%, 5,4 mmol) en 8 ml de N,N'-dimetilformamida a temperatura ambiente, se agregó etantiol (0,45 ml, 6,0 mmol) en gotas. Al cabo de 5 minutos, la mezcla se tornó una solución transparente, y se agregó a una solución agitada del producto obtenido del Paso B anterior (0,45 g, 1,56 mmoL) en 2 ml de N,N'-dimetilformamida en un frasco de base redonda. El recipiente se selló con un cierre de vidrio molido, y la mezcla se calentó a 90-95ºC durante 4 horas. Una vez enfriado a temperatura ambiente, la mezcla se vertió en 20 ml de una solución acuosa de NaOH 1,0 M, se enjuagó con 20 ml de H_2O. La mezcla acuosa se lavó dietil éter (30 ml x 2), se ajustó a pH ~ 5 utilizando una solución acuosa de HCl 0,5 M, y se extrajo con CH_2Cl_2 (50 ml x

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96

4). Los extractos combinados se lavaron con salmuera, se secaron en Na_2SO_4 y se concentraron hasta una solución amarilla oscura. Esta se disolvió en 50 ml de acetato de etilo ,se lavó con H_2O (30 ml x 2) y salmuera (30 ml), se secó en Na_2SO_4. La evaporación del solvente dio 0,422 g del producto de alcohol (99%, $MH^+ = 275.0$).

Paso D

El alcohol obtenido del Paso C anterior (0,467 g, 1,70 mmol) se brominó utilizando el procedimiento establecido en el Ejemplo de Preparación 13.29, Paso D, para dar el correspondiente bromuro en 0,607 g (100%).

Paso E

El bromuro obtenido del Paso D anterior (0,607 g, 1,72 mmoL) se metiló utilizando el procedimiento establecido en el Ejemplo de Preparación 13.29 Paso E, para dar el producto deseado en 0,408 g (65%, $M^+ = 367$, M+2 = 369.1).

Paso F

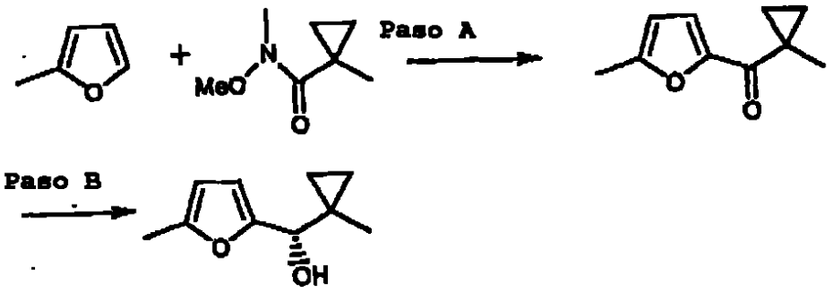
El producto (0,405 g, 1,103 mmol) del Paso E anterior se convirtió al compuesto imina (0,29 g, 56%) utilizando el procedimiento establecido en el Ejemplo de Preparación 13.29, paso E.

Paso G

El producto imina obtenido del Paso F anterior (0,29 g, 0,61 mmol) se demetiló utilizando el procedimiento establecido en el Paso C anterior para dar el correspondiente alcohol en forma de un aceite de color amarillo oscuro, el cual se disolvió en 5 ml de metanol y se agregó con acetato de sodio (0,12 g, 1,46 mmoL) y clorhidrato de hidroxiamina (0,075 g, 1,08 mmol). La mezcla resultante se agitó

a temperatura ambiente durante 3 horas, y se vertió en 10 ml de una solución acuosa de NaOH 1,0 M. Se utilizó 30 ml de H_2O como enjuague y se combinó con la capa acuosa. La mezcla acuosa se lavó con dietil éter (40 ml x 3), se ajustó a pH ~ 6 utilizando una solución acuosa de HCl 1,0 M, y se extrajo con acetato de etilo (40 ml x 3). Los extractos orgánicos se lavaron con H_2O (20 ml x 2), salmuera (20 ml), se secaron en Na_2SO_4, y se concentraron a vacío para dar 0,112 g de la hidroxi-amino tiofeno sulfonamida deseada (64%, MH^+ = 290).

EJEMPLO DE PREPARACIÓN 13.35



Paso A

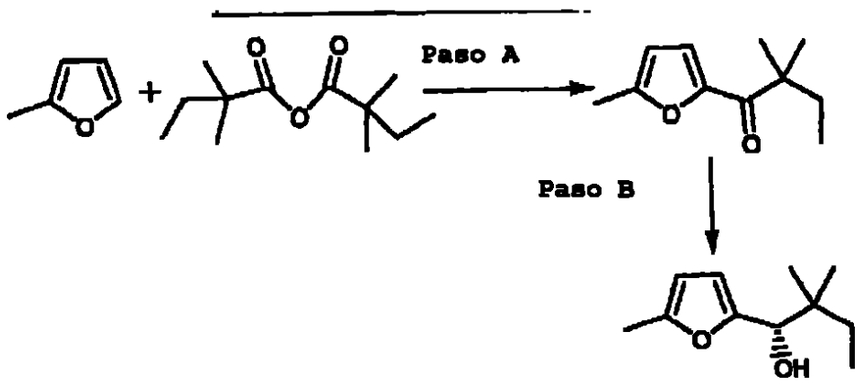
A una solución de 2-metil furano (1,72 g) en éter se agregó BuLi (8,38 ml) a –78ºC y se agitó a temperatura ambiente durante media hora. La mezcla de reacción se enfrió nuevamente a –78ºC y se templó con ciclopropil amida 1 y se agitó durante dos horas a –78ºC y se entibió lentamente a temperatura ambiente. La mezcla de reacción se agitó durante tres horas a temperatura ambiente y se templó con la adición de una solución de cloruro de amonio saturado. La mezcla se llevó a un embudo separador, se lavó con agua, salmuera y se secó en sulfato de sodio anhidro. La filtración y eliminación del solvente dio la cetona cruda, la cual se purificó utilizando cromatografía de columna para dar la cetona 3,0 g (87%) en forma de un aceite de color amarillo pálido.

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Paso B

A una solución de cetona (1,0 g) en THF (5,0 ml) a 0ºC se agregó R-metil oxazoborolidina (1,2 Ml, 1M en tolueno) en gotas seguido de la adición de una solución de boro complejado con sulfuro de dimetilo (1,85 ml, 2M en THF). La mezcla de reacción se agitó durante 30 minutos a 0ºC y luego a temperatura ambiente durante una hora. La mezcla de reacción se enfrió a 0ºC y MeOH se agregó cuidadosamente. La mezcla se agitó durante 20 minutos y se concentró a presión reducida. El residuo se extrajo con éter, se lavó con agua, HCl 1M (10 ml), bicarbonato de sodio saturado (10,0 ml), agua y salmuera. La capa orgánica se secó en sulfato de sodio anhidro, se filtró y la eliminación del solvente dio el alcohol crudo que se purificó mediante cromatografía de gel de sílice para dar el alcohol puro 0,91 g (91%) en forma de un aceite de color amarillo.

EJEMPLO DE PREPARACIÓN 13.36



Paso A

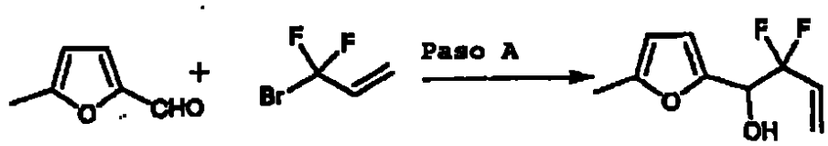
Una mezcla equimolar de 2-metilfurano (1,0 g) y anhídrido (2,6 g) se mezcló con $SnCl_4$ (0,05 ml) y se calentó a 100ºC durante 3 horas. Al cabo de enfriar la mezcla de reacción, se agregó agua (10 ml), seguido de la solución de

carbonato de sodio saturado hasta que se convierte alcalino. La mezcla de reacción se extrajo con éter varias veces y la capa de éter combinada se lavó con agua, salmuera y se secó en sulfato de sodio anhidro. La filtración y eliminación del solvente dio la cetona cruda, la cual se purificó utilizando cromatografía de gel de sílice para dar la cetona 0,9 g (43%) en forma de un aceite amarillo.

Paso B

El alcohol del Paso B se obtuvo siguiendo un procedimiento similar al establecido en el Ejemplo de Preparación 13.35 Paso B.

EJEMPLO DE PREPARACIÓN 13.37



Paso A.

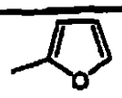
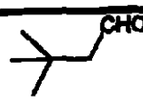
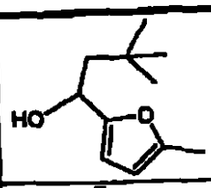
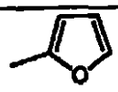
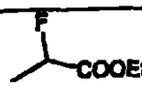
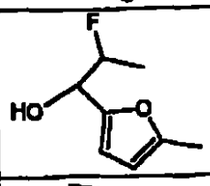
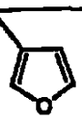
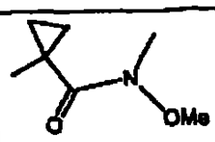
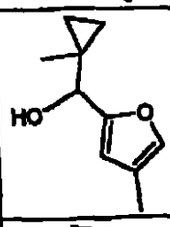
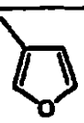
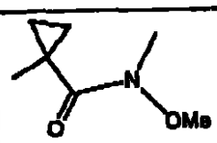
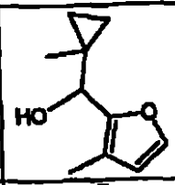
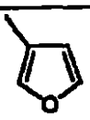
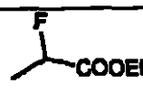
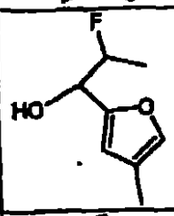
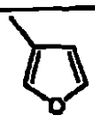
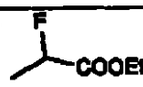
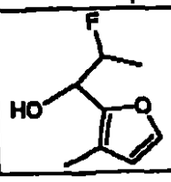
A una solución de 5-metil- furan-2-aldehido (1,0 g) y 3-bromo-3,3-difluorpropeno (2,24 g) en DMF (30 ml) se agregó polvo de indio (1,66 g) y yoduro de litio (50,0 mg). La mezcla de reacción se agitó durante la noche, se diluyó con agua y se extrajo con éter. La capa de éter se lavó con agua, salmuera y se purificó mediante cromatografía de gel de sílice para dar 2,8 g del alcohol puro (92%).

EJEMPLOS PREPARATIVOS 13.38 – 13.45

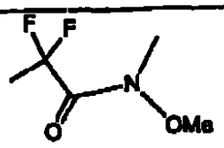
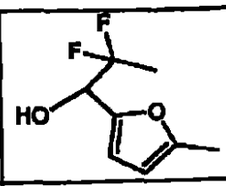
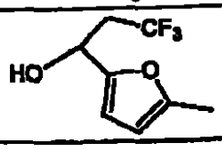
Siguiendo un procedimiento similar al establecido en el Ejemplo de Preparación 13.25 de WO 02/083624 publicada el 24 de octubre de 2002, y el

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300

Ejemplo de Preparación 13.35, y utilizando el furano y electrófilo indicado, se prepararon los siguientes alcoholes en la siguiente Tabla

Ej. Prep	Furano	Electrófilo	Alcohol	Rendim.
13.38				86%
13.39				69%
13.40				84%
13.41				82%
13.42				60%
13.43				65%

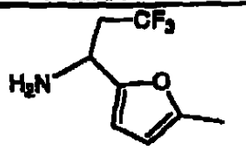
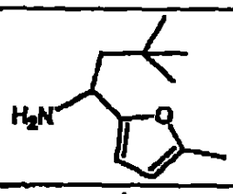
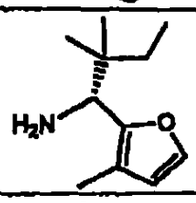
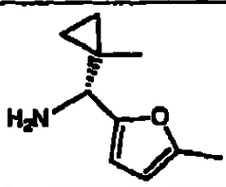
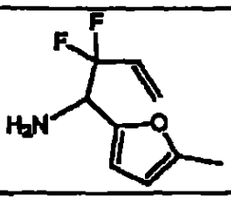
299
301

13.44				82%
13.45				89%

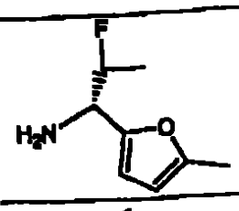
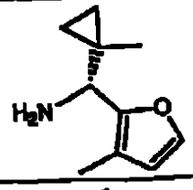
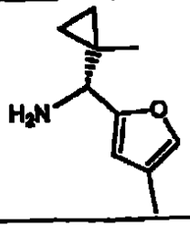
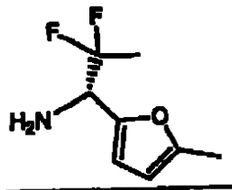
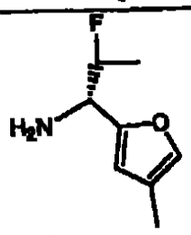
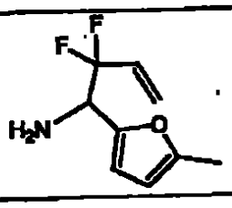
EJEMPLOS PREPARATIVOS 13.50 – 13.61

Siguiendo un procedimiento similar al establecido en los Ejemplos Preparativos 13.25 del documento WO 02/083624 publicada el 24 de octubre de 2002, y utilizando el Alcohol indicado, se prepararon las siguientes Aminas en la Tabla a continuación.

300
302

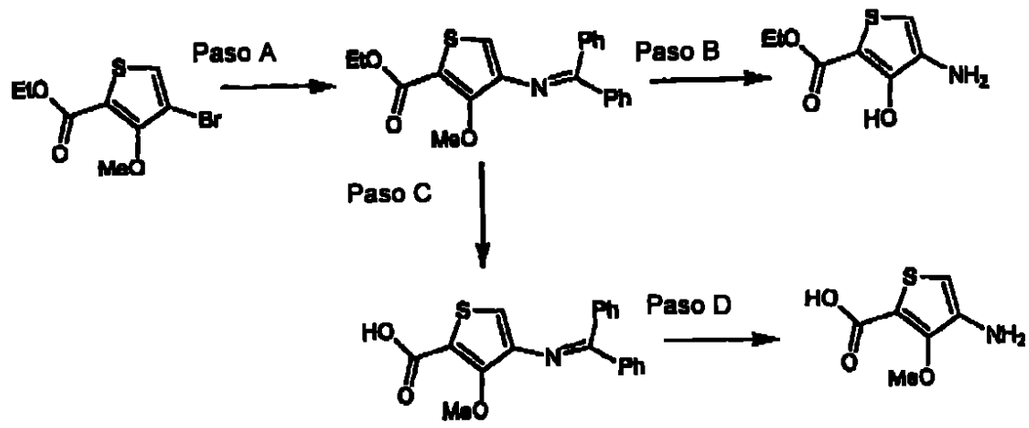
Ej. Prep	ALCOHOL	AMINA	% Rend
13.50	13.45		28%
13.51	13.38		58%
13.52	13.36		69%
13.53	13.35		81%
13.54	13.37		82%

301
303

13.55	13.39		45%
13.56	13.41		57%
13.57	13.40		58%
13.58	13.44		54%
13.59	13.42		53%
13.61	13.37		82%

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304

EJEMPLO DE PREPARACIÓN 13.70



Paso A

La imina se preparó siguiendo el procedimiento establecido en el Ejemplo de Preparación 13.19 del documento WO 02/083624 publicada el 24 de octubre de 2002, a partir del bromoester conocido (1,0 g) en forma de un sólido color amarillo, Paso A para dar 1,1 g (79%).

Paso B

El producto del Paso A (0,6 g) se hizo reaccionar siguiente el procedimiento establecido en el Ejemplo de Preparación 13.19 del documento WO 02/083624 publicada el 24 de octubre de 2002, para dar 0,19 g del producto amina (64%).

Paso C

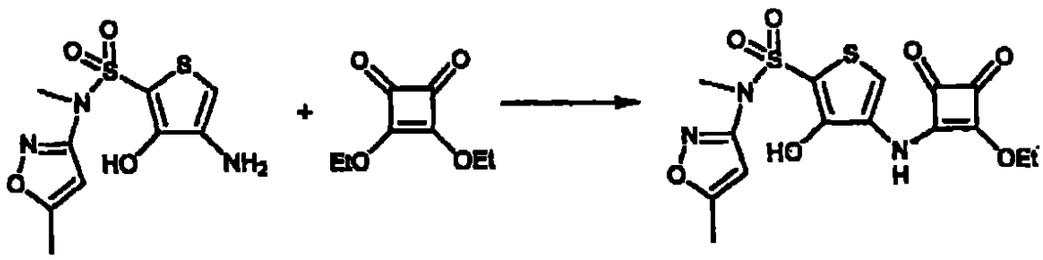
El producto del Paso B (1,0 g) se hizo reaccionar siguiendo el procedimiento establecido en el Ejemplo de Preparación 13.19 del documento WO 02/083624 publicado el 24 de octubre de 2002, para dar el 0,9 g del ácido en forma de un sólido amarillo (94%).

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Paso D

El producto del Paso C (0,35 g) se hizo reaccionar siguiendo el procedimiento establecido en el Ejemplo de Preparación 13.19 del I documento WO 02/083624 publicado el 24 de octubre de 2002, para dar 0,167 g del aminoácido en forma de un sólido amarillo (93%).

EJEMPLO DE PREPARACIÓN 19.2



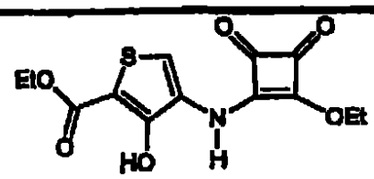
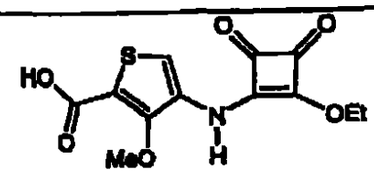
La hidroxi tiofen amina del Ejemplo de Preparación 13.34 (108 mg, 0,37 mmol) se disolvió en 5 ml de etanol y se agitó con dietoxiesquarato (0,14 ml, 0,95 mmol) y carbonato de potasio (52 mg, 0,38 mmol) a temperatura ambiente durante la noche. La mezcla se diluyó con H_2O (25 ml), se ajustó a pH ~ 6 utilizando una solución acuosa de HCl 1,0 M, y se extrajo con acetato de etilo (40 ml x 3). Los extractos orgánicos combinados se lavaron con salmuera, se secaron en Na_2SO_4, y se concentraron hasta un aceite, el cual se purificó mediante cromatografía de columna flash, eluyendo con CH_2Cl_2-MeOH (100:1, v/v). La eliminación de los solventes dio 83,5 mg del producto del título (MH+ = 414).

EJEMPLOS PREPARATIVOS 23.14A y 23.14B

Siguiendo los procedimientos establecidos en el Ejemplo de Preparación 19 del documento WO 02/83624 publicado el 24 de octubre de 2002, pero

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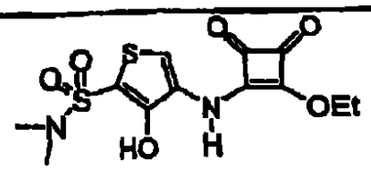
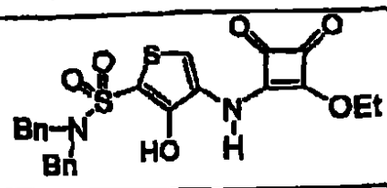
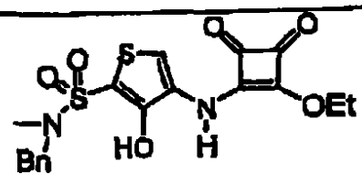
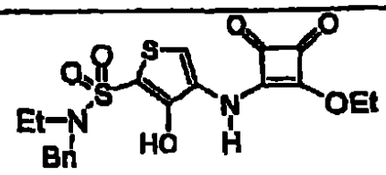
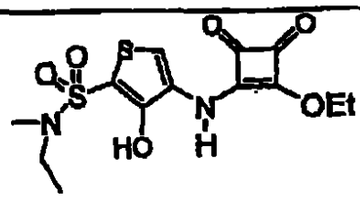
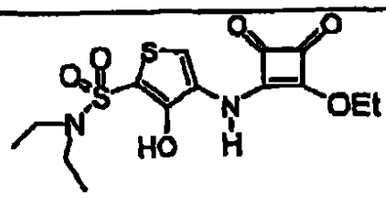
utilizando la amina del Ejemplo de Preparación indicado en la Tabla a continuación, se obtuvieron los intermediarios de ciclobutendiona.

Ej. Prep	Amina del Ej. Prep.	Producto	1. Rend (%) 2. MH^+
23.14A	13.70 Step B		1. 60% 2. 138
23.14B	13.70 Step D		1. 65%

EJEMPLO DE PREPARACIÓN 23.15A - 23.15F

Siguiendo los procedimientos establecidos en el Ejemplo de Preparación 19.2 pero utilizando las aminas del Ejemplo de Preparación indicado en la Tabla a continuación, se prepararon los intermediarios de ciclobutendiona.

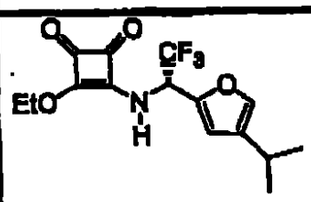
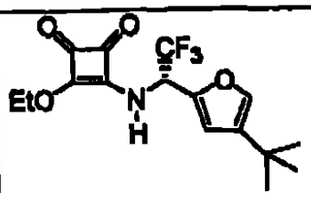
305
309

Ej. Prep	Amina del Ej. Prep.	Producto	1. Rend (%) 2. MH^+
23.15A	13.29		1. 66 % 2. 347
23.15B	13.30		1. 21% 2. 499
23.15C	13.31		1. 41% 2. 423
23.15D	13.32		1. 28% 2. 437
23.15E	13.33		1. 48% 2. 361,1
23.15F	13.32A		1. 68% 2. 375.1

EJEMPLO DE PREPARACIÓN 23.16 – 23.26

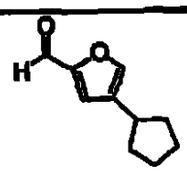
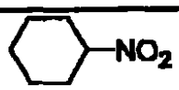
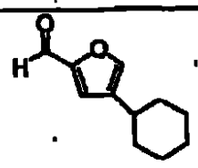
Siguiendo los procedimientos establecidos en el Ejemplo de Preparación 19 del documento WO 02/83624 publicado el 24 de octubre de 2002, pero utilizando la amina del Ejemplo de Preparación indicado en la Tabla a continuación, se obtuvieron los intermediarios de ciclobutendiona.

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308

Ej. Prep.	Amina del Ej. Prep.	Producto	Rend (%)
23.25	13.17A		48%
23.26	13.17B		66%

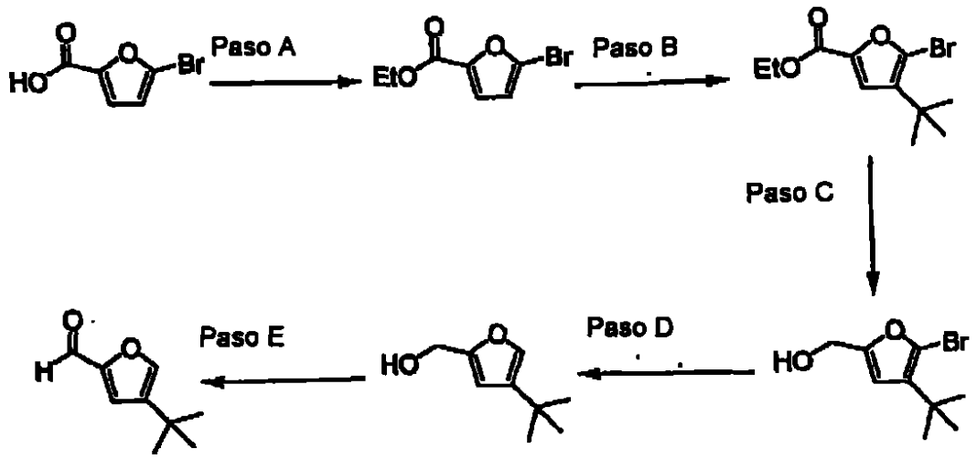
EJEMPLO DE PREPARACIÓN 34.15 – 34.16

Siguiendo los procedimientos establecidos en el Ejemplo de Preparación 34.8 del documento WO 02/83624 publicado el 24 de octubre de 2002, pero utilizando los nitroalcanos indicados en la Tabla a continuación, se prepararon los aldehidos.

Ej. Prep	Nitroalcano	Aldehido	Rend.
34.15			17%
34.16			21%

EJEMPLO DE PREPARACIÓN 34.17

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Paso A

A una suspensión agitada del ácido 5-bromo-2-furoico (15,0 g, 78,54 mmol) en 225 ml de CH_2Cl_2 a temperatura ambiente se agregó cloruro de oxalilo seguido de una cantidad catalítica de N,N'-dimetilformamida. Al cabo de 1 hora, se agregó etanol (20 ml) seguido de trietilamina (22 ml). La reacción se continuó durante 15 horas. La mezcla se concentró a presión reducida hasta un residuo, el cual se extrajo con un exceso de volumen de hexanos, y hexanos-CH_2Cl_2 (3:1, v/v). Los extractos se filtraron, el filtrado se concentró hasta un aceite de color amarillo, se secó en alto vacío, dando 17,2 g (93%) del éster deseado.

Paso B

El producto éster obtenido del Paso A anterior (17,2 g, 73,18 mmol) se convirtió a 2-etil-4-tercbutil-5-bromo-furoato (7,9 g, 37%) utilizando el procedimiento de literatura: *J. Am. Chem. Soc.*, 1939, 61, 473-478.

Paso C

El producto éster obtenido del Paso B anterior (7,9 g, 27,13 mol) se redujo al alcohol (6,32 g) utilizando el procedimiento establecido en el Ejemplo de

Preparación 34.8, Paso C, del documento WO 02/083624 publicado el 24 de octubre de 2002.

Paso D

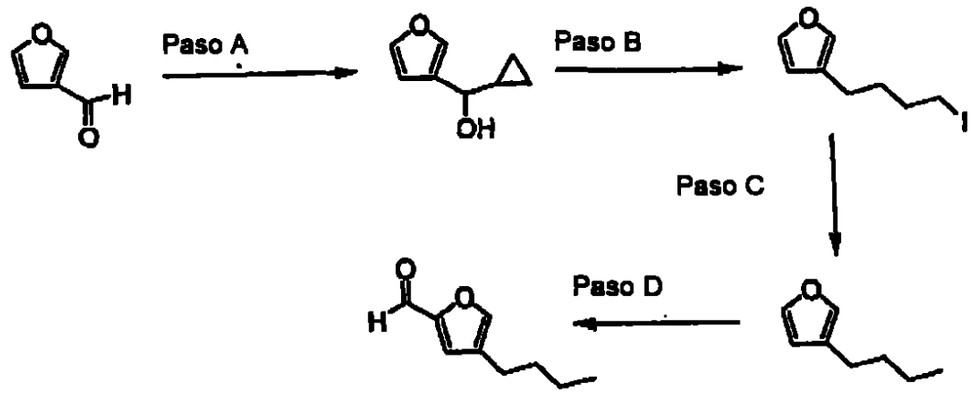
El producto obtenido del Paso C anterior (6,32 g) se disolvió en 140 ml de THF y se enfrió en un baño a –78ºC. Una solución 2,5 M de n-butillitio en hexanos (22 ml, 55,0 mmol) se agregó en gotas a lo largo de la pared lateral del matraz. Al cabo de 15 min, se agregó H_2O (~ 70 ml). Se eliminó el baño de enfriamiento, la mezcla se agitó durante 1 hora adicional. Se agregó salmuera (50 ml) y CH_2Cl_2 (300 ml), las dos capas se separaron, la capa acuosa se extrajo con CH_2Cl_2 (100 ml), y las capas orgánicas combinadas se secaron con Na_2SO_4. La evaporación de solventes dio 5,33 g (crudo) del producto desbrominado en forma de un aceite de color marrón rojizo.

Paso E

El producto de alcohol obtenido del Paso D anterior (5,33 g) se oxidó al correspondiente aldehído (3,06 g, 74% en tres pasos) utilizando el procedimiento establecido en el Ejemplo de Preparación 34.8, Paso D.

EJEMPLO DE PREPARACIÓN 34.18

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311



Paso A

A una solución agitada de bromuro de ciclopropilo (4,0 ml, 50 mmol) en 120 ml de éter a –78ºC se agregó en gotas una solución de 1,7M de t-butillitio en pentano (44,5 ml, 75,7 mmol). Al cabo de 10 minutos, se eliminó el baño de enfriamiento, se continuó la agitación durante 1,5 hora. La mezcla se enfrió nuevamente en un baño a –78ºC, y se agregó 3-furaldehido (3,5 ml, 41,9 mmol). La reacción se continuó durante 1 hora, y se templó con una solución acuosa de NH4Cl saturado. La mezcla acuosa se extrajo con CH_2Cl_2 (100 ml x 3). Los extractos orgánicos se lavaron con salmuera, se secaron en Na_2SO_4, se filtraron y se concentraron a vacío para dar 5,3 g (91%) del producto de alcohol en forma de un sólido amarillo.

Paso B

Cloro trimetilsilano (27,2 ml, 214,2 mmol) se agregó en gotas hasta una suspensión vigorosamente agitada de yoduro de sodio (32 g, 213,5 mmol) en 100 ml de acetonitrilo. Al cabo de 5 minutos, una solución del alcohol obtenido del Paso A anterior (4,93 g, 35,68 mmol) en 100 ml de acetonitrilo se agregó en gotas. Se continuó la agitación durante 5 minutos. Se agregó H_2O (100 ml), las capas se separaron, y la capa acuosa se extrajo con éter (100 ml x 2). Las capas orgánicas se combinaron, se lavaron con una solución acuosa de $Na_2S_2O_3$ al 10%

y salmuera, y se secaron en Na_2SO_4. La evaporación de los solventes dio un aceite de color marrón oscuro, el cual se filtró a través de una columna de gel de sílice de 5 pulgadas, eluyendo con CH_2Cl_2-hexanos (1:3,5, v/v). La eliminación de los solventes dio 4,22 g (47%) del producto yodo en forma de un aceite color amarillo claro.

Paso C

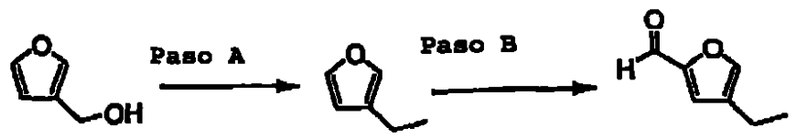
El producto yodo obtenido del Paso B anterior (2,2 g, 8,8 mmol) se disolvió en 60 ml de éter, y se agitó en un baño a –78ºC. Una solución de 1,7M de t-butillitio en pentano (10,4 ml, 17,7 mmol) se agregó en gotas. Al cabo de 20 min. el baño de enfriamiento se eliminó. La reacción se continuó durante 2,5 horas, y se templó con H_2O (20 ml). La mezcla acuosa se agitó durante la noche y se separó. La capa acuosa se extrajo con éter (30 ml). Las capas orgánicas combinadas se lavaron con salmuera, se secaron en Na_2SO_4, y se filtraron en una almohadilla de celite. La eliminación del solvente dio 1,10 g (100%) de 3-butilfurano en forma de un aceite rojizo-amarillo.

Paso D

3-butilfurano (1,1 g, 8,8 mmol), obtenido del Paso C anterior, se disolvió en 60 ml de éter, y se agitó en un baño a –78ºC. Una solución de 1,7M de t-butillitio en pentano (10,4 ml, 17,7 mmol) se agregó en gotas a lo largo de la pared lateral del matraz. La mezcla se agitó durante 3 horas desde –78ºC hasta 0ºC, y continuó durante 1 hora a temperatura ambiente. Se agregó una solución de N,N'-dimetilformamida (1,1 ml, 14,23 mmol). La reacción se continuó durante la noche, y se templó con una solución acuosa de NH_4Cl saturado. Las dos capas se separaron, la capa acuosa se extrajo con CH_2Cl_2 (30 ml x 2). Las capas orgánicas combinadas se lavaron con salmuera, se secaron con Na_2SO_4, y se concentraron

hasta un aceite, el cual fue purificado mediante TLC preparativa (CH_2Cl_2-hexanos = 1:1.5, v/v) para dar 0,48 g (36%) del aldehido (contaminado mediante algo de 3-butil-2-furaldehido).

EJEMPLO DE PREPARACIÓN 34.19



Paso A

Se preparó 3-etilfurano a partir de 3-hidroximetilfurano de acuerdo con el procedimiento de la literatura: *J. Org. Chem.*, 1983, 48, 1106-1107.

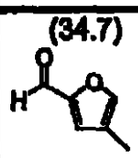
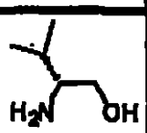
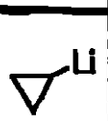
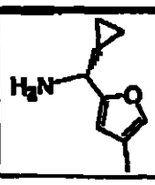
Paso B

3-etilfurano obtenido del Paso A anterior se convirtió a 4-etil-2-furaldehido utilizando el procedimiento establecido en el Ejemplo de Preparación 34.32, Paso D, del documento WO 02/083624 publicado el 24 de octubre de 2002.

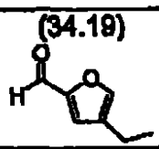
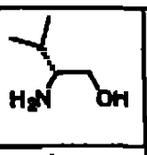
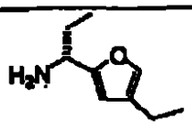
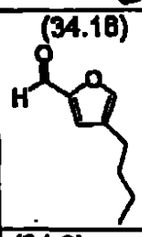
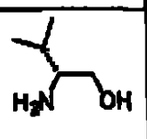
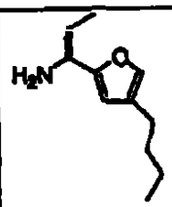
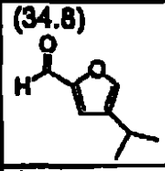
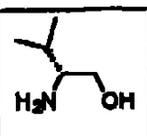
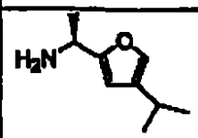
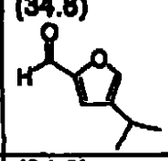
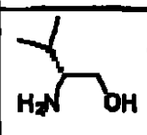
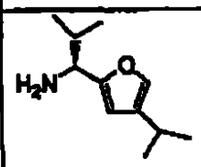
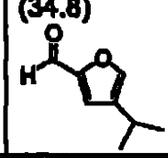
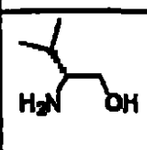
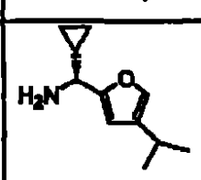
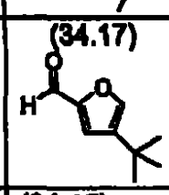
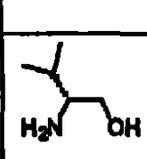
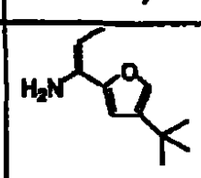
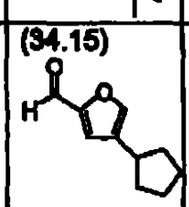
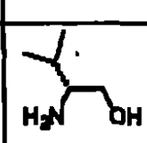
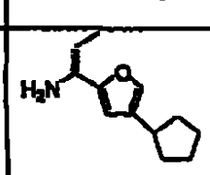
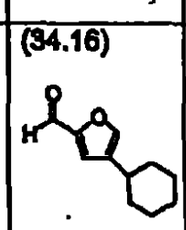
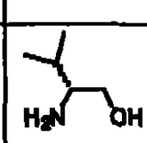
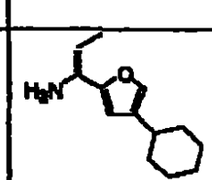
EJEMPLO DE PREPARACIÓN 75.10A - 75.10J

Siguiendo el procedimiento establecido en el Ejemplo de Preparación 64 del documento WO 02/083624 publicado el 24 de octubre de 2002, pero utilizando los aldehidos disponibles comercialmente, los amino alcoholes, y los reactivos organolitios en la Tabla siguiente, se obtuvieron los productos amina ópticamente puros. Los números en la columna "Aldehido" se refieren a los ejemplos preparativos en la presente o en WO 02/083624.

~~312~~
314

Ej. Prep	Aldehido	Amino Alcohol	Organo Litio	Producto	1.\ 2. MH^+
75.10A	(34.7) 				1. 61% 2. 135 $[M-NH_2]^+$

~~313~~
315

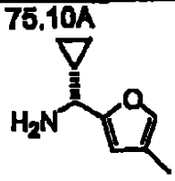
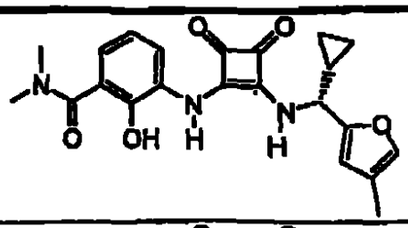
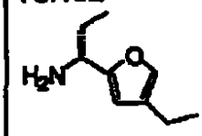
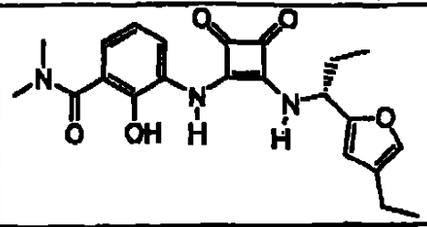
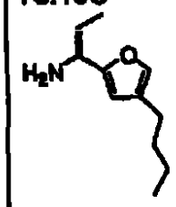
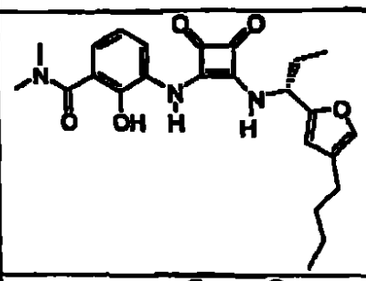
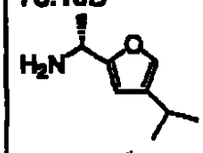
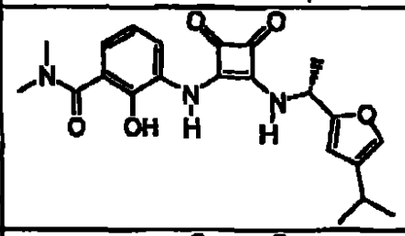
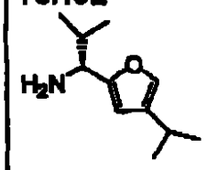
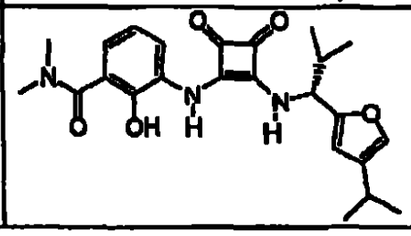
75.10B	(34.19) 		EtLi		1. 24% 2. 154
75.10C	(34.18) 		EtLi		1. 32% 2. 165 $[M-NH_2]^+$
75.10D	(34.8) 		MeLi		1. 47% 2. 137 $[M-NH_2]^+$
75.10E	(34.8) 		iPrLi		1. 30% 2. 165 $[M-NH_2]^+$
75.10F	(34.8) 				1. 67% 2. 163.0 $[M-NH_2]^+$
75.10G	(34.17) 		EtLi		1. 24% 2. 165 $[M-NH_2]^+$
75.10H	(34.15) 		EtLi		1. 70% 2. 194
75.10J	(34.16) 		EtLi		1. 54% 2. 208

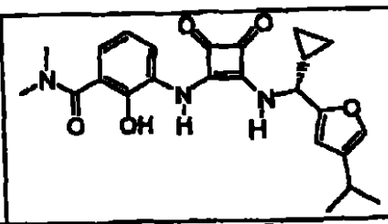
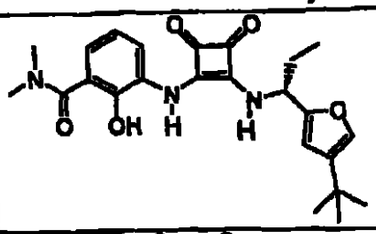
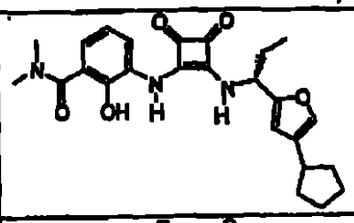
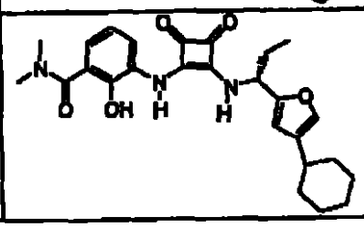
~~314~~
316

EJEMPLOS 360.109 – 360.117

Siguiendo el procedimiento establecido en el Ejemplo de Preparación 261 del documento WO 02/083624 publicado el 24 de octubre de 2002, pero utilizando la amina comercialmente disponible o la amina preparada a partir del Ejemplo de Preparación indicado en la Tabla siguiente, se obtuvieron los siguientes productos de ciclobutendiona.

315
317

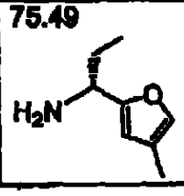
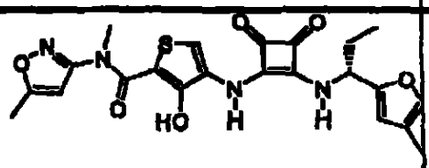
Ej.	Amina	Producto	1. Rend. 2. MH^+ 3. pf (°C)
360.109	75.10A 		1. 67% 2. 410.1 3. 119-121
360.110	75.10B 		1. 71% 2. 412 3. 102
360.111	75.10C 		1. 64% 2. 440.1 3. 91-93
360.112	75.10D 		1. 79% 2. 412 3. 111-113
360.113	75.10E 		1. 20% 2. 440.1 3. 130 (DEC)

380.114	75.10F		1. 61% 2. 438.1 3. 117-119
380.115	75.10G		1. 61% 2. 440.1 3. 117-119
380.116	75.10H		1. 61% 2. 452 3. 116
380.117	75.10J		1. 65% 2. 466 3. 109

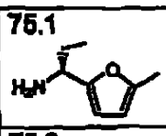
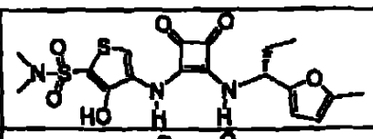
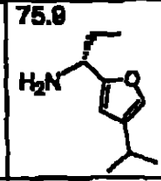
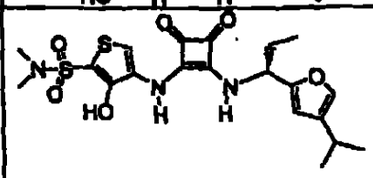
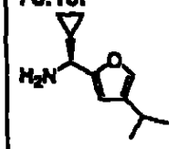
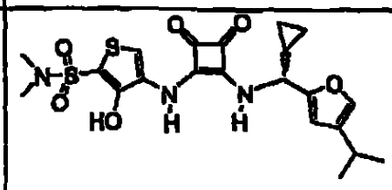
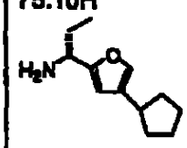
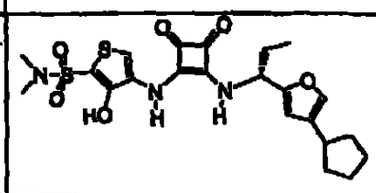
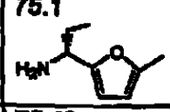
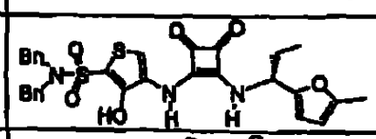
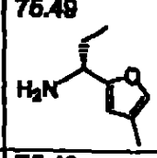
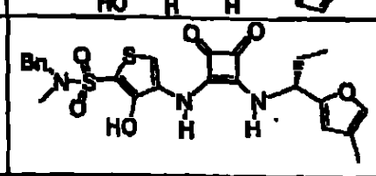
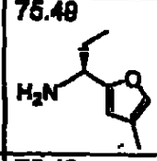
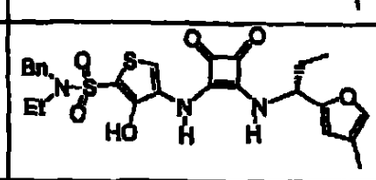
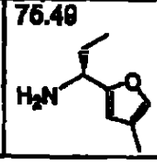
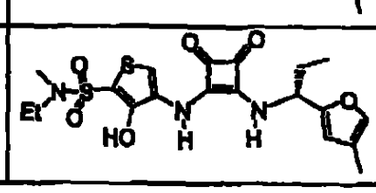
EJEMPLOS 368.32 – 368.45

Siguiendo el procedimiento establecido en el Ejemplo 261 del documento WO 02/083624 publicado el 24 de octubre de 2002, pero utilizando la amina comercialmente disponible en la tabla siguiente y el intermediario de ciclobutendiona del Ejemplo de Preparación indicado, se obtuvieron los siguientes productos de ciclobutendiona. Los números en las columnas "Amina" y "Ej. prep." se refieren a los ejemplos preparativos en la presente o en el WO 02/083624.

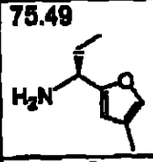
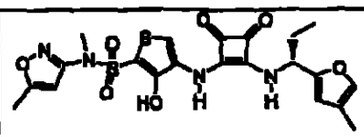
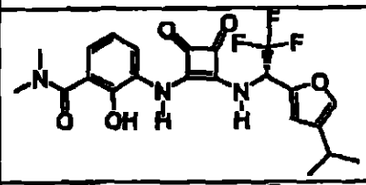
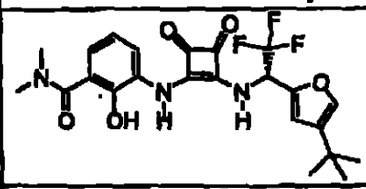
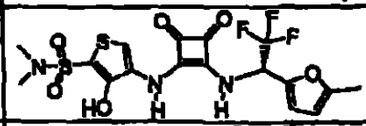
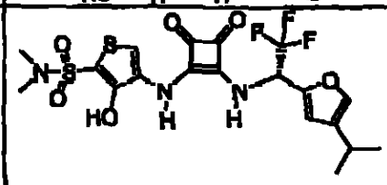
317
319

Ej.	Amina	Ej. Prep.	Producto	1. Rend (%) 2. MH+ 3. pf (°C)
368.32	75.49 	23.14		1. 68% 2. 471.1 3. 148

~~318~~ 320

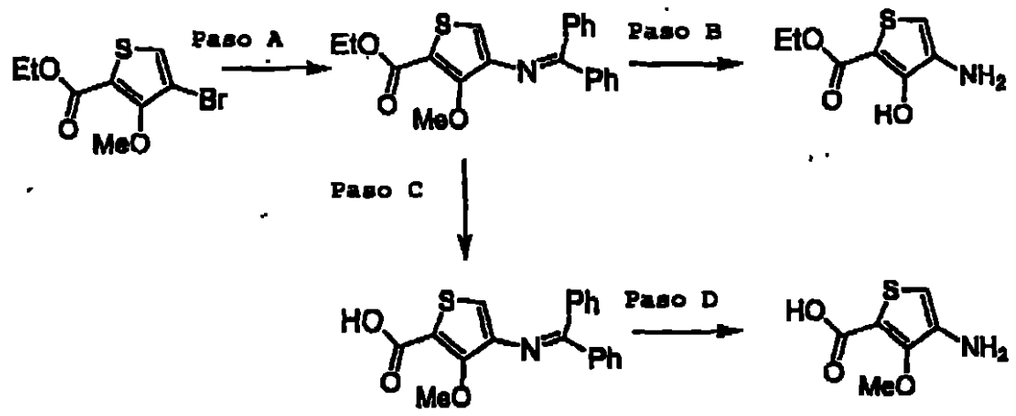
368.33	75.1 	23.15A		1. 33% 2. 440.1 3. 181
368.34	75.9 	23.15A		1. 56% 2. 468 3. 180
368.35	75.10F 	23.15A		1. 28% 2. 480 3. 186
368.36	75.10H 	23.15A		1. 48% 2. 494 3. 112.5
368.37	75.1 	23.15B		1. 58% 2. 592 3. 177-179
368.38	75.49 	23.15C		1. 69% 2. 516 3. 88-90
368.39	75.49 	23.15D		1. 80% 2. 530 3. 134-137
368.40	75.49 	23.15E		1. 87% 2. 454 3. 138-140

~~319~~
321

368.41	75.49 	19.2		1. 26% 2. 507 3. 162-164
368.42	3	23.25		1. 82% 2. 466 3. 141-143
368.43	3	23.26		1. 67% 2. 480 3. 139 dec
368.44	13.29	23.16		1. 29% 2. 480 3. 112-114
368.45	13.29	23.26		1. 88% 2. 508 3. 190 dec

EJEMPLOS PREPARATIVOS 600

320
322



Paso A

Siguiendo el procedimiento establecido en el Ejemplo de Preparación 13.19 Paso D, del documento WO 02/083624 publicado el 24 de octubre de 2002, se preparó la imina del bromoéster conocido (1,0 g) para dar 1,1 g (79%) en forma de un sólido color amarillo.

Paso B

El producto del Paso A (0,6 g) se hizo reaccionar siguiendo el procedimiento establecido en el Ejemplo de Preparación 13.19, Paso E, del documento WO 02/083624 publicado el 24 de octubre de 2002, para dar 0,19 g del producto amina (64%).

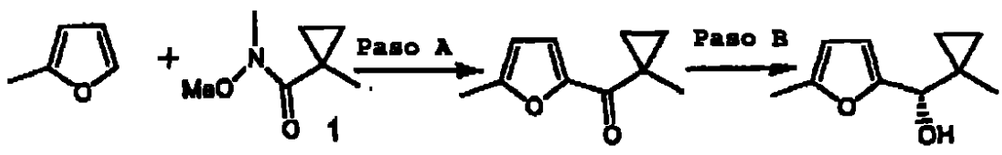
Paso C

El producto del Paso B (1,0 g) se hizo reaccionar siguiendo el procedimiento establecido en el Ejemplo de Preparación 13.19, Paso B, del documento WO 02/083624 publicado el 24 de octubre de 2002, para dar 0,9 g del ácido en forma de un sólido amarillo (94%).

Paso D

El producto del Paso C (0,35 g) se hizo reaccionar siguiendo el procedimiento establecido en el Ejemplo de Preparación 13.19, Paso E, del documento WO 02/083624 publicado el 24 de octubre de 2002, para dar 0,167 g del aminoácido en forma de un sólido amarillo (93%).

EJEMPLOS PREPARATIVOS 601



Paso A

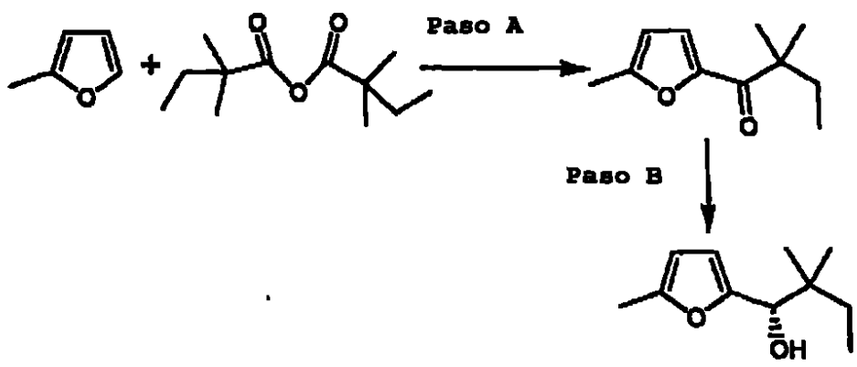
A una solución de 2-metil furano (1,72 g) en éter se agregó BuLi (8,38 ml) a –78ºC y se agitó a temperatura ambiente durante media hora. La mezcla de reacción se enfrió nuevamente a –78ºC y se templó con ciclopropil amida 1 y se agitó durante dos horas a –78ºC y se entibió lentamente a temperatura ambiente. La mezcla de reacción se agitó durante tres horas a temperatura ambiente y se templó con la adición de una solución de cloruro de amonio saturado. La mezcla se llevó a un embudo separador, se lavó con agua, salmuera y se secó en sulfato de sodio anhidro. La filtración y la eliminación del solvente dio la cetona cruda, la cual se purificó utilizando cromatografía de columna para dar la cetona 3,0 g (87%) en forma de un aceite de color amarillo pálido.

Paso B

A una solución de cetona (1,0 g) del Paso A anterior en THF (5,0 ml) a 0ºC se agregó R-metil oxazoborolidina (1,2 Ml, 1M en tolueno) en gotas seguido de la adición de una solución de borano complejada con dimetil sulfuro (1,85 ml, 2M en

THF). La mezcla de reacción se agitó durante 30 minutos a 0ºC y luego a temperatura ambiente durante una hora. La mezcla de reacción se enfrió a 0ºC y se agregó MeOH cuidadosamente. La mezcla se agitó durante 20 minutos y se concentró a presión reducida. El residuo se extrajo con éter, se lavó con agua, HCl 1M (10 ml), bicarbonato de sodio saturado (10,0 ml) agua y salmuera. La capa orgánica se secó en sulfato de sodio anhidro, se filtró y la eliminación del solvente dio el alcohol crudo que se purificó mediante cromatografía de gel de sílice para dar 0,91 g del alcohol puro (91%) en forma de un aceite amarillo.

EJEMPLOS PREPARATIVOS 602



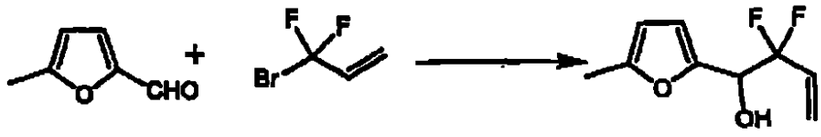
Paso A

Una mezcla equimolar de 2-metilfurano (1,0 g) y anhídrido (2,6 g) se mezcló con $SnCl_4$ (0,05 ml) y se calentó a 100ºC durante 3 horas. Al cabo de enfriar la mezcla de reacción, se agregó agua (10 ml), seguido de una solución de carbonato de sodio saturado hasta que se tornó alcalina. La mezcla de reacción se extrajo con éter varias veces y la capa de éter combinada se lavó con agua, salmuera y se secó en sulfato de sodio anhidro. La filtración y la eliminación del solvente dio la cetona cruda, la cual fue purificada mediante cromatografía de gel de sílice para dar 0,9 g de cetona (43%) en forma de un aceite de color amarillo.

Paso B

El alcohol del título se obtuvo siguiendo un procedimiento similar al establecido en el Ejemplo de Preparación 601.

EJEMPLOS PREPARATIVOS 603

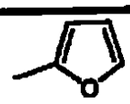
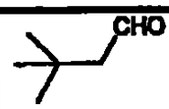
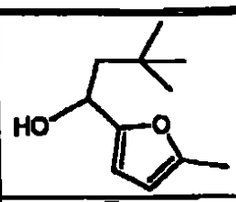
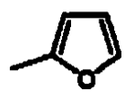
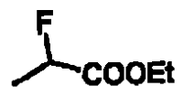
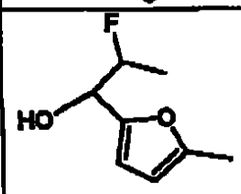


A una solución de 5-metil furan-2-aldehido (1,0 g) y 3-bromo-3,3-difluorpropeno (2,24 g) en DMF (30 ml) se agregó polvo de indio (1,66 g) y yoduro de litio (50,0 mg). La mezcla de reacción se agitó durante la noche, se diluyó con agua y se extrajo con éter. La capa de éter se lavó con agua, salmuera y se purificó mediante cromatografía de gel de sílice para dar 2,8 g del alcohol puro (92%).

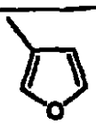
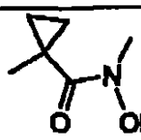
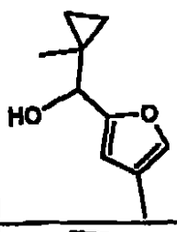
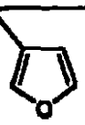
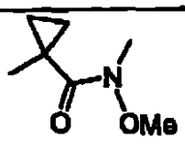
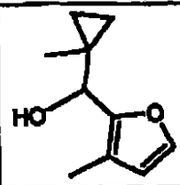
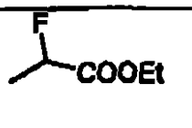
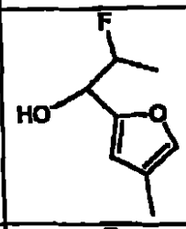
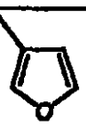
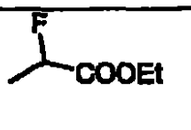
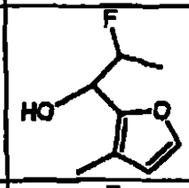
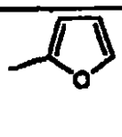
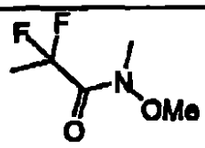
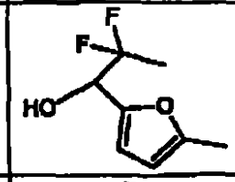
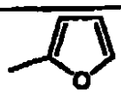
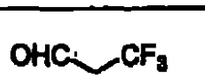
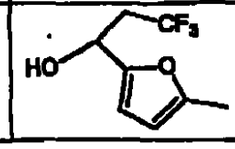
EJEMPLOS PREPARATIVOS 604-611

Siguiendo un procedimiento similar al establecido en el Ejemplo de Preparación 13.25 del documento WO 02/083624 publicado el 24 de octubre de 2002, o el Ejemplo de Preparación 601, se prepararon los siguientes alcoholes.

324
326

Ej. Prep'	Furano	Electrófilo	Alcohol	Rend
604				86%
605				69%

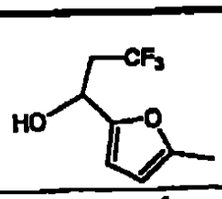
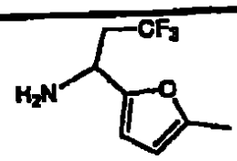
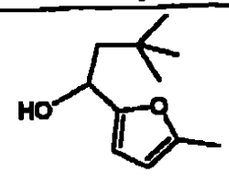
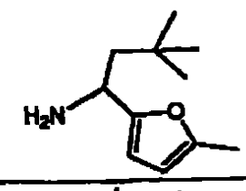
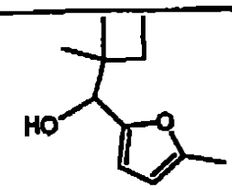
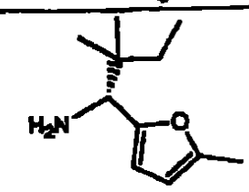
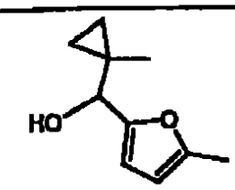
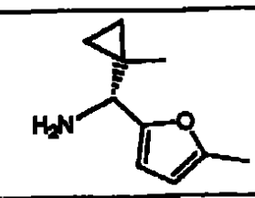
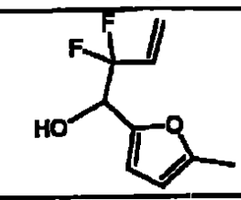
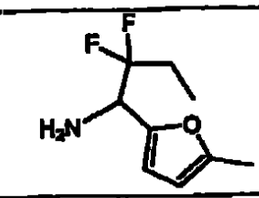
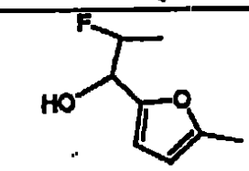
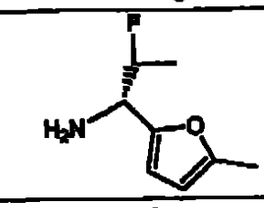
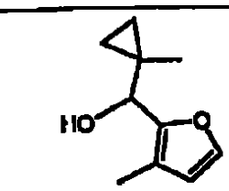
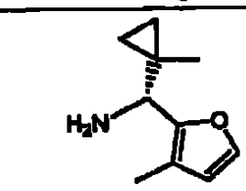
~~325~~
327

606				84%
607				82%
608				60%
609				65%
610				82%
611				89%

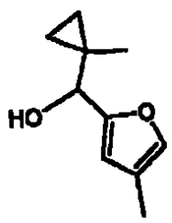
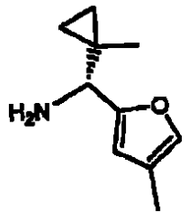
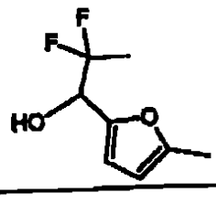
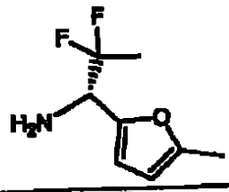
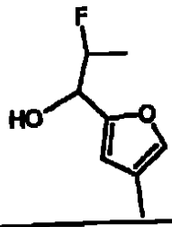
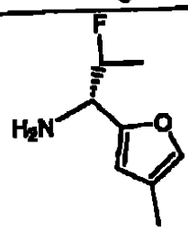
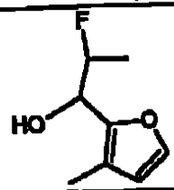
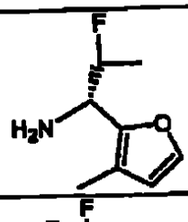
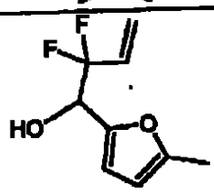
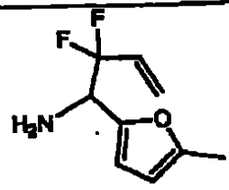
EJEMPLOS PREPARATIVOS 620 – 631

Siguiendo un procedimiento similar al establecido en los Ejemplos Preparativos 13.25 se prepararon las siguientes aminas a partir de los correspondientes alcoholes.

326
328

EJ. PREP	ALCOHOL	AMINA	REND
620			28%
621			58%
622			69%
623			81%
624			82%
625			45%
626			57%

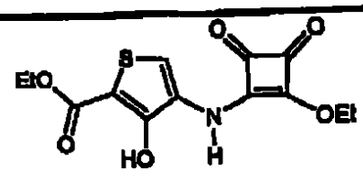
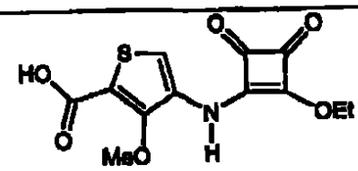
327
329

627			58%
628			54%
629			53%
630			50%
631			82%

328
330

EJEMPLO DE PREPARACIÓN 640 – 641

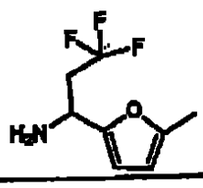
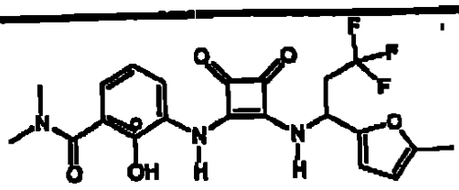
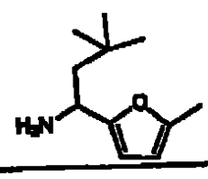
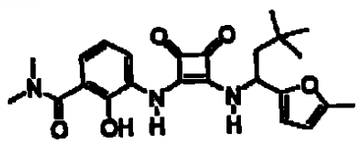
Siguiendo los procedimientos establecidos en el Ejemplo de Preparación 19 del documento WO 02/83624 publicado el 24 de octubre de 2002, pero utilizando la amina del Ejemplo de Preparación indicado en la Tabla a continuación, se obtuvieron los intermediarios de ciclobutendiona.

Ej.Prep	Amina del Ej. Prep	Producto	^{1}Rend (%) 2. MH^+
640	600 Step B		1. 60% 2. 138
641	600 Step D		1. 66 2. 136

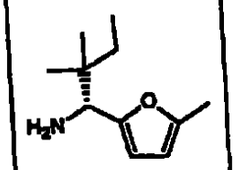
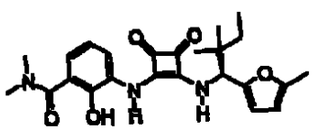
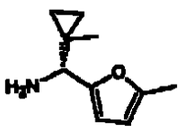
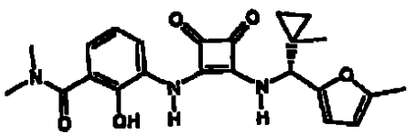
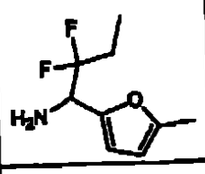
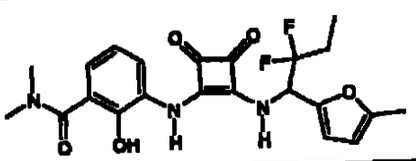
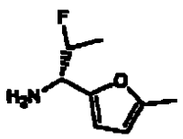
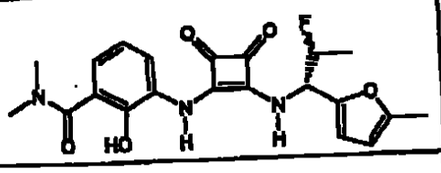
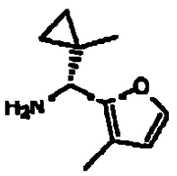
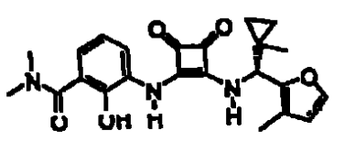
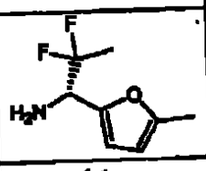
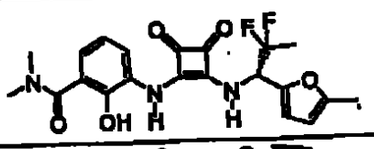
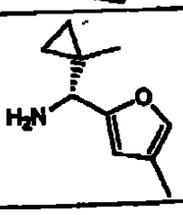
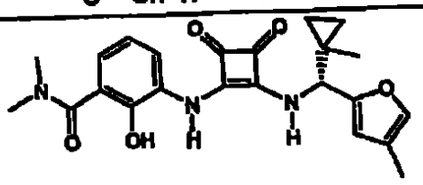
EJEMPLOS 1200 – 1211

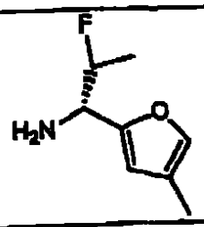
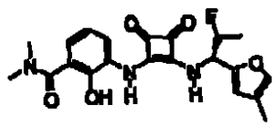
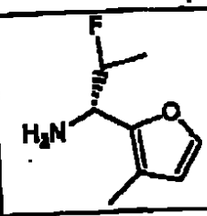
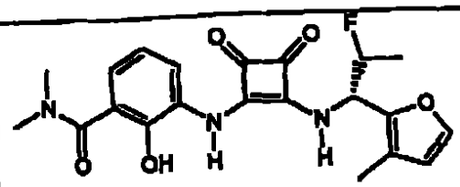
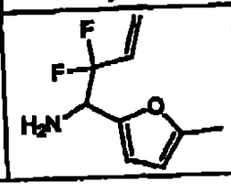
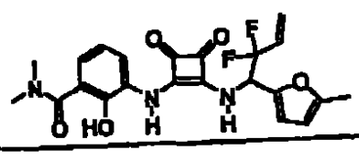
Siguiendo el procedimiento establecido en el Ejemplo de Preparación 261 del documento WO 02/083624 publicado el 24 de octubre de 2002, pero utilizando la amina comercialmente disponible o la amina preparada a partir del Ejemplo de Preparación indicado en la Tabla siguiente, se obtuvieron los siguientes productos de ciclobutendiona.

329
331

Ej	Amina	Producto	1. Rend (%) 2. MH+ 3. pf (°C)
1200			1. 61.3 2. 451.4 3. 108.6
1201			1. 54 2. 439.5 3. 117.8

~~330~~
332

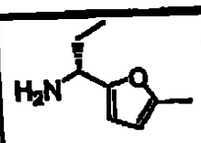
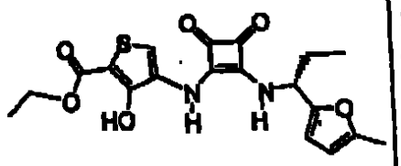
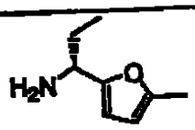
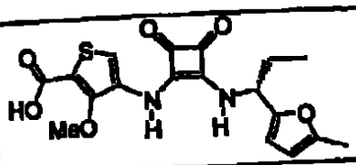
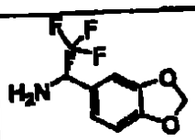
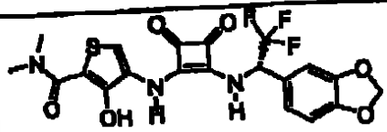
1202			1. RT 2. 439.5 3. 128-131.8
1203			1. 75 2. 423.4 3. 118-119
1204			1. 74 2. 447.4 3. 108-111
1205			1. 42 2. 415.42 3. 136-140
1206			1. 46 2. 423.4 3. 114-117
1207			1. 35 2. 433.1 3. 123-128
1208			1. 42 2. 423.4 3. 118-121

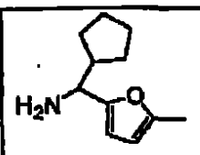
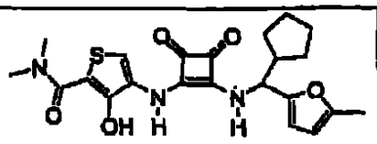
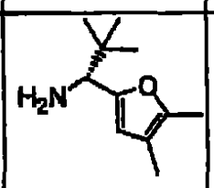
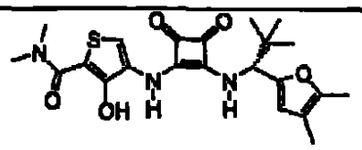
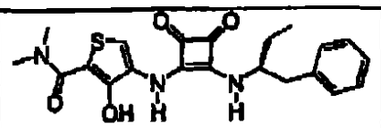
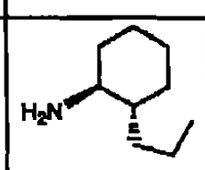
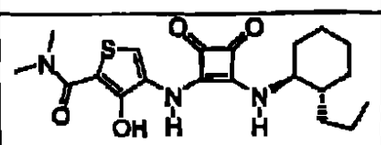
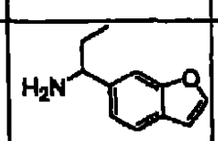
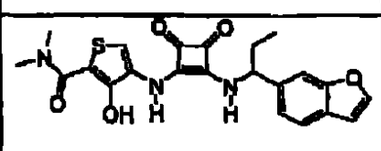
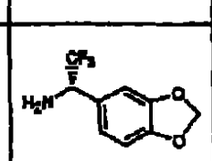
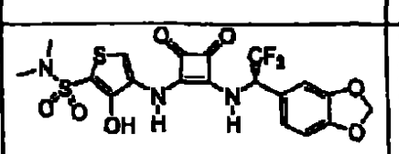
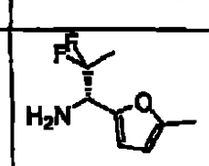
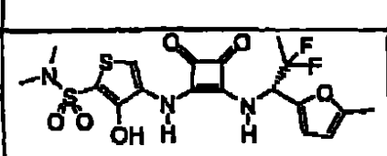
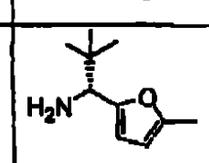
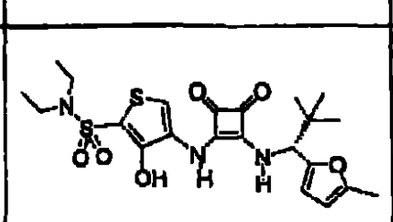
1209			1. 51 2. 415.4 3. 112-117
1210			1. 44 2. 415.4% 3. 115-120
1211			1. 48 2. 445.4 3. 105-110

EJEMPLOS 1300 – 1311

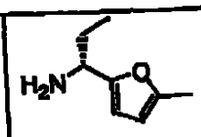
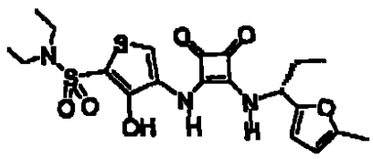
Siguiendo el procedimiento establecido en el Ejemplo de Preparación 261 del documento WO 02/083624 publicado el 24 de octubre de 2002, pero utilizando la amina comercialmente disponible en la Tabla siguiente y el intermediario de ciclobutandiona a partir del Ejemplo de Preparación indicado, se obtuvieron los siguientes productos de ciclobutendiona. El Ejemplo de Preparación 23.9 está en el documento WO 02/083624, publicado el 24 de octubre de 2002.

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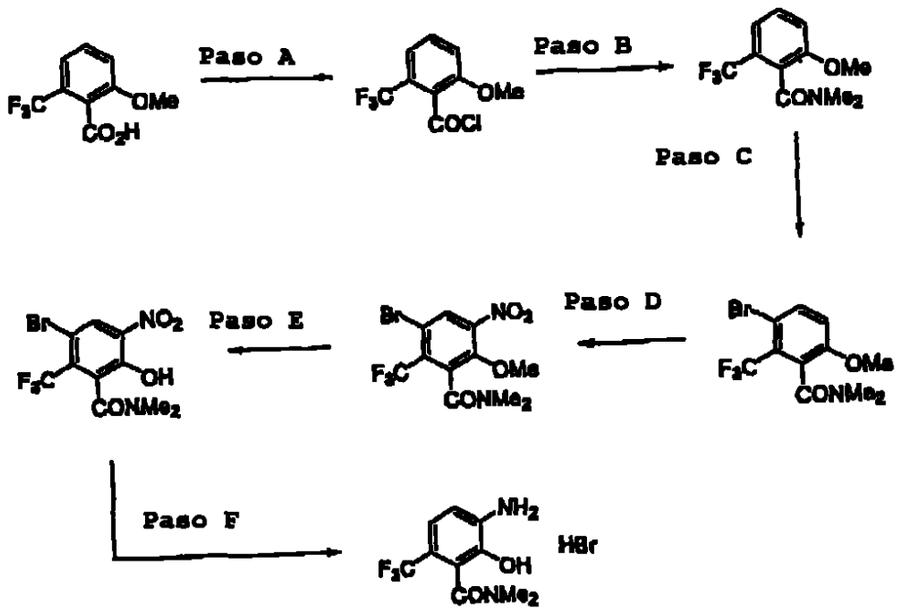
Ej.	Amina	Ej. Prep	Producto	1.Rend (%) 2. MH^+ 3.Pf (°C)
1300		640		1. 35% 2. 380.4 3. 100
1301		641		1.78% 2. 390.4 3. 130
1302		23.9		1. 48% 2. 483.4 3. 116

1303		23.9		1. 46% 2. 443.5 3. 106
1304		23.9		1. 40% 2. 445.54 3. 102
1305		23.9		1. 51% 2. 413.4 3. 98
1306		23.9		1.78% 2. 405.5 3. 246
1307		23.9		1. 83% 2. 439.5 3. 129
1308		23.15A		1. 11% 2. 519.47 3. 123
1309		23.15A		1. 47% 2. 475 3. 113
1310		640		1. 55% 2. 496.1 3. 123- 125

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1311		640		1. 74% 2. 466.1 3. 116-118

EJEMPLO DE PREPARACIÓN 1001



Paso A

Se agregó en gotas cloruro de oxalilo (3 ml, 34,27 mmol) a una mezcla de ácido 2-metoxi-6-(trifluormetil)benzoico (1,5 g, 6,81 mmol) (preparada de acuerdo con el método conocido, ver: EP0897904B1), N,N-dimetilformamida (0,3 ml), y diclorometano (40 ml) con agitación a temperatura ambiente. La mezcla de reacción se agitó durante la noche. La evaporación del solvente y el exceso de cloruro de oxalilo y el secado a vacío dio cloruro 2-metoxi-6-(trifluormetil)benzoilo

en forma de un sólido, el cual se utilizó sin purificación.

Paso B

Una solución de cloruro 2-metoxi-6-(trifluormetil)benzoilo (ca. 6,81 mmol) del Paso A anterior en diclorometano (20 ml) se agregó en gotas a una mezcla de 4-(dimetilamino)piridina (42 mg, 0,34 mmol), trietilamina (2,8 ml, 20,09 mmol), y solución 2M de dimetilamina en tetrahidrofurano (7 ml, 14 mmol), y diclorometano (30 ml) con agitación a temperatura ambiente. La mezcla de reacción se agitó durante la noche. Se agregó una mezcla de diclorometano y agua. La fase orgánica se separó, se lavó con una solución de HCl 1N, agua, y solución de bicarbonato de sodio saturado y se concentró. El residuo se purificó mediante cromatografía de columna (acetato de etilo:hexanos, 3:1 v/v) para dar el producto en forma de un sólido blanco (1,24 g, 74% en dos pasos).

Paso C

Una mezcla de la amida del Paso B anterior (1,8 g, 7,28 mmol), tetracloruro de carbono (25 ml), y polvo de hierro (305 mg, 5,46 mmol) se enfrió a 0ºC. Se agregó bromo (0,94 ml, 18,34 mmol) en gotas con agitación. Al cabo de la adición, la mezcla se agitó a temperatura ambiente durante 1 hora y a 50ºC durante 3 horas. La mezcla se enfrió a temperatura ambiente, se diluyó con diclorometano, y se vertió lentamente a una solución de $NaHSO_3$ al 10% fría. Al cabo de la agitación a temperatura ambiente durante 0,5 horas, la capa orgánica se separó y se concentró para dar el producto en forma de un sólido blanco (2,26 g, 95%).

Paso D

Ácido sulfúrico concentrado (10 ml) se agregó en gotas a un matraz cargado con el bromuro del Paso C anterior (600 mg, 1,84 mmol) a 0ºC con

agitación. Una mezcla de ácido nítrico (0,2 ml, 4,76 mmol) y ácido sulfúrico concentrado (0,3 ml) luego se agregó en gotas. Al cabo de la adición, la mezcla se agitó a temperatura ambiente durante 3 horas. La mezcla se agregó a agua helada, se neutralizó con 15% de solución de NaOH a pH 7, y se extrajo con diclorometano. La capa orgánica se concentró para dar el producto en forma de un sólido blanco (621 mg, 91%). Pf 92ºC, m/e 371 (MH^+).

Paso E

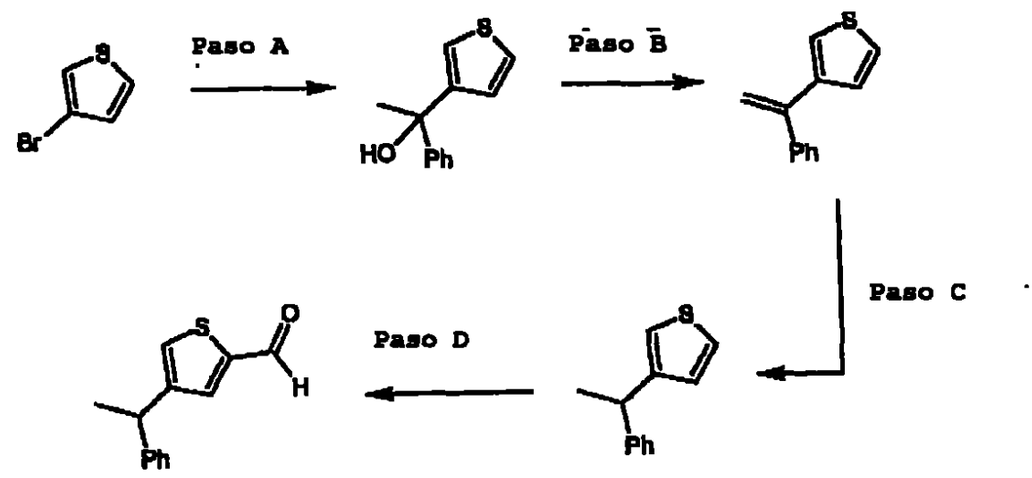
Una solución del compuesto del Paso D anterior (1,2 g, 3,23 mmol) en diclorometano (50 ml) se enfrió a –75ºC. La solución de BBr_3 1M en diclorometano (7,5 ml, 7,5 mmol) se agregó en gotas con agitación. La mezcla se agitó a –75ºC durante 2 horas. La mezcla se agregó a agua helada. Al cabo de la agitación a temperatura ambiente durante 0,5 horas, la mezcla se extrajo con diclorometano. La capa orgánica se concentró y el residuo se purificó mediante cromatografía de columna (diclorometano-metanol, 9:1 v/v) para dar el producto en forma de un sólido amarillo (1,05 g, 91%). m/e 357 ((MH^+).

Paso F

Una mezcla del compuesto del Paso E anterior (1,08 g, 3,02 mmol), metanol (30 ml), y 10% de Pd-C (250 mg) se sometió a hidrogenación a 50 psi a temperatura ambiente durante 6 horas. La mezcla se filtró a través de una capa de celite. El filtrado se concentró para dar el compuesto del título en forma de un sólido amarillo pálido (930 mg, 96%). Pf 132ºC, m/e 249.

EJEMPLO DE PREPARACIÓN 1002

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Paso A

A una solución enfriada (-70ºC) eterial (45 ml seca) de 3-bromotiofeno (3,8 ml) se agregó BuLi (30 ml de 1,6M en hexano) en gotas, y la mezcla se agitó a 70ºC durante 20 minutos. Se agregó acetofenona (4,6 ml) en éter (6 ml) en gotas con agitación a –70ºC. Al cabo de 3 horas, la mezcla se entibió a temperatura ambiente y se agregó NH_4Cl (ac) sat. Y la mezcla se extrajo con éter. La fase orgánica se secó (Na_2SO_4) y se concentró a vacío para dar el compuesto del título el cual se utilizó en el Paso B sin purificación adicional.

Paso B

El producto crudo del Paso A anterior se agitó con ácido oxálico (0,375 g) a 70ºC a presión reducida durante 3 horas, luego se enfrió a temperatura ambiente y se extrajo con éter. La fase orgánica se secó en Na_2SO_4 y se concentró a vacío para dar el producto en forma de un líquido de color amarillo pálido (5,7 g, 78% para los Pasos A-B).

Paso C

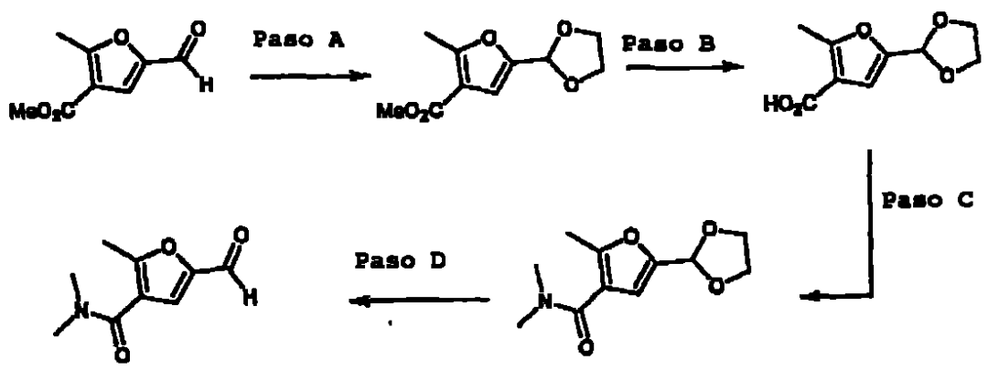
Al producto de la Etapa B anterior (4,2 g) diluida con diclorometano (30 ml) y con contenido de trietilsilano (6 ml) se agregó TFA (3 ml) en diclorometano (7,5

ml). Al cabo de agitar a temperatura ambiente durante 10 minutos, la mezcla se concentró a vacío para dar el producto en forma de un líquido incoloro (4,61 g, 80%).

Paso D

A una solución eterial (3,5 ml seca) del producto tiofeno (1,5 g) del Paso C anterior se agregó BuLi (3,2 ml de 2,5M), y la mezcla se calentó a reflujo durante 15 min., se enfrió a temperatura ambiente, se agregó en gotas DMF (0,8 ml) en éter (3,5 ml). Al cabo de agitación durante 30 min. se agregó NH_4Cl sat. (ac) y la mezcla se extrajo con éter. La fase orgánica se secó en Na_2SO_4 y se concentró a vacío para dar el compuesto del título (1,71 g, 98%).

EJEMPLO DE PREPARACIÓN 1003



Paso A

El aldehído (0,50 g) se combinó con etilen glicol (1 ml), benceno (40 ml) y pTSA monohidrato (30 mg) y se agitó a reflujo durante 20 horas. Se enfrió a temperatura ambiente, se agregó EtOAc y solución de $NaCHO_3$ sat (ac), se separó la fase orgánica, se concentró a vacío, y se purificó mediante cromatografía flash (EtOAc-Hex, 1:4) para dar un líquido incoloro (60 mg).

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Paso B

El producto del Paso A anterior (0,607 g) se agitó a 45ºC durante la noche con NaOH 1N (ac), luego se enfrió a temperatura ambiente, se acidificó con HCl 3N y se extrajo con EtOAc. El lavado con salmuera y la concentración a vacío dio un sólido (5,0 g).

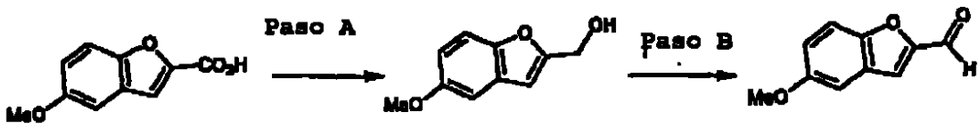
Paso C

Siguiendo un procedimiento similar al utilizado en el Ejemplo de Preparación 1, salvo utilizando el producto del Paso B anterior y dimetilamina en THF (2M), se obtuvo el producto (1,21 g crudo).

Paso D

El producto del paso C anterior se disolvió en THF y se agitó con HCl 0,3N (ac) y se agitó a temperatura ambiente durante 4 horas. La concentración a vacío dio un aceite de color amarillo pálido (1,1 g, 67%).

EJEMPLO DE PREPARACIÓN 1004



Paso A

A una solución enfriada (-78ºC) de ácido metoxibenzofurano-2-carboxílico (1 g) se agregó DIBAL (30 ml, 1M en THF). Al cabo de agitar durante 20 min., la mezcla se entibió a temperatura ambiente y se agitó durante 4 horas, luego se vertió en NH4Cl sat. (ac) (35 m). Al cabo de agitar a temperatura ambiente

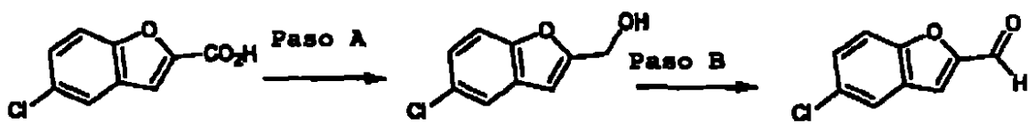
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durante 20 min., se agregó HCl 6M (ac) y la mezcla se extrajo con EtOAc, la fase orgánica se secó y luego se concentró a vacío. La purificación mediante cromatografía de gel de sílice (EtOAc-hexano, 3:7) dio el alcohol en forma de un sólido (0,4 g, 97%).

Paso B

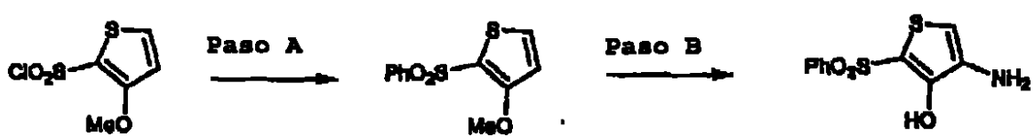
Una mezcla del producto del Paso A anterior (0,9 g), EtOAc (50 ml) y MnO2 (5,2 g) se agitó a temperatura ambiente durante 22 horas, luego se filtró y se concentró a vacío. El sólido se redisolvió en EtOAc (50 ml), se agregó MnO2 (5,2 g) y la mezcla se agitó durante 4 horas adicionales. La filtración, la concentración y la purificación en gel de sílice (EtOAc-Hexano, 1:3) dio el compuesto del título en forma de un sólido (0,60 g, 67%).

EJEMPLO DE PREPARACIÓN 1005



Siguiendo un procedimiento similar al detallado en el Ejemplo de Preparación 1004, salvo utilizando ácido 5-clorobenzofuran-2-carboxílico (1,5 g), se obtuvo el compuesto del título (sólido, 0,31 g, 24%).

EJEMPLO DE PREPARACIÓN 1006



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Paso A

El cloruro de sulfonilo del Ejemplo de Preparación 13.29 del Paso A (1,5g) se agitó con AlCl3 y benceno durante 15 min. a 20ºC. El tratamiento con NaOH, la extracción con Et_2O, la concentración a vacío, y la purificación mediante cromatografía flash (sílice, hexano-EtOAc, 5:2) dio la fenilsulfona (1,5 g, 84%, $MH^+ = 255$).

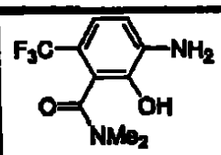
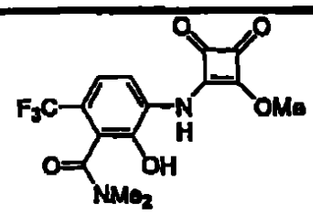
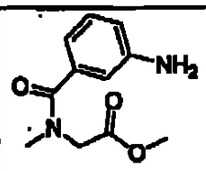
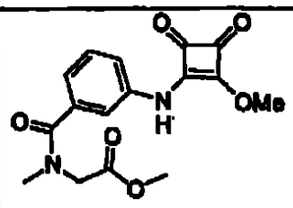
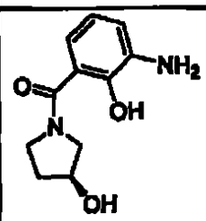
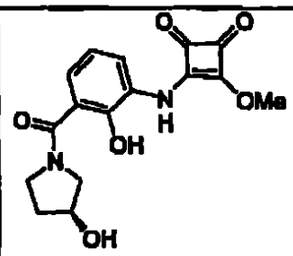
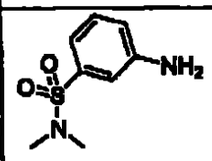
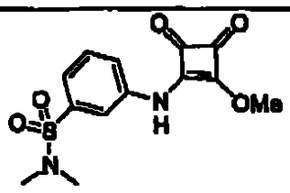
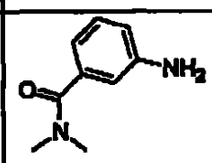
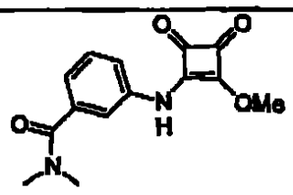
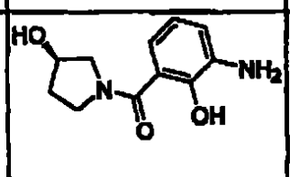
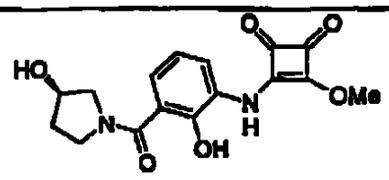
Paso B

Siguiendo los mismos procedimientos que los utilizados en el Ejemplo de Preparación 13.29 Pasos C-G, salvo utilizando la sulfona del Paso A anterior, se preparó el compuesto del título (0,04 g, 27%, $MH^+ = 256$).

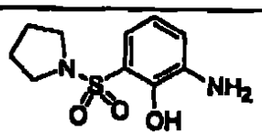
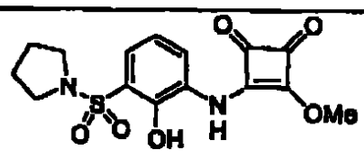
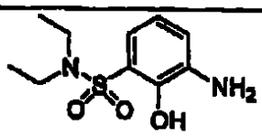
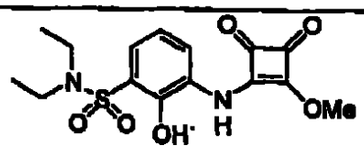
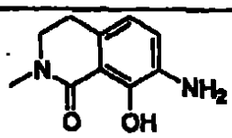
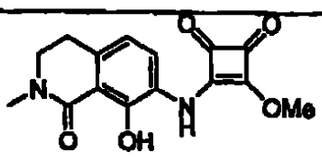
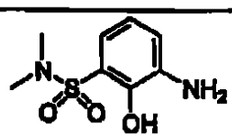
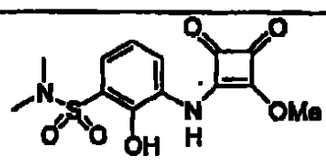
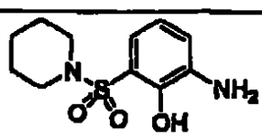
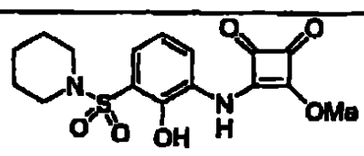
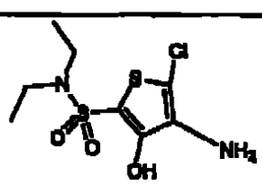
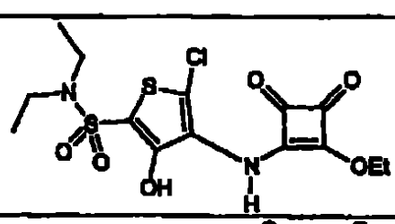
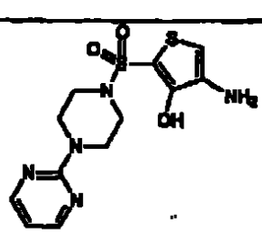
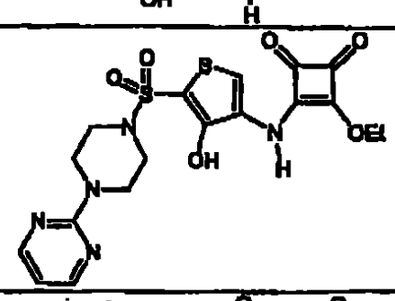
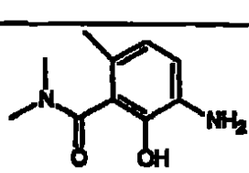
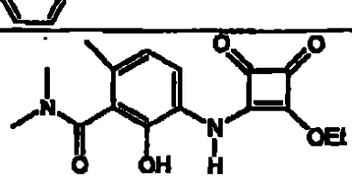
EJEMPLO PREPARTIVO 1007 – 1029

Siguiendo un procedimiento similar al establecido en el Ejemplo de Preparación 19.1 del documento WO 02/083624 publicado el 24 de octubre de 2002 o el Ejemplo de Preparación 19.2, pero utilizando la amina (anilinas) enumeradas en al tabla a continuación, se prepararon los siguientes intermediarios esquarato.

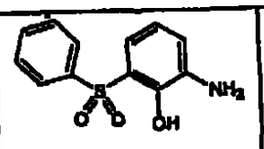
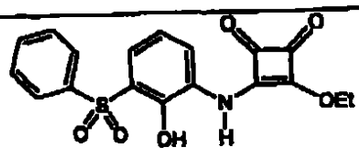
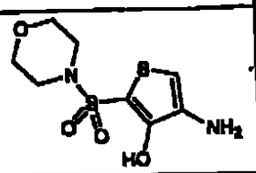
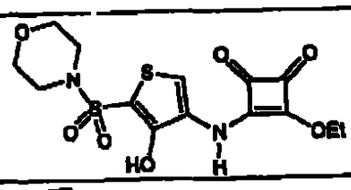
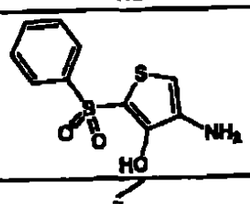
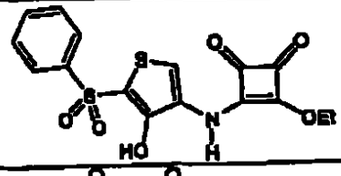
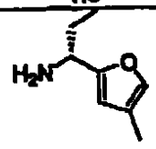
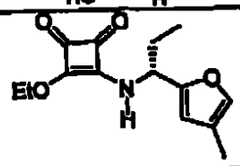
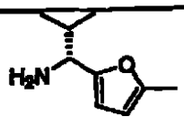
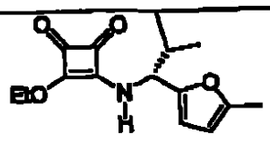
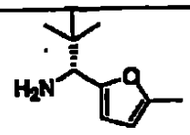
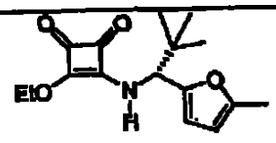
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Ejemplo	Amina/Anilina	Producto	1.Rend(%) 2. (M+1)+
1007			1. 95% 2. 359
1008			1. 99% 2. 333
1009			1. 99% 2. 333
1010			1. 99% 2. 311
1011			1. 99% 2. 275
1012			1. 99% 2. 333

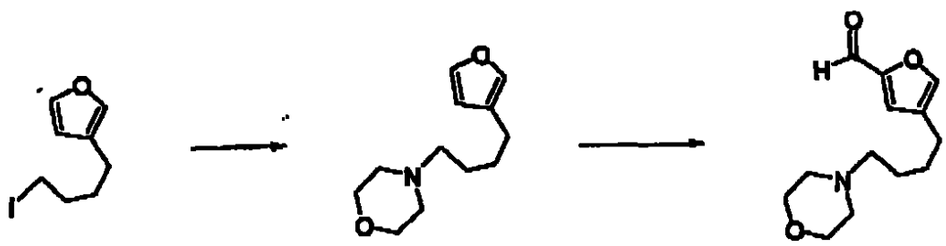
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1013			1. 72% 2. 383.0
1014			1. 60% 2. 355.1
1015			1. 70% 2. 303.1
1016			1. 45% 2. 327.0
1017			1. 70% 2. 367.0
1019			1. 32% 2. 409
1020			1. 48% 2. 466
1021			1. ~60% (crude)

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1022			1. 21%
1023			1. 45% 2. 389
1024			1. 30% 2. 380
1027			1. 44% 2. 284
1028			1. 56% 2. 278
1029			1. 47% 2. 292

EJEMPLO DE PREPARACIÓN 1030



Paso A

El producto del Ejemplo de Preparación 34.18 Paso B (2 g, 8 mmol) se agitó con morfolina (0,9 ml, 10,29 mmol) y K2CO3 (2,2 g, 15,9 mmol) en 50 ml de

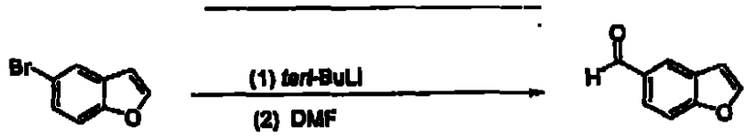
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34

acetona a temperatura ambiente para obtener el derivado de morfolinobutilfurano (1,22 g, 73%).

Paso B

Siguiendo un procedimiento similar al del Ejemplo de Preparación 34.18 Paso D, pero utilizando el producto (1,2 g) del Paso A anterior, se preparó el aldehido del título (0,9 g, 66%, 1:0,7 mezcla regioisomérica).

EJEMPLO DE PREPARACIÓN 1031



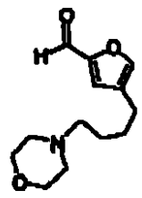
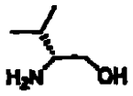
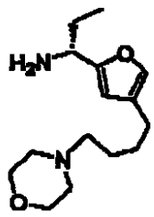
Una solución de 5-bromobenzofurano (950 mg, 4,82 mmol) en éter anhidro (12 ml) se enfrió a –78ºC. Se agregó en gotas bajo argón solución 1,7 M de terc-BuLi en pentano (6 ml, 10,2 mmol). Al cabo de la adición, la mezclase agitó a –78ºC durante 20 min., seguido de la adición de una mezcla de DMF (0,8 ml) y éter (1 ml). La mezcla se dejó entibiar a temperatura ambiente y se agitó durante 0,5 horas. Se agregó acetato de etilo. La mezcla se vertió a solución de cloruro de amonio saturado. La capa orgánica se separó y se concentró. El residuo se purificó mediante cromatografía de columna (acetato de etilo-hexanos, 1:5 v/v) para dar el compuesto del título en forma de un sólido de color amarillo pálido (490 mg, 70%).

EJEMPLOS PREPARATIVOS 1040 – 1054

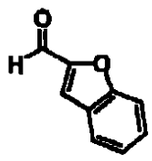
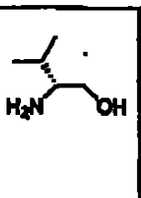
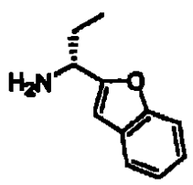
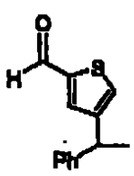
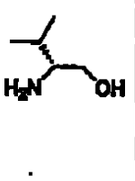
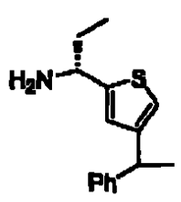
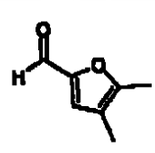
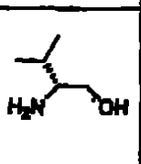
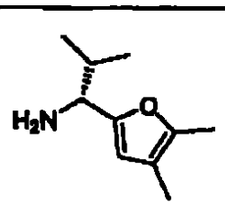
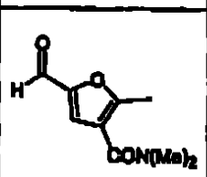
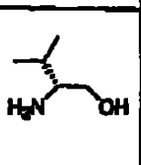
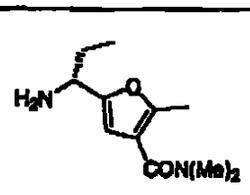
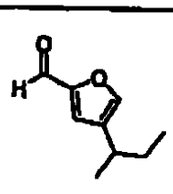
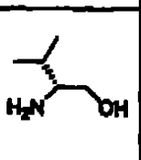
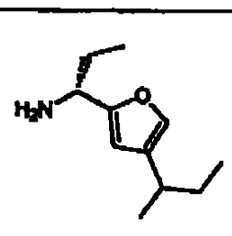
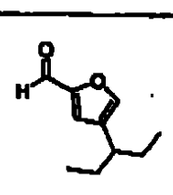
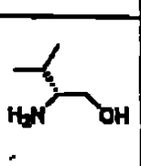
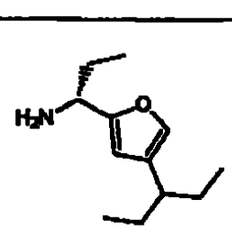
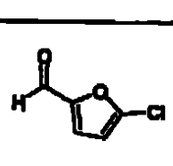
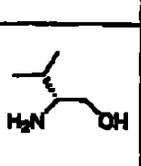
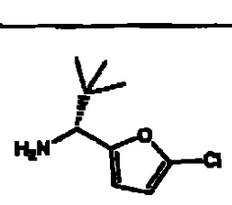
Siguiendo el procedimiento establecido en el Ejemplo de Preparación 64 del documento WO 02/083624 publicado el 24 de octubre de 2002, pero utilizando

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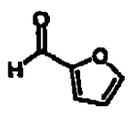
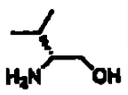
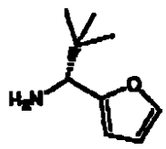
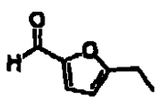
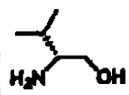
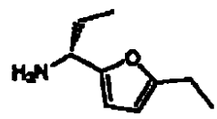
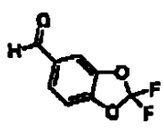
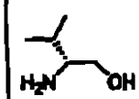
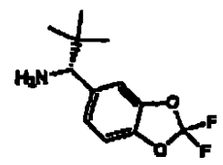
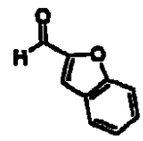
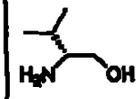
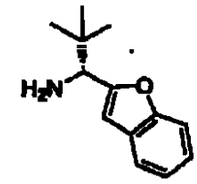
el aldehido comercialmente disponible (o preparado), los aminoalcoholes, y los reactivos de organolitio de la tabla a continuación, se obtuvieron los productos amina ópticamente puros.

Ej. Prep	Aldehido	Amino Alcohol	Organo-Litio	Producto	1. Rend(%) 2. (M+1)+
1040			EtLi		1. 24% 2. 267

347
349

1041			EtLi		1. 94% 2. 176 (m/e)
1042			EtLi		1. 67% 2. 229 (M-16)
1043			i-PrLi		1. 80% 2. 151 [M-16]
1044			EtLi		1. 74% 2. 194 (M-16)
1045			EtLi		1. 33% 2. 166 [M-NH2]+
1046			EtLi		1. 31 2. 179 [M-NH2]+
1047			t-BuLi		1. 31% 2. 188

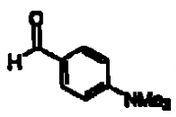
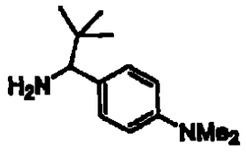
348
350

1048			t-BuLi		1. 10% 2. 154
1049			EtLi		1. 73% 2. 137 [M-NH2]°
1051			t-BuLi		1. 17%
1054			t-BuLi		1. 79% 2. 151 (M-16)

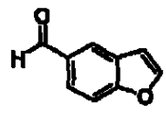
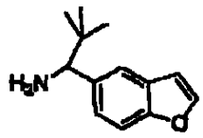
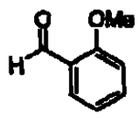
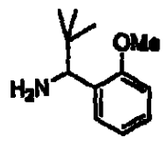
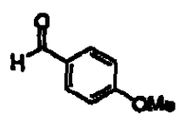
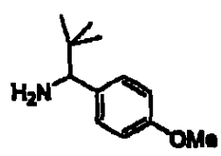
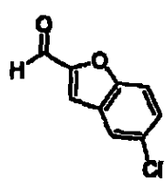
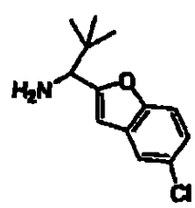
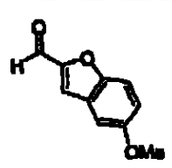
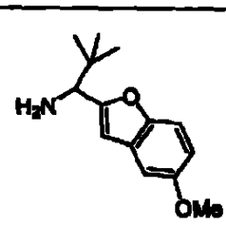
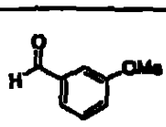
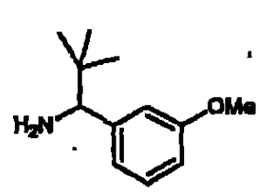
EJEMPLOS PREPARATIVOS 1100 – 1126

Siguiendo el procedimiento establecido en el Ejemplo de Preparación 34 del documento WO 02/083624 publicado el 24 de octubre de 2002, pero utilizando los aldehidos comercialmente disponibles reactivos de Grignard/organolitio enumerados en la tabla a continuación, se obtuvieron los productos amina.

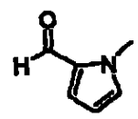
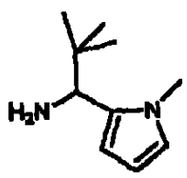
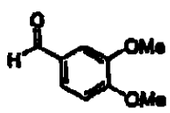
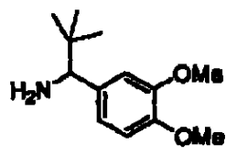
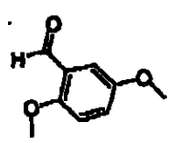
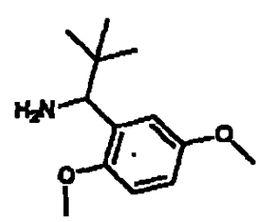
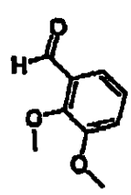
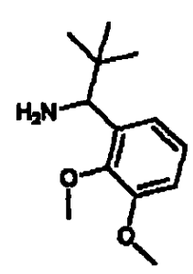
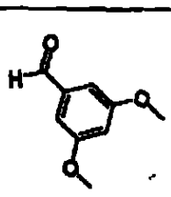
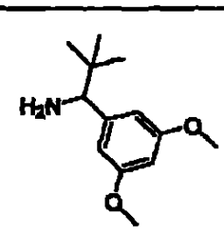
3449
351

Ej. Prep	Aldehido	Reactivo Organo-metálico	Producto	1Ren (%) 2. (M+1)°
1100		t-BuLi		1. 83% 2. 190 (M-16)

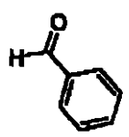
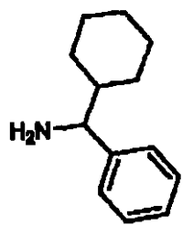
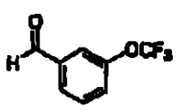
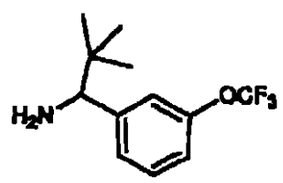
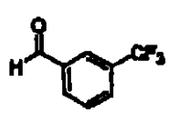
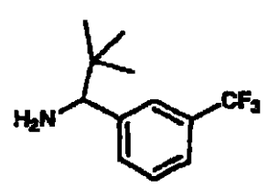
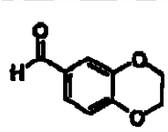
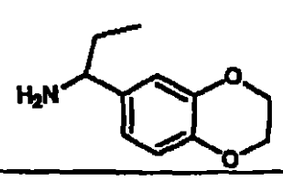
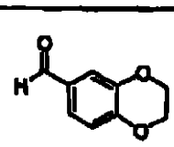
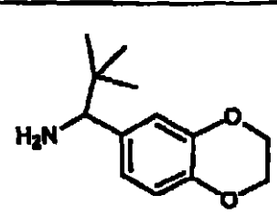
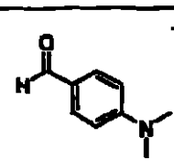
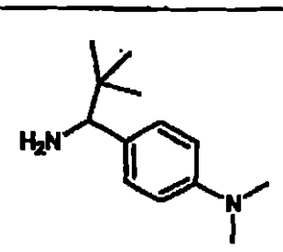
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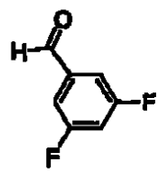
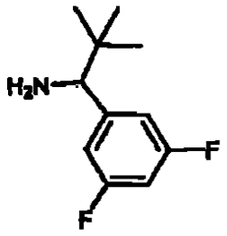
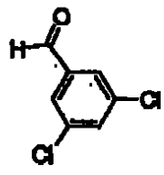
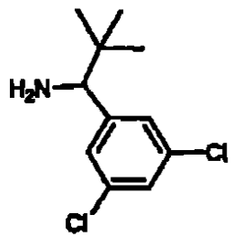
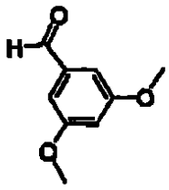
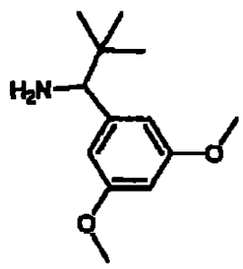
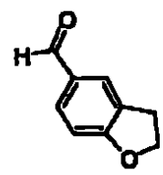
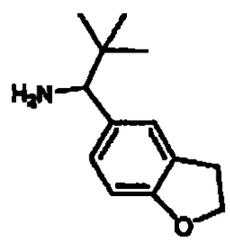
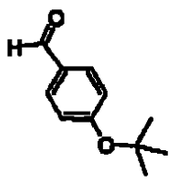
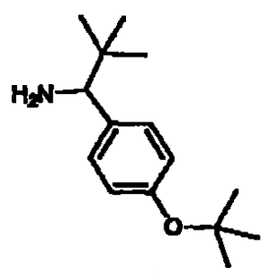
1101		t-BuLi		1. 48% 2. 204
1102		t-BuLi		1. 48% 2. 194
1103		t-BuLi		1. 51% 2. 194
1104		t-BuLi		1. 12% 2. 238
1105		t-BuLi		1. 39% 2. 234
1106		t-BuLi		1. 44% 2. 194 (m/e)

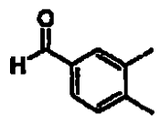
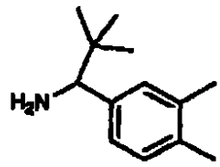
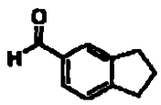
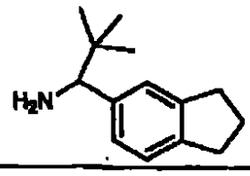
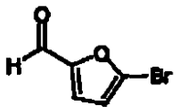
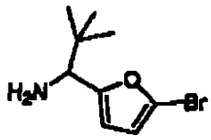
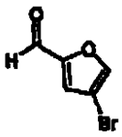
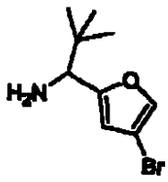
351
353

1107		t-BuLi		1. 57% 2. 150 (M-16)
1108		t-BuLi		1. 31% 2. 224
1109		t-BuLi		1. 11% 2. 224
1110		t-BuLi		1. 57% 2. 224
1111		t-BuLi		1. 21% 2. 224

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354

1112		c-Pentyl-Li		1. 58% 2. 190
1113		t-BuLi		1. 20% 2. 248
1114		t-BuLi		1. 24% 2. 232
1115		EtLi		1. 32% 2. 177 (M-NH2)
1116		t-BuLi		1. 28% 2. 205 (M-NH2)
1117		t-BuLi		1. 50% 2. 190 (M-NH2)

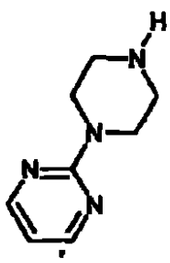
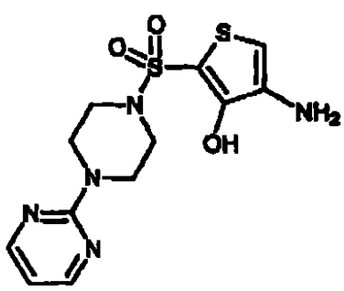
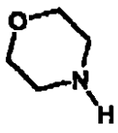
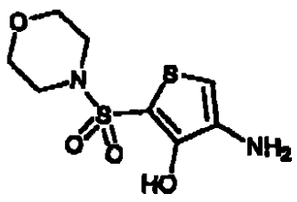
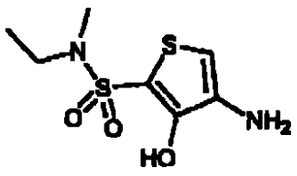
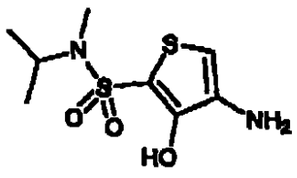
1118		t-BuLi		1. 29% 2. 200
1119		t-BuLi		1. 28% 2. 232
1120		t-BuLi		1. 76% 2. 224
1121		t-BuLi		1. 40% 2. 206
1122		t-BuLi		1. 38% 2. 236

1123		t-BuLi		1. 70% 2. 182
1124		t-BuLi		1. 81% 2. 204
1125		t-BuLi		33%
1126		t-BuLi		50%

EJEMPLOS PREPARATIVOS 1200 – 1203

Siguiendo el procedimiento establecido en el Ejemplo de Preparación 13.29 pero utilizando las aminas comercialmente disponibles, se obtuvieron los productos hidroxiaminotiofeno enumerados en la Tabla a continuación.

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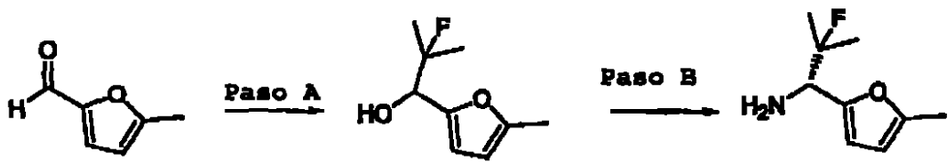
Ej. Prep	Amina	Producto	1.Ren (%) 2. (M+1)$^+$
1200			1. 3% 2. 342
1201			1. 41% 2. 266
1202			1. 17% 2. 237
1203			1. 1%

EJEMPLO DE PREPARACIÓN 1300



El compuesto del título del Ejemplo de Preparación 13.32 (0,35 g) se trató con ácido sulfúrico concentrado (3 ml) durante 6 horas, luego se vertió en hielo, y el pH se ajustó a 4 con NaOH. La extracción con EtOAc, y el secado de la fase orgánica en Na_2SO_4 dio el compuesto del título (159 mg, 64%, $MH^+ = 223$).

EJEMPLO DE PREPARACIÓN 1301



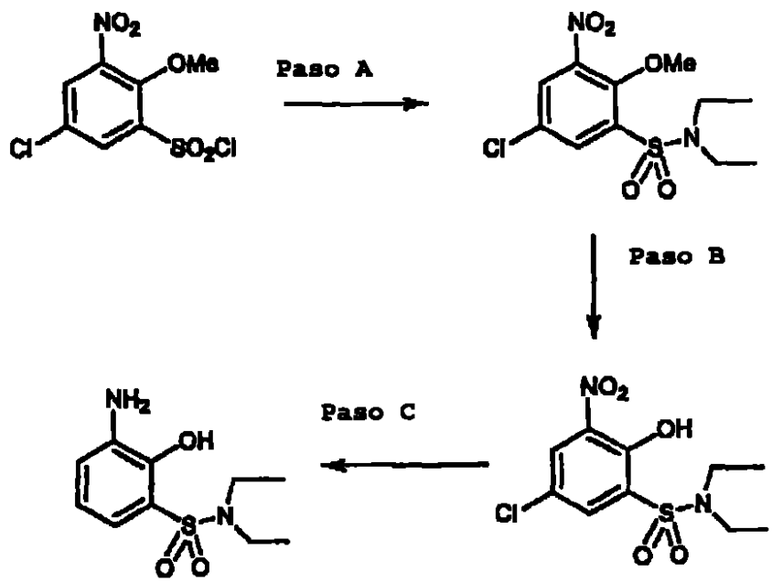
Paso A

Siguiendo un procedimiento similar al utilizado en el Ejemplo de Preparación 605 pero utilizando el fluorisopropilester comercialmente disponible, se obtuvo el producto alcohol (1,2 g, 84%, M-OH = 155).

Paso B

Siguiendo un procedimiento similar al utilizado en el Ejemplo de Preparación 625 pero utilizando el alcohol del Paso A anterior, se obtuvo el producto amina (350 mg, 35%, M-NH2 = 155).

EJEMPLO DE PREPARACIÓN 1302



Paso A

Siguiendo un procedimiento similar al utilizado en el Ejemplo de Preparación 13.29 Paso B, salvo utilizando el arilsulfonilcloruro disponible comercialmente (0,15 g) y dietilamina (2,2 eq), se obtuvo la dimetilsulfonamida (0,12 g, 71%), $MH^+ = 323$).

Paso B

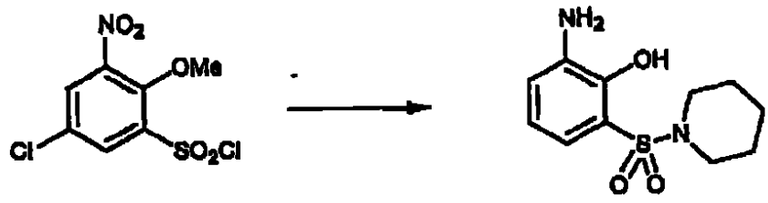
Siguiendo un procedimiento similar al utilizado en el Ejemplo de Preparación 13.29 Paso C, salvo utilizando el producto del Paso A anterior (0,12 g), se obtuvo el fenol (0,112 g, 98%).

Paso C

Siguiendo un procedimiento similar al utilizado en el Ejemplo de Preparación 10.55 Paso C, del documento WO 02/083624 publicado el 24 de octubre de 2002, salvo utilizando el producto del Paso B anterior (0,112 g), se obtuvo el compuesto del título (0,1 g, 99%, $MH^+ = 245$).

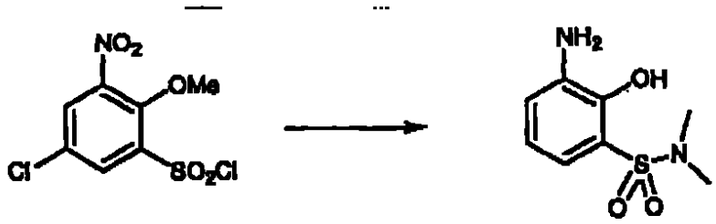
~~350~~
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EJEMPLO DE PREPARACIÓN 1303



Siguiendo un procedimiento similar al utilizado en el Ejemplo de Preparación 1302 Pasos A-C, salvo utilizando piperidina en el Paso A (0,078 g) en lugar de dietilamina, se obtuvo el compuesto del título (0,070 g, 35%, MH^+ = 257).

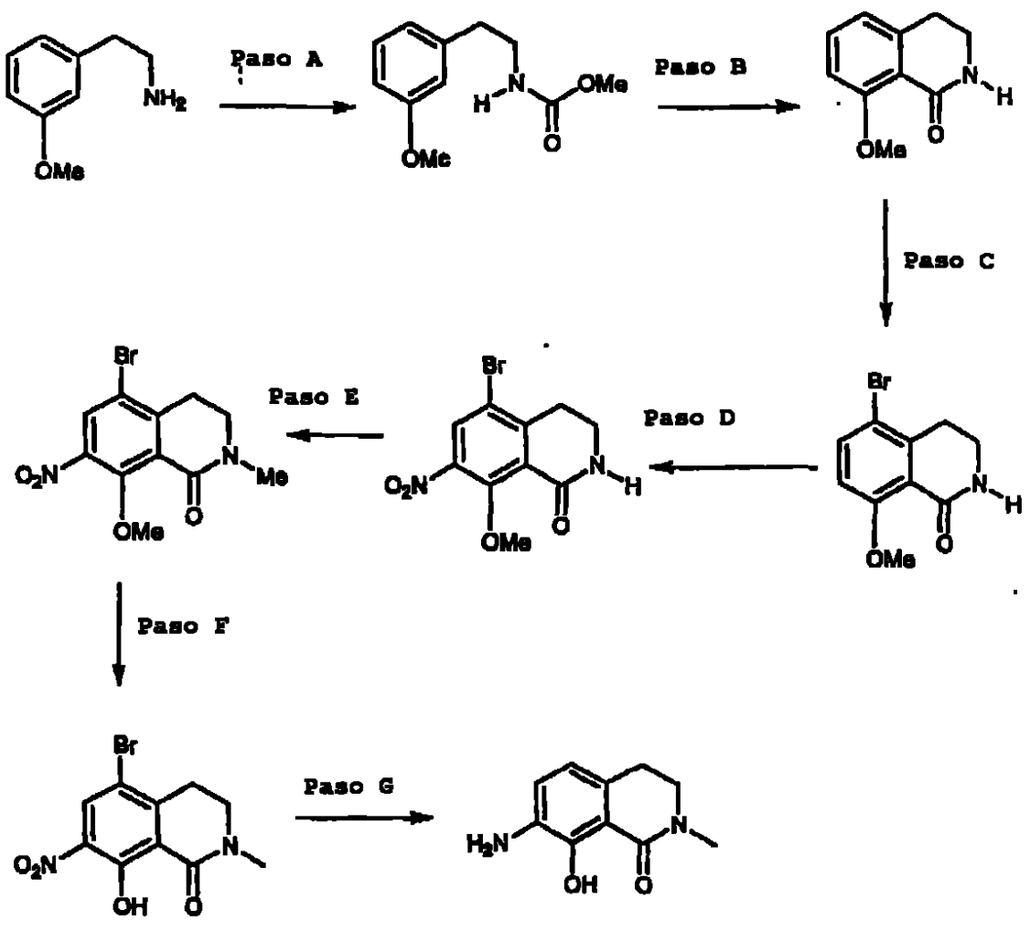
EJEMPLO DE PREPARACIÓN 1304



Siguiendo un procedimiento similar al utilizado en el Ejemplo de Preparación 1302 Pasos A-C, salvo utilizando dimetilamina (2M en THF) en el Paso A en lugar de dietilamina, se obtuvo el compuesto del título (1,92 g, 72%, MH^+ = 217).

EJEMPLO DE PREPARACIÓN 1305

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Paso A

Siguiendo un procedimiento similar al utilizado en el Ejemplo de Preparación 1302 Paso A, salvo utilizando la fenetilmaina indicada (4,99 g), se obtuvo el producto del título (5,96 g, 86%, $MH^+ = 210$).

Paso B

El compuesto del Paso A anterior (5,0 g) se agregó a 30 g de PPA a 150ºC y la mezcla resultante se agitó durante 20 min, antes de ser vertida en hielo y se extrajo con diclorometano. La fase orgánica se secó en MgSO4, se concentró a vacío y se purificó mediante cromatografía de gel de sílice (EtOAc:MeOH) para dar el producto (0,5 g, 9%).

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360.

Paso C

Siguiendo un procedimiento similar al utilizado en el Ejemplo de Preparación 13.3 Paso D, del documento WO 02/083624 publicado el 24 de octubre de 2002, salvo utilizando el compuesto del Paso B anterior (0,14 g), se obtuvo el producto (0,18 g, 87%, $MH^+ = 256$).

Paso D

Siguiendo un procedimiento similar al utilizado en el Ejemplo de Preparación 11 Paso B, del documento WO 02/083624 publicado el 24 de octubre de 2002, salvo utilizando el compuesto del Paso C anterior (0,18 g), se obtuvo el producto (0,17 g).

Paso E

Siguiendo un procedimiento similar al utilizado en el Ejemplo de Preparación 13.3 Paso B, del documento WO 02/083624 publicado el 24 de octubre de 2002, salvo utilizando el compuesto del Paso D anterior (0,17 g), se obtuvo el producto (0,17 g, 95%, $MH^+ = 315$).

Paso F

Siguiendo un procedimiento similar al utilizado en el Ejemplo de Preparación 13.29 Paso C, salvo utilizando el producto del Paso E anterior (0,17 g), se obtuvo el nitrofenol (0,165 g, 99%, $MH^+ = 303$).

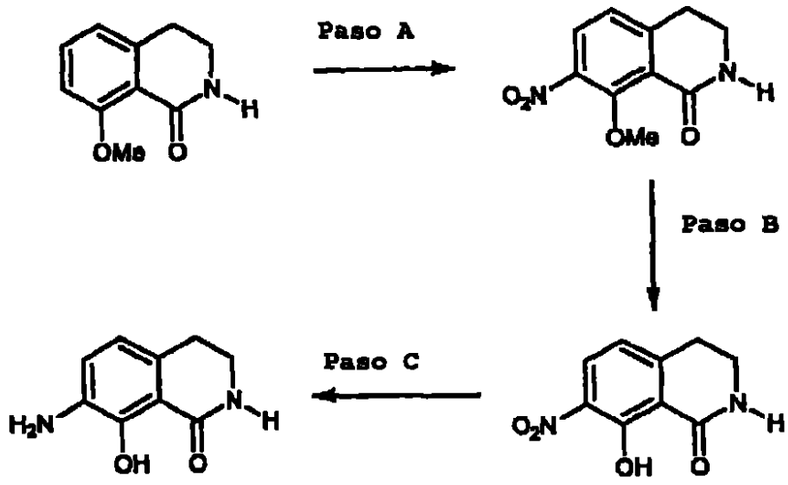
Paso G

Siguiendo un procedimiento similar al utilizado en el Ejemplo de Preparación 10.55 Paso C, del documento WO 02/083624 publicado el 24 de

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octubre de 2002, salvo utilizando el producto del Paso F anterior (0,165 g), se obtuvo el compuesto del título (0,128 g, 86%, MH^+ = 193).

EJEMPLO DE PREPARACIÓN 1306



Paso A

Siguiendo un procedimiento similar al utilizado en el Ejemplo de Preparación 11 Paso B, del documento WO 02/083624 publicado el 24 de octubre de 2002, salvo utilizando el lactam (0,179 g), se obtuvo el compuesto del título (0,25 g, 25%).

Paso B

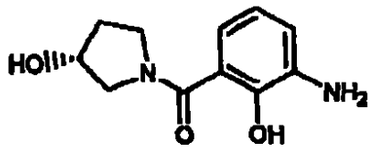
Siguiendo un procedimiento similar al utilizado en el Ejemplo de Preparación 13.29 Paso C, salvo utilizando el producto del Paso A anterior (0,055 g), se obtuvo el fenol (0,045 g, 99%).

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Paso C

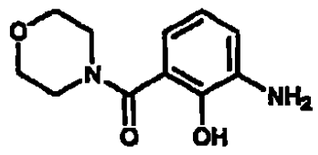
Siguiendo un procedimiento similar al utilizado en el Ejemplo de Preparación 10.55 Paso C, del documento WO 02/083624 publicado el 24 de octubre de 2002, salvo utilizando el producto del Paso B anterior (0,0454 g), se obtuvo el compuesto del título (0,022 g, 57%, MH^+ = 179).

EJEMPLO DE PREPARACIÓN 1307



Siguiendo un procedimiento similar al utilizado en el Ejemplo de Preparación 2, del documento WO 02/083624 publicado el 24 de octubre de 2002, salvo utilizando HCl 3-(R)-hidroxipirrolidina (1,36 g), se obtuvo el compuesto del título (2,25 g, 89%).

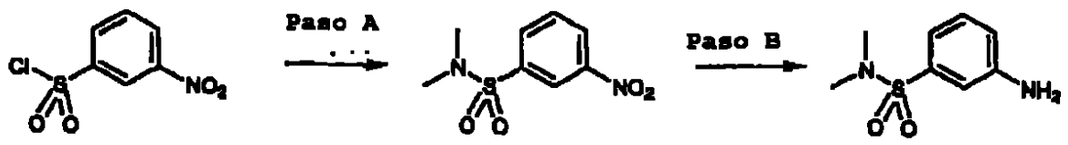
EJEMPLO DE PREPARACIÓN 1308



Siguiendo un procedimiento similar al utilizado en el Ejemplo de Preparación 2, del documento WO 02/083624 publicado el 24 de octubre de 2002, salvo utilizando morfolina, se obtuvo el compuesto del título (3,79 g).

EJEMPLO DE PREPARACIÓN 1309

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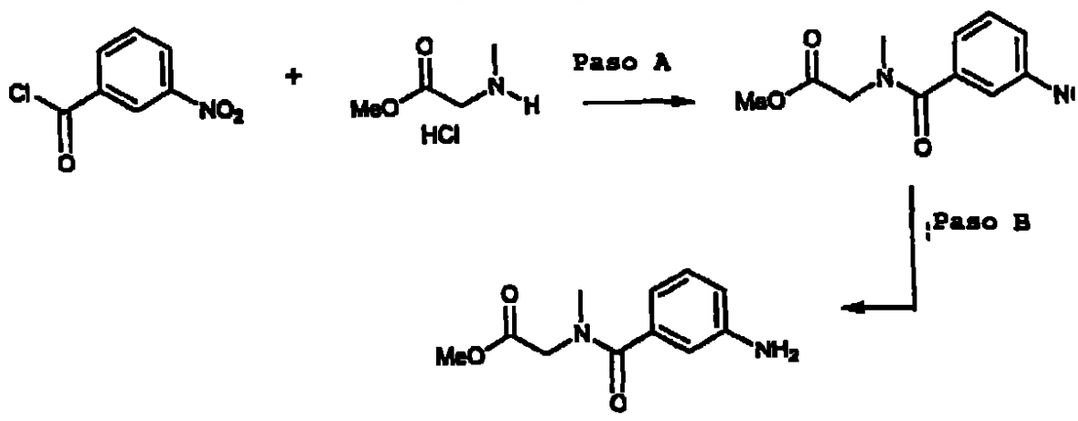
Paso A

Siguiendo un procedimiento similar al utilizado en el Ejemplo de Preparación 13.29 Paso B, salvo utilizando el nitrofenilsulfonilcloruro y dietilamina comercialmente disponibles (2,2 eq), se obtuvo la dimetilsfulonamida (90%, MH^+ = 231).

Paso B

Siguiendo un procedimiento similar al utilizado en el Ejemplo de Preparación 10.55 Paso C, del documento WO 02/083624 publicado el 24 de octubre de 2002, salvo utilizando el producto del Paso B anterior, se obtuvo el compuesto del título (45%, MH^+ = 201).

EJEMPLO DE PREPARACIÓN 1310



Paso A

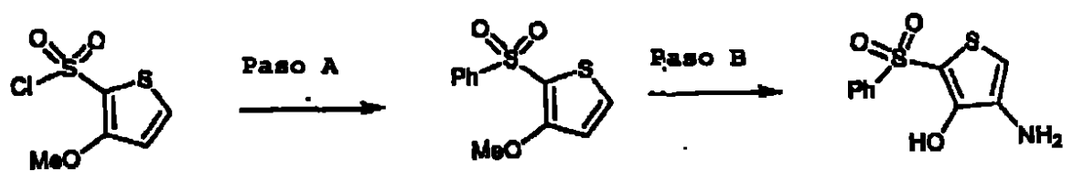
Siguiendo un procedimiento similar al utilizado en el Ejemplo de Preparación 13.29 Paso B, salvo utilizando el nitrobenzoilcloruro comercialmente

disponible y la amina indicada comercialmente disponible, se obtuvo la benzamida (13%, MH^+ = 253).

Paso B

Siguiendo un procedimiento similar al utilizado en el Ejemplo de Preparación 10.55 Paso C, del documento WO 02/083624 publicado el 24 de octubre de 2002, salvo utilizando el producto del Paso B anterior, se obtuvo el compuesto del título (94%, MH^+ = 223).

EJEMPLO DE PREPARACIÓN 1311



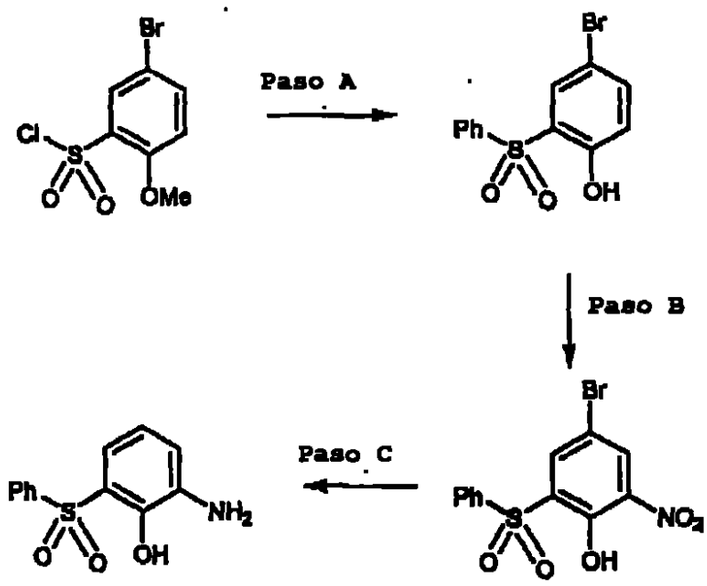
Paso A

A una solución en benceno (20 ml) de metoxitiofensulfonilcloruro (1,5 g) se agregó $AlCl_3$ (2,0 g) a temperatura ambiente. Al cabo de 15min, la mezcla se agregó a HCL 0,1N (ac) con agitación, luego se extrajo con Et_2O. El lavado de la fase orgánica con salmuera, el secado en $MgSO_4$, la concentración a vacío y la purificación mediante cromatografía de gel de sílice (Hexano:EtOAc, 5:2) dio el compuesto del título (1,5 g, 84%).

Paso B

Siguiendo un procedimiento similar al utilizado en el Ejemplo de Preparación 13.29 Pasos C-G, salvo utilizando el producto del Paso A anterior, se obtuvo el compuesto del título (3%, MH^+ = 380).

EJEMPLO DE PREPARACIÓN 1312



Paso A

Siguiendo un procedimiento similar al utilizado en el Ejemplo de Preparación 1311 Paso A, salvo utilizando el sulfonilcloruro comercialmente disponible, se obtuvo la difenilsulfona (880 mg, 80%).

Paso B

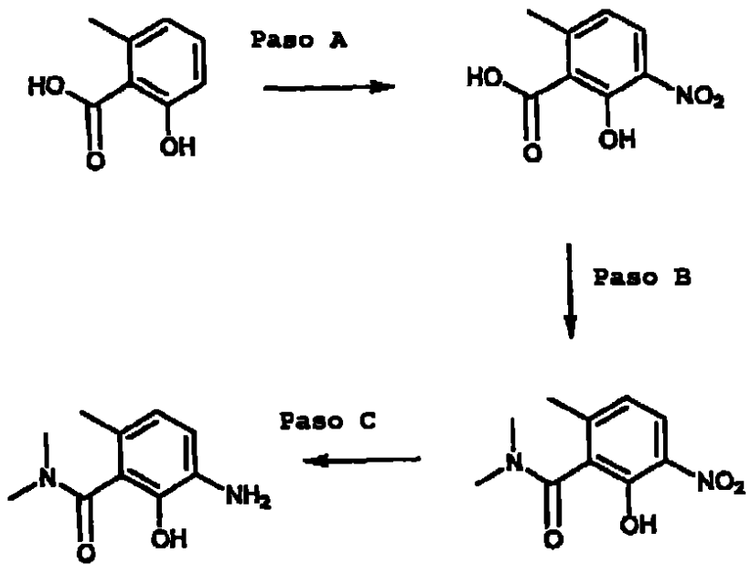
Siguiendo un procedimiento similar al utilizado en el Ejemplo de Preparación 11 Paso B, del documento WO 02/083624 publicado el 24 de octubre de 2002, salvo utilizando el producto del Paso A anterior, se obtuvo el compuesto del título (0,90 g, 97%).

Paso C

Siguiendo un procedimiento similar al utilizado en el Ejemplo de Preparación 10.55 Paso C, del documento WO 02/083624 publicado el 24 de

octubre de 2002, salvo utilizando el producto del Paso B anterior, se obtuvo el compuesto del título (0,106 g, 95%).

EJEMPLO DE PREPARACIÓN 1313



Paso A

Siguiendo un procedimiento similar al utilizado en el Ejemplo de Preparación 1311 Paso A, salvo utilizando el fenol comercialmente disponible (2 g), se obtuvo el nitroácido (~ 13 mmol).

Paso B

Cloruro de oxallilo (3,5 ml) y dos gotas de DMF se agregaron al producto del Paso A anterior (~ 13 mmol) disuelto en diclorometano (100 ml). Al cabo de la agitación a temperatura ambiente durante la noche, la mezcla se concentró a vacío, se diluyó con diclorometano (50 ml), se enfrió a 0ºC. Se agregaron dimetilamina en THF (20 ml de 2N) y TEA (8 ml). Al cabo de 3 horas de agitación, la mezcla se concentró a vacío, se agregó NaOH ac (1M), y la mezcla se extrajo

con diclorometano. El pH de la capa acuosa se ajustó a pH = 2 utilizando HCl 6N (ac), y se extrajo con diclorometano. Los extractos orgánicos combinados se lavaron con salmuera, se secaron ,se concentraron a vacío, y el producto purificado mediante cromatografía de gel de sílice (700 ml de diclorometano / 20 ml de MeOH / 1 ml d AcOH) para dar el compuesto del título (800 mg, 27% para dos pasos).

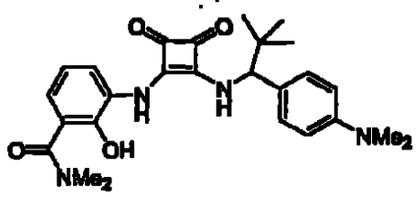
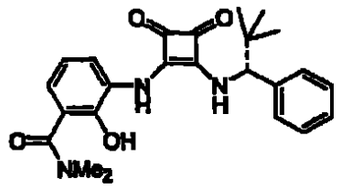
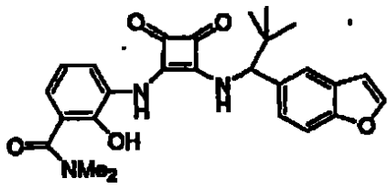
Paso C

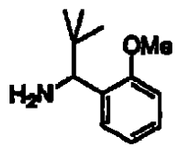
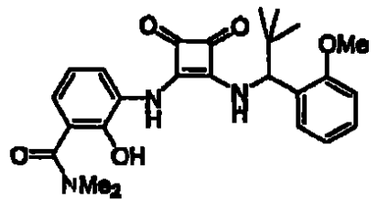
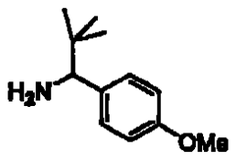
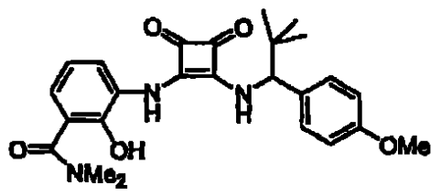
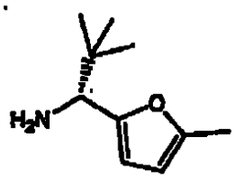
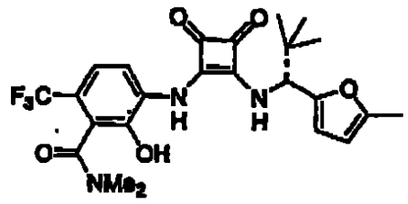
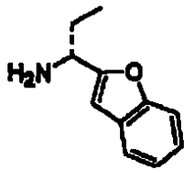
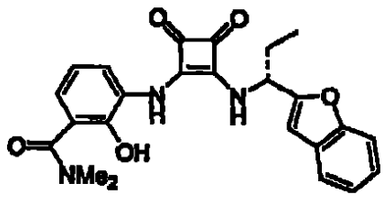
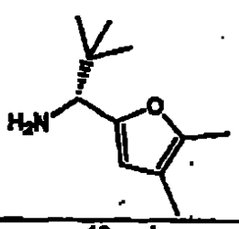
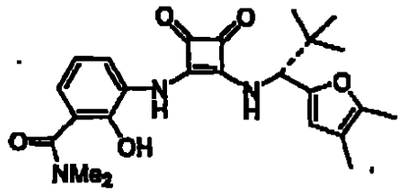
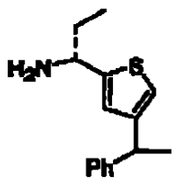
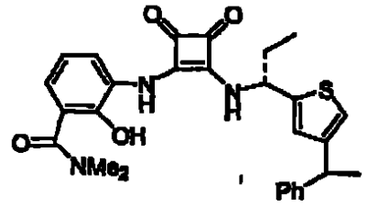
Siguiendo un procedimiento similar al utilizado en el Ejemplo de Preparación 10.55 Paso C, del documento WO 02/083624 publicado el 24 de octubre de 2002, salvo utilizando el producto del Paso B anterior (780 mg), se obtuvo el compuesto del título (0,46 g, 68%).

EJEMPLOS PREPARATIVOS 2001 – 2088

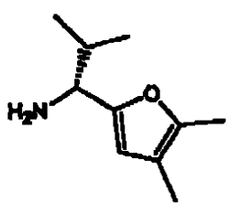
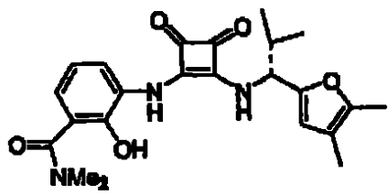
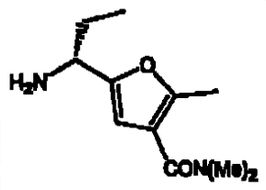
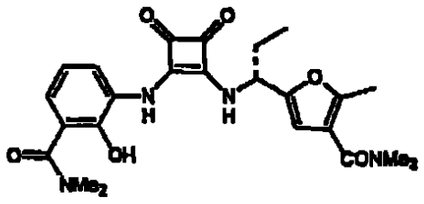
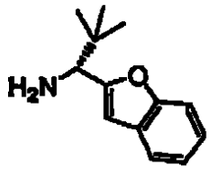
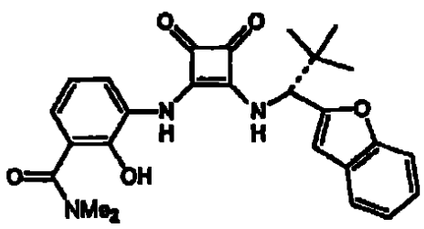
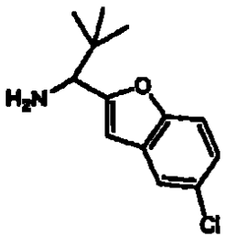
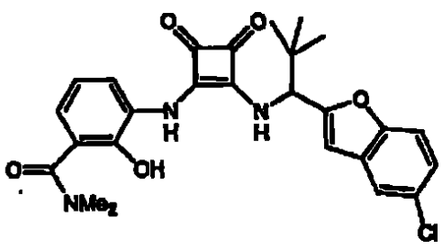
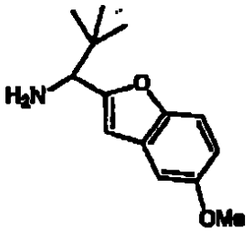
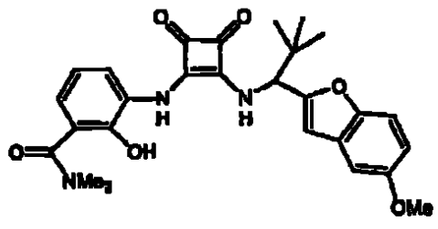
Siguiendo un procedimiento similar al utilizado en el Ejemplo 210, del documento WO 02/083624 publicado el 24 de octubre de 2002, pero utilizando el intermediario de ciclobutendiona y la amina indicada en la Tabla a continuación, se obtuvieron los productos de ciclobutendiona siguientes. Ver WO 02/083624, publicada el 24 de octubre de 2002, para los Ejemplos Preparativos 19, 19.2, 22, 23.14, y 87.1

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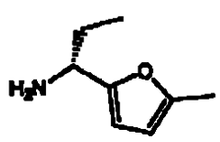
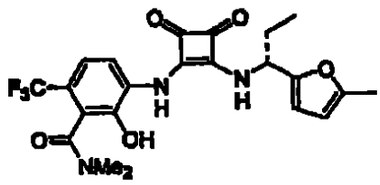
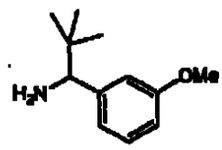
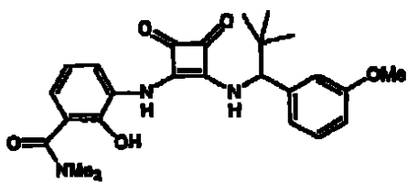
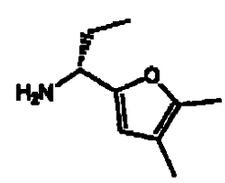
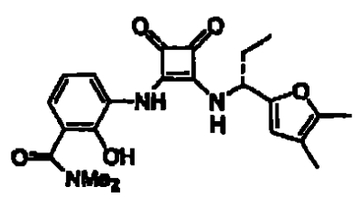
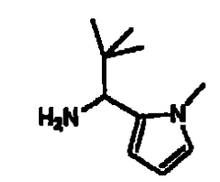
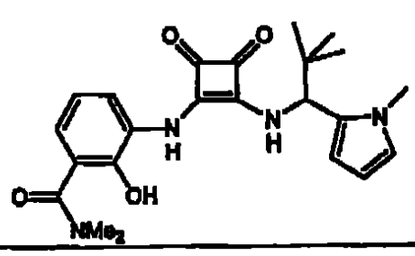
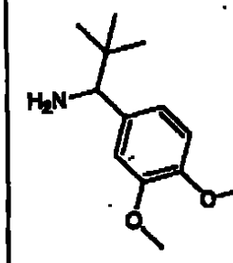
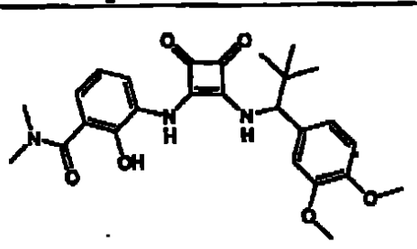
Ejemplo	Ej Prep del Intermediario y la Amina	Producto	1Ran (%) 2. (M+1)+
2001	19 y		3. 65% 4. 465
2002	19 y		1. 5% 2. 422
2003	19 y		1. 47% 2. 462

2004	19 y 		1. 74% 2. 452
2005	19 y 		1. 71% 2. 452
2006	1007 y 		1. 18% 2. 494
2007	19 y 		1. 38% 2. 434
2008	19 y 		1. 18% 2. 440
2009	19 y 		1. 45% 2. 504

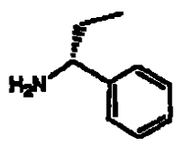
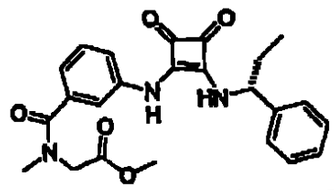
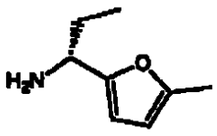
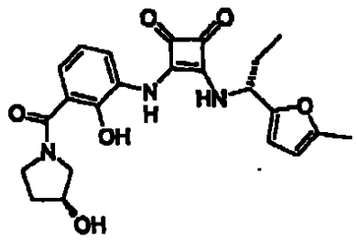
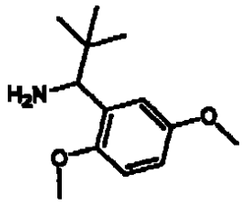
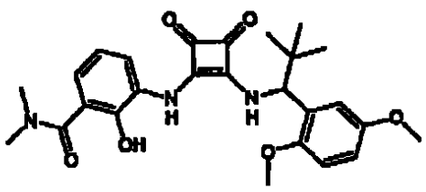
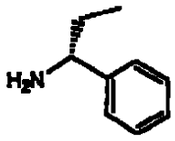
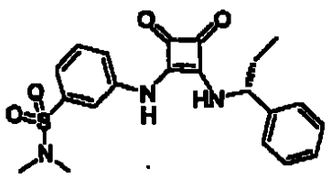
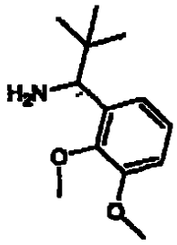
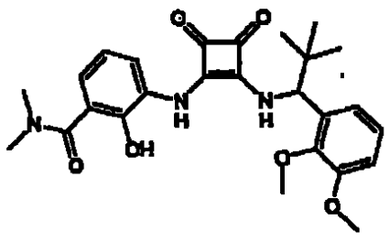
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2010	19 y 		1. 57% 2. 426
2011	19 y 		1. 6% 2. 469
2012	19 y 		1. 4% 2. 462
2013	19 y 		1. 29% 2. 496
2014	19 y 		1. 17% 2. 492

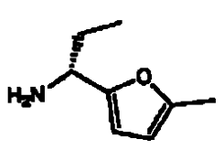
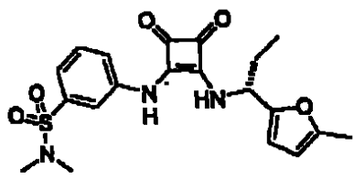
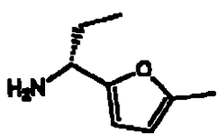
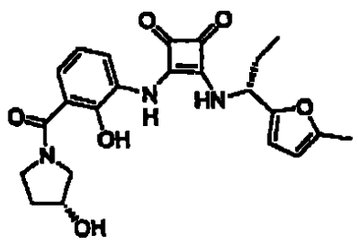
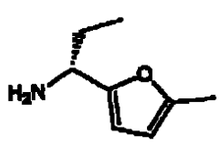
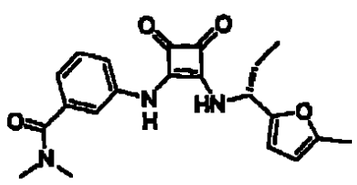
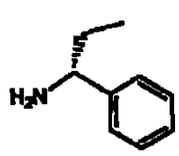
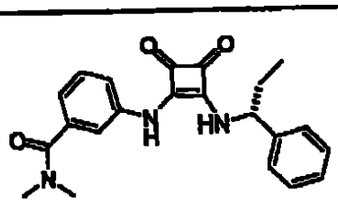
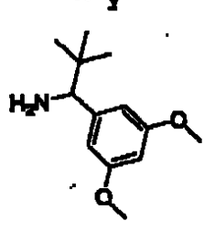
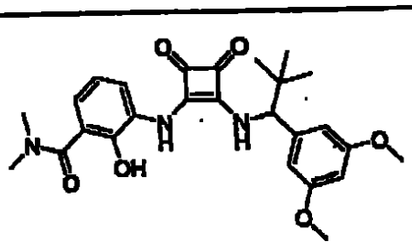
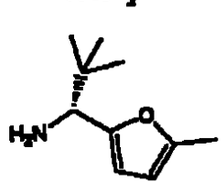
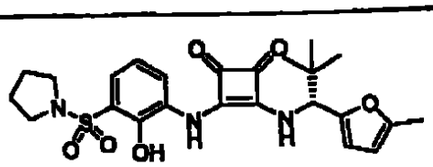
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2015	1007 y 		1. 65% 2. 466
2016	19 i y 		1. 72% 2. 452
2017	19 y 		1. 22% 2. 412
2018	19 y 		1. 5% 2. 425
2019	19 y 		1. 82% 2. 482

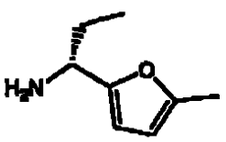
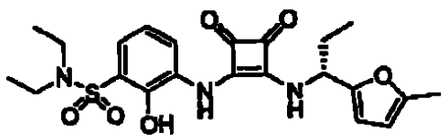
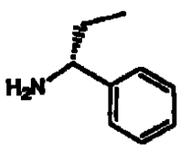
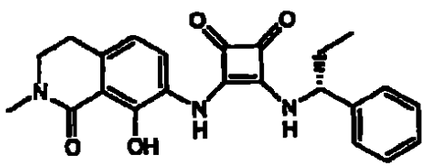
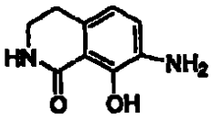
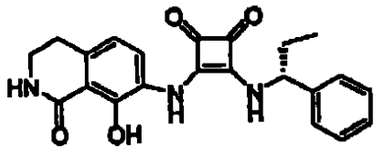
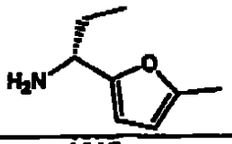
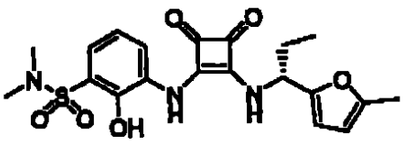
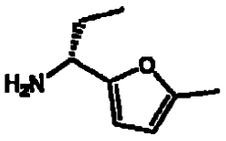
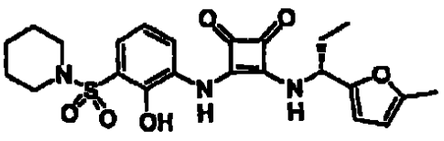
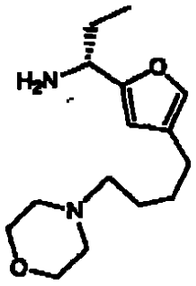
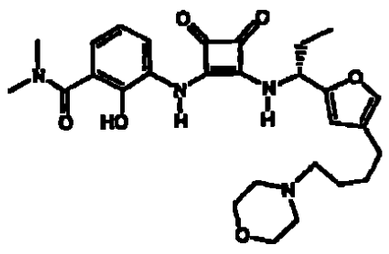
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374

2020	1008 y 		1. 49% 2. 438
2021	22 y 		1. 46% 2. 440
2022	18 y 		1. 35% 2. 482
2024	1010 y 		1. 16% 2. 414
2026	19 y 		1. 46% 2. 482

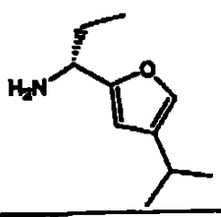
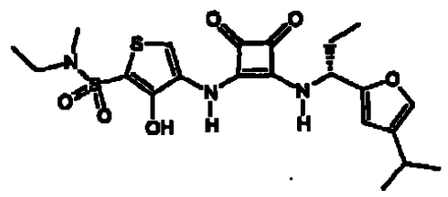
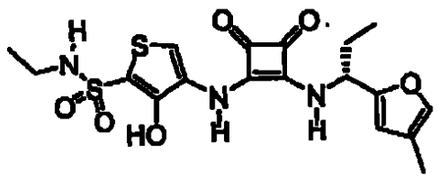
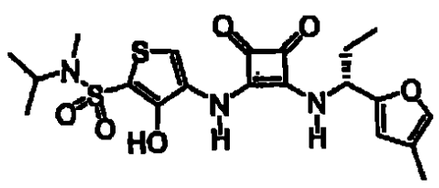
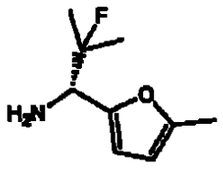
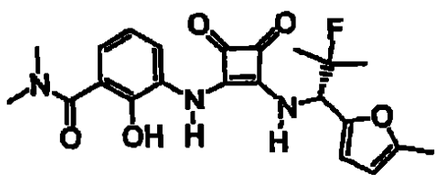
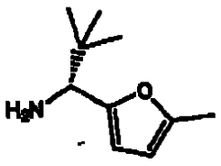
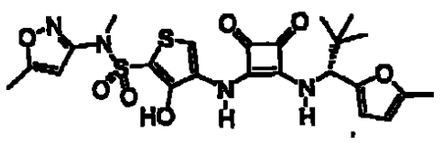
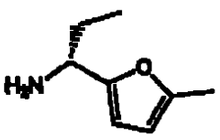
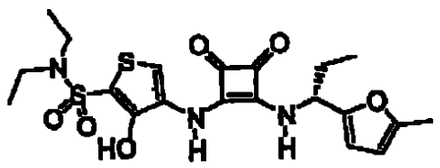
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375

2027	1010 y 		1. 13% 2. 418
2028	1012 y 		1. 39% 2. 440
2029	19 ¼ 		1. 66% 2. 382
2030	19 y 		1. 39% 2. 378
2033	19 y 		1. 71% 2. 482
2034	1013 iy 		1. 45% 2. 467.9

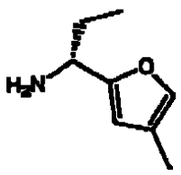
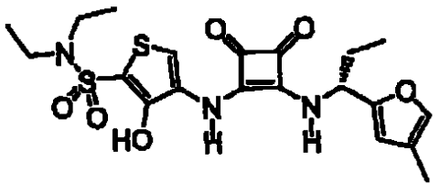
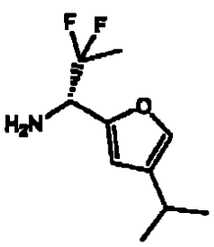
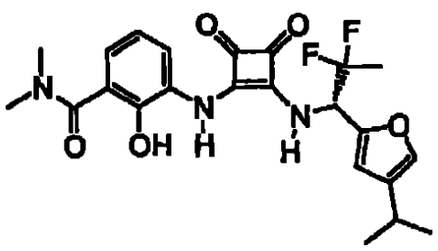
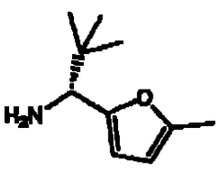
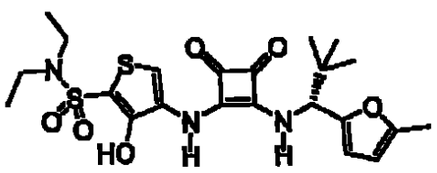
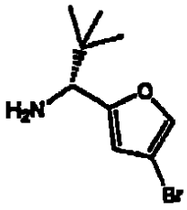
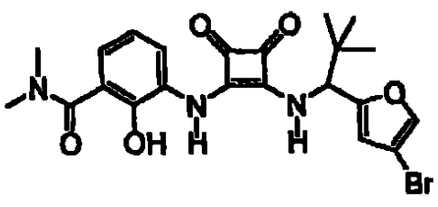
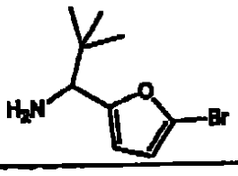
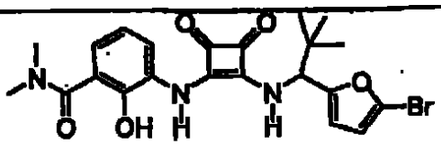
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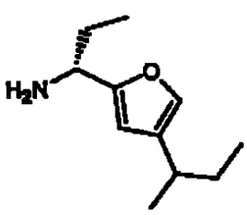
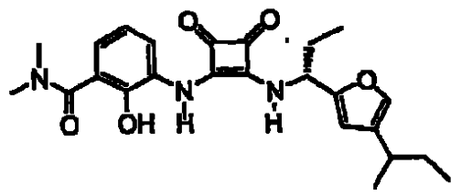
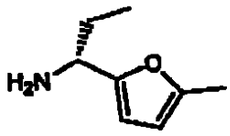
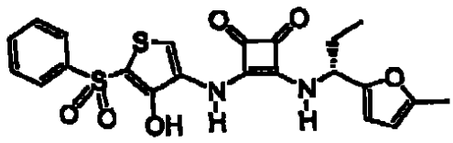
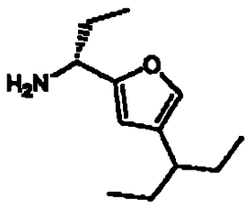
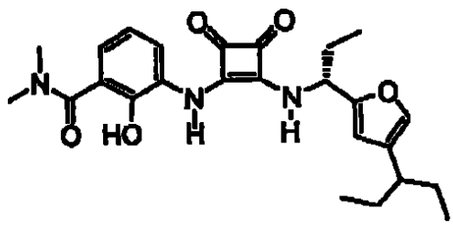
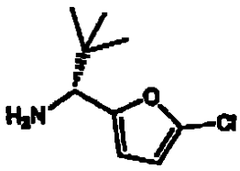
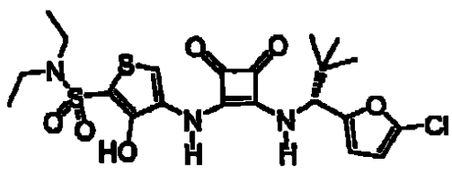
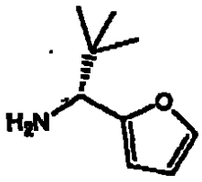
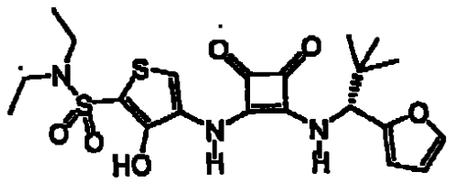
2035	1014 y 		1. 22% 2. 461.8
2036	1015 y 		1. 27% 2. 405.9
2037	87.1 y 		1. 26% 2. 392.0
2038	1016 		1. 28% 2. 433.8
2039	1017y 		1. 34% 2. 473.9
2040	19 y 		1. 34% 2. 525

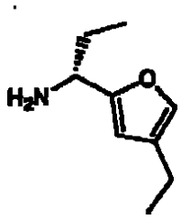
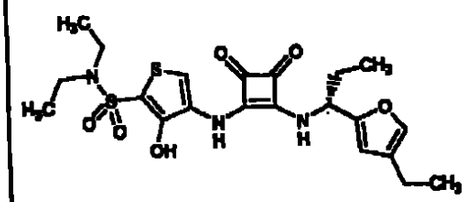
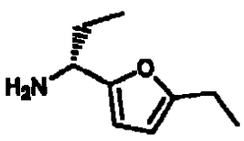
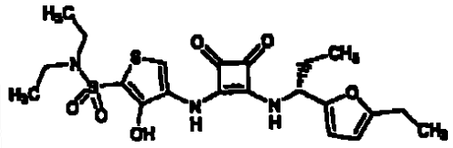
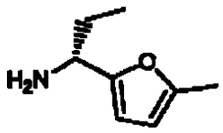
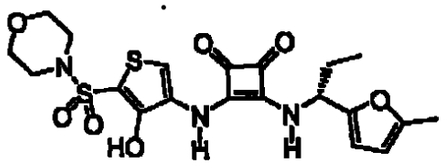
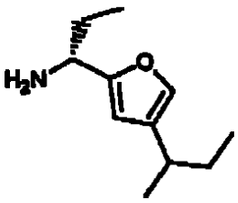
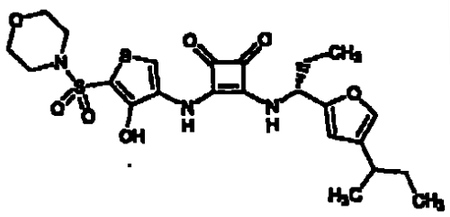
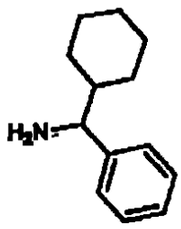
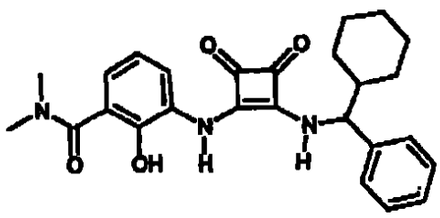
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2041	23.15E y 		1. 67% 2. 482
2042	1300 y 1027		1. 33% 2. 440
2043	1203 y 1027		1. 24% 2. 466
2044	19 y 		1. 26% 2. 486
2046	19.2 y 		1. 27% 2. 535
2047	23.15F y 		1. 74% 2. 488

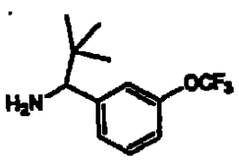
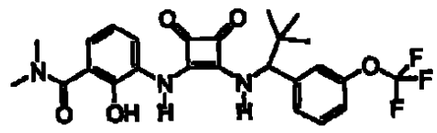
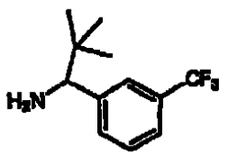
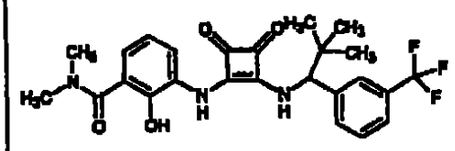
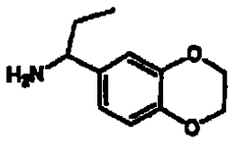
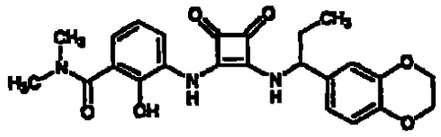
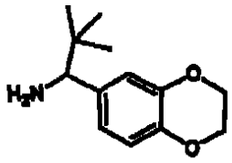
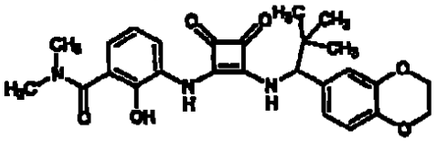
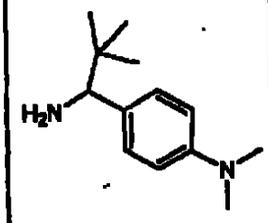
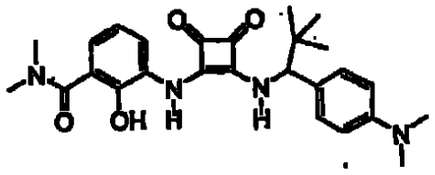
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2048	23.15F y 		1. 68% 2. 488
2049	19 y 		1. 31% 2. 462
2050	23.15F y 		1. 41% 2. 486
2051	19 y 		1. 68% 2. 490
2052	19 y 		1. 43% 2. 490

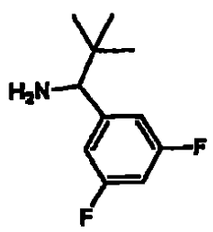
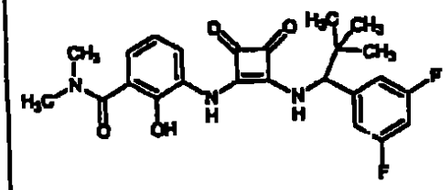
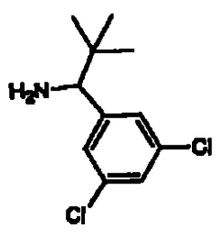
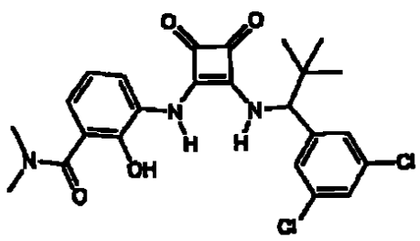
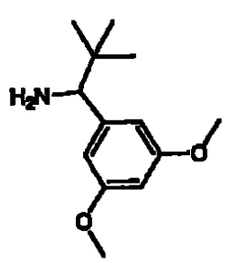
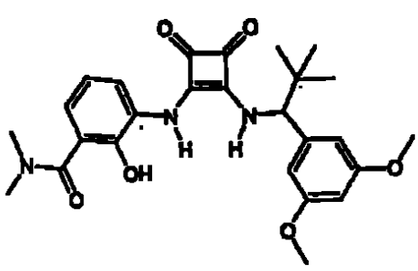
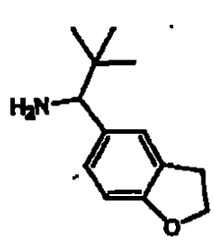
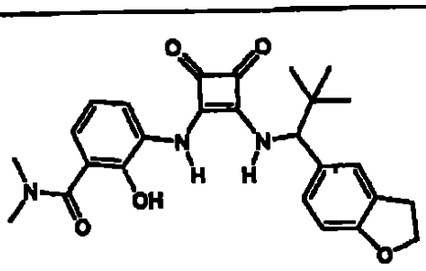
2053	19 y 		1. 76% 2. 440
2054	1024 y 		1. 16% 2. 473
2055	19 y 		1. 87% 2. 454
2056	23.15F y 		1. 52% 2. 516
2056A	23.15F y 		1. 62% 2. 482

2057	23.15F y 		1. 40% 2. 482
2058	23.15F y 		1. 71% 2. 482
2059	1023 y 		1. 67% 2. 482
2060	1023 y 		1. 60% 2. 524
2061	19 y 		1. 34% 2. 448

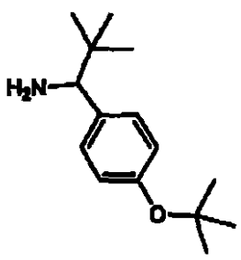
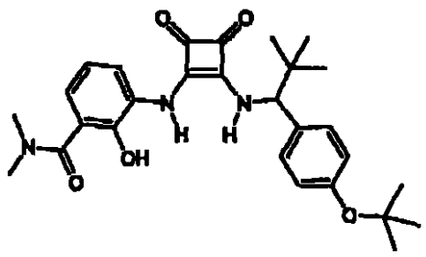
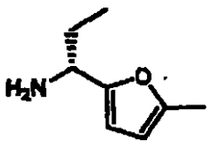
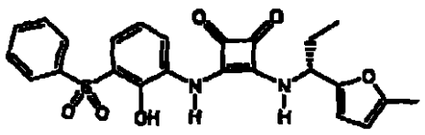
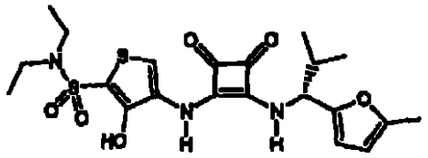
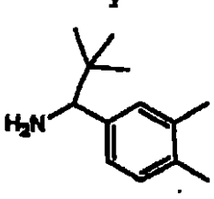
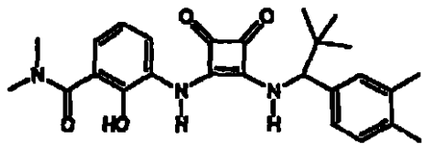
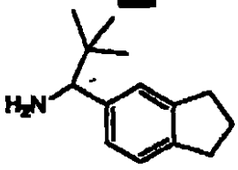
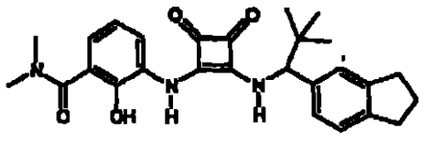
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381

2062	19 y 		1. 43% 2. 506
2063	19 y 		1. 63% 2. 480
2064	19 y 		1. 26% 2. 462
2065	19 y 		1. 24% 2. 480
2066	19 y 		1. 37% 2. 485

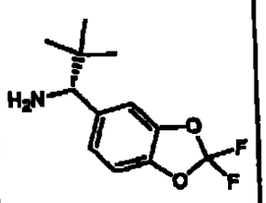
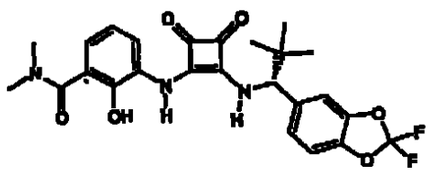
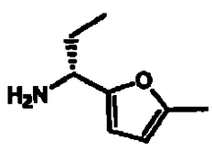
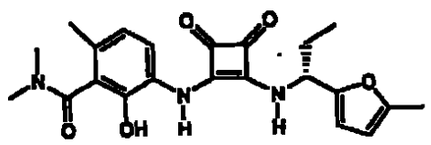
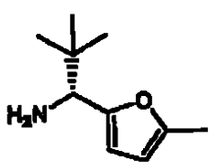
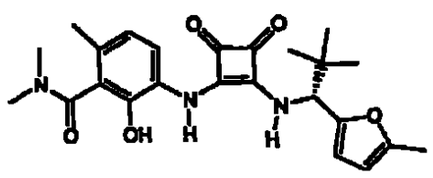
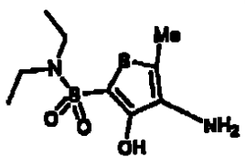
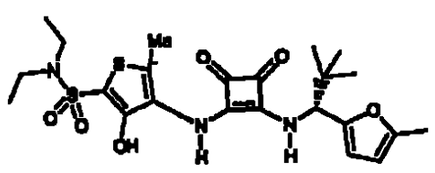
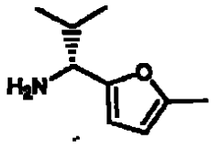
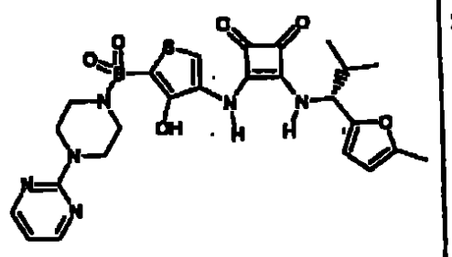
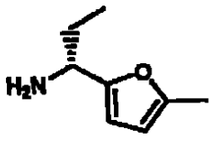
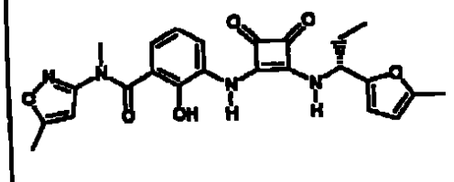
~~300~~
382

2067	19 y 		1. 38% 2. 468
2068	19 y 		1. 35% 2. 490
2069	19 y 		1. 73% 2. 482
2070	19 y 		1. 69% 2. 484

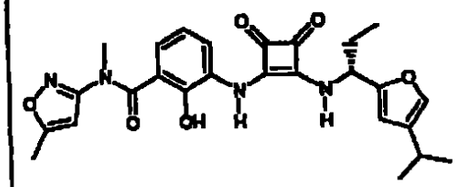
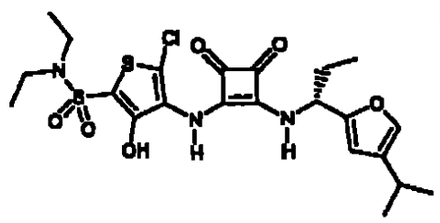
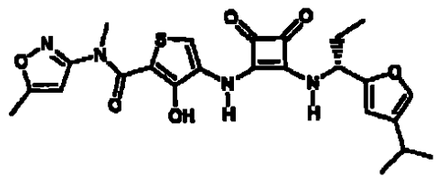
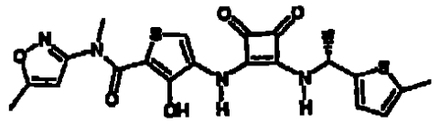
381
383

2071	19 y 		1. 71% 2. 494
2072	1022 y 		1. 54% 2. 467
2074	13.32A y 1028 		1. 42% 2. 482
2075	19 y 		1. 78% 2. 450
2076	19 [redacted] 		1. 25% 2. 402

382
384

2077	19 y 		1. 38% 2. 502
2079	1021 y 		1. 23% 2. 440
2080	1021 y 		1. 15% 2. 476
2081	1029 y 		1. 17% 2. 510
2083	1020 y 		1. 46% 2. 573
2084	23.14 y 		1. 80% 2. 486

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385

2085	23.14 y		1. 82% 2. 493
2086	1019 y		1. 29% 2. 530
2087	23.14 y		1. 30% 2. 499
2088	23.14 y		1. 13% 2. 473

Otra forma de realización de la presente invención está dirigida al uso de cualquiera de los compuestos descriptos anteriormente (por ejemplo, los compuestos de las fórmulas IA, IB, 1.0A, 3.0A y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311 y 2001-2088 o una sal (por ejemplo, de calcio o sodio) o solvato farmacéuticamente aceptable de los mismos) para la elaboración de un medicamento para el tratamiento de inflamación aguda.

Otra forma de realización de la presente invención está dirigida al uso de cualquiera de los compuestos descriptos anteriormente (por ejemplo, los compuestos de las fórmulas IA, IB, 1.0A, 3.0A y los compuestos finales de los

ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311 y 2001-2088 o una sal (por ejemplo; de calcio o sodio) o solvato farmacéuticamente aceptable de los mismos) para la elaboración de un medicamento para el tratamiento de artritis reumatoide.

Otra forma de realización de la presente invención está dirigida a un compuesto final de los ejemplos 2006. 2010, 2015, 2029, 2034, 2035. 2038, 2039. 2047, 2050. 2074, 2079 y 2087 o una sal (por ejemplo, de calcio o sodio) o solvato farmacéuticamente aceptable de los mismos. Otras formas de realización están dirigidas al uso de estos compuestos para la elaboración de un medicamento para el tratamiento de la inflamación aguda, o para la elaboración de un medicamento para el tratamiento de la inflamación crónica, o para la elaboración de un medicamento para el tratamiento de artritis reumatoide, o para la elaboración de un medicamento para el tratamiento de dolor inflamatorio agudo, o para la elaboración de un medicamento para el tratamiento de dolor inflamatorio crónico, o para la elaboración de un medicamento para el tratamiento de dolor neuropático agudo, o para la elaboración de un medicamento para el tratamiento de dolor neuropático crónico, o para la elaboración de un medicamento para el tratamiento de COPD.

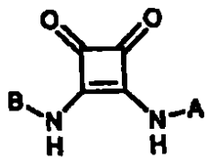
Si bien la presente invención ha sido descripta juntamente con las realizaciones específicas establecidas anteriormente, muchas alternativas, modificaciones y variantes de las mismas serán evidentes para los expertos en la técnica. Dichas alternativas, modificaciones y variantes estarán dentro del espíritu y alcance de la presente invención.

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REIVINDICACIONES

Habiendo así descripto y determinado la naturaleza de la presente invención y la forma como la misma ha de ser llevada a la práctica, se declara reivindicar como de propiedad y derecho exclusivo:

1. Un compuesto de la fórmula:

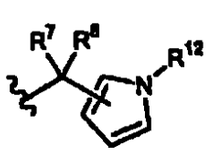


(IB)

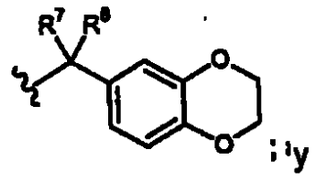
y las sales y solvatos farmacéuticamente aceptables de los mismos, en donde:

A es seleccionado del grupo que consiste de:

(1)

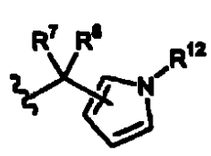


y

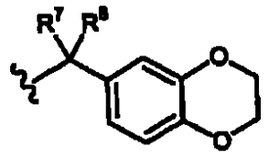


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(2)



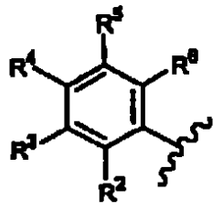
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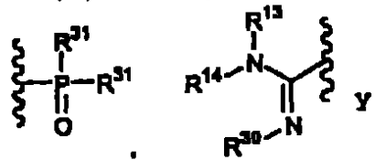
en donde dichos anillos de dichos grupos A están sustituidos con 1 a 6 sustituyentes cada uno independientemente seleccionado del grupo que consiste de: grupos R^9; y

B está seleccionado del grupo que consiste de:

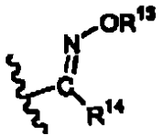
(1)



siempre que R^3 para este grupo esté seleccionado del grupo que consiste de: $-C(O)NR^{13}R^{14}$,



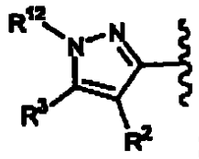
y



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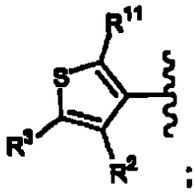
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(2)



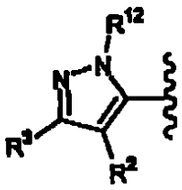
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(3)



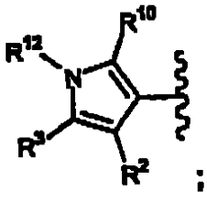
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(4)



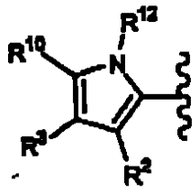
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(5)



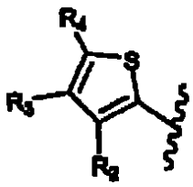
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(6)



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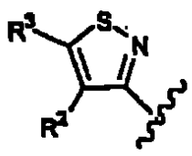
(7)



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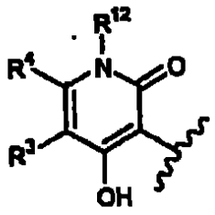
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(8)



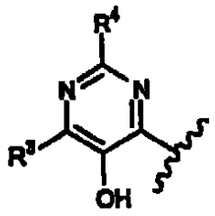
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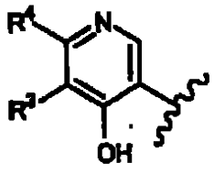
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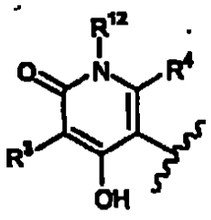
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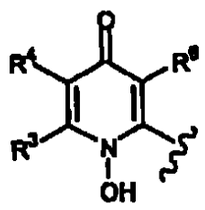
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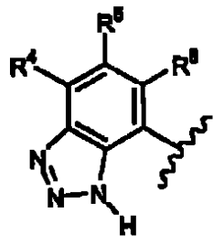
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(13)



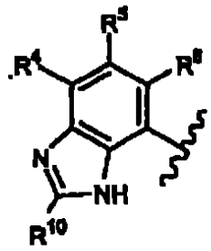
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(14)



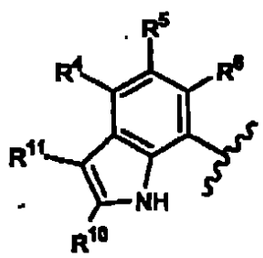
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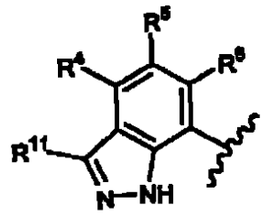
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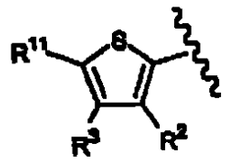
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(17)



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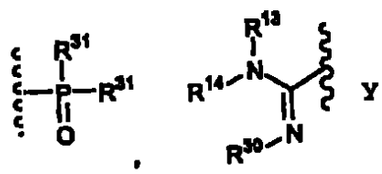
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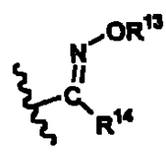
;

R^2 está seleccionado del grupo que consiste de: hidrógeno, OH, -C(O)OH, -SH, $-SO_2NR^{13}R^{14}$, $-NHC(O)R^{13}$, $-NHSO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, $-NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, $-C(O)NHOR^{13}$, $-C(O)NR^{13}OH$, $-S(O_2)OH$, $-OC(O)R^{13}$, un grupo funcional ácido heterocíclico no sustituido, y un grupo funcional ácido heterocíclico sustituido, en donde hay 1 a 6 sustituyentes sobre dicho grupo funcional ácido heterocíclico sustituido, cada sustituyente está independientemente seleccionado del grupo que consiste de: grupos R^9;

cada R^3 y R^4 es independientemente seleccionado del grupo que consiste de: hidrógeno, ciano, halógeno, alquilo, alcoxi, -OH, $-CF_3$, $-OCF_3$, $-NO_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NHR^{17}$, $-C(O)NR^{13}R^{14}$, $-SO_{(t)}NR^{13}R^{14}$, $-SO_{(t)}R^{13}$, $-C(O)NR^{13}OR^{14}$, arilo no sustituido o sustituido, heteroarilo no sustituido o sustituido,



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donde hay 1 a 6 sustituyentes en dicho grupo arilo sustituido y cada sustituyente es independientemente seleccionado del grupo que consiste de: grupos R^9; y en donde hay 1 a 6 sustituyentes en dicho grupo heteroarilo sustituido y cada sustituyente es independientemente seleccionado del grupo que consiste de: grupos R^9;

cada R^5 y R^6 son iguales o diferentes y son independientemente seleccionados del grupo que consiste de hidrógeno, halógeno, alquilo, alcoxi, -CF_3, -OCF_3, -NO_2, -$C(O)R^{13}$, -$C(O)OR^{13}$, -$C(O)NR^{13}R^{14}$, -$SO_{(t)}NR^{13}R^{14}$, -$C(O)NR^{13}OR^{14}$, ciano, arilo sustituido o no sustituido, y grupo heteroarilo no sustituido o sustituido; donde hay 1 a 6 sustituyentes en dicho grupo arilo sustituido y cada sustituyente es independientemente seleccionado del grupo que consiste de: grupos R^9; y donde hay 1 a 6 sustituyentes en dicho grupo heteroarilo sustituido y cada sustituyentes es independientemente seleccionado del grupo que consiste de: grupos R^9;

cada R^7 y R^8 es independientemente seleccionado del grupo que consiste de. H, alquilo no sustituido o sustituido, arilo no sustituido o sustituido, heteroarilo no sustituido o sustituido, arilalquilo no sustituido o sustituido, heteroarilalquilo no sustituido o sustituido, cicloalquilo no sustituido o sustituido, cicloalquilalquilo no sustituido o sustituido, -CO_2R^{13}, -$CONR^{13}R^{14}$, alquinilo, alquenilo, y cicloalquenilo; y donde hay uno o más sustituyentes en dichos grupos R^7 y R^8, donde cada sustituyente es independientemente seleccionado del grupo que consiste de:

t) halógeno,

u) –CF_3,

v) –COR^{13},

w) –OR^{13},

x) –$NR^{13}R^{14}$,

y) NO_2,

z) –CN,

aa) $-SO_2OR^{13}$,

bb) $-Si(alquilo)_3$, donde cada alquilo es independientemente seleccionado,

cc) $-Si(arilo)_3$, donde cada alquilo es independientemente seleccionado,

dd) $-(R^{13})_2R^{14}Si$, donde cada R^{13} es independientemente seleccionado,

ee) $-CO_2R^{13}$,

ff) $-C(O)NR^{13}R^{14}$,

gg) $-SO_2NR^{13}R^{14}$,

hh) $-SO_2R^{13}$,

ii) $-OC(O)R^{13}$,

jj) $-OC(O)NR^{13}R^{14}$,

kk) $-NR^{13}C(O)R^{14}$, y

ll) $-NR^{13}CO_2R^{14}$;

cada R^9 es independientemente seleccionado del grupo que consiste de:

o) $-R^{13}$,

p) halógeno,

q) $-CF_3$,

r) $-COR^{13}$,

s) $-OR^{13}$,

t) $-NR^{13}R^{14}$,

u) $-NO_2$,

v) –CN,

w) $-SO_2R^{13}$,

x) $-SO_2NR^{13}R^{14}$,

y) $-NR^{13}COR^{14}$,

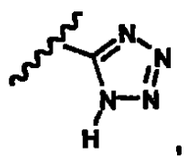
z) $-CONR^{13}R^{14}$,

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aa) $-NR^{13}CO_2R^{14}$,

bb) $-CO_2R^{13}$,

cc)



,

dd) alquilo sustituido con uno o más o más grupos –OH,

ee) alquilo sustituido con uno o más grupos $-NR^{13}R^{14}$, y

ff) $-N(R^{13})SO_2R^{14}$;

cada R^{10} y R^{11} es independientemente seleccionado a partir del grupo que consiste de R^{13}, hidrógeno, alquilo $-CF_3$, $-OCF_3$, $-NR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, -OH, $-C(O)OR^{13}$, -SH, $-SO_{(t)}NR^{13}R^{14}$, $-SO_2R^{13}$, $-NHC(O)R^{13}$, $-NHSO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, $-C(O)NR^{13}R^{14}$, $-C(O)NR^{13}OR^{14}$, $-OC(O)R^{13}$ y ciano;

R^{12} es seleccionado del grupo que consiste de : hidrógeno, $-C(O)OR^{13}$, grupo arilo no sustituido o sustituido, heteroarilo no sustituido o sustituido, arilalquilo no sustituido o sustituido, cicloalquilo no sustituido o sustituido, alquilo no sustituido o sustituido, cicloalquilalquilo no sustituido o sustituido, y heteroarilalquilo no sustituido o sustituido; donde hay 1 a 6 sustituyentes en los grupos R^{12} sustituido y cada sustituyente es independientemente seleccionado del grupo que consiste de: grupos R^9;

cada R^{13} y R^{14} es independientemente seleccionado del grupo que consiste de: H, alquilo no sustituido o sustituido, arilo no sustituido o sustituido, heteroarilo no sustituido o sustituido, arilalquilo no sustituido o sustituido, heteroarilalquilo no sustituido o sustituido, cicloalquilo no sustituido o sustituido, cicloalquilalquilo no sustituido o sustituido, heterocíclico no sustituido o sustituido, fluoralquilo no sustituido o sustituido, heterocicloalquilalquilo no sustituido o sustituido; donde

hay 1 a 6 sustituyentes en dichos grupos R^{13} y R^{14} sustituidos y cada sustituyente es independientemente seleccionado del grupo que consiste de: alquilo, $-CF_3$, -OH, alcoxi, arilo, arilalquilo, fluoralquilo, cicloalquilo, cicloalquilalquilo, heteroarilo, heteroarilalquilo, $-N(R^{40})_2$, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-S(O)_tNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ siempre que R^{15} no sea H, halógeno y $-NHC(O)NR^{15}R^{16}$; o

R^{13} y R^{14} tomados juntos con el nitrógeno al cual están unidos en los grupos $-C(O)NR^{13}R^{14}$ y $-SO_2NR^{13}R^{14}$ forman un anillo heterocíclico saturado no sustituido o sustituido, dicho anillo opcionalmente contiene un heteroátomo adicional seleccionado del grupo que consiste de: O, S y NR^{18}; en donde hay 1 a 3 sustituyentes en los grupos R^{13} y R^{14} ciclados sustituidos y cada sustituyente es independientemente seleccionado del grupo que consiste de: alquilo, arilo, hidroxi, hidroxialquilo, alcoxi, alcoxialquilo, arilalquilo, fluoralquilo, cicloalquilo, cicloalquilalquilo, heteroarilo, heteroarilalquilo, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-SO_tNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ siempre que R^{15} no sea H, $-NHC(O)NR^{15}R^{16}$, $NHC(O)OR^{15}$, halógeno, y un grupo heterocicloalquenilo

cada R^{15} y R^{16} es independientemente seleccionado a partir del grupo que consiste de: H, alquilo, arilo, arilalquilo, cicloalquilo y heteroarilo;

R^{17} es seleccionado a partir del grupo que consiste de: $-SO_2$alquilo, $-SO_2$arilo, $-SO_2$cicloalquilo, y $-SO_2$heteroarilo;

R^{18} es seleccionado del grupo que consiste de: H, alquilo, arilo, heteroarilo, $-C(O)R^{19}$, $-SO_2R^{19}$ y $-C(O)NR^{19}R^{20}$;

cada R^{19} y R^{20} es independientemente seleccionado del grupo que consiste de: alquilo, arilo y heteroarilo;

R^{30} es seleccionado del grupo que consiste de: alquilo, cicloalquilo, -CN, $-NO_2$, o $-SO_2R^{15}$ siempre que R^{15} no sea H;

cada R^{31} es independientemente seleccionado del grupo que consiste de: alquilo no sustituido o sustituido, arilo no sustituido o sustituido, heteroarilo no

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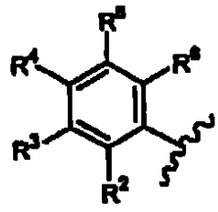
sustituido o sustituido y cicloalquilo no sustituido o sustituido, en donde hay 1 a 6 sustituyentes en dichos grupos R^{31} sustituidos y cada sustituyente es independientemente seleccionado del grupo que consiste de: alquilo, halógeno y $-CF_3$;

cada R^{40} es independientemente seleccionado del grupo que consiste de: H, alquilo y cicloalquilo; y

t es 0, 1 o 2.

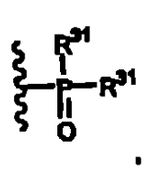
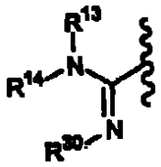
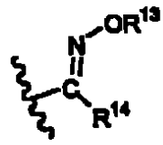
2. El compuesto de la reivindicación 1 en donde B es seleccionado del grupo que consiste de:

(1)

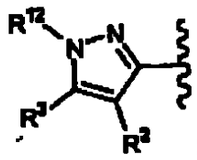


siempre que R^3 para este grupo esté seleccionado del grupo que consiste de: $-C(O)NR^{13}R^{14}$,

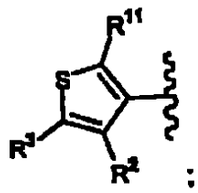
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(2)

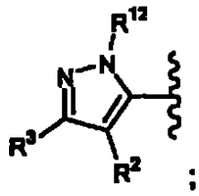

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(3)


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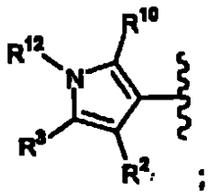
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(4)



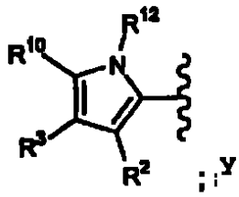
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(5)



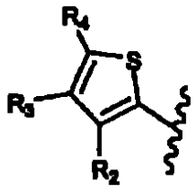
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(6)



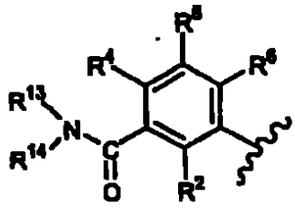
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(7)



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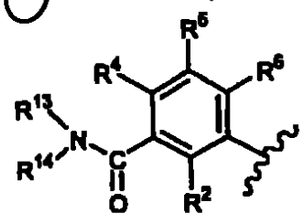
3. El compuesto de la reivindicación 1 en donde B es:



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4. El compuesto de la reivindicación 1 en donde B es:



R^2 es –OH, y R^{13} y R^{14} son cada uno de ellos el mismo o diferente grupo alquilo.

5. El compuesto de la reivindicación 1 en donde B es



6. El compuesto de la reivindicación 5 en donde R^2 es –OH.

7. El compuesto de la reivindicación 6 en donde R^{13} y R^{14} son el mismo o diferente grupo alquilo.

8. El compuesto de la reivindicación 7 en donde R^{13} y R^{14} son metilo.

9. Un compuesto seleccionado del grupo que consiste de los compuestos de las fórmulas 1.0A, 3.0A, y los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088.

10. El compuesto de la reivindicación 9 seleccionado del grupo que consiste de los compuestos 1.0A, 3.0A, .

11. El compuesto de la reivindicación 9 seleccionado del grupo que consiste de los compuestos finales de los ejemplos 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, y 2001-2088.

12. El compuesto de cualquiera de las reivindicaciones 1 a 8 en donde dicho compuesto es una sal de calcio o sodio.

13. El compuesto de cualquiera de las reivindicaciones 9 a 11 en donde dicho compuesto es una sal de calcio o sodio.

14. Una composición farmacéutica que comprende una cantidad efectiva

de al menos un compuesto de cualquiera de las reivindicaciones 1 a 11 y un portador farmacéuticamente aceptable.

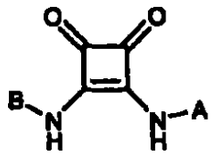
15. Una composición farmacéutica que comprende una cantidad efectiva de una sal de calcio o una sal de sodio de al menos un compuesto de cualquiera de las reivindicaciones 1 a 11 y un portador farmacéuticamente aceptable.

16. El uso de al menos un compuesto de fórmula IA para la fabricación de un medicamento para tratar una enfermedad mediada por la quimiocina,

dicha enfermedad mediada por la quimiocina está seleccionada del grupo que consiste de: dolor inflamatorio agudo, dolor inflamatorio crónico, dolor neuropático agudo, dolor neuropático crónico, síndrome disneico agudo, reacción de hipersensibilidad del tipo retardada, aterosclerosis, isquemia cardiaca y cerebral, osteoartritis, esclerosis múltiple, restinosis, angiogénesis, osteoporosis, gingivitis, virus respiratorio, virus herpes, virus de la hepatitis, HIV, virus asociado con el sarcoma de Kaposi, meningitis, fibrosis cística, trabajo de pre-parto, tos, prurito, disfunción multiorgánica, trauma, torceduras, luxaciones, contusiones, artritis psoriática, herpes, encefalitis, vasculitis SNC, daño cerebral traumático, tumores en el SNC, hemorragia subaracnoidea, trauma pos quirúrgico, pneumonitis intersticial, hipersensibilidad, artritis inducida por cristal, pancreatitis aguda y crónica, hepatitis alcohólica aguda, enterocolitis necrotizante, sinusitis crónica, enfermedad ocular angiogénica, inflamación ocular, retinopatía del prematuro, retinopatía diabética, degeneración macular siendo el tipo húmedo preferido y neovascularización córneal, polimiositis, vasculitis, acné, úlceras gástricas y duodenales, enfermedad celíaca, esofagitis, glositis, obstrucción de vías respiratorias, hipersensibilidad de las vías respiratorias, bronquiectasia, bronquiolitos, bronquiolitos obliteran, bronquitis crónica, cor pulmón ale, tos, disnea, enfisema, hipercapnea, hiperinflación, hipoxemia, inflamaciones inducidas por hiperoxia, hipoxia, reducción de volumen del pulmón quirúrgica, fibrosis

pulmonar, hipertensión pulmonar. hipertrofia ventricular derecha. peritonitis asociada con la diálisis peritoneal ambulatoria continua (CAPD). erliquiosis granulocítica, sacoidosis. enfermedad de la vía respiratoria menor. desequilibrio de ventilación-perfusión. respiración sibilante, resfríos, gota. enfermedad del hígado por alcohol, lupus, tratamiento de quemaduras. periodontitis. daño de reperfusión de transplante, rechazo de transplante prematuro, inflamación aguda, inflamación crónica y artritis reumatoide, y

dichos compuestos de fórmula IA están representados por la fórmula:



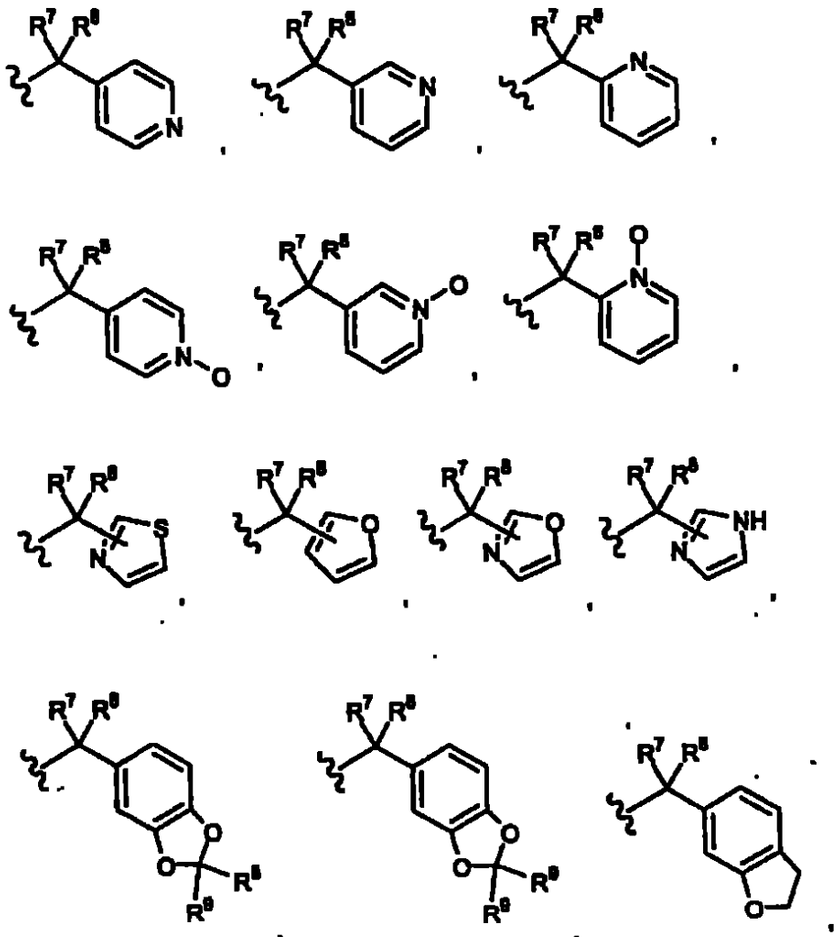
(IA)

y las sales o solvatos farmacéuticamente aceptables de los mismos, en donde:

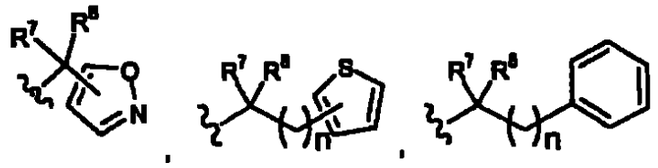
A es seleccionado del grupo que consiste de:

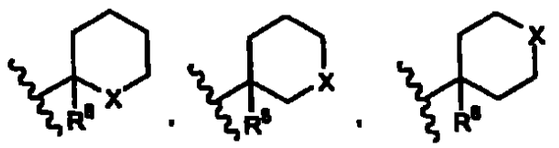
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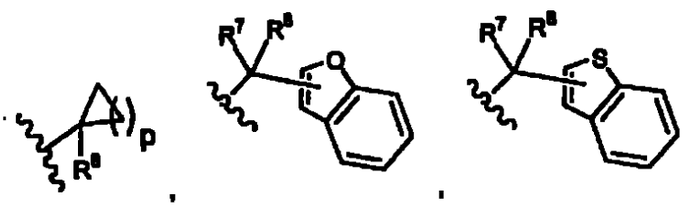
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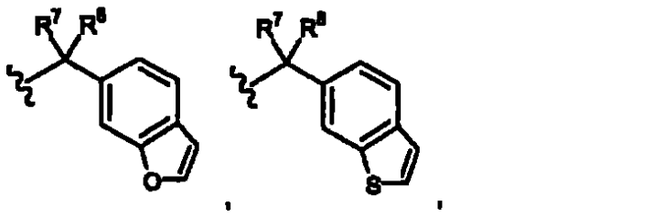


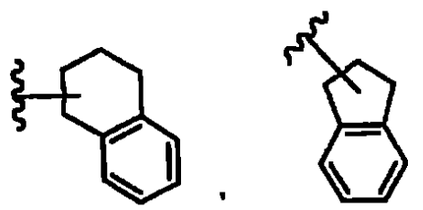
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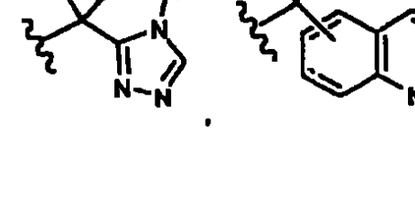




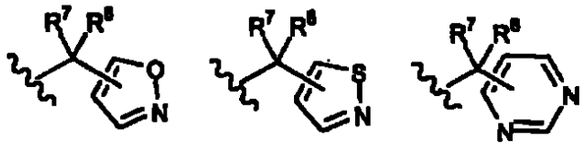


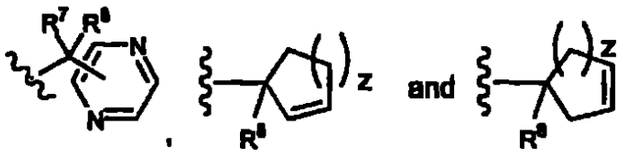




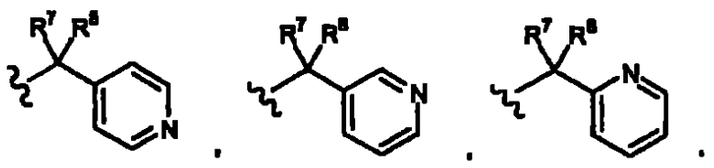


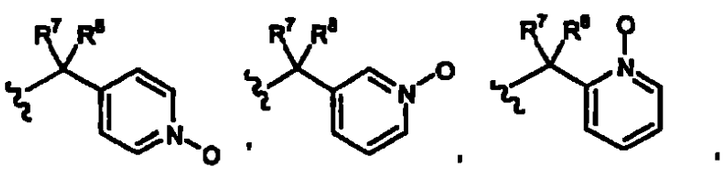
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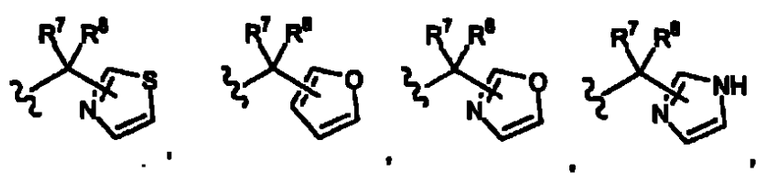


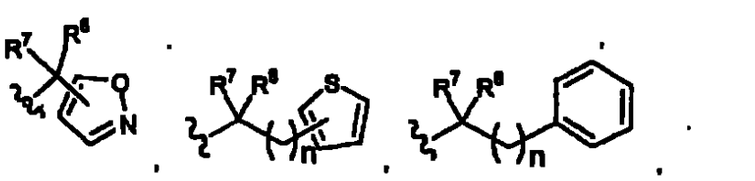


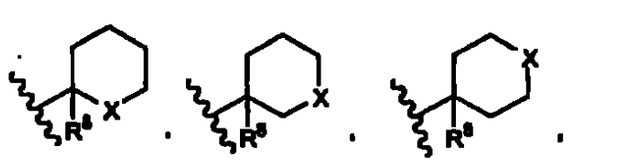
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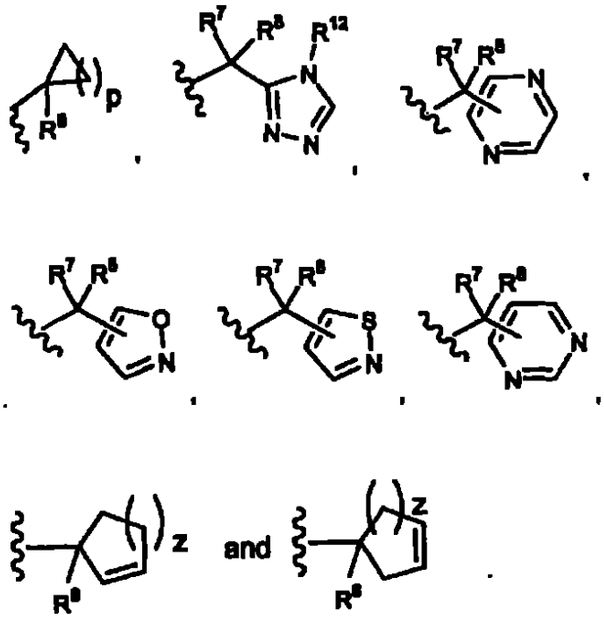






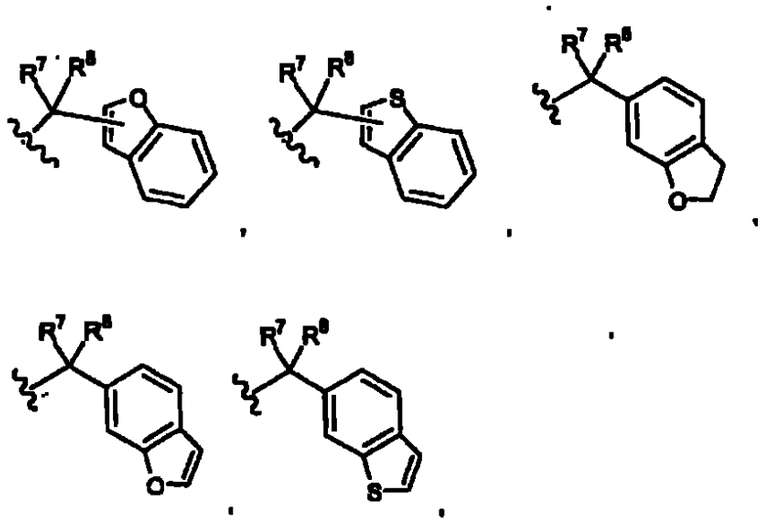


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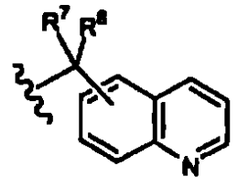
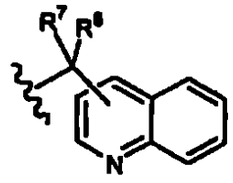


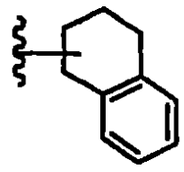
en donde los anillos anteriores de dichos grupos A están sustituidos con 1 a 6 sustituyentes cada uno independientemente seleccionado del grupo que consiste de: grupos R^9;

(3)



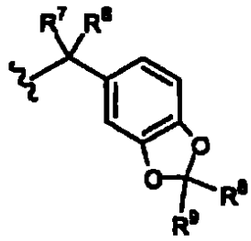
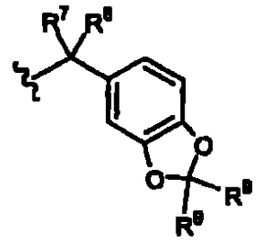
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en donde uno o ambos de los anillos anteriores de dichos grupos A están sustituidos con 1 a 6 sustituyentes cada uno independientemente seleccionado del grupo que consiste de: grupos R^9;

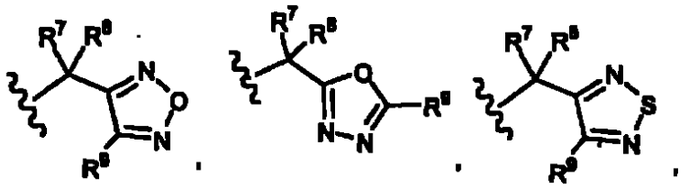
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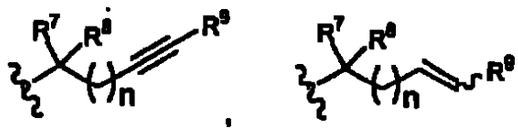

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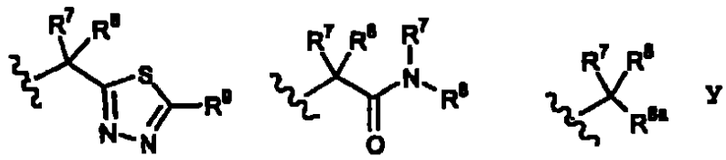
en donde los anillos fenilo anteriores de dichos grupos A están sustituidos con 1 a 3 sustituyentes cada uno independientemente seleccionado del grupo que consiste de: grupos R^9; y

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(5)

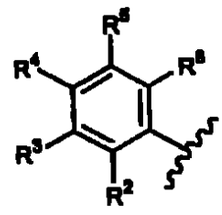
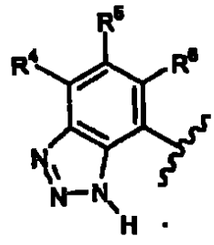
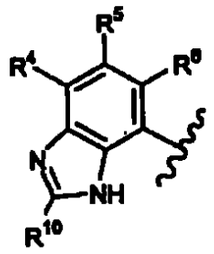
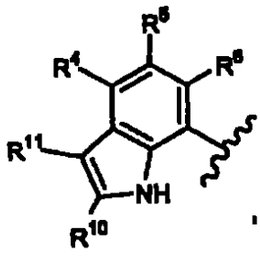
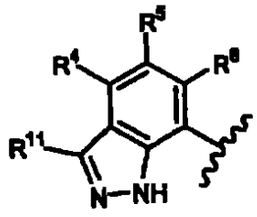
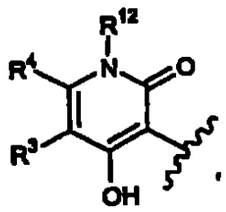
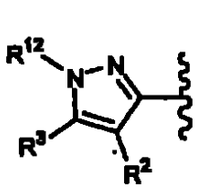
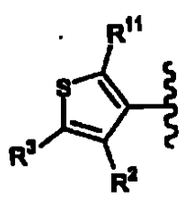
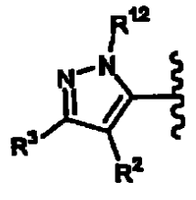
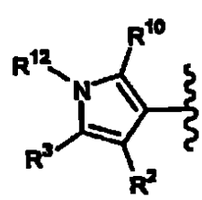
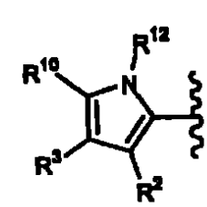
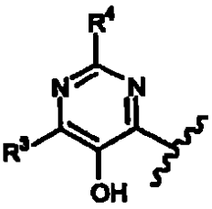




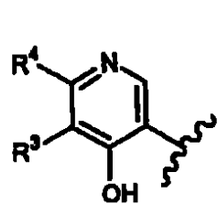
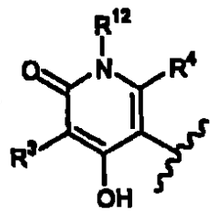
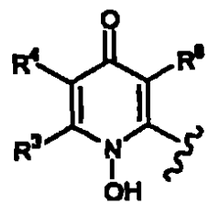


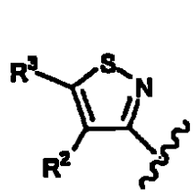
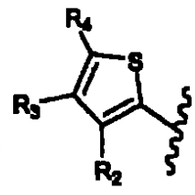
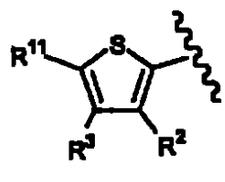


B está seleccionado del grupo que consiste de:

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n es 0 a 6;

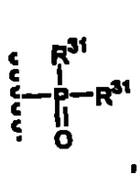
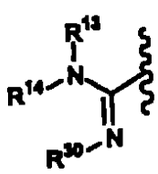
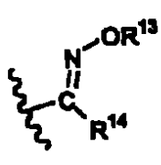
p es 1 a 5;

X es O. NH, o S;

Z es 1 a 3;

R^2 está seleccionado del grupo que consiste de: hidrógeno, OH, -C(O)OH, -SH, $-SO_2NR^{13}R^{14}$, $-NHC(O)R^{13}$, $-NHSO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, $-NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, $-C(O)NHOR^{13}$, $-C(O)NR^{13}OH$, $-S(O_2)OH$, $-OC(O)R^{13}$, un grupo funcional ácido heterocíclico no sustituido, y un grupo funcional ácido heterocíclico sustituido, en donde hay 1 a 6 sustituyentes sobre dicho grupo funcional ácido heterocíclico sustituido, cada sustituyente está independientemente seleccionado del grupo que consiste de: grupos R^9;

cada R^3 y R^4 es independientemente seleccionado del grupo que consiste de: hidrógeno, ciano, halógeno, alquilo, alcoxi, -OH, $-CF_3$, $-OCF_3$, $-NO_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NHR^{17}$, $-C(O)NR^{13}R^{14}$, $-SO_{(t)}NR^{13}R^{14}$, $-SO_{(t)}R^{13}$, $-C(O)NR^{13}OR^{14}$, arilo no sustituido o sustituido, heteroarilo no sustituido o sustituido,


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donde hay 1 a 6 sustituyentes en dicho grupo arilo sustituido y cada sustituyente es independientemente seleccionado del grupo que consiste de: grupos R^9; y en donde hay 1 a 6 sustituyentes en dicho grupo heteroarilo sustituido y cada sustituyente es independientemente seleccionado del grupo que consiste de: grupos R^9;

cada R^5 y R^6 son iguales o diferentes y son independientemente seleccionados del grupo que consiste de hidrógeno, halógeno, alquilo, alcoxi, -CF_3, -OCF_3, -NO_2, -$C(O)R^{13}$, -$C(O)OR^{13}$, -$C(O)NR^{13}R^{14}$, -$SO_{(t)}NR^{13}R^{14}$, -$C(O)NR^{13}OR^{14}$, ciano, arilo sustituido o no sustituido, y grupo heteroarilo no sustituido o sustituido; donde hay 1 a 6 sustituyentes en dicho grupo arilo sustituido y cada sustituyente es independientemente seleccionado del grupo que consiste de: grupos R^9; y donde hay 1 a 6 sustituyentes en dicho grupo heteroarilo sustituido y cada sustituyentes es independientemente seleccionado del grupo que consiste de: grupos R^9;

cada R^7 y R^8 es independientemente seleccionado del grupo que consiste de. H, alquilo no sustituido o sustituido, arilo no sustituido o sustituido, heteroarilo no sustituido o sustituido, arilalquilo no sustituido o sustituido, heteroarilalquilo no sustituido o sustituido, cicloalquilo no sustituido o sustituido, cicloalquilalquilo no sustituido o sustituido, -CO_2R^{13}, -$CONR^{13}R^{14}$, alquinilo, alquenilo, y cicloalquenilo; y donde hay uno o más sustituyentes en dichos grupos R^7 y R^8, donde cada sustituyente es independientemente seleccionado del grupo que consiste de:

a) halógeno,

b) –CF_3,

c) –COR^{13},

d) –OR^{13},

e) –$NR^{13}R^{14}$,

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f) NO_2,

g) –CN,

h) $–SO_2OR^{13}$,

i) –Si(alquilo)$_3$, donde cada alquilo es independientemente seleccionado,

j) –Si(arilo)$_3$, donde cada alquilo es independientemente seleccionado,

k) $–(R^{13})_2R^{14}Si$, donde cada R^{13} es independientemente seleccionado,

l) $–CO_2R^{13}$,

m) $–C(O)NR^{13}R^{14}$,

n) $–SO_2NR^{13}R^{14}$,

o) $–SO_2R^{13}$,

p) $–OC(O)R^{13}$,

q) $–OC(O)NR^{13}R^{14}$,

r) $–NR^{13}C(O)R^{14}$, y

s) $–NR^{13}CO_2R^{14}$;

R^{8a} es seleccionado del grupo que consiste de: hidrógeno, alquilo, cicloalquilo y cicloalquilalquilo;

cada R^9 es independientemente seleccionado del grupo que consiste de:

a) $-R^{13}$,

b) halógeno,

c) $–CF_3$,

d) $–COR^{13}$,

e) $–OR^{13}$,

f) $–NR^{13}R^{14}$,

g) $–NO_2$,

h) –CN,

i) $–SO_2R^{13}$,

j) $-SO_2NR^{13}R^{14}$,

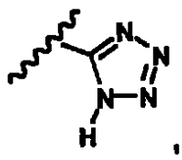
k) $-NR^{13}COR^{14}$,

l) $-CONR^{13}R^{14}$,

m) $-NR^{13}CO_2R^{14}$,

n) $-CO_2R^{13}$,

o)



,

p) alquilo sustituido con uno o más o más grupos –OH,

q) alquilo sustituido con uno o más grupos $-NR^{13}R^{14}$, y

r) $-N(R^{13})SO_2R^{14}$;

cada R^{10} y R^{11} es independientemente seleccionado a partir del grupo que consiste de R^{13}, hidrógeno, alquilo $-CF_3$, $-OCF_3$, $-NR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, -OH, $-C(O)OR^{13}$, -SH, $-SO_{(t)}NR^{13}R^{14}$, $-SO_2R^{13}$, $-NHC(O)R^{13}$, $-NHSO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, $-C(O)NR^{13}R^{14}$, $-C(O)NR^{13}OR^{14}$, $-OC(O)R^{13}$ y ciano;

R^{12} es seleccionado del grupo que consiste de : hidrógeno, $-C(O)OR^{13}$, grupo arilo no sustituido o sustituido, heteroarilo no sustituido o sustituido, arilalquilo no sustituido o sustituido, cicloalquilo no sustituido o sustituido, alquilo no sustituido o sustituido, cicloalquilalquilo no sustituido o sustituido, y heteroarilalquilo no sustituido o sustituido; donde hay 1 a 6 sustituyentes en los grupos R^{12} sustituido y cada sustituyente es independientemente seleccionado del grupo que consiste de: grupos R^9;

cada R^{13} y R^{14} es independientemente seleccionado del grupo que consiste de: H, alquilo no sustituido o sustituido, arilo no sustituido o sustituido, heteroarilo no sustituido o sustituido, arilalquilo no sustituido o sustituido, heteroarilalquilo no

412
414

sustituido o sustituido, cicloalquilo no sustituido o sustituido, cicloalquilalquilo no sustituido o sustituido, heterocíclico no sustituido o sustituido, fluoralquilo no sustituido o sustituido, heterocicloalquilalquilo no sustituido o sustituido; donde hay 1 a 6 sustituyentes en dichos grupos R^{13} y R^{14} sustituidos y cada sustituyente es independientemente seleccionado del grupo que consiste de: alquilo, $-CF_3$, -OH, alcoxi, arilo, arilalquilo, fluoralquilo, cicloalquilo, cicloalquilalquilo, heteroarilo, heteroarilalquilo, $-N(R^{40})_2$, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-S(O)_tNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ siempre que R^{15} no sea H, halógeno y $-NHC(O)NR^{15}R^{16}$; o

R^{13} y R^{14} tomados juntos con el nitrógeno al cual están unidos en los grupos $-C(O)NR^{13}R^{14}$ y $-SO_2NR^{13}R^{14}$ forman un anillo heterocíclico saturado no sustituido o sustituido, dicho anillo opcionalmente contiene un heteroátomo adicional seleccionado del grupo que consiste de: O, S y NR^{18}; en donde hay 1 a 3 sustituyentes en los grupos R^{13} y R^{14} ciclados sustituidos y cada sustituyente es independientemente seleccionado del grupo que consiste de: alquilo, arilo, hidroxi, hidroxialquilo, alcoxi, alcoxialquilo, arilalquilo, fluoralquilo, cicloalquilo, cicloalquilalquilo, heteroarilo, heteroarilalquilo, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-SO_tNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ siempre que R^{15} no sea H, $-NHC(O)NR^{15}R^{16}$, $NHC(O)OR^{15}$, halógeno, y un grupo heterocicloalquenilo

cada R^{15} y R^{16} es independientemente seleccionado a partir del grupo que consiste de: H, alquilo, arilo, arilalquilo, cicloalquilo y heteroarilo;

R^{17} es seleccionado a partir del grupo que consiste de: $-SO_2$alquilo, $-SO_2$arilo, $-SO_2$cicloalquilo, y $-SO_2$heteroarilo;

R^{18} es seleccionado del grupo que consiste de: H, alquilo, arilo, heteroarilo, $-C(O)R^{19}$, $-SO_2R^{19}$ y $-C(O)NR^{19}R^{20}$;

cada R^{19} y R^{20} es independientemente seleccionado del grupo que consiste de: alquilo, arilo y heteroarilo;

R^{30} es seleccionado del grupo que consiste de: alquilo, cicloalquilo, -CN, -

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NO_2, o $-SO_2R^{15}$ siempre que R^{15} no sea H;

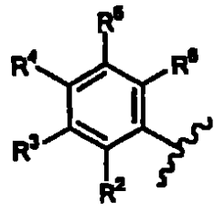
cada R^{31} es independientemente seleccionado del grupo que consiste de: alquilo no sustituido o sustituido, arilo no sustituido o sustituido, heteroarilo no sustituido o sustituido y cicloalquilo no sustituido o sustituido, en donde hay 1 a 6 sustituyentes en dichos grupos R^{31} sustituidos y cada sustituyente es independientemente seleccionado del grupo que consiste de: alquilo, halógeno y $-CF_3$;

cada R^{40} es independientemente seleccionado del grupo que consiste de: H, alquilo y cicloalquilo; y

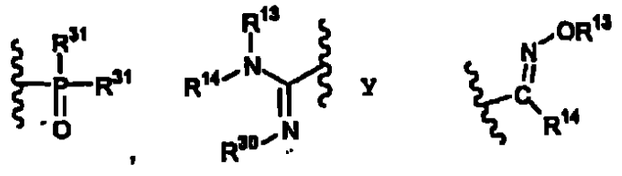
t es 0, 1 o 2.

17. El uso de la reivindicación 16 en donde B es seleccionado del grupo que consiste de:

(1)



siempre que R^3 para este grupo sea seleccionado del grupo que consiste de: $-C(O)NR^{13}R^{14}$,

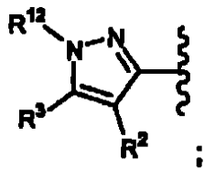


y

;

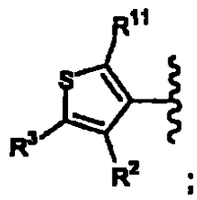
414
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(2)



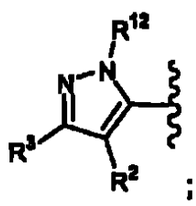
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(3)



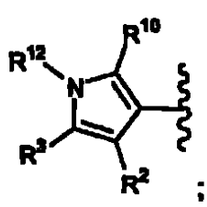
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(4)



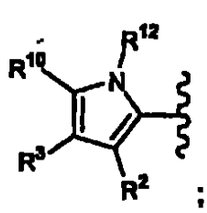
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(5)



;

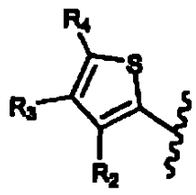
(6)



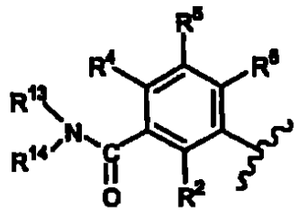
; y

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417

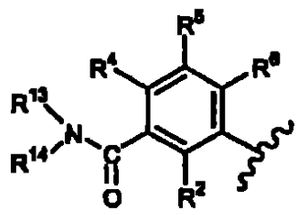
(7)



18. El uso de la reivindicación 16 en donde B es:

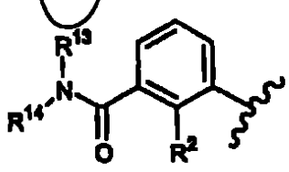


19. El uso de la reivindicación 16 en donde B es:



R^2 es –OH, y R^{13} y R^{14} son cada uno el mismo o diferente grupo alquilo.

20. El uso de la reivindicación 16 en donde B es:

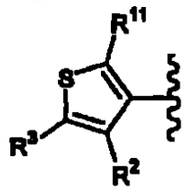


21. El uso de la reivindicación 20 en donde R^2 es –OH.

22. El uso de la reivindicación 21 en donde R^{13} y R^{14} son el mismo o diferente grupo alquilo.

23. El uso de la reivindicación 22 en donde R^{13} y R^{14} son metilo.

24. El uso de la reivindicación 16 en donde B es



25. El uso de la reivindicación 24 en donde R^{11} es H.

26. El uso de la reivindicación 25 en donde R^2 es –OH.

27. El uso de la reivindicación 26 en donde R^3 es $-C(O)NR^{13}R^{14}$.

28. El uso de la reivindicación 27 en donde R^{13} y R^{14} son cada uno independientemente seleccionados del grupo que consiste de: alquilo, heteroarilo no sustituido y heteroarilo sustituido.

29. El uso de la reivindicación 24 en donde R^3 es $-S(O)_tNR^{13}R^{14}$.

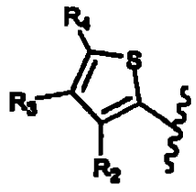
30. El uso de la reivindicación 29 en donde R^2 es –OH.

31. El uso de la reivindicación 30 en donde los sustituyentes R^{13} y R^{14} son iguales o diferentes y son seleccionados del grupo que consiste de: H y alquilo.

32. El uso de la reivindicación 31 en donde cada R^{13} y R^{14} son independientemente seleccionados del grupo que consiste de: H, metilo, etilo, isopropilo y t-butilo.

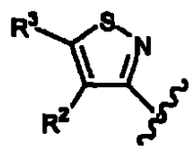
33. El uso de la reivindicación 32 en donde R^{13} y R^{14} son etilo.

34. El uso de la reivindicación 16 en donde B es

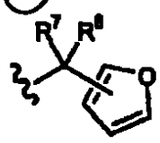


35. El uso de la reivindicación 16 en donde B es:

447
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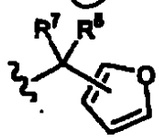


36. El uso de cualquiera de las reivindicaciones 16 a 35 en donde A es:



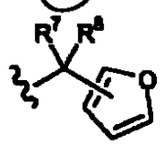
en donde el anillo furano es no sustituido o sustituido.

37. El uso de la reivindicación 36 en donde A es



en donde el anillo furano es sustituido.

38. El uso de la reivindicación 37 en donde A es



en donde el anillo furano es sustituido con al menos un grupo alquilo.

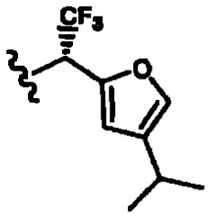
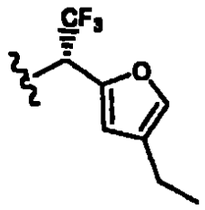
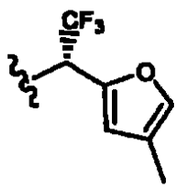
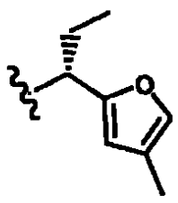
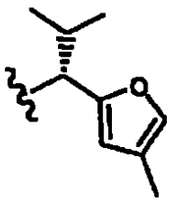
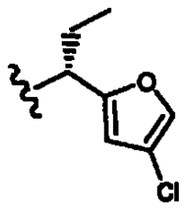
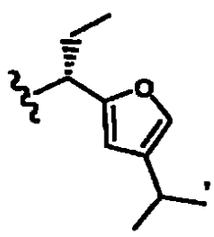
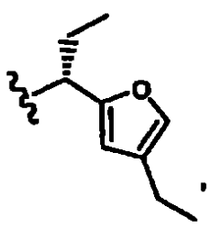
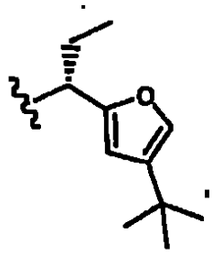
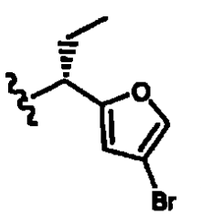
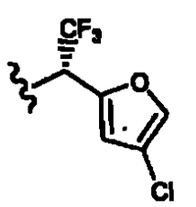
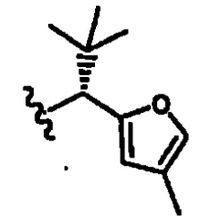
39. El uso de la reivindicación 38 en donde R^7 y R^8 son independientemente seleccionados del grupo que consiste de: H y alquilo.

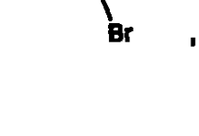
40. El uso de la reivindicación 39 en donde R^7 es H, y R^8 es alquilo.

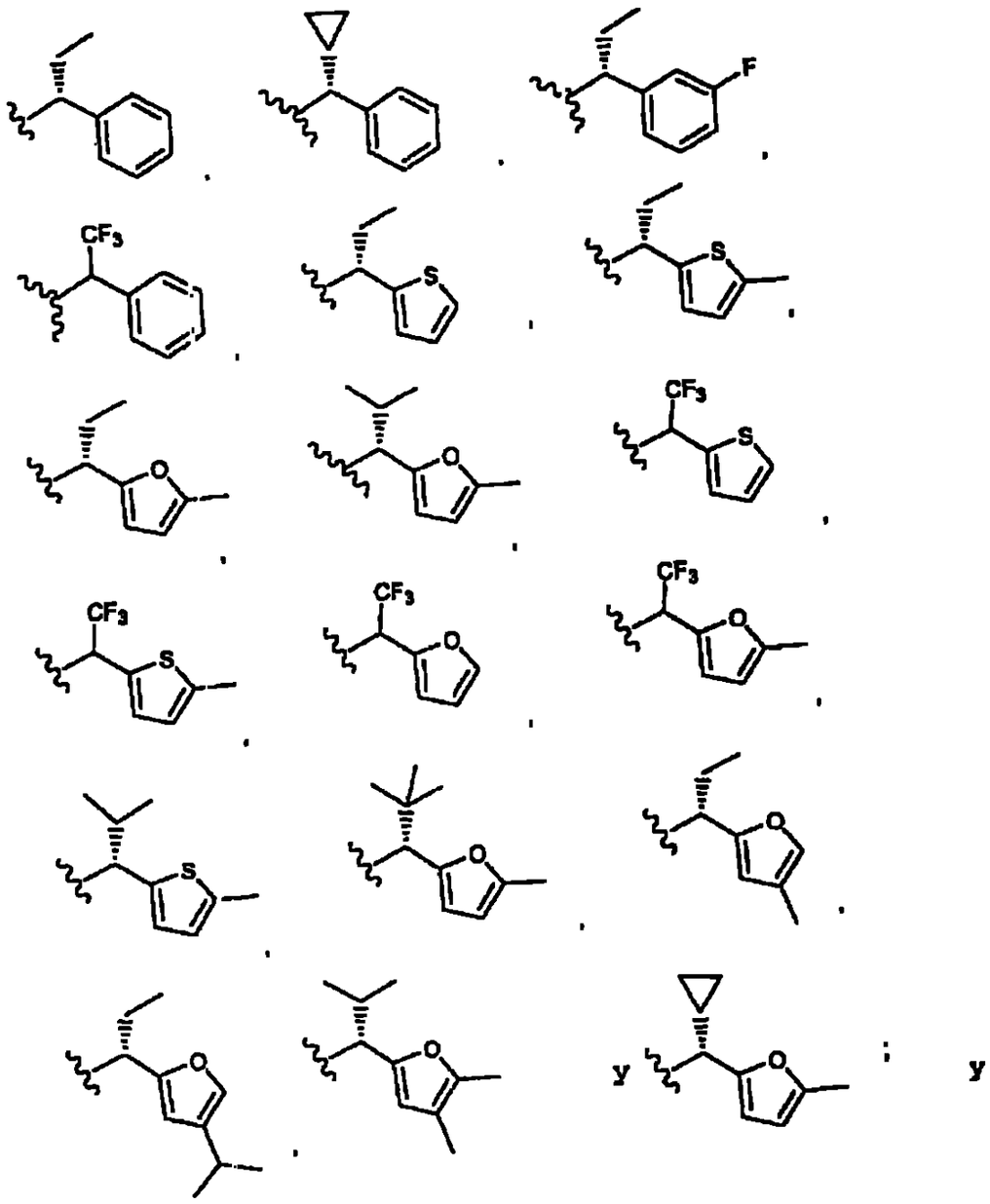
41. El uso de la reivindicación 16 en donde

(1) A es seleccionado del grupo que consiste de:

1418
420

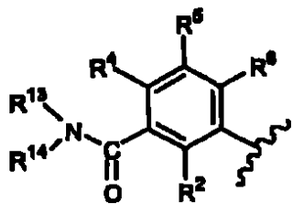

















(2) B es:

~~420~~
422



en donde:

R^2 es –OH;

R^4 es seleccionado del grupo que consiste de: H, $-CH_3$ y $-CF_3$;

R^5 es seleccionado del grupo que consiste de: H y ciano;

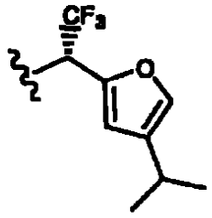
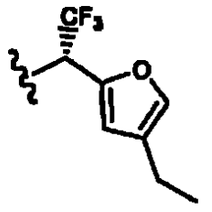
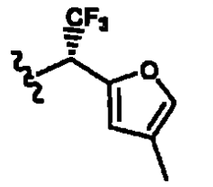
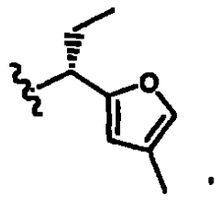
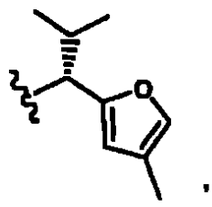
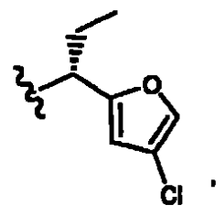
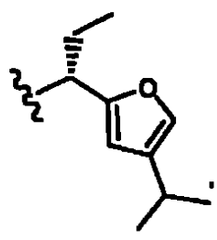
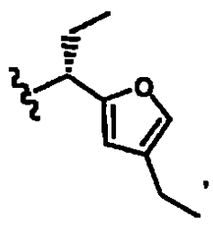
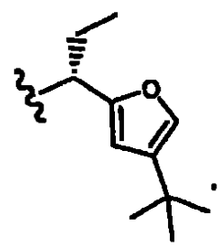
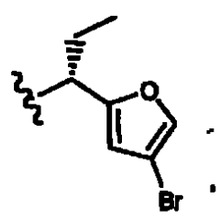
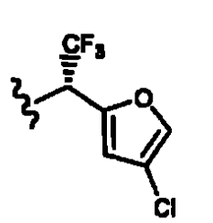
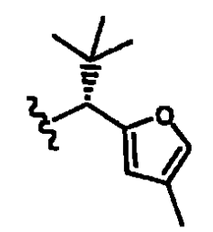
R^6 es seleccionado del grupo que consiste de: H, $-CH_3$ y $-CF_3$;

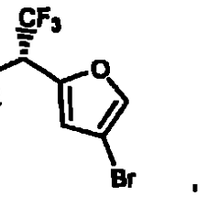
R^{13} y R^{14} son *metilo*.

42 El uso de la reivindicación 16 en donde

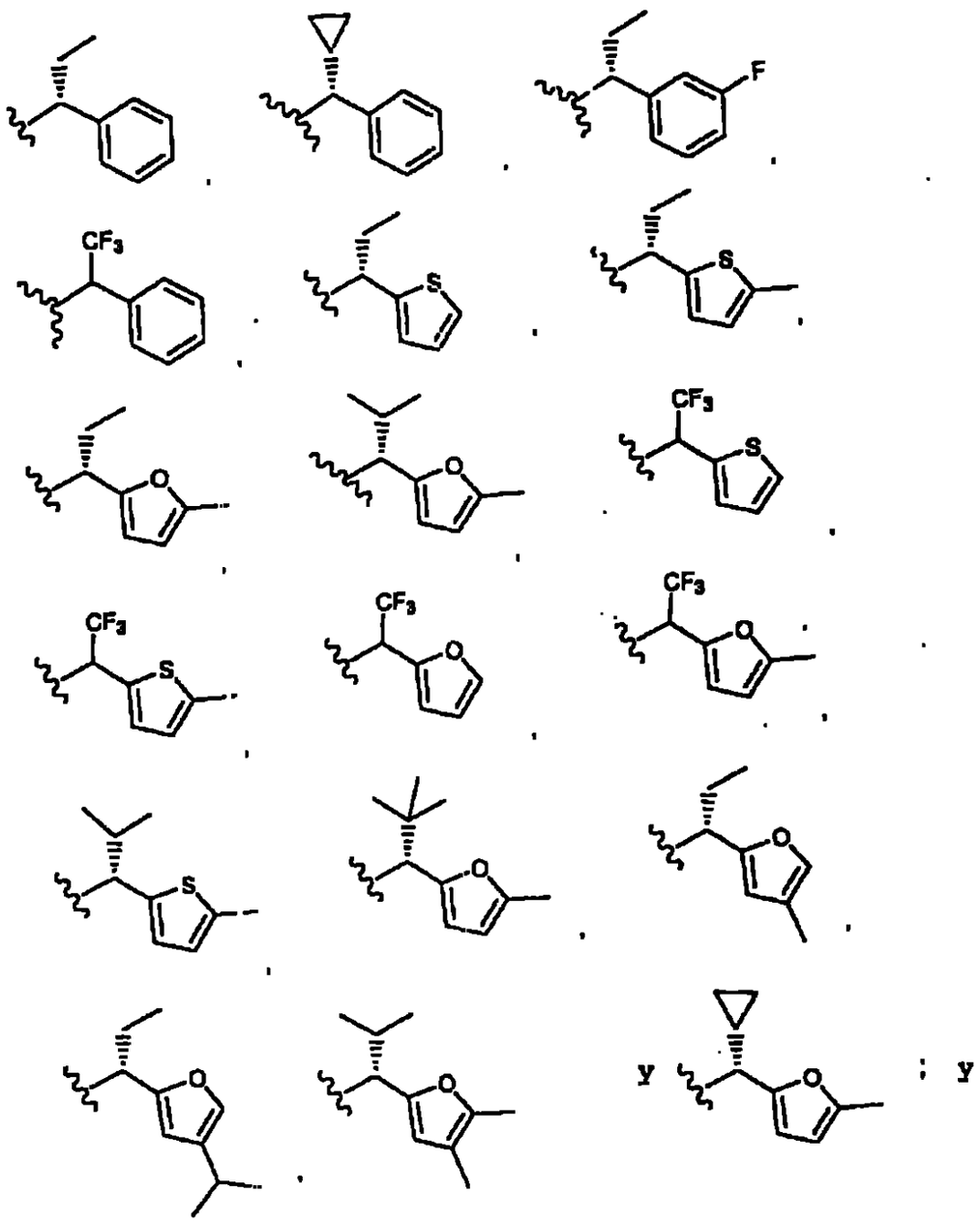
(1) A es seleccionado del grupo que consiste de:

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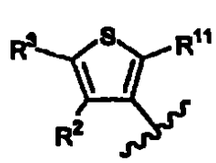















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424



(2) B es:



en donde:

R^2 es –OH;

R^3 es seleccionado del grupo que consiste de: $-SO_2NR^{13}R^{14}$ y $–CONR^{13}R^{14}$;

R^{11} es H; y

cada R^{13} y R^{14} son independientemente seleccionados del grupo que consiste de: H, metilo, etilo, isopropilo y t-butilo.

43. El uso de la reivindicación 42 en donde R^3 es $–SO_2NR^{13}R^{14}$.

44. El uso de la reivindicación 43 en donde R^{13} y R^{14} son etilo.

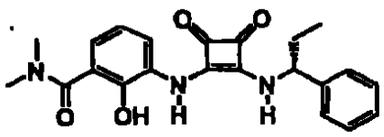
45. El uso de la reivindicación 16 en donde dicho compuesto es una sal de calcio.

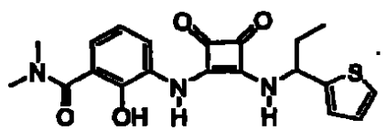
46. El uso de la reivindicación 16 en donde dicho compuesto es una sal de sodio.

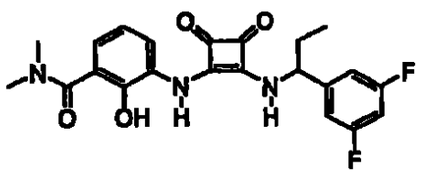
47. El uso de la reivindicación 16 en donde dicha enfermedad es seleccionada del grupo que consiste de: dolor inflamatorio agudo, dolor inflamatorio crónico, dolor neuropático agudo, y dolor neuropático crónico.

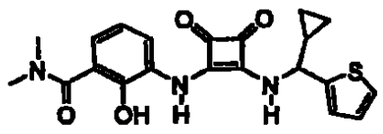
48. El uso de la reivindicación 16 en donde dicho compuesto es seleccionado del grupo que consiste de:

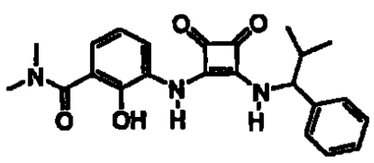
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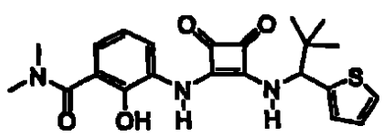


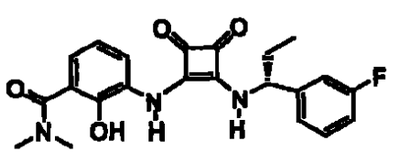


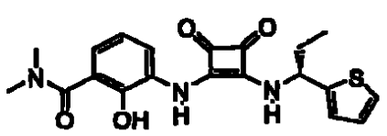


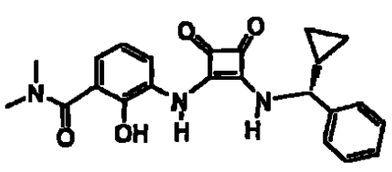


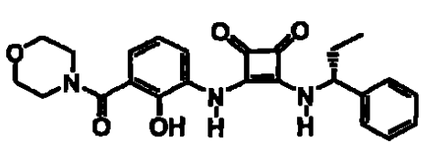


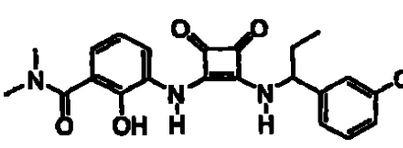


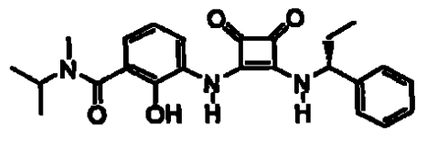


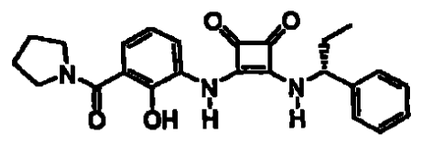


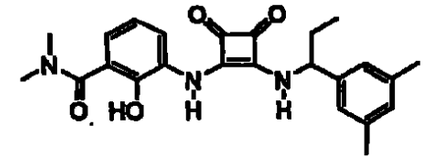


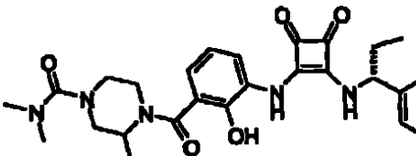


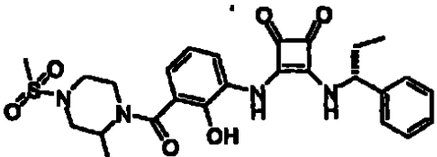


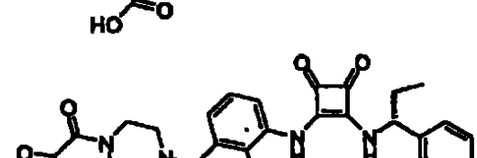


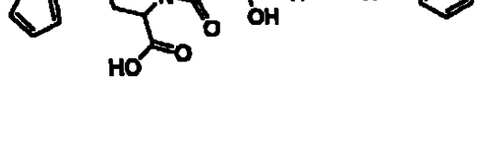




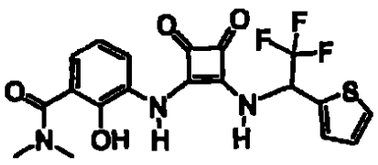


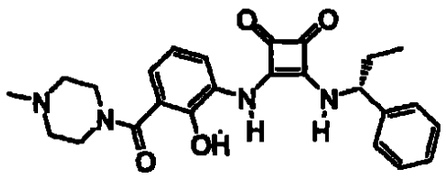


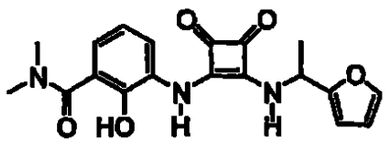


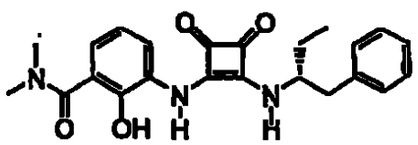


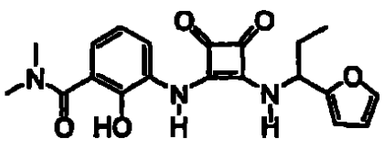
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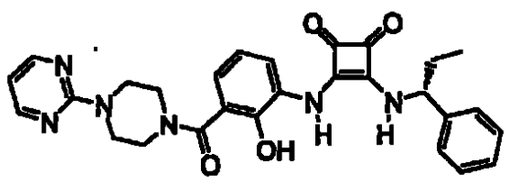


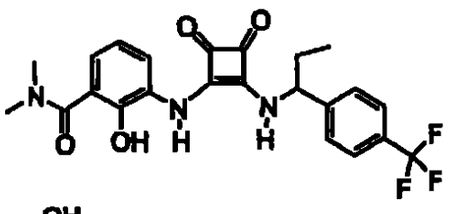


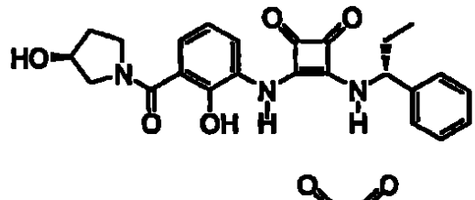


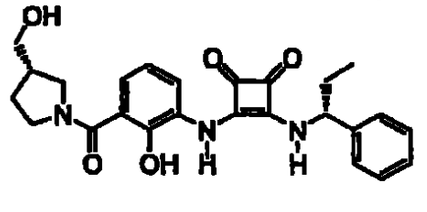


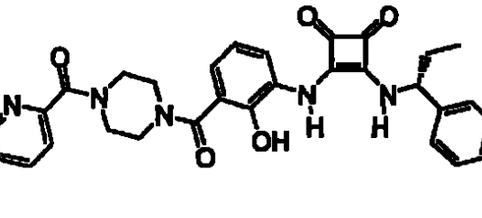


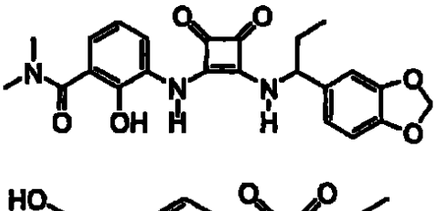


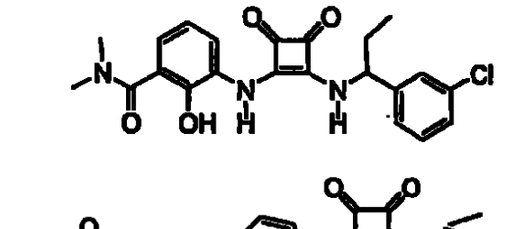


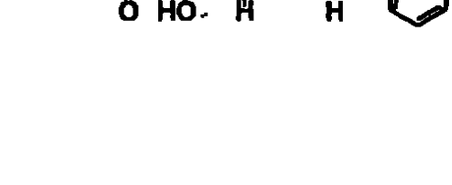


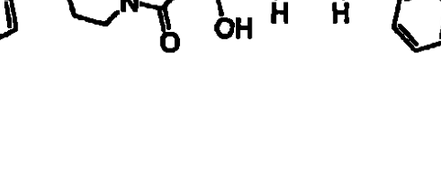




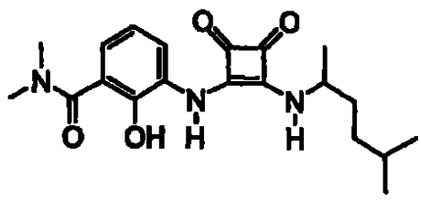


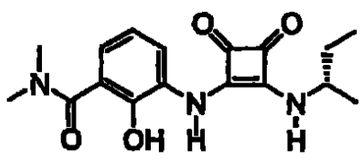


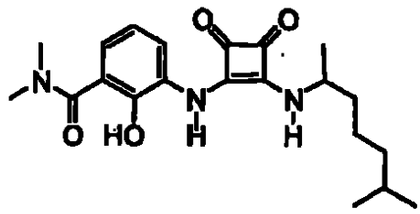


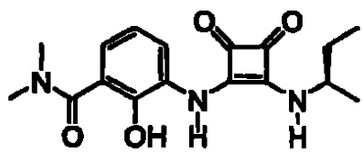


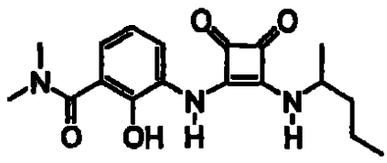
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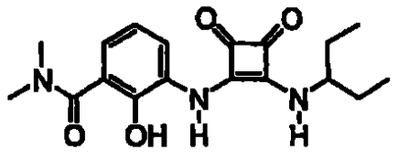


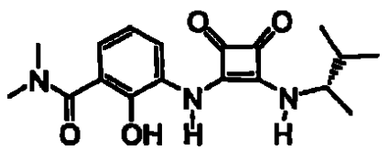


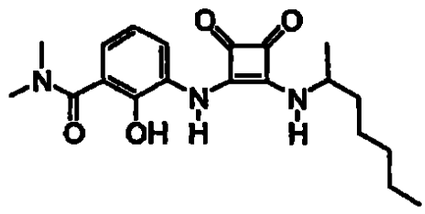


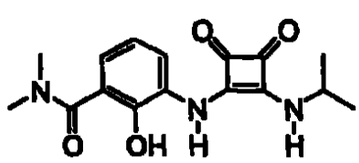


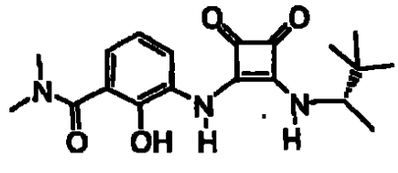


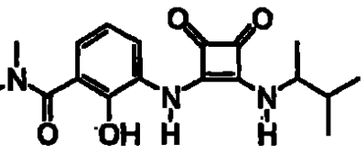


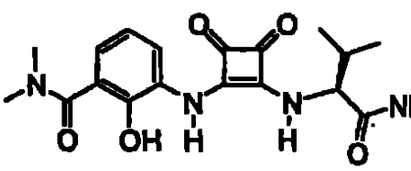


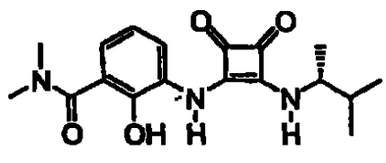


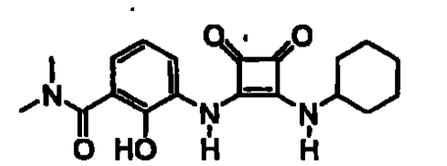




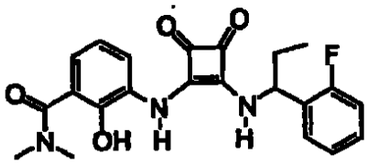


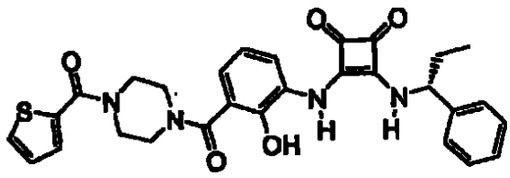


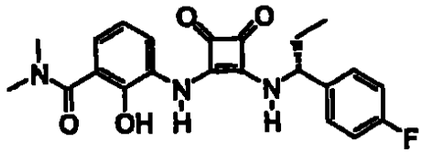


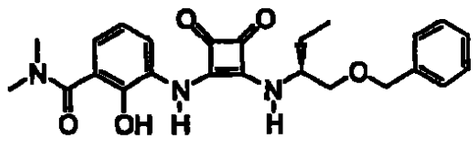


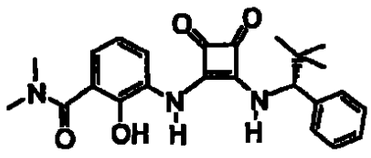
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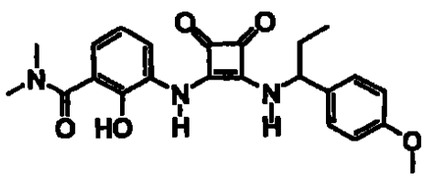


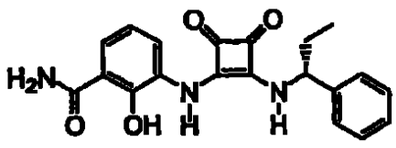


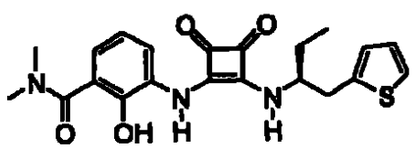


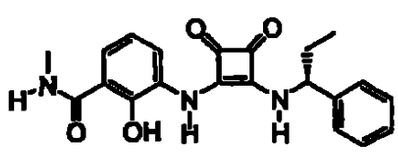


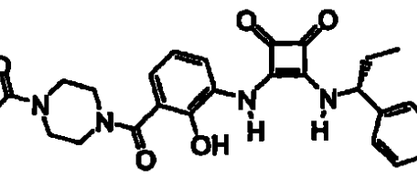


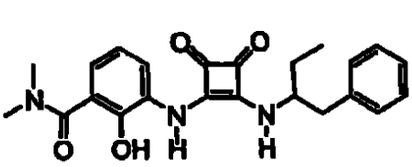


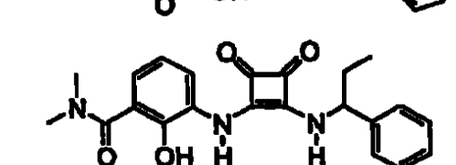


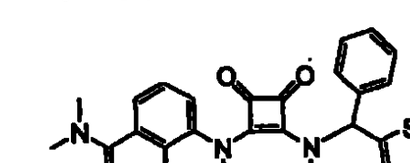


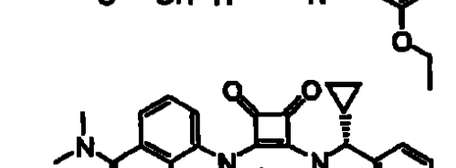


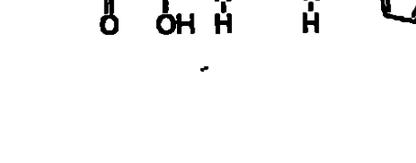


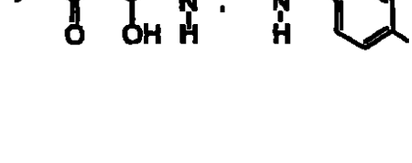


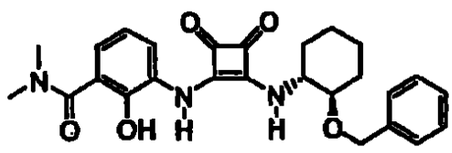


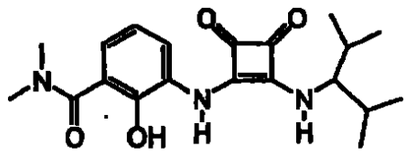


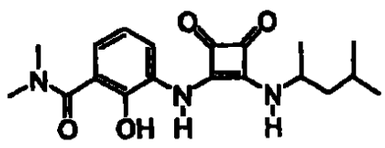


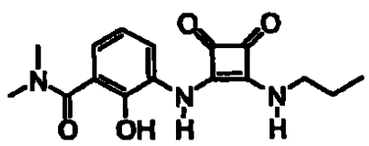


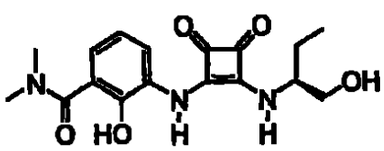


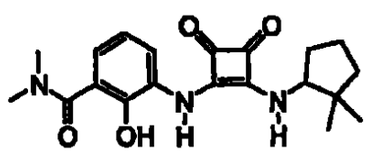


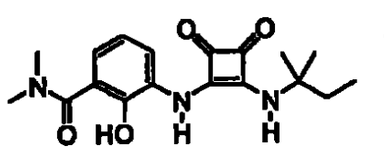


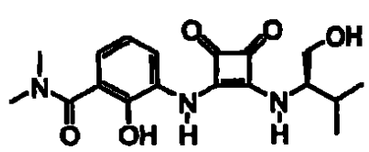


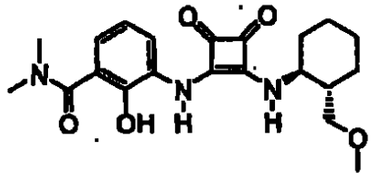


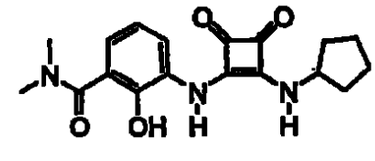


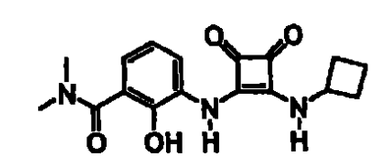


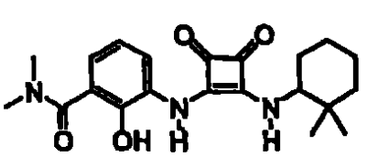


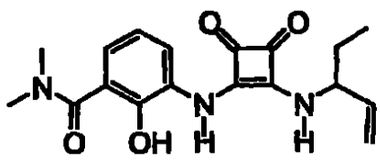


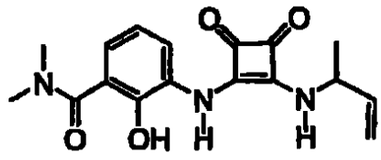


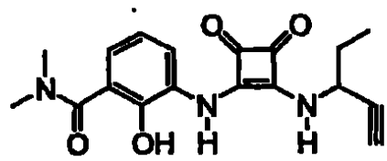


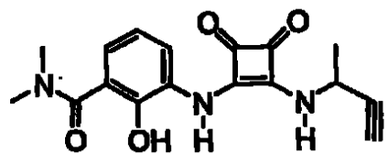


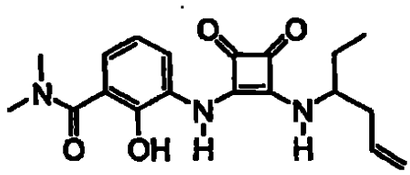


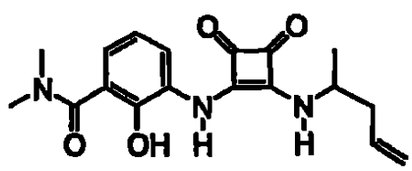


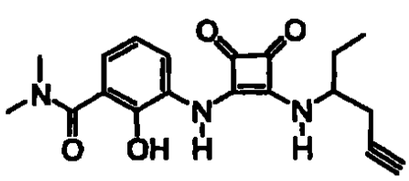


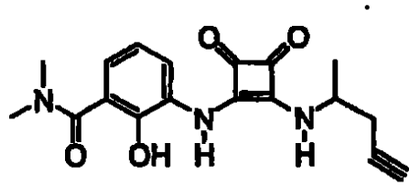


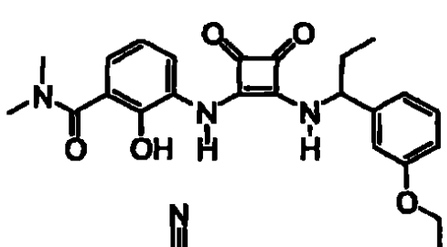


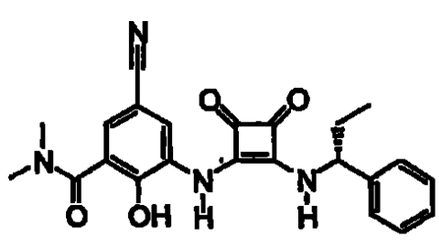




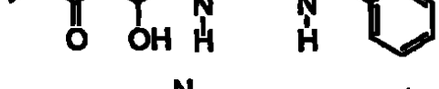


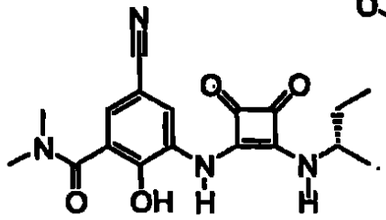


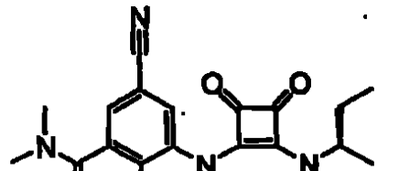


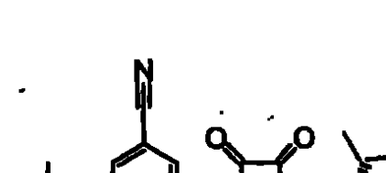


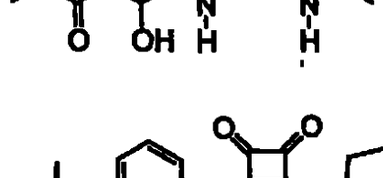


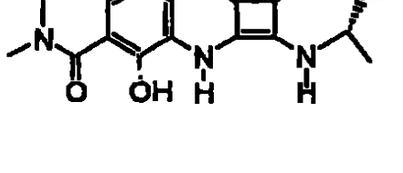


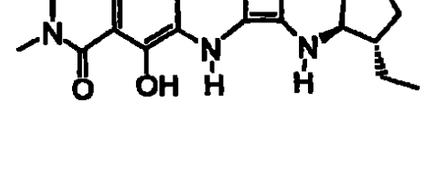


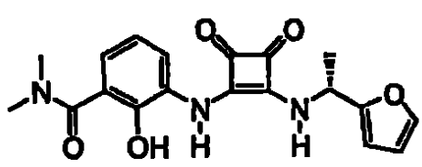


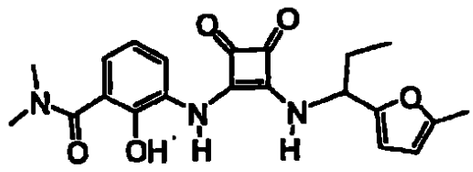


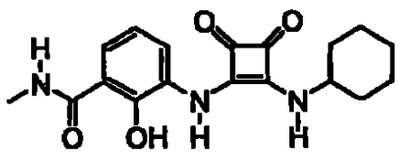


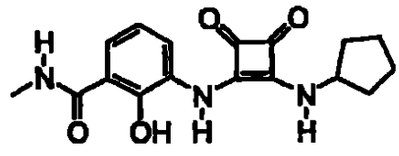


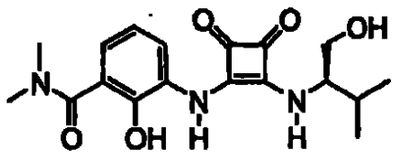


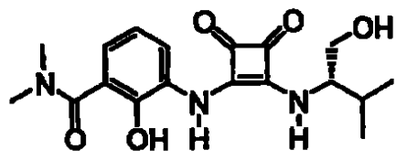


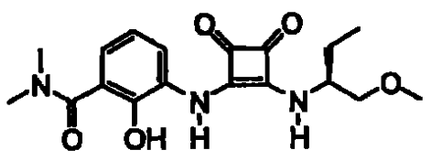


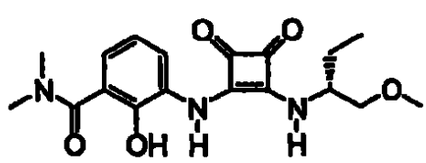


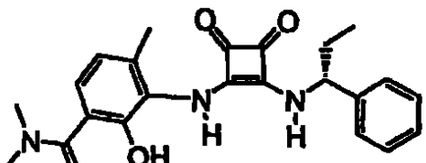


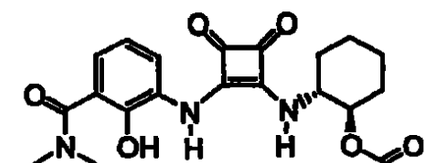


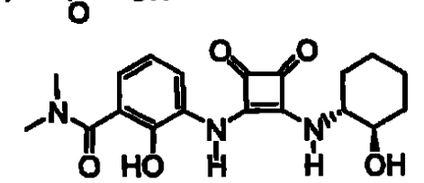




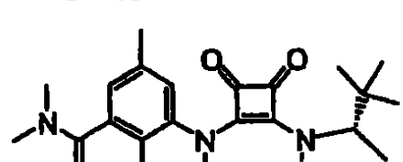


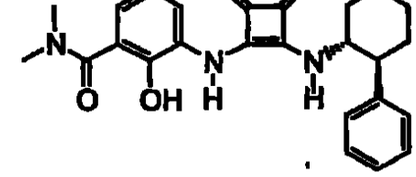


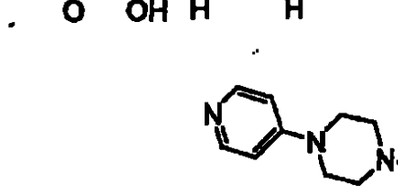


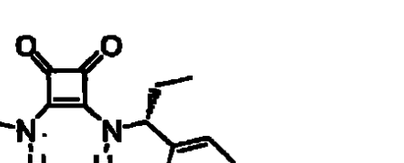




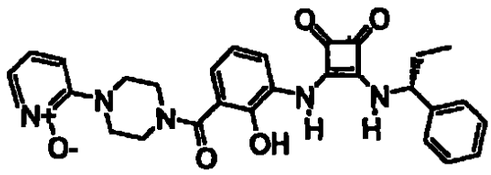


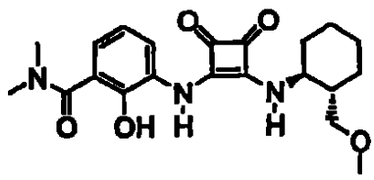


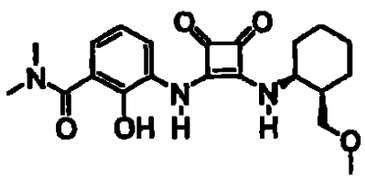


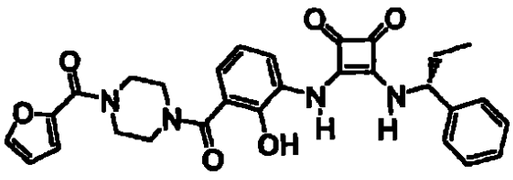


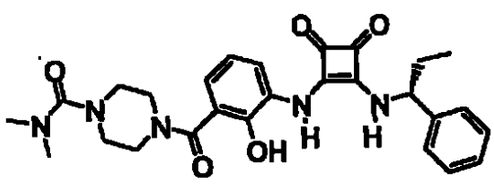
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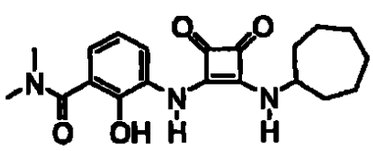


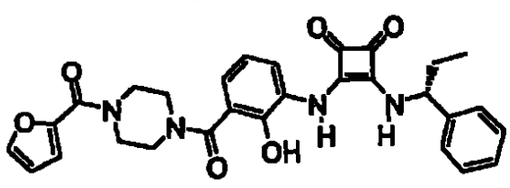


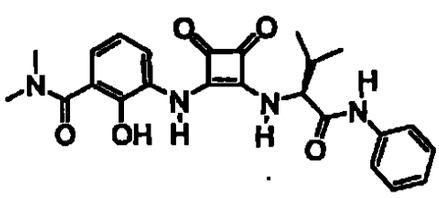


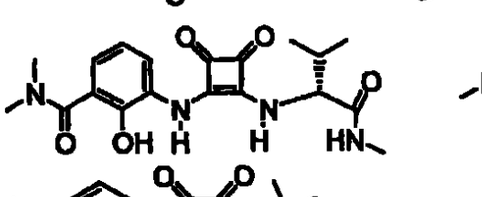


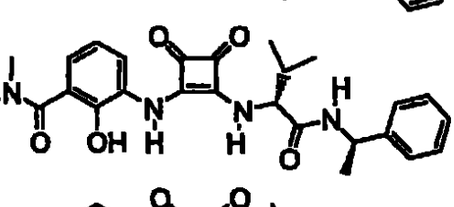


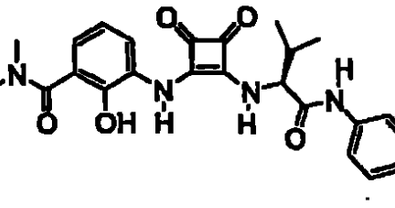


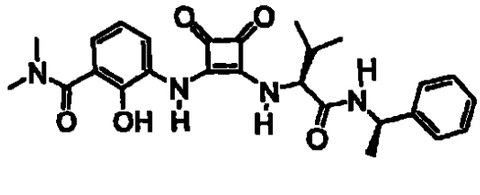


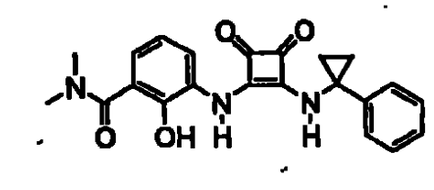


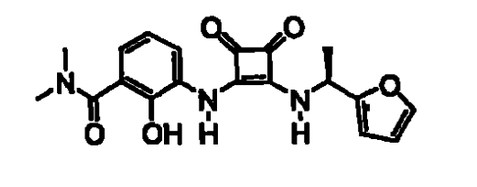


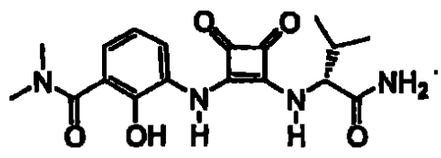


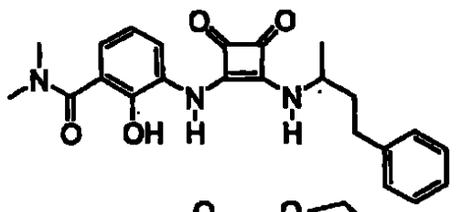


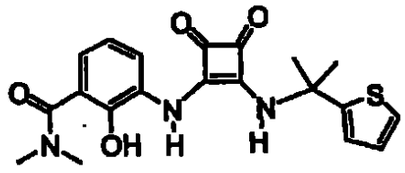


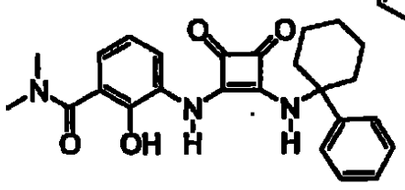


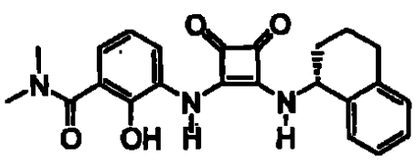


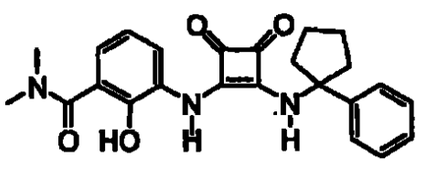


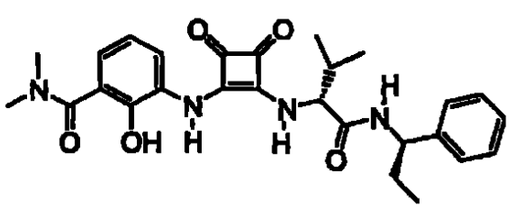


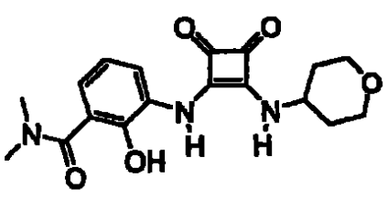


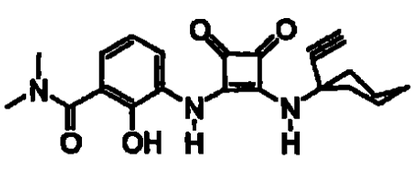


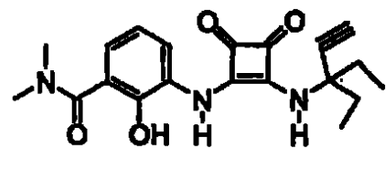


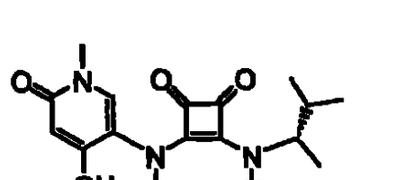


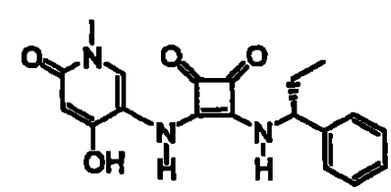


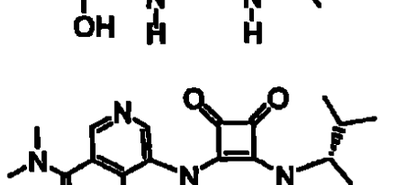


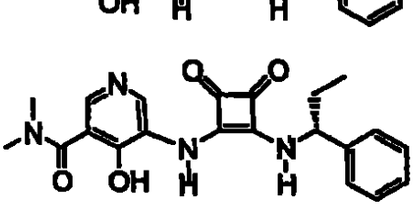


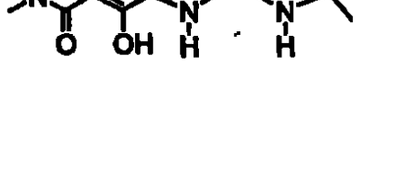


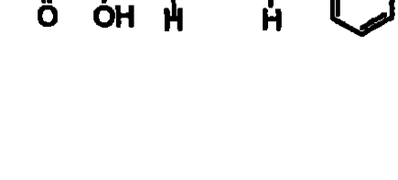


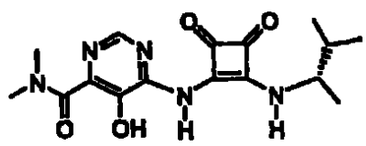


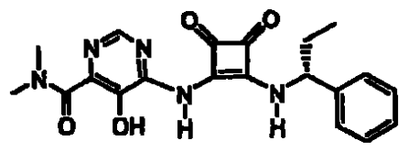


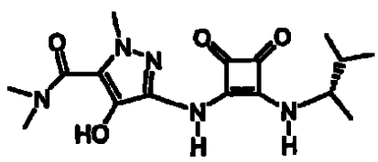


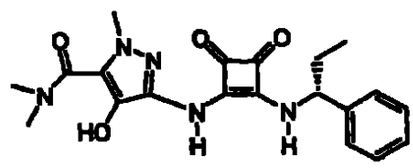


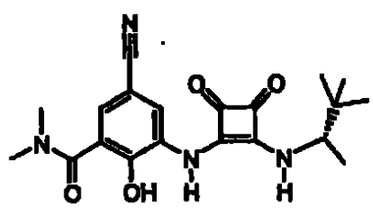


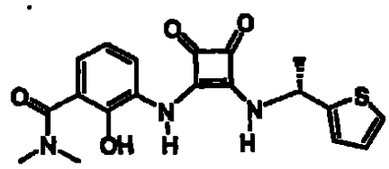


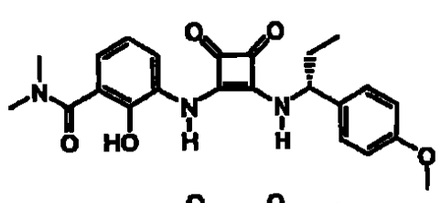


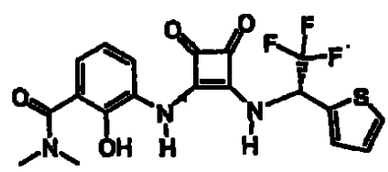


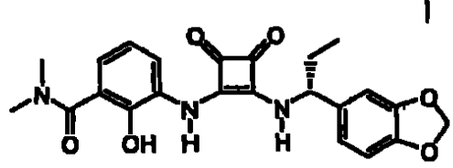


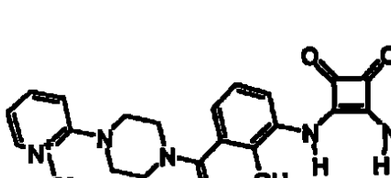


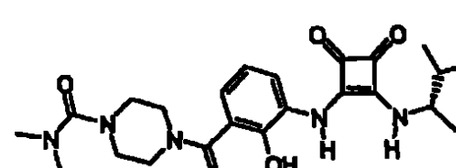


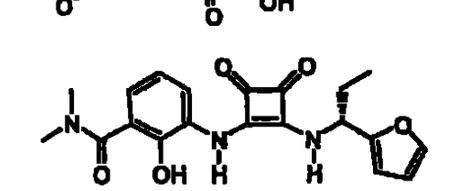


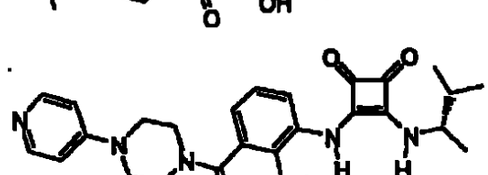


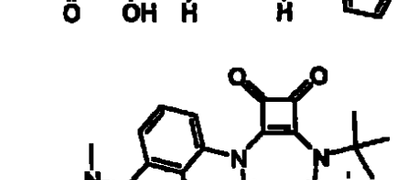


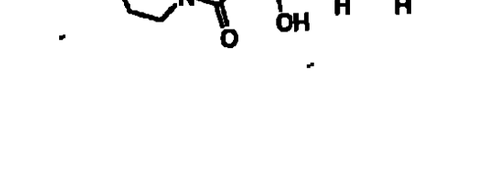


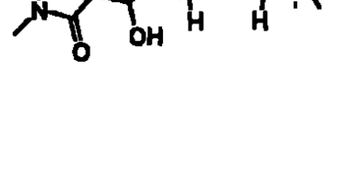


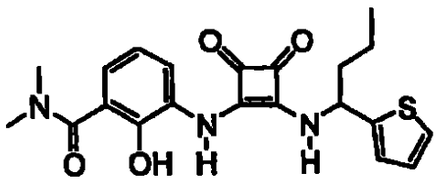


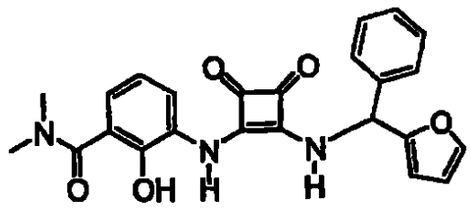


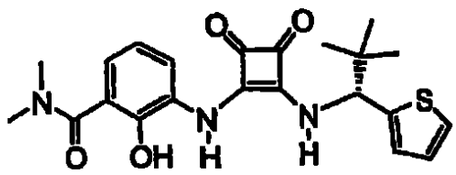


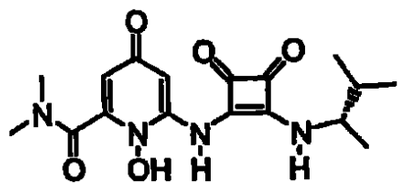


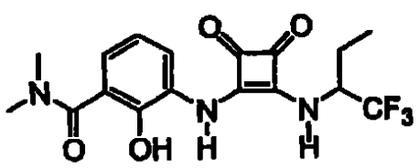


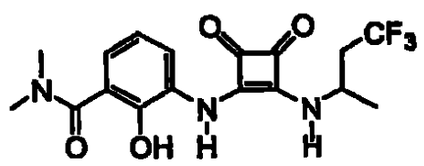


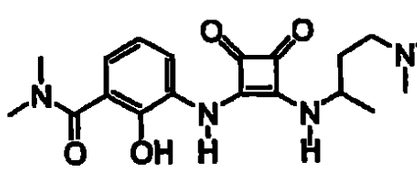


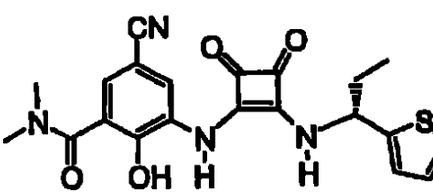


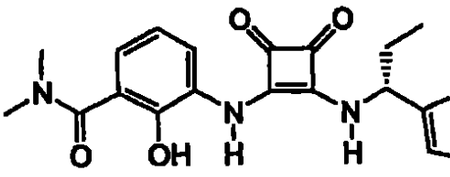


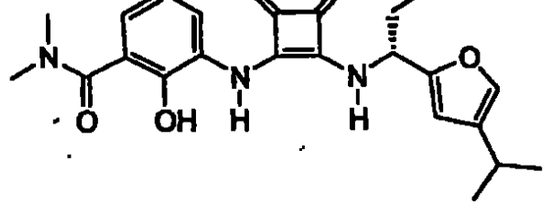


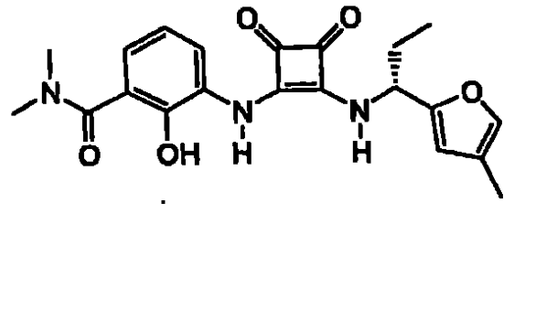


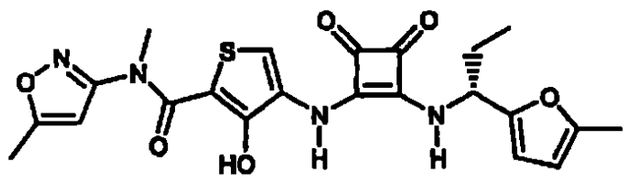


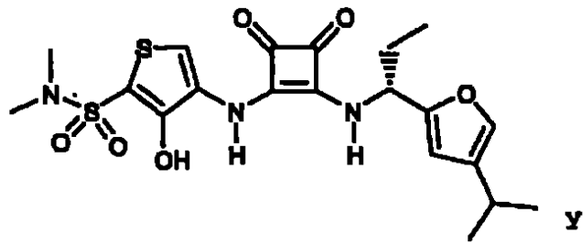




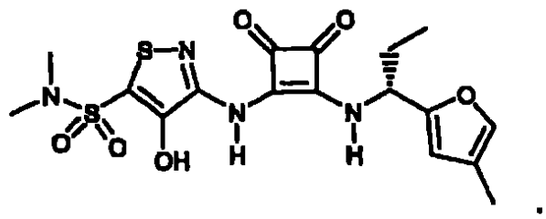






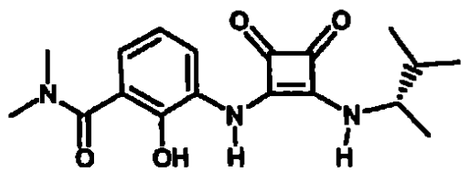


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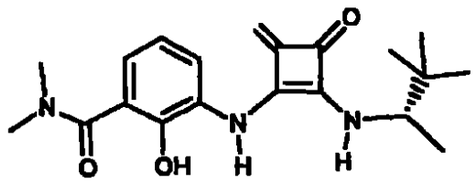
49. El uso de la reivindicación 48 en donde se utiliza una sal de calcio o sodio de los compuestos.

50. El uso de la reivindicación 16 en donde dicho compuesto es:



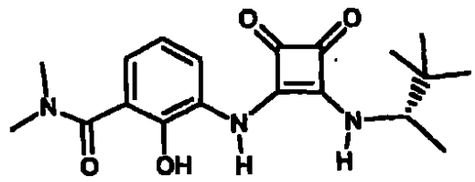
o una sal o solvato farmacéuticamente aceptable del mismo.

51. El uso de la reivindicación 16 en donde dicho compuesto es:



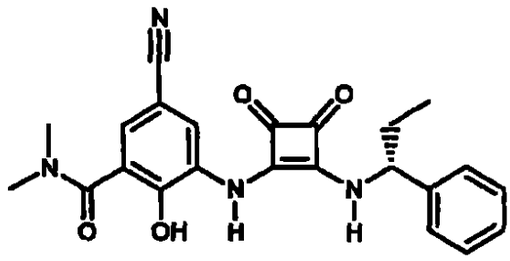
o una sal o solvato farmacéuticamente aceptable del mismo.

52. El uso de la reivindicación 16 en donde dicho compuesto es:



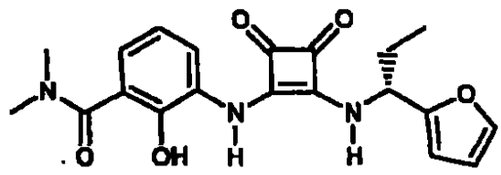
o una sal o solvato farmacéuticamente aceptable del mismo.

53. El uso de la reivindicación 16 en donde dicho compuesto es:



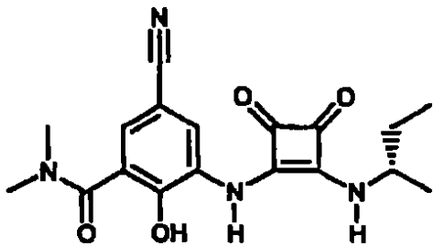
o una sal o solvato farmacéuticamente aceptable del mismo.

54. El uso de la reivindicación 16 en donde dicho compuesto es:



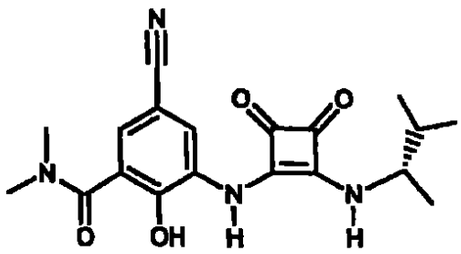
o una sal o solvato farmacéuticamente aceptable del mismo.

55. El uso de la reivindicación 16 en donde dicho compuesto es:



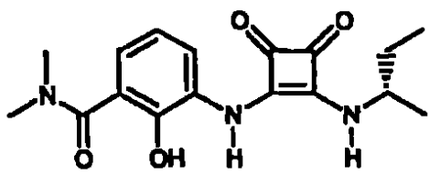
o una sal o solvato farmacéuticamente aceptable del mismo.

56. El uso de la reivindicación 16 en donde dicho compuesto es:



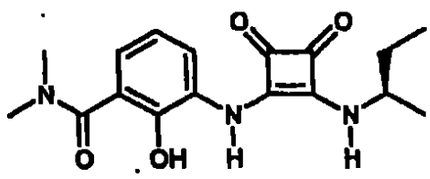
o una sal o solvato farmacéuticamente aceptable del mismo.

57. El uso de la reivindicación 16 en donde dicho compuesto es:



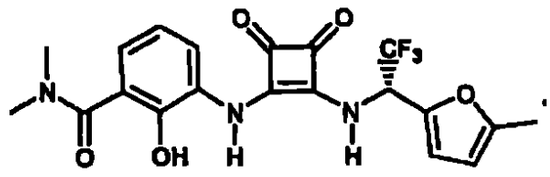
o una sal o solvato farmacéuticamente aceptable del mismo.

58. El uso de la reivindicación 16 en donde dicho compuesto es:



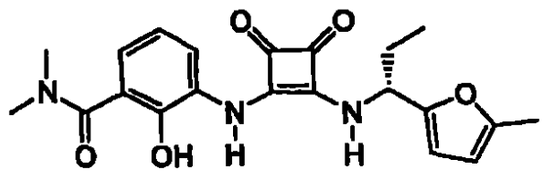
o una sal o solvato farmacéuticamente aceptable del mismo.

59. El uso de la reivindicación 16 en donde dicho compuesto es:



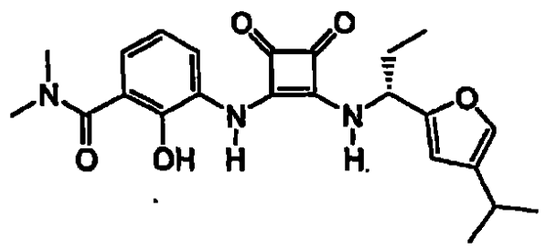
o una sal o solvato farmacéuticamente aceptable del mismo.

60. El uso de la reivindicación 16 en donde dicho compuesto es:



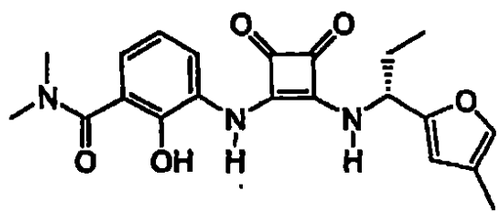
o una sal o solvato farmacéuticamente aceptable del mismo.

61. El uso de la reivindicación 16 en donde dicho compuesto es:



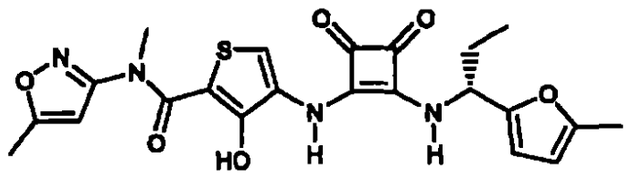
o una sal o solvato farmacéuticamente aceptable del mismo.

62. El uso de la reivindicación 16 en donde dicho compuesto es:



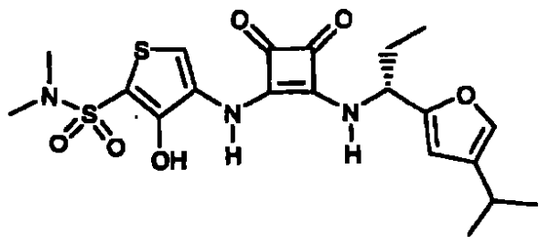
o una sal o solvato farmacéuticamente aceptable del mismo.

63. El uso de la reivindicación 16 en donde dicho compuesto es:



o una sal o solvato farmacéuticamente aceptable del mismo.

64. El uso de la reivindicación 16 en donde dicho compuesto es:



o una sal o solvato farmacéuticamente aceptable del mismo.

65. El uso de cualquiera de las reivindicaciones 50 a 64 en donde se utiliza una sal de calcio o sodio de dicho compuesto.

66. Un uso de al menos un compuesto de cualquiera de las reivindicaciones 1 a 13 para fabricar un medicamento para tratar una enfermedad mediada por quimiocina, en donde la quimiocina se liga a un receptor CXCR2 y/o CXCR1 en un paciente.

67. Un uso de al menos un compuesto de cualquiera de las reivindicaciones 1 a 13 para fabricar un medicamento para tratar una enfermedad mediada por quimiocina, en donde la quimiocina se liga a un receptor CXC en un paciente.

68. El uso de la reivindicación 66 en donde la enfermedad mediada por quimiocina es seleccionada del grupo que consiste de: inflamación crónica, dolor inflamatorio agudo, dolor inflamatorio crónico, dolor neuropático agudo, dolor neuropático crónico. psoriasis. dermatitis atópica. asma, COPD (enfermedad de obstrucción pulmonar crónica), enfermedad respiratoria del adulto, enfermedad del intestino inflamatoria, enfermedad de Crohn, colitis ulcerativa, choque séptico, choque endotóxico,

sepsia gram negativa, síndrome del choque tóxico, apoplejía, daño por reperfusión cardiaca y renal, glomerulonefritis, trombosis, enfermedad de Alzheimer, reacción injerto vs. huésped, rechazos aloinjertos, malaria, síndrome disneico agudo, reacción de hipersensibilidad del tipo retardada, aterosclerosis, isquemia cardiaca y cerebral, osteoartritis, esclerosis múltiple, restinosis, angiogénesis, osteoporosis, gingivitis, virus respiratorio, virus herpes, virus de la hepatitis, HIV, virus asociado con el sarcoma de Kaposi, meningitis, fibrosis cística, trabajo de pre-parto, tos, prurito, disfunción multiorgánica, trauma, torceduras, luxaciones, contusiones, artritis psoriática, herpes, encefalitis, vasculitis SNC, daño cerebral traumático, tumores en el SNC, hemorragia subaracnoidea, trauma pos quirúrgico, pneumonitis intersticial, hipersensibilidad, artritis inducida por cristal, pancreatitis aguda y crónica, hepatitis alcohólica aguda, enterocolitis necrotizante, sinusitis crónica, enfermedad ocular angiogénica, inflamación ocular, retinopatía del prematuro, retinopatía diabética, degeneración macular siendo el tipo húmedo preferido y neovascularización córneal, polimiositis, vasculitis, acné, úlceras gástricas y duodenales, enfermedad celíaca, esofagitis, glositis, obstrucción de vías respiratorias, hipersensibilidad de las vías respiratorias, bronquiectasis, bronquiolitis, bronquiolitis obliterans, bronquitis crónica, cor pulmonale, tos, disnea, enfisema, hipercapnea, hiperinflación, hipoxemia, inflamaciones inducidas por hiperoxia, hipoxia, reducción de volumen del pulmón quirúrgica, fibrosis pulmonar, hipertensión pulmonar, hipertrofia ventricular derecha, peritonitis asociada con la diálisis peritoneal ambulatoria continua (CAPD), erliquiosis granulocítica, sacoidosis, enfermedad de la vía respiratoria menor, desequilibrio de ventilación-perfusión, respiración sibilante, resfríos, gota, enfermedad del hígado por alcohol, lupus, tratamiento de quemaduras, periodontitis, daño de reperfusión de transplante y rechazo de transplante temprano.

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69. Un uso de al menos un compuesto de cualquiera de las reivindicaciones 1 a 13 para la fabricación de un medicamento para tratar cáncer.

70. Un uso de al menos un compuesto de cualquiera de las reivindicaciones 1 a 13 para la fabricación de un medicamento para tratar cáncer, el tratamiento comprende administrar dicho medicamento en combinación con la administración de al menos un agente anticancerígeno.

71. El uso de la reivindicación 70 en donde dicho agente anticancerígeno es seleccionado del grupo que consiste de: agentes alquilantes, antimetabolitos, productos naturales y sus derivados, hormonas, anti-hormonas, agentes anti-angiogénicos y esteroides, y sintéticos.

72. Un uso de al menos un compuesto de cualquiera de las reivindicaciones 1 a 13 para la fabricación de un medicamento para inhibir la angiogenesis.

73. Un uso de al menos un compuesto de cualquiera de las reivindicaciones 1 a 13 para la fabricación de un medicamento para inhibir la angiogenesis, la inhibición comprende administrar dicho medicamento en combinación con la administración de al menos un compuesto anti-angiogénesis.

74. Un uso de al menos un compuesto de cualquiera de las reivindicaciones 1 a 13 para la fabricación de un medicamento para tratar una enfermedad seleccionado del grupo que consiste de: gingivitis, virus respiratorio, virus herpes, virus de la hepatitis, HIV, virus asociado con el sarcoma de Kaposi y aterosclerosis.

75. El uso de la reivindicación 66 en donde la enfermedad mediada por quimiocina es una enfermedad ocular angiogénica.

76. El uso de la reivindicación 75 en donde dicha enfermedad ocular angiogénica es seleccionada del grupo que consiste de: inflamación ocular, retinopatía del prematuro, retinopatía diabética, degeneración macular del tipo

húmedo y neovascularización córneal.

77. El uso de la reivindicación 69 en donde el cáncer tratado es melanoma, carcinoma gástrico, o carcinoma de pulmón de células no-pequeñas.

78. El uso de la reivindicación 70 en donde el cáncer tratado es melanoma, carcinoma gástrico, o carcinoma de pulmón de células no-pequeñas.

79. El uso de la reivindicación 71, en donde el cáncer tratado es melanoma, carcinoma gástrico, o carcinoma de pulmón de células no-pequeñas.

80. Un uso de al menos un compuesto de cualquiera de las reivindicaciones 1 a 13 para la fabricación de un medicamento para tratar dolor inflamatorio agudo.

81. Un uso de al menos un compuesto de cualquiera de las reivindicaciones 1 a 13 para la fabricación de un medicamento para tratar dolor inflamatorio crónico.

82. Un uso de al menos un compuesto de cualquiera de las reivindicaciones 1 a 13 para la fabricación de un medicamento para tratar dolor neuropático agudo.

83. Un uso de al menos un compuesto de cualquiera de las reivindicaciones 1 a 13 para la fabricación de un medicamento para tratar dolor neuropático crónico.

84. Un uso de al menos un compuesto de cualquiera de las reivindicaciones 1 a 13 para la fabricación de un medicamento para tratar COPD (enfermedad de obstrucción pulmonar crónica).

85. El uso de la reivindicación 16 en donde dicha enfermedad es dolor inflamatorio agudo.

86. El uso de la reivindicación 16 en donde dicha enfermedad es dolor inflamatorio crónico.

87. El uso de la reivindicación 16 en donde dicha enfermedad es dolor

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neuropático agudo.

88. El uso de la reivindicación 16 en donde dicha enfermedad es dolor neuropático crónico.

89. El uso de la reivindicación 16 en donde dicha enfermedad es inflamación aguda.

90. El uso de la reivindicación 16 en donde dicha enfermedad es artritis reumatoide.

91. El uso de cualquiera de las reivindicaciones 48 a 64 en donde dicha enfermedad es inflamación aguda.

92. El uso de cualquiera de las reivindicaciones 48 a 64 en donde dicha enfermedad es artritis reumatoide.

93. El uso de la reivindicación 91 en donde el medicamento es elaborado a partir de una sal de calcio o sodio del compuesto.

94. El uso de la reivindicación 92 en donde el medicamento es elaborado a partir de una sal de calcio o sodio del compuesto.

95. Un compuesto seleccionado del grupo formado por los compuestos finales de los ejemplos 2006, 2010, 2015, 2029, 2034, 2035, 2038, 2039, 2047, 2050, 2074, 2079 y 2087.

96. El compuesto de la reivindicación 95 en donde el compuesto es una sal de calcio o sodio del compuesto.

97. Una composición farmacéutica que comprende una cantidad efectiva de por lo menos un compuesto de cualquiera de las reivindicaciones 95 a 96 y un portador farmacéuticamente aceptable.

98. Un uso de por lo menos un compuesto de cualquiera de las reivindicaciones 1 a 13, 95 y 96 para la elaboración de un medicamento para el tratamiento de dolor inflamatorio agudo.

99. Un uso de por lo menos un compuesto de cualquiera de las

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reivindicaciones 1 a 13, 95 y 96 para la elaboración de un medicamento para el tratamiento de artritis reumatoide.

100. Un uso de por lo menos un compuesto de cualquiera de las reivindicaciones 95 y 96 para la elaboración de un medicamento para el tratamiento de COPD.

101. Un uso de por lo menos un compuesto de cualquiera de las reivindicaciones 95 y 96 para la elaboración de un medicamento para el tratamiento de dolor inflamatorio agudo.

102. Un uso de por lo menos un compuesto de cualquiera de las reivindicaciones 95 y 96 para la elaboración de un medicamento para el tratamiento de dolor inflamatorio crónico.

103. Un uso de por lo menos un compuesto de cualquiera de las reivindicaciones 95 y 96 para la elaboración de un medicamento para el tratamiento de dolor neuropático agudo.

104. Un uso de por lo menos un compuesto de cualquiera de las reivindicaciones 95 y 96 para la elaboración de un medicamento para el tratamiento de dolor neuropático crónico.

105. Un uso de por lo menos un compuesto de cualquiera de las reivindicaciones 1 a 13, 95 y 96 para la elaboración de un medicamento para el tratamiento de la inflamación crónica.

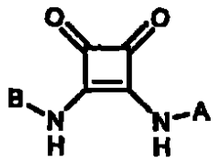
106. Un uso de por lo menos un compuesto de cualquiera de las reivindicaciones 16 y 48 a 64 y 96 para la elaboración de un medicamento para el tratamiento de la inflamación crónica.

p. SCHERING CORPORATION * PHARMACOPEIA, INC.

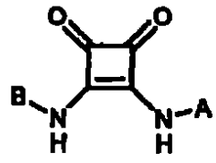
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RESUMEN

Se revelan nuevos compuestos de la fórmula:



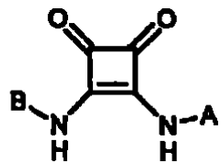
o una sal o solvato farmacéuticamente aceptable de los mismos. Además se revela el tratamiento de las enfermedades mediadas por quimiocina utilizando los compuestos de la fórmula:



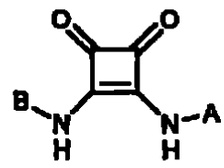
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RESUMEN

Se revelan nuevos compuestos de la fórmula:



o una sal o solvato farmacéuticamente aceptable de los mismos. Además se revela el tratamiento de las enfermedades mediadas por quimiocina utilizando los compuestos de la fórmula:



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)
OC01406K7RFD		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US03/23785	30/07/2003	30/07/2002
International Patent Classification (IPC) or national classification and IPC		
C07C237/36		
Applicant		
SCHERING CORPORATION		

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
20/02/2004	26/05/2004
Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	GELLIE B R Tel. (+49-89) 2399 2828

Form PCT/IPEA/409 (cover sheet) P20476 (October 2002)

I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 03/23785

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C237/36 C07C237/44 C07C311/39 C07D207/323 C07D217/24
C07D307/52 C07D307/68 C07D307/81 C07D307/82 C07D307/83
C07D317/46 C07D319/18 C07D333/20 C07D405/12 C07D409/12

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 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02 083624 A (SCHERING CORP ;PHARMACOPEIA INC (US)) 24 October 2002 (2002-10-24) cited in the application page 61; claims; example 360.63	1-107
Y	WO 01 92202 A (SMITHKLINE BEECHAM CORP ;WIDDOWSON KATHERINE L (US); BI GUANGPING) 6 December 2001 (2001-12-06) page 16, line 2 -page 17, line 18; claims	1-107
Y	WO 01 68569 A (SMITHKLINE BEECHAM CORP ;WIDDOWSON KATHERINE L (US); JIN QI (US)) 20 September 2001 (2001-09-20) page 19, line 20 -page 21, line 6; claims 1,14-16	1-107

-/--

[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
4 November 2003	17/11/2003

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	Hanisch, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/23785

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

☐ Further documents are listed in the continuation of box C.

☒ 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

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"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
4 November 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	Hanisch, I

Form PCT/ISA/210 (second sheet) (July 1992)

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451

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 solicitante 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:

Fecha:

SUPERINDUSTRIA Y COMERCIO
Radicacion : 05007006 00000000 Folios: 450
Fecha (AMD): 2005-01-28 10:12:17
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

454

Industria y Comercio
SUPERINTENDENCIA

Folio 452

2020
Bogotá, D.C.,

Doctor
CARLOS R. OLARTE

Oficio N° 12459

ASUNTO:	Radicación N°	05-7006
	Solicitud internacional	PCT/US2003/0023785
	Fecha inicio fase nacional	28/02/2005
	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:

- Debe aclarar el número de reivindicaciones por cuanto en la solicitud internacional figuran 107 y la solicitud en fase nacional contiene únicamente 106.

- Debe allegar el documento que acredita la existencia y representación de la sociedad Pharmacopeia Drug Discovery, Inc.

- La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486/00.

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 N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha, 01 ABR 2005.

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5, 7 y 10
Sede CAN: Tr. 40A No. 38-50 Conmutador: 3820840
Fax: 382 26 95. Línea 9800-910 165
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. - Colombia

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