CSA716747
Organizacion y Digitalizacion CSA Ltda

Industria y Comercio

SUPERINTENDENCIA

1/47

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

Delegatura de Propiedad Industrial

División de Nuevas Creciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

09-20345

21. **EXPEDIENTE No.**

54. **TÍTULO** MODULADORES DEL RECEPTOR GLUCOCORTICOIDE Y/O DE AP-1 Y/O DE LA ACTIVIDAD DE NF-KB Y SU USO

51. **CLASIFICACIÓN INTERNACIONAL** C07D 277/46 C07D 405/12

71. **SOLICITANTE** BRISTOL MYERS SQUIBB COMPANY

DOMICILIO NEW JERSEY USA

74. **APODERADO** ÁLVARO CORREA ORDOÑEZ

22. **BOGOTÁ, D. C.** 27 DE FEBRERO DE 2009

(FORMA P-10)

09-03-2009

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-020345- -00000-0000
Fecha: 2009-02-27 16:43:35 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 869

FORMULARIO ÚNICO DE SO
PCT
ENTRADA EN FASE NACIONAL

1 SOLICITUD DE :

[X] Patente de Invención
[X] Capítulo I.

[ ] Patente de Modelo de Utilidad
[ ] Capítulo II.

2 SOLICITANTE (71)

Nombre: **BRISTOL-MYERS SQUIBB COMPANY**

Dirección: Route 206 and Province Line Road, Princeton, New Jersey 08543-4000, Estados Unidos de América

Nacionalidad o Domicilio: Estados Unidos de América

Lugar de Constitución: Estados Unidos de América

Teléfono: Fax:

E-Mail

IDENTIFICACION

C.C. [ ] NIT [ ]

C.E. [ ] Otro [ ]

Cual

Número

3 REPRESENTANTE O APODERADO

Nombre: ALVARO CORREA ORDOÑEZ

Dirección: Avenida 82 No. 10-62 Piso 6

Teléfono: 6341500 Fax: 3762211

E-Mail: office.bogota@bakernet.com

IDENTIFICACION

C.C. [X] NIT [ ]

C.E. [ ] Otro [ ]

Cual

Número 79.143.366 Usaquén TP 28281

4 INVENTOR (ES) (72)

Nombre: WEINSTEIN, David, S; GONG, Hua; DUAN, Jingwu; DHAR, T.G. Murali; YANG, Bingwei Vera; CHEN, Ping; JiANG, Bin;

Dirección: c/o Bristol-Myers Squibb Company, Route 206 and Province Line Road, Princeton, New Jersey 08543-4000, Estados Unidos de América; c/o Bristol-Myers Squibb Company, Route 206 and Province Line Road, Princeton, New Jersey 08543-4000, Estados Unidos de América; c/o Bristol-Myers Squibb Company, Route 206 and Province Line Road, Princeton, New Jersey 08543-4000, Estados Unidos de América; c/o Bristol-Myers Squibb Company, Route 206 and Province Line Road, Princeton, New Jersey 08543-4000, Estados Unidos de América; c/o Bristol-Myers Squibb Company, Route 206 and Province Line Road, Princeton, New Jersey 08543-4000, Estados Unidos de América; c/o Bristol-Myers Squibb Company, Route 206 and Province Line Road, Princeton, New Jersey 08543-4000, Estados Unidos de América;

Nacionalidad o Domicilio: Estados Unidos de América

5 PCT (85)

Solicitud Internacional No. PCT/US2007/075543 Fecha 09.08.2007

Publicación Internacional No. WO/2008/021926 Fecha 21.02.2008

6 Título (54) MODULADORES DEL RECEPTOR GLUCOCORTICOIDE, Y/O DE AP-1, Y/O DE LA ACTIVIDAD DE NF-κB Y SU USO

7 Clasificación Internacional (51) C07D 277/46; C07D 405/12; C07D 417/12; C07D 417/14 ; C07D 491/04

8 Prioridad

SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	09.08.2006	60/836,496
US	08.08.2007	11/835,438

9 Comprobante de pago No.

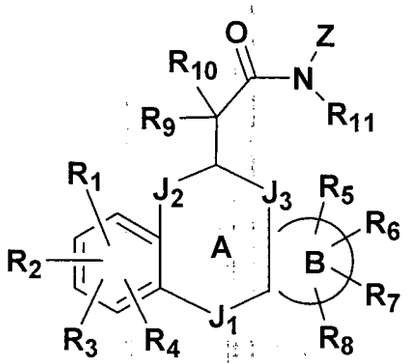
	Fecha
09-5,903	ENE-26-2009
09-5,850	ENE-26-2009
08-100,489	DIC-26-2008
08-100,490	DIC-26-2008
08-100,240	DIC-26-2008
08-100,332	DIC-26-2008

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

(10) **ANEXOS**

- [X] Comprobante de pago de la tasa de presentación de la solicitud
- [X] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- [X] Poderes, si fuere el caso (ver radicado No. 08.129.339 del 04-DIC-08 Poder General de Bristol-Myers Squibb Company)
- [x] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [X] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [X] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- [ ] De ser el caso, certificado de depósito del material biológico
- [X] 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 está solicitud
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional..
- [X] Otros: Extractos

(11) **FIGURA CARATERISTICA**



I

(12) Solicito la concesión de la patente.

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA:

C.C. 79.143.366 de Usaquén T.P. 20.284

Instrucciones para la presentación de los anexos, ver reverso de esta página

TRADUCCIÓN OFICIAL Nº 108/2009 de un documento escrito en inglés el cual para su identificación se sella con el sello del traductor. Esta es una traducción oficial efectuada el día 16 de febrero de 2009 por la señora Teresa Jiménez de Montes, con cc 41.569.149 de Bogotá, traductora oficial según Resolución Nº 220 del 6 de febrero de 1978, expedida por el Ministerio de Justicia de la República de Colombia

==========

60/836,496 – 10367

CERTIFICACIÓN NOTARIAL

Yo, Maura O. Knobl, Notaria Pública, Oficina de Patentes, Bristol-Myers Squibb Company, certifico que este documento es una copia fiel y exacta de las cesión original firmada por los inventores.

Estado de New Jersey)
) suscrito y jurado
Condado de Mercer)

Fecha **29 de enero de 2009**

Firmado, **Maura O. Knobl**
MAURA O. KNOBL

[SELLO]
MAURA O. KNOBL
Notaria Pública de New Jersey
Mi comisión vence el 23 de julio de 2013

Mundial
Caso 10367 (PSP)

CESIÓN

Nosotros,		
David S. Weinstein	Residente en	10 Inverness Lane East Windsor, New Jersey 08520 Estados Unidos de América
Ping Chen	Residente en	21 Derby Chase Court Belle Mead, New Jersey 08502 Estados Unidos de América
Hua Gong	Residente en	2000 Veterans Highway Apt. E12 Levittown Pennsylvania 19056 Estados Unidos de América
Bingwei Vera Yang	Residente en	15 Regents Court Belle Mead, New Jersey 08502 Estados Unidos de América

TERESA J. DE MONTES
TRADUCTORA OFICIAL
RES. 220 MIN. JUSTICIA

De acuerdo con las obligaciones contractuales asumidas hasta ahora por nosotros y/o a cambio de una contraprestación válida y efectiva cuyo recibo y suficiencia se acusan por el presente documento, mediante el presente vendemos y cedemos a **Bristol-Myers Squibb Company**, una sociedad de Delaware, con domicilio de negocios en Lawrenceville-Princeton Road, Princeton, NJ 08543-4000, a sus sucesores, causahabientes y representantes legales, la totalidad de nuestros derechos, títulos y participación los cuales incluyen el derecho y el beneficio total sobre las prioridades que puedan otorgarse ahora o en el futuro, a nosotros, por las leyes locales o por tratado, incluida la convención internacional para la protección de propiedad industrial en y para todos los países del mundo incluidos los Estados Unidos y sus territorios y posesiones, en y sobre la invención titulada:

MODULADORES DE RECEPTOR DE GLUCOCORTICOIDE, ACTIVIDAD AP-1, Y/O NF-kB Y USO DE LOS MISMOS

Inventado por nosotros y descritos en la solicitud de patente provisional de los Estados Unidos

Solicitud No. 60/836,496, presentada 9 de agosto, 2006

Incluyendo la citada solicitud de patente provisional de los Estados Unidos y cualquier solicitud que reclame antigüedad de la citada solicitud provisional presentada en cualquier país y con respecto a cualquier patente que pueda ser emitida y/u otorgada con respecto a la misma y todas las divisiones, continuaciones, reexpediciones, certificados de re-examen, y extensiones de las mismas en todos los países, cuya participación constituye la propiedad total sobre dicha invención y sobre todas las citadas solicitudes, patentes (incluyendo reemisión de patentes) extensiones, y certificados de re-examen pertenecerán y serán disfrutados por Bristol-Myers Squibb Company y sus sucesores y causahabientes hasta el máximo de los términos para los cuales esas patentes (incluidas las reexpediciones de patentes), certificados de extensión y de re-examen puedan otorgarse y/o emitirse en su totalidad como si los mismos hubieren sido mantenidos y disfrutadas por nosotros, si esta venta, cesión y transferencia no se hubiere realizado;

Y por el presente aceptamos que se le comunique al citado cesionario o a su representante sobre cualquier hecho del que tengamos conocimiento con respecto a dicha invención, a dar testimonio en cualquier proceso legal, a firmar y/o suscribir cualquier otro documento adicional y/o instrumento que pueda ser necesario, legítimo y adecuado para la presentación y/o proceso judicial de todas las solicitudes, incluyendo solicitudes divisionales, de continuación y de reemisión, certificados de extensiones y reexamen y/o el otorgamiento y/o extensión de los mismos y/o de otra manera garantizar el título de dicha invención y de todas las solicitudes, patentes (incluidas las re-emisiones de patentes, certificados de extensiones y reexamen de las mismas, en dicho cesionario y en general, a revisar todos los actos que sean necesarios para colaborar con el cesionario, sus sucesores y causahabientes para obtener y hacer cumplir la adecuada protección de dicha invención en todos los países.

Firmado el 20 de septiembre de 2006 por [Firma ilegible]
David S. Weinstein

TERESA J. DE MONTES
TRADUCTORA OFICIAL
RES. 220 MINJUSTICIA

ESTADO DE NEW JERSEY)
) suscrito y jurado
CONDADO DE MERCER)

Hoy 20 de septiembre de 2006, compareció ante mí David S. Weinstein, a quien conozco como la persona mencionada y quien firmó la cesión que antecede y reconoció ante mí su firma.

Firmado [ilegible]
Notario Público

[SELLO]
DEBRA A. WOJCIK
NOTARIA PÚBLICA DE NEW JERSEY
Mi comisión vence mayo 30, 2008

Mundial
Caso 10367 (PSP)

Firmado hoy 14 de septiembre de 2006, por [Firma ilegible]
Ping Chen

Estado de New Jersey)
) suscrito y jurado
Condado de Mercer)

Hoy 14 de septiembre de 2006, compareció ante mí Ping Chen a quien conozco como la persona mencionada y quien firmó la cesión que antecede y reconoció ante mí su firma.

Firmado, Lisa B. Swidra
Notaria Pública

[SELLO]
LISA B. SWIDRA
Notaria Pública, Estado de New Jersey
Vencimiento comisión abril 22, 2009

Firmado el 8 de septiembre de 2006, por [firma ilegible]
Hua Gong

Estado de New Jersey)
) suscrito y jurado
Condado de Mercer)

Hoy 8 de septiembre de 2006, compareció ante mí Hua Gong a quien conozco como la persona mencionada y quien firmó la cesión anterior y reconoció ante mí su firma.

Firmado, Lisa B. Swidra
Notaria Pública

[SELLO]
LISA B. SWIDRA

TERESA J. DE MONTES
TRADUCTORA OFICIAL
RES. 220 MINJUSTICIA

Notaria Pública, Estado de New Jersey
Vencimiento comisión abril 22, 2009

Firmado el 24 de septiembre de 2006, por [Firma ilegible]
Bingwei Vera Yang

Estado de New Jersey)
) suscrito y jurado
Condado de Mercer)

Hoy 28 de septiembre de 2006, compareció ante mí Bingwei Vera Yang a quien conozco como la persona mencionada y quien firmó la cesión anterior y reconoció ante mí su firma.

Firmado, Lisa B. Swidra
Notaria Pública

[SELLO]
LISA B. SWIDRA
Notaria Pública, Estado de New Jersey
Vencimiento comisión abril 22, 2009

10367 - US - (PSP)
Rodney

Oficina Patentes y Marcas Registradas de los Estados Unidos
UNITED STATES DEPARTMENT OF COMMERCE
Oficina de Patentes y Marcas Registradas de los Estados Unidos
Dirección: COMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria Virginia 22313-1450
www.uspto.gov

Solicitud No.	Fecha de solicitud o 371(c)	Art Unit	Derechos solicitud pagados	Expediente del apoderado No.	Dibujos	Total reivindicaciones	Reivindicaciones IND
60/836,496	08/09/2006		950	10367 (PSP)			

CONFIRMACIÓN No. 5918
RECIBO DE PRESENTACIÓN DE LA SOLICITUD CORREGIDO
Código de Barras
OC000000020434463*

23914
LOUIS J. WILLE
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P.O. BOX 4000
PRINCETON, NJ 08543-4000

Fecha de envío por correo: 09/14/2006

Se acusa recibo de esta solicitud provisional de patente. No se examinará para patentabilidad y quedará abandonada a más tardar doce meses después de su fecha de presentación. Asegúrese de suministrar el NÚMERO, FECHA DE PRESENTACIÓN, NOMBRE DEL SOLICITANTE Y TÍTULO DE LA INVENCIÓN DE

TERESA J. DE MONTES
TRADUCTORA OFICIAL
RES. 220 MINJUSTICIA

LA SOLICITUD U.S. al hacer preguntas sobre su solicitud. Los derechos enviados por cheque o giro están sujetos a cobro. Por favor, verifique la exactitud de la información presentada en este recibo. **Si se observa un error en este Recibo de Presentación de la solicitud, por favor envíe un correo al Comisionado de Patentas a P.O. Box 1450 Alexandria Va 22313-1450. Por favor, envíe una copia de este recibo de presentación con los cambios anotados. Si usted recibió un "Aviso para diligenciar partes que faltan" en esta solicitud, por favor presente cualquier corrección a este Recibo de Presentación con su respuesta a la notificación. Cuando la USPTO procesa la respuesta a la notificación, la USPTO expedirá otro Recibo de Presentación incluyendo las correcciones solicitadas (si es apropiado.**

Solicitante(s)

David S. Weinstein, East Windsor, NJ;
Ping Chen, Belle Mead, NJ;
Hua Gong, Levittown, PA;
Bingwei Vera Yang, Belle Mead, NJ;

RECIBIDO
LEY DE PATENTES BMS
Septiembre 19 de 2006
Docketed Item CFR
Fecha Vencimiento
Abogado BR

Poder:
Burton Rodney – 22076

Si se requiere, Licencia para presentación en el exterior otorgada: 08/21/2006

El código y número del país de su solicitud de prioridad que se utilizará para la presentación en el exterior, de acuerdo con la Convención de París es: **US60/836,496**

Fecha proyectada de la publicación: Ninguna, la solicitud no cumple los requisitos para publicación pre-otorgamiento.

Solicitud de no publicación: No aplicable

Solicitud de publicación anticipada: No aplicable.

Título:
Moduladores del receptor de glucocorticoides, Actividad de AP-1 y/o de NF-kB y uso de los mismos

PROTECCIÓN DE SU INVENCIÓN FUERA DE LOS ESTADOS UNIDOS

Dado que los derechos que otorga una patente US. se extienden sólo en el territorio de los Estados Unidos y no tienen efecto en un país del exterior, un inventor que desee proteger la patente en otro país debe solicitar una patente en un país específico o en las oficinas regionales de patentes. Es posible que los solicitantes deseen considerar presentar una solicitud internacional de acuerdo con el Tratado de Cooperación de Patentes (PCT). Una solicitud PCT generalmente tiene el mismo efecto que una solicitud de patente nacional en cada país miembro de PCT. El proceso PCT **simplifica** la presentación de solicitudes de patente sobre la misma

TERESA J. [illegible]
TRADUCTORA OFICIAL
RES 220 MINJUSTICIA

invención en los países miembros pero no resulta en el otorgamiento de una patente internacional y no elimina la necesidad de que los solicitantes presenten documentos adicionales y paguen derechos en países donde se desea la protección de la patente.

Casi todos los países tienen sus propias leyes de patentes y una persona que desea una patente en un país específico debe presentar una solicitud para la patente en ese país conforme a esas leyes específicas. Dado que las leyes de muchos países difieren en diversos aspectos de la ley de patentes de los Estados Unidos, se recomienda a los solicitantes buscar orientación en los países específicos del exterior para garantizar que los derechos a la patente no se pierdan prematuramente.

También se les informa a los solicitantes que en el caso de las invenciones hechas en los Estados Unidos el director de la USPTO debe expedir una licencia antes que los solicitantes puedan solicitar una patente en un país del exterior. La presentación de una solicitud de patente U.S. sirve como solicitud de una licencia para presentación de la solicitud en el exterior. El recibo de presentación de la solicitud contiene información adicional e información con respecto al estado de la licencia del solicitante para solicitud en el exterior.

Es posible que los solicitantes deseen consultar el folleto USPTO "Información general concerniente a las patentes" (específicamente, la sección titulada "Tratados y Patentes del Exterior") para más información sobre los marcos de tiempo y fechas límite para presentación de solicitudes de patentes en el exterior. La guía está disponible contactando al centro de contacto USPTO en 800-786-9199, o puede consultarse en el sitio de internet de USPTO en: http://www.uspto.gov/web/offices/pac/doc /general/index.html.

Para información sobre cómo prevenir el robo de su propiedad intelectual (patentes, marcas registradas y derechos de autor) usted puede consultar el sitio de internet del Gobierno de los Estados Unidos: http://www.stopfakes.gov. Parte de una iniciativa del Departamento de Comercio este sitio de internet incluye "herramientas" de autoayuda que les dan a los inventores orientación sobre cómo proteger la propiedad intelectual en casos específicos tales como China, Corea y México. Para preguntas sobre cómo proteger las patentes, los solicitantes pueden llamar a la línea gratuita del gobierno de los Estados Unidos en el teléfono 1-866-999 HALT (1-866-999-4158).

LICENCIA PARA PRESENTACIÓN EN EL EXTERIOR DE ACUERDO CON EL
Título 35, Código de los Estados Unidos, Sección 184
Título 37, Código de Regulaciones Federales, 5.11 & 5.15

OTORGADO

Se le ha otorgado al solicitante una licencia de acuerdo con el Título 35 Código de los Estados Unidos, Sección 184, si la frase "SI SE REQUIERE, SE HA OTORGADO UNA LICENCIA PARA PRESENTACIÓN EN EL EXTERIOR" seguida por una fecha aparece en este formulario. Estas licencias se expiden en todas las solicitudes donde las condiciones para expedición de una licencia se han cumplido, indistintamente si la licencia se requiere como se establece en 37 CFR 5.15. El alcance y limitaciones de esta licencia se estipulan en 37 CFR 5.15(a) a menos que haya sido expedida antes una licencia de acuerdo con 37 CFR 5.15(b). La licencia está sujeta a revocación, previa notificación por escrito. La fecha indicada es la fecha de vigencia de la licencia a menos que se haya otorgado antes una licencia con un alcance similar, de acuerdo con 37 CFR 5.13 o 5.14.

TERESA J. DE MONTES
TRADUCTORA OFICIAL
RES. 220 MINJUSTICIA

Esta licencia debe conservarla el licenciatario y puede ser utilizada en cualquier momento en o después de su fecha de vigencia a menos que será revocada. Esta licencia se transfiere automática a cualquier solicitud o solicitudes presentada(s) de acuerdo con 37 CFR 1.53©. Esta licencia no es retroactiva.

El otorgamiento de una licencia en ninguna forma disminuye la responsabilidad de un licenciatario por la seguridad del asunto objeto según lo señalado en cualquier conTrato con el Gobierno o eb las disposiciones de leyes existentes relacionadas con espionaje y la seguridad nacional o la exportación de información técnica. Los licenciatarios deben informarse sobre las regulaciones vigentes, especialmente con respecto a algunos países, de otras agencias, particularmente la Oficina de Controles Comerciales de Defensa (Office of Defense Trade Controls), Departamento de Estado (con respecto a armas, municiones, implementos de guerra (22 CFR 121-128)); la Oficina de Industria y Seguridad, Departamento de Comercio (15 CFR partes 730-774); la Oficina de Control de Activos del Exterior, Departamento de Tesorería (31 CFR partes 500+) y el Departamento de Energía.

NO OTORGADA

No se ha otorgado ninguna licencia de acuerdo con el Título 35 del Código de los Estados Unidos, Sección 184 en esta fecha, si la frase "SI SE REQUIERE LICENCIA PARA PRESENTACIÓN EN EL EXTERIOR OTORGADA" no aparece en este formulario. El solicitante debe solicitar una licencia de acuerdo con 37 CFR 5.12, si desea una licencia antes del vencimiento de los 6 meses después de la fecha de presentación de la solicitud. Si han transcurrido 6 meses desde la fecha de presentación de esta solicitud y el licenciatario no ha recibido ninguna indicación de una orden de confidencialidad de acuerdo con 35 U.S.C. 181, el licenciatario puede presentar en el exterior la solicitud conforme a 37 CFR 5, 15(b).

10367 NP

CESIÓN

Nosotros,

David S. Weinstein, Ping Chen, T.G. Murali Dhar, Jinwu Duan, Hua Gong, Bin Jiang, Bingwei Vera Yang

De acuerdo con las obligaciones contractuales asumidas hasta ahora por nosotros y/o a cambio de una contraprestación válida y efectiva cuyo recibo y suficiencia se acusan por el presente documento, mediante el presente vendemos y cedemos a **Bristol-Myers Squibb Company**, una sociedad de Delaware, con domicilio de negocios en Rt. 206 & Province Line Road, Princeton Road, Princeton, NJ 08543-4000, a sus sucesores, causahabientes y representantes legales, la totalidad de nuestros derechos, títulos y participación los cuales incluyen el derecho y el beneficio total sobre las prioridades que puedan otorgarse ahora o en el futuro, a nosotros, por las leyes locales o por tratado, incluida la convención internacional para la protección de propiedad industrial en y para todos los países del mundo incluidos los Estados Unidos y sus territorios y posesiones, en y sobre la invención titulada:

MODULADORES DE RECEPTOR DE GLUCOCORTICOIDE, ACTIVIDAD AP-1, Y/O NF-kB Y USO DE LOS MISMOS

TERESA J. DE MONTES
TRADUCTORA OFICIAL
RES. 220 MINJUSTICIA

Inventado por nosotros y descritos en la solicitud de patente no provisional de los Estados Unidos

Solicitud No. 11/835,438, presentada 8 de agosto, 2007

Incluyendo la citada solicitud de patente no provisional de los Estados Unidos y cualquier solicitud que reclame antigüedad de la citada solicitud no provisional presentada en cualquier país y con respecto a cualquier patente que pueda ser emitida y/u otorgada con respecto a la misma y todas las divisiones, continuaciones, reexpediciones, certificados de re-examen, y extensiones de las mismas en todos los países, cuya participación constituye la propiedad total sobre dicha invención y sobre todas las citadas solicitudes, patentes (incluyendo reemisión de patentes) extensiones, y certificados de re-examen pertenecerán y serán disfrutados por Bristol-Myers Squibb Company y sus sucesores y causahabientes hasta el máximo de los términos para los cuales esas patentes (incluidas las reexpediciones de patentes), certificados de extensión y de re-examen puedan otorgarse y/o emitirse en su totalidad como si los mismos hubieren sido mantenidos y disfrutadas por nosotros, si esta venta, cesión y transferencia no se hubiere realizado;

Y por el presente aceptamos comunicar al mencionado cesionario o a su representante sobre cualquier hecho del que tengamos conocimiento con respecto a dicha invención, a dar testimonio en cualquier proceso legal, a firmar y/o suscribir cualquier otro documento adicional y/o instrumento que pueda ser necesario, legítimo y adecuado para la presentación y/o proceso judicial de todas las solicitudes, incluyendo solicitudes divisionales, de continuación y de reemisión, certificados de extensiones y reexamen y/o el otorgamiento y/o extensión de los mismos y/o de otra manera garantizar el título de dicha invención y de todas las solicitudes, patentes (incluidas las re-emisiones de patentes, certificados de extensiones y reexamen de las mismas, en dicho cesionario y en general, a revisar todos los actos que sean necesarios para colaborar con el cesionario, sus sucesores y causahabientes para obtener y hacer cumplir la adecuada protección de dicha invención en todos los países.

Firmado el 10 de agosto de 2007 por [Firma ilegible]
David S. Weinstein

Estado de New Jersey)
) suscrito y jurado
Condado de Somerset)

Hoy 10 de agosto de 2007, compareció ante mí David S. Weinstein, a quien conozco como la persona mencionada y quien firmó la cesión que antecede y reconoció ante mí su firma.

Firmado Dawnet Bragg
Notaria Público

[SELLO]
DAWNET BRAGG
NOTARIA PÚBLICA DE NEW JERSEY
Mi comisión vence septiembre 22, 2009

10367 NP
TERESA J. DE MONTES
TRADUCTORA OFICIAL
RES. 220 MINJUSTICIA

Firmado hoy 13 de agosto de 2007, por [Firma ilegible]
Ping Chen

Estado de New Jersey)
) suscrito y jurado
Condado de Somerset)

Hoy 13 de septiembre de 2007, compareció ante mí Ping Chen a quien conozco como la persona mencionada y quien firmó la cesión que antecede y reconoció ante mí su firma.

Firmado, Dawnet Bragg
Notaria Pública

[SELLO]
DAWNET BRAGG
Notaria Pública, Estado de New Jersey
Vencimiento comisión septiembre 22, 2009

10367 NP

Firmado el 13 de agosto de 2007 por T.G. Murali Dhar
T.G. Murali Dhar

Estado de New Jersey)
)
Condado de Somerset)

Hoy 13 de agosto de 2007, ante mí, compareció T.G. Murali Dhar a quien conozco como la persona que firmó la cesión adjunta y reconoció ante mí que la firmó.

Firmado, Dawnet Bragg
Notaria Pública

[SELLO]

DAWNET BRAGG
Notaria Pública de New Jersey
Mi comisión vence septiembre 22, 2009

10367 NP

Firmado el 15 de agosto de 2007, por [firma ilegible]
Jingwu Duan

Estado de New Jersey)
)
Condado de Somerset)

Hoy 15 de agosto de 2007, compareció ante mí Jingwu Duan a quien conozco como la persona mencionada y quien firmó la cesión anterior y reconoció ante mí su firma.

TERESA J. DE MONTES
TRADUCTORA OFICIAL
REG. 220 MINJUSTICIA

Firmado, Dawnet Bragg
Notaria Pública

[SELLO]

DAWNETT BRAGG
Notaria Pública, Estado de New Jersey
Vencimiento comisión septiembre 22, 2009

10367 NP

Firmado el 15de agosto de 2007, por [firma ilegible]
Hua Gong

Estado de New Jersey)
)
Condado de Somerset)

Hoy 15 de agosto de 2007, compareció ante mí Hua Gong a quien conozco como la persona mencionada y quien firmó la cesión anterior y reconoció ante mí su firma.

Firmado, Dawnet Bragg
Notaria Pública

[SELLO]

DAWNET BRAGG
Notaria Pública, Estado de New Jersey
Vencimiento comisión septiembre 22, 2009

10367 NP

Firmado el 15 de agosto de 2007, por Bin Jiang
Bin Jiang

Estado de New Jersey)
)
Condado de Somerset)

Hoy 15 de agosto de 2007, compareció ante mí Bin Jiang a quien conozco como la persona mencionada y quien firmó la cesión anterior y reconoció ante mí su firma.

Firmado, Dawnet Bragg
Notaria Pública

[SELLO]

DAWNET BRAGG
Notaria Pública, Estado de New Jersey
Vencimiento comisión septiembre 22, 2009

10367 NP

Firmado el 15 de agosto de 2007, por Bingwei Vera Yang

TERESA J. DE MONTES
TRADUCTORA OFICIAL
RES. 220 MINJUSTICIA

Bingwei Vera Yang

Estado de New Jersey)
)
Condado de Somerset)

Hoy 15 de agosto de 2007, compareció ante mí Bingwei Vera Yang a quien conozco como la persona mencionada y quien firmó la cesión anterior y reconoció ante mí su firma.

Firmado, Dawnet Bragg
Notaria Pública

[SELLO]

DAWNETT BRAGG
Notaria Pública, Estado de New Jersey
Vencimiento comisión septiembre 22, 2009

10367 NP

CESIÓN

Yo,
Arthur M. Doweyko

De acuerdo con las obligaciones contractuales asumidas hasta ahora por mi y/o a cambio de una contraprestación válida y efectiva cuyo recibo y suficiencia se acusan por el presente documento, mediante el presente vendemos y cedemos a **Bristol-Myers Squibb Company**, una sociedad de Delaware, con domicilio de negocios en Rt. 206 & Province Line Road, Princeton Road, Princeton, NJ 08543-4000, a sus sucesores, causahabientes y representantes legales, la totalidad de mis derechos, títulos y participación los cuales incluyen el derecho y el beneficio total sobre las prioridades que puedan otorgarse ahora o en el futuro, a mi, por las leyes locales o por tratado, incluida la convención internacional para la protección de propiedad industrial en y para todos los países del mundo incluidos los Estados Unidos y sus territorios y posesiones, en y sobre la invención titulada:

MODULADORES DE RECEPTOR DE GLUCOCORTICOIDE, ACTIVIDAD AP-1, Y/O NF-kB Y USO DE LOS MISMOS

Inventado por mí y descrito en la solicitud de patentes de los Estados Unidos no provisional

Solicitud No. 11/835,438, presentada 8 de agosto, 2007

Incluyendo la citada solicitud de patentes de los Estados Unidos no provisional y cualquier solicitud que reclame antigüedad de la citada solicitud no provisional presentada en cualquier país y con respecto a cualquier patente que pueda ser emitida y/u otorgada con respecto a la misma y todas las divisiones, continuaciones, reexpediciones, certificados de re-examen y de extensiones de las mismas en todos los países, cuya participación constituye la propiedad total sobre dicha invención y sobre todas las citadas solicitudes, patentes (incluyendo reemisión de patentes) extensiones, y certificados de re-examen que serán de propiedad de y disfrutados por

TERESA J. DE MO...
TRADUCTORA OFICIAL
RES. 220 MIN...

Bristol-Myers Squibb Company y sus sucesores y causahabientes hasta el máximo de los términos para los cuales esas patentes (incluidas las reexpediciones de patentes), certificados de extensión y de re-examen puedan otorgarse y/o emitirse en su totalidad como si las mismas hubieren sido mantenidos y disfrutados por nosotros, si esta venta, cesión y transferencia no se hubiere realizado;

Y por el presente acepto comunicar al mencionado cesionario o a su representante sobre cualquier hecho del que tenga conocimiento con respecto a dicha invención, a dar testimonio en cualquier proceso legal, a firmar y/o suscribir cualquier otro documento adicional y/o instrumento que pueda ser necesario, legítimo y adecuado para la presentación y/o proceso judicial de todas las solicitudes, incluyendo solicitudes divisionales, de continuación y de reemisión, certificados de reextensiones y de re-examen y/o el otorgamiento y/o extensión de los mismos y/o de otra manera garantizar el título de dicha invención y de todas las solicitudes, patentes (incluidas las re-expediciones de patentes, certificados de extensiones, re-examen de las mismas, en dicho escenario y en general, a revisar todos los actos que sean necesarios para colaborar al cesionario, sus sucesores y causahabientes en la obtención y aplicación de la protección debida para dicha invención en todos los países.

Firmado el 27 de septiembre de 2007 por [Firma ilegible]
Arthur M. Doweyko

Estado de New Jersey)
)
Condado de Somerset)

Hoy 27 de septiembre de 2007, ante mí, compareció Arthur M. Doweyko a quien conozco como la persona que firmó la cesión adjunta y reconoció ante mí que la firmó.

Firmado [ilegible]
Notario Público

[SELLO]
DAWNET BRAGG
Notaria Pública de New Jersey
Mi comisión vence septiembre 22, 2009

Oficina Patentes y Marcas Registradas de los Estados Unidos

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS
Oficina de Patentes y Marcas Registradas de los Estados Unidos
Dirección: COMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria Virginia 22313-1450
www.uspto.gov

SOLICITUD NO.	FECHA DE SOLICITUD O 371(C)	GRP ART UNIT	DERECHOS SOLICITUD PAGADOS	EXPEDIENTE DEL APODERADO NO.	TOTAL REIVINDICACIONES	REIVINDICACIONES IND
11/835,438	08/08/2007	1624	2530	10367 NP	28	3

TERESA J. DE MONTES
TRADUCTORA OFICIAL
RES. 220 MINJUSTICIA

CONFIRMACIÓN No. 1442
RECIBO DE PRESENTACIÓN DE LA SOLICITUD ACTUALIZADO

Código de Barras
OC000000030283012

23914
LOUIS J. WILLE
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P.O. BOX 4000
PRINCETON, NJ 08543-4000

Fecha de envío por correo: 06/05/2008

Se acusa recibo de esta solicitud de patente no provisional. La solicitud pasará a examen a su debido tiempo. El solicitante será notificado de los resultados del examen. Cualquier correspondencia relacionada con la solicitud debe incluir la siguiente información de identificación: NÚMERO DE SOLICITUD U.S., FECHA DE PRESENTACIÓN, NOMBRE DEL SOLICITANTE y TÍTULO DE LA INVENCIÓN. Los derechos enviados por cheque o giro están condicionados al cobro. Por favor, verificar la exactitud de los datos presentados en este recibo. **Si se observa un error en este Recibo de Presentación de solicitud, por favor presente una solicitud por escrito para corrección del recibo de presentación de la solicitud. Por favor, envíe una copia de este recibo de presentación con los cambios anotados. Si usted recibió un "Aviso para diligenciar partes que faltan" en esta solicitud, por favor presente cualquier corrección a este Recibo de Presentación con su respuesta a la notificación. Cuando la USPTO procesa la respuesta a la notificación, la USPTO expedirá otro Recibo de Presentación de solicitud incorporando las correcciones solicitadas.**

Solicitante(s)

David S. Weinstein, East Windsor, NJ;
Ping Chen, Belle Mead, NJ;
T.G. Murali Dhar, Newtown, PA;
Jingwu Duan, Yardley, PA;
Hua Gong, King of Prussia, PA;
Bin Jiang, Norristown, PA;
Bingwei Vera Yang, Belle Mead, NJ;
Arthur M. Doweyko, Long Valley, NJ;

Cesión para Solicitud de Patente publicada

Bristol-Myers Squibb Company

Poder: Los profesionales de patentes relacionados con el número de cliente 23914.

Información de Prioridad Nacional reivindicada por el solicitante
Esta solicitud reivindica el beneficio de 60/836,496 08/09/2006

Solicitudes en el exterior

Si se requiere, Licencia para presentación en el exterior otorgada: 09/21/2007

TERESA J. DE MONTES
TRADUCTORA OFICIAL

El código y número del país de su solicitud de prioridad que se utilizará para la presentación en el exterior, de acuerdo con la Convención de París es: **US 11/835,438**

Fecha proyectada de la publicación: 09/11/2008.

Solicitud de no publicación: No

Solicitud de publicación anterior: No.

Título:

Moduladores del receptor de glucocorticoides, Actividad de AP-1 y/o NF-kB y uso de los mismos

Clase preliminar

514

PROTECCIÓN DE SU INVENCIÓN FUERA DE LOS ESTADOS UNIDOS

Dado que los derechos que otorga una patente US. se extienden sólo en el territorio de los Estados Unidos y no tienen efecto en un país del exterior, un inventor que desee proteger la patente en otro país debe solicitar una patente en un país específico o en las oficinas regionales de patentes. Es posible que los solicitantes deseen considerar presentar una solicitud internacional de acuerdo con el Tratado de Cooperación de Patentes (PCT). Una solicitud PCT generalmente tiene el mismo efecto que una solicitud de patente nacional en cada país miembro de PCT. El proceso PCT **simplifica** la presentación de solicitudes de patente sobre la misma invención en los países miembros pero no resulta en el otorgamiento de una patente internacional y no elimina la necesidad de que los solicitantes presenten documentos adicionales y paguen derechos en países donde se desea la protección de la patente.

Casi todos los países cada país tienen sus propias leyes de patentes, una persona que desea una patente en un país específico debe presentar una solicitud para la patente en ese país conforme a estas leyes particulares. Dado que las leyes de muchos países difieren en diversos aspectos de la ley de patentes de los Estados Unidos, se recomienda a los solicitantes buscar orientación en los países específicos del exterior para garantizar que los derechos a la patente no se pierdan prematuramente.

También se les informa a los solicitantes que en el caso de las invenciones hechas en los Estados Unidos el director de la USPTO debe expedir una licencia antes que los solicitantes puedan solicitar una patente en un país del exterior. La presentación de una solicitud de patente U.S. sirve como una solicitud para una licencia para presentación de la solicitud en el exterior.. El recibo de presentación de la solicitud contiene información adicional e información con respecto al estado de la licencia del solicitante para solicitud en el exterior.

Es posible que los solicitantes deseen consultar el folleto USPTO "Información general concerniente a las patentes" (específicamente, la sección titulada "Tratados y Patentes del Exterior") para más información sobre los marcos de tiempo y fechas límite para presentación de solicitudes de patentes en el exterior. La guía está disponible contactando al centro de contacto USPTO en 800-786-9199, o puede consultarse en el sitio de internet de USPTO en: http://www.uspto.gov/web/offices/pac/doc /general/index.html.

TERESA J. DE MONTES
TRADUCTORA OFICIAL
RES. 220 MINJUSTICIA

Para información sobre cómo prevenir el robo de su propiedad intelectual (patentes, marcas registradas y derechos de autor) usted puede consultar el sitio de internet del Gobierno de los Estados Unidos: http://www.stopfakes.gov. Parte de una iniciativa del Departamento de Comercio este sitio de internet incluye "herramientas" de autoayuda que les dan a los inventores orientación sobre cómo proteger la propiedad intelectual en casos específicos tales como China, Corea y México. Para preguntas relacionadas con la protección de patentes, los solicitantes pueden llamar a la línea gratuita del gobierno de los Estados Unidos en el teléfono 1-866-999 HALT (1-866-999-4158).

LICENCIA PARA PRESENTACIÓN EN EL EXTERIOR DE ACUERDO CON EL Título 35, Código de los Estados Unidos, Sección 184 Título 37, Código de Regulaciones Federales, 5.11 & 5.15

OTORGADO

Se le ha otorgado al solicitante una licencia de acuerdo con el Título 35 Código de los Estados Unidos, Sección 184, si la frase "SI SE REQUIERE, SE HA OTORGADO UNA LICENCIA PARA PRESENTACIÓN EN EL EXTERIOR" seguida por una fecha aparece en este formulario. Estas licencias se expiden en todas las solicitudes donde las condiciones para expedición de una licencia se han cumplido, indistintamente si la licencia se requiere como se establece en 37 CFR 5.15. El alcance y limitaciones de esta licencia se estipulan en 37 CFR 5.15(a) a menos que haya sido expedida antes una licencia de acuerdo con 37 CFR 5.15(b). La licencia está sujeta a revocación, previa notificación por escrito. La fecha indicada es la fecha de vigencia de la licencia a menos que se haya otorgado antes una licencia con un alcance similar, de acuerdo con 37 CFR 5.13 o 5.14.

Esta licencia debe conservarla el licenciatario y puede ser utilizada en cualquier momento en o después de su fecha de vigencia a menos que será revocada. Esta licencia se transfiere automática a cualquier solicitud o solicitudes presentada(s) de acuerdo con 37 CFR 1.53(c). Esta licencia no es retroactiva.

El otorgamiento de una licencia en ninguna forma disminuye la responsabilidad de un licenciatario por la seguridad del asunto según lo señalan cualquier contrato del gobierno o las disposiciones de leyes existentes relacionadas con espionaje y la seguridad nacional o la exportación de información técnica. Los licenciatarios deben informarse sobre las regulaciones vigentes, especialmente con respecto a algunos países, de otras agencias, particularmente la Oficina de Controles Comerciales de Defensa, Departamento de Estado (con respecto a armas, municiones, implementos de guerra (22 CFR 121-128)); la Oficina de Industria y Seguridad, Departamento de Comercio (15 CFR partes 730-774); la Oficina de Control de Activos del Exterior, Departamento de Tesorería (31 CFR partes 500+) y el Departamento de Energía.

NO OTORGADA

No se ha otorgado ninguna licencia de acuerdo con el Título 35 del Código de los Estados Unidos, Sección 184 en esta fecha, si la frase "SI SE REQUIERE LICENCIA PARA PRESENTACIÓN EN EL EXTERIOR OTORGADA" no aparece en este formulario. El solicitante debe solicitar una licencia de acuerdo con 37 CFR 5.12, si desea una licencia antes del vencimiento de los 6 meses después de la fecha de presentación de la solicitud. Si han transcurrido 6 meses desde la fecha de presentación de esta solicitud y el licenciatario no ha recibido ninguna indicación de

TERESA J. DE MONTES
TRADUCTORA OFICIAL

una orden de confidencialidad de acuerdo con 35 U.S.C. 181, el licenciatario puede presentar en el exterior la solicitud conforme a 37 CFR 5, 15(b).

APOSTILLE
(Convention de La Haye du octobre 5, 1961)

1. País	Estados Unidos de America
Este documento público	
2. Fue firmado por	MAURA O KNOBL
3. actuando en su carácter de	Notaria Pública, Estado de New Jersey
4. lleva el sello/timbre de	MAURA O KNOBL, NOTARIA

CERTIFICADO

5. EN	TRENTON, NEW JERSEY
6. el	2 DE FEBRERO DE 2009
7. por	R. David Rousseau, Tesorero de New Jersey
8. Número	A353082
9. Sello/Estampilla	10. Firma
Gran Sello del Estado de New Jersey	ILEGIBLE

Certificado Número: 113568367
Verifique este certificado en línea en
http://www1.state.nj.us/TYTR_StandingCert/JSP/Verify_Cert.jsp

La anterior es traducción fiel y completa del documento en referencia, de la cual se deja copia en este archivo para su confrontación.

Teresa Jiménez de Montes
c.c. 41.569.149 de Bogotá
Traductora Oficial según
Resolución No.220 del
6 de febrero de 1978,
expedida por el Ministerio de Justicia.

una orden de confidencialidad de acuerdo con 35 U.S.C. 181, el licenciatario puede presentar en el exterior la solicitud conforme a 37 CFR 5, 15(b).

APOSTILLE
(Convention de La Haye du octobre 5, 1961)

1. País	Estados Unidos de America
Este documento público	
2. Fue firmado por	MAURA O KNOBL
3. actuando en su carácter de	Notaria Pública, Estado de New Jersey
4. lleva el sello/timbre de	MAURA O KNOBL, NOTARIA

CERTIFICADO

5. EN	TRENTON, NEW JERSEY
6. el	2 DE FEBRERO DE 2009
7. por	R. David Rousseau, Tesorero de New Jersey
8. Número	A353082
9. Sello/Estampilla	10. Firma
Gran Sello del Estado de New Jersey	ILEGIBLE

Certificado Número: 113568367
Verifique este certificado en línea en
http://www1.state.nj.us/TYTR_StandingCert/JSP/Verify_Cert.jsp

La anterior es traducción fiel y completa del documento en referencia, de la cual se deja copia en este archivo para su confrontación.

TERESA J. DE MONTES
TRADUCTORA OFICIAL
RES 220 MINJUSTICIA

Teresa Jiménez de Montes
c.c. 41.569.149 de Bogotá
Traductora Oficial según
Resolución No.220 del
6 de febrero de 1978,
expedida por el Ministerio de Justicia.

000021

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
MAURA O KNOBL

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

4. BEARS THE SEAL/STAMP OF:
MAURA O KNOBL, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY

6. THE 2ND DAY OF FEBRUARY 2009

7. BY: R. David Rousseau, NEW JERSEY TREASURER

8. NO. A353082

9. SEAL/STAMP:

10. SIGNATURE



Certificate Number: 113568367
Verify this certificate online at
https://www1.state.nj.us/TYTR_StandingCert/JSP/Verify_Cert.jsp

CERTIFICATION

I, Maura O. Knobl, Notary Public, Patent Department, Bristol-Myers Squibb Company, do hereby certify that this document is a true and accurate copy of the original assignments signed by the inventors.

STATE OF NEW JERSEY)
) ss.
COUNTY OF MERCER)

Date January 29, 2009

Maura O. Knobl
Maura O. Knobl

MAURA O. KNOBL
Notary Public of New Jersey
My Commission Expires July. 23, 2013

ASSIGNMENT

We,

David S. Weinstein	residing at	10 Inverness Lane East Windsor, New Jersey 08520 United States of America
Ping Chen	residing at	21 Derby Chase Court Belle Mead, New Jersey 08502 United States of America
Hua Gong	residing at	2000 Veterans Highway Apt. E12 Levittown, Pennsylvania 19056 United States of America
Bingwei Vera Yang	residing at	15 Regents Court Belle Mead, New Jersey 08502 United States of America,

pursuant to contractual obligations heretofore assumed by us and/or for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, do hereby sell and assign to **Bristol-Myers Squibb Company**, a Delaware corporation, having a place of business at Lawrenceville-Princeton Road, Princeton, NJ 08543-4000, its successors, assigns and legal representatives, all our right, title and interest, which includes the right to and full benefit of such priorities as may now or hereafter be granted to us by local laws or by treaty, including any international convention for the protection of industrial property, in and for all countries of the world, including the United States and its territories and possessions, in and to the invention entitled:

MODULATORS OF GLUCOCORTICOID RECEPTOR, AP-1, AND/OR NF-kB ACTIVITY AND USE THEREOF

invented by us and described in the provisional United States patent application

Application No. 60/836,496, filed August 9, 2006,

including said provisional United States patent application and any application claiming priority from said provisional application, filed in any country, and any patents which may be issued and/or granted thereon, and all divisions, continuations, reissues, reexamination certificates and extensions thereof in all countries, the said interest being the entire ownership of said invention and all of said applications, patents (including reissue patents), extensions and reexamination

certificates to be held and enjoyed by the said Bristol-Myers Squibb Company and its successors and assigns to the full end of the terms to which said patents (including reissue patents), extensions and reexamination certificates may be granted and/or issued, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made;

And we hereby agree to communicate to said assignee or its representatives any facts known to us respecting said invention, to testify in any legal proceedings, to sign and/or execute any further documents and/or instruments which may be necessary, lawful and proper in and/or for the filing and/or prosecution of all applications, including divisional, continuation and reissue applications, extensions and reexamination certificates and/or the granting and/or issuance thereof and/or to otherwise secure title to said invention and all of said applications, patents (including reissue patents, extensions and reexamination certificates in said assignee, and in general to do everything possible to aid said assignee, its successors and assigns to obtain and enforce proper protection for said invention in all countries.

Signed this 20th day of September, 2006 by _____
David S. Weinstein

STATE OF NEW JERSEY)
) ss.
COUNTY OF MERCER)

On this day 20th of September, 2006, before me came David S. Weinstein, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

[SEAL]

_____
Notary Public

DEBRA A. WOJCIK
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires May 30, 2008

Signed this 14th day of Sept, 2006 by _____
Ping Chen

STATE OF NEW JERSEY)
) ss.
COUNTY OF MERCER)

On this day 14th of September, 2006, before me came Ping Chen, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

[SEAL] LISA B. SWIDRA
Notary Public of New Jersey
My Commission Expires April 22, 2009

_____
Notary Public

Signed this 8th day of Sept., 2006 by _____
Hua Gong

STATE OF NEW JERSEY)
) ss.
COUNTY OF MERCER)

On this day 8th of September, 2006, before me came Hua Gong, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

[SEAL] LISA B. SWIDRA
Notary Public of New Jersey
My Commission Expires April 22, 2009

_____
Notary Public

Signed this 28th day of September, 2006 by _____
Bingwei Vera Yang

STATE OF NEW JERSEY)
) ss.
COUNTY OF MERCER)

On this day 28th of September, 2006, before me came Bingwei Vera Yang, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

[SEAL]

_____
Notary Public

LISA B. SWIDRA
Notary Public of New Jersey
My Commission Expires April 22, 2009

000026

10367-US-PSP
Rodney

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPL NO.	FILING OR 371 (c) DATE	ART UNIT	FIL FEE REC'D	ATTY.DOCKET NO	DRAWINGS	TOT CLMS	IND CLMS
60/836,496	08/09/2006		950	10367 (PSP)			

CONFIRMATION NO. 5918

CORRECTED FILING RECEIPT

OC000000020434463

23914
LOUIS J. WILLE
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P O BOX 4000
PRINCETON, NJ 08543-4000

Date Mailed: 09/14/2006

Receipt is acknowledged of this provisional Patent Application. It will not be examined for patentability and will become abandoned not later than twelve months after its filing date. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please mail to the Commissioner for Patents P.O. Box 1450 Alexandria Va 22313-1450. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).**

RECEIVED
BMS PATENT LAW
SEP 19 2006
Docketed Item QFR
Due Date
Attorney BR

Applicant(s)

David S. Weinstein, East Windsor, NJ;
Ping Chen, Belle Mead, NJ;
Hua Gong, Levittown, PA;
Bingwei Vera Yang, Belle Mead, NJ;

Power of Attorney:

Burton Rodney--22076

If Required, Foreign Filing License Granted: 08/21/2006

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is US60/836,496

Projected Publication Date: None, application is not eligible for pre-grant publication

Non-Publication Request: Not applicable

Early-Publication Request: Not applicable

Title

Modulators of glucocorticoid receptor, AP-1, and/or NF-kB activity and use thereof

6

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES 030027

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

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Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER
Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations

especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

ASSIGNMENT

We,

David S. Weinstein, Ping Chen, T. G. Murali Dhar, Jingwu Duan, Hua Gong, Bin Jiang, Bingwei Vera Yang

pursuant to contractual obligations heretofore assumed by us and/or for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, do hereby sell and assign to **Bristol-Myers Squibb Company**, a Delaware corporation, having a place of business at Rt. 206 & Province Line Road, Princeton Road, Princeton, NJ 08543-4000, its successors, assigns and legal representatives, all our right, title and interest, which includes the right to and full benefit of such priorities as may now or hereafter be granted to us by local laws or by treaty, including any international convention for the protection of industrial property, in and for all countries of the world, including the United States and its territories and possessions, in and to the invention entitled:

MODULATORS OF GLUCOCORTICOID RECEPTOR, AP-1, AND/OR NF-κB ACTIVITY AND USE THEREOF

invented by us and described in the non-provisional United States patent application

Application No. 11/835,438, filed August 8, 2007

including said non-provisional United States patent application and any application claiming priority from said non-provisional application, filed in any country, and any patents which may be issued and/or granted thereon, and all divisions, continuations, reissues, reexamination certificates and extensions thereof in all countries, the said interest being the entire ownership of said invention and all of said applications, patents (including reissue patents), extensions and reexamination certificates to be held and enjoyed by the said Bristol-Myers Squibb Company and its successors and assigns to the full end of the terms to which said patents (including reissue patents), extensions and reexamination certificates may be granted and/or issued, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made;

And we hereby agree to communicate to said assignee or its representatives any facts known to us respecting said invention, to testify in any legal proceedings, to sign and/or execute any further documents and/or instruments which may be necessary, lawful and proper in and/or for the filing and/or prosecution of all applications, including divisional, continuation and reissue applications, extensions and reexamination certificates and/or the granting and/or issuance thereof and/or to otherwise secure title to said invention and all of said applications, patents (including reissue patents, extensions and reexamination certificates in said assignee, and in general to do everything possible to aid said assignee, its successors and assigns to obtain and enforce proper protection for said invention in all countries.

Signed this 10th day of August, 2007 by _____
David S. Weinstein

STATE OF New Jersey)
)
COUNTY OF Somerset)

On the 10th day of August, 2007, before me came David S. Weinstein to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

[SEAL]

_____
Notary Public

DAWNET BRAGG
Notary Public of New Jersey
My Commission Expires Sept. 22, 2009

Signed this 13th day of August, 2007 by

Ping Chen

STATE OF New Jersey)
)
COUNTY OF Somerset)

On the 13th day of August, 2007, before me came Ping Chen to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

[SEAL]

Notary Public

DAWNET BRAGG
Notary Public of New Jersey
My Commission Expires Sept. 22, 2009

Signed this 13 day of AUGUST, 2007 by T.G. Murali Dhar.
T. G. Murali Dhar

STATE OF New Jersey)
)
COUNTY OF Somerset)

On the 13th day of August, 2007, before me came T. G. Murali Dhar to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

Dawnet Bragg
Notary Public

[SEAL]

DAWNET BRAGG
Notary Public of New Jersey
My Commission Expires Sept. 22, 2009

Signed this 15th day of August, 2007 by

Jingwu Duan

STATE OF New Jersey)
)
COUNTY OF Somerset)

On the 15th day of August, 2007, before me came Jingwu Duan to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and *acknowledged* that he/she executed it.

[SEAL]

Notary Public

DAWNET BRAGG
Notary Public of New Jersey
My Commission Expires Sept. 22, 2009

Signed this 15 day of August, 2007 by Hua Gong

STATE OF New Jersey)
)
COUNTY OF Somerset)

On the 15th day of August, 2007, before me came Hua Gong to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

[SEAL]

Notary Public

DAWNET BRAGG
Notary Public of New Jersey
My Commission Expires Sept. 22, 2009

000035

Signed this 15th day of August, 2007 by Bin Jiang
Bin Jiang

STATE OF New Jersey)
COUNTY OF Somerset)

On the 15th day of August, 2007, before me came Bin Jiang to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

[SEAL]

Dawnet Bragg
Notary Public

DAWNET BRAGG
Notary Public of New Jersey
My Commission Expires Sept. 22, 2009

Signed this 15th day of August, 2007 by Bingwei Vera Yang
Bingwei Vera Yang

STATE OF New Jersey)
COUNTY OF Somerset)

On the 15th day of August, 2007, before me came Bingwei Vera Yang to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

[SEAL]

Notary Public

DAWNET BRAGG
Notary Public of New Jersey
My Commission Expires Sept. 22, 2009

- 030037

ASSIGNMENT

I,

Arthur M. Doweyko

pursuant to contractual obligations heretofore assumed by me and/or for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, do hereby sell and assign to **Bristol-Myers Squibb Company**, a Delaware corporation, having a place of business at Rt. 206 & Province Line Road, Princeton Road, Princeton, NJ 08543-4000, its successors, assigns and legal representatives, all my right, title and interest, which includes the right to and full benefit of such priorities as may now or hereafter be granted to me by local laws or by treaty, including any international convention for the protection of industrial property, in and for all countries of the world, including the United States and its territories and possessions, in and to the invention entitled:

MODULATORS OF GLUCOCORTICOID RECEPTOR, AP-1, AND/OR NF-κB ACTIVITY AND USE THEREOF

invented by me and described in the non-provisional United States patent application

Application No. 11/835,438, filed August 8, 2007

including said non-provisional United States patent application and any application claiming priority from said non-provisional application, filed in any country, and any patents which may be issued and/or granted thereon, and all divisions, continuations, reissues, reexamination certificates and extensions thereof in all countries, the said interest being the entire ownership of said invention and all of said applications, patents (including reissue patents), extensions and reexamination certificates to be held and enjoyed by the said Bristol-Myers Squibb Company and its successors and assigns to the full end of the terms to which said patents (including reissue patents), extensions and reexamination certificates may be granted and/or issued, as fully and entirely as the same would have been held and enjoyed by me if this sale, assignment and transfer had not been made;

And I hereby agree to communicate to said assignee or its representatives any facts known to me respecting said invention, to testify in any legal proceedings, to sign and/or execute any further documents and/or instruments which may be necessary, lawful and proper in and/or for the filing and/or prosecution of all applications, including divisional, continuation and reissue applications, extensions and reexamination certificates and/or the granting and/or issuance thereof and/or to otherwise secure title to said invention and all of said applications, patents (including reissue patents, extensions and reexamination certificates in said assignee, and in general to do everything possible to aid said assignee, its successors and assigns to obtain and enforce proper protection for said invention in all countries.

Signed this 27 day of SEPTEMBER, 2007 by _____
Arthur M. Doweyko

STATE OF New Jersey)
)
COUNTY OF Somerset)

On the 27th day of September, 2007, before me came Arthur M. Doweyko to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

[SEAL]

_____
Notary Public

DAWNET BRAGG
Notary Public of New Jersey
My Commission Expires Sept. 22, 2009

UNITED STATES PATENT AND TRADEMARK OFFICE 000039

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
11/835,438	08/08/2007	1624	2530	10367 NP	28	3

CONFIRMATION NO. 1442

UPDATED FILING RECEIPT

OC000000030283012

23914
LOUIS J. WILLE
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P O BOX 4000
PRINCETON, NJ 08543-4000

Date Mailed: 06/05/2008

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

David S. Weinstein, East Windsor, NJ;
Ping Chen, Belle Mead, NJ;
T.G. Murali Dhar, Newtown, PA;
Jingwu Duan, Yardley, PA;
Hua Gong, King of Prussia, PA;
Bin Jiang, Norristown, PA;
Bingwei Vera Yang, Belle Mead, NJ;
Arthur M. Doweyko, Long Valley, NJ;

Assignment For Published Patent Application

Bristol-Myers Squibb Company

Power of Attorney: The patent practitioners associated with Customer Number 23914

Domestic Priority data as claimed by applicant

This appln claims benefit of 60/836,496 08/09/2006

Foreign Applications

If Required, Foreign Filing License Granted: 09/21/2007

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 11/835,438**

Projected Publication Date: 09/11/2008

Non-Publication Request: No

Early Publication Request: No

Title

MODULATORS OF GLUCOCORTICOID RECEPTOR, AP-1, AND/OR NF-kB ACTIVITY AND USE THEREOF

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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Title 37, Code of Federal Regulations, 5.11 & 5.15

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the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

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000342

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

(19) World Intellectual Property Organization
International Bureau

PCT

(43) International Publication Date
21 February 2008 (21.02.2008)

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(21) International Application Number:
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(26) Publication Language: English

(30) Priority Data:

60/836,496	9 August 2006 (09.08.2006)	US
11/835,438	8 August 2007 (08.08.2007)	US

(71) Applicant *(for all designated States except US)*: **BRISTOL-MYERS SQUIBB COMPANY** [US/US]; Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **WEINSTEIN, David, S.** [US/US]; c/o Bristol-Myers Squibb Company, Route 206 and Proviince Line Road, Princeton, New Jersey 08543-4000 (US). **GONG, Hua** [CN/US]; c/o Bristol-Myers Squibb Company, Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 (US). **DUAN, Jingwu** [US/US]; c/o Bristol-Myers Squibb Company, Route 206 and Proviince Line Road, Princeton, New Jersey 08543-4000 (US). **DHAR, T.G. Murali** [US/US]; c/o Bristol-Myers Squibb Company, Route 206 and Proviince Line Road, Princeton, New Jersey 08543-4000 (US). **YANG, Bingwei Vera** [US/US]; c/o Bristol-Myers Squibb Company, Route 206 and Proviince Line Road, Princeton, New Jersey 08543-4000 (US). **CHEN, Ping** [US/US]; c/o Bristol-Myers Squibb Company, Route 206 and Proviince Line Road, Princeton, New Jersey 08543-4000 (US). **JIANG, Bin** [US/US]; c/o Bristol-Myers Squibb Company, Route 206 and Proviince Line Road, Princeton, New Jersey 08543-4000 (US).

(74) Agents: **DUNCAN, Laurelee A.** et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, New Jersey 08543-4000 (US).

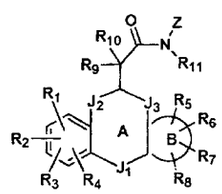
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN,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

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

Published:

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

(54) Title: MODULATORS OF GLUCOCORTICOID RECEPTOR, AP-1, AND/OR NF-KB ACTIVITY AND USE THEREOF



(I)

(57) Abstract: Novel non-steroidal compounds are provided which are useful in treating diseases associated with modulation of the glucocorticoid receptor, AP-1, and/or NF-KB activity, including inflammatory and immune diseases, having the structure of formula (I), an enantiomer, diastereomer, or tautomer thereof, or a prodrug ester thereof, or a pharmaceutically-acceptable salt thereof, in which: Z is heterocyclo or heteroaryl; A is a 5- to 8- membered carbocyclic ring or a 5- to 8-membered heterocyclic ring; B is a cycloalkyl, cycloalkenyl, aryl, heterocyclo, or heteroaryl ring, wherein each ring is fused to the A ring on adjacent atoms and optionally substituted by one to four groups which are the same or different and are independently selected from R_5, R_6, R_7, and R_8; J_1, J_2, and J3 are at each occurrence the same or different and are independently $-A_1QA_2-$; Q is a bond, O, S, S(O), or S(O)2; A_1 and A_2 are the same or different and are at each occurrence independently selected from a bond, C1-3alkylene, substituted C_{1-3}alkylene, C_2-4alkenylene, and substituted C_{2-4}alkenylene, provided that A_1 and A_2 are chosen so that ring A is a 5- to 8-membered carbocyclic or heterocyclic ring; R_1 to R_{11} are as defined herein. Also provided are pharmaceutical compositions and methods of treating inflammatory- or immune-associated diseases and obesity and diabetes employing said compounds.

WO 2008/021926 A2

MODULATORS OF GLUCOCORTICOID RECEPTOR, AP-1, AND/OR NF-κB ACTIVITY AND USE THEREOF

[0001] This application claims a benefit of priority from U.S. Provisional Application No. 60/836,496, filed August 9, 2006, the entire disclosure of which is incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to new non-steroidal compounds which are effective modulators of the glucocorticoid receptor, and/or AP-1, and/or NF-κB activity and thus are useful in treating diseases such as inflammatory or immune associated diseases , and to a method for using such compounds to treat these and related diseases.

BACKGROUND OF THE INVENTION

[0003] The transcription factors NF-κB and AP-1 are involved in regulating the expression of a number of genes involved in mediating inflammatory and immune responses. NF-κB regulates the transcription of genes including TNF-α, IL-1, IL-2, IL-6, adhesion molecules (such as E-selectin) and chemokines (such as Rantes), among others. AP-1 regulates the production of the cytokines TNF-α, IL-1, IL-2, as well as, matrix metalloproteases. Drug therapies targeting TNF-α, a gene whose expression is regulated by both NF-κB and AP-1, have been shown to be highly efficacious in several inflammatory human diseases including rheumatoid arthritis and Crohn's disease. Accordingly, NF-κB and AP-1 play key roles in the initiation and perpetuation of inflammatory and immunological disorders. *See* Baldwin, A.S., *Journal of Clin. Investigation*, 107, 3 (2001); Firestein, G.S., and Manning, A.M., *Arthritis and Rheumatism*, 42, 609 (1999); and Peltz, G., *Curr. Opin. in Biotech.*, 8, 467 (1997).

[0004] There are many signaling molecules (kinases and phosphatases) upstream of AP-1 and NF-κB which are potential therapeutic drug targets. The kinase JNK plays an essential role in regulating the phosphorylation and subsequent activation of c-jun, one of the subunits which constitute the AP-1 complex (fos/c-jun). Compounds

which inhibit JNK have been shown to be efficacious in animal models of inflammatory disease. *See* Manning, A.M. and Davis, R.J., *Nature Rev. Drug Disc.*, V. 2, 554 (2003). A kinase critical to the activation of NF-κB is the IκB kinase (IKK). This kinase plays a key role in the phosphorylation of IκB. Once IκB is phosphorylated it undergoes degradation leading to the release of NF-κB which can translocate into the nucleus and activate the transcription of the genes described above. An inhibitor of IKK has been shown to be efficacious in animal models of inflammatory disease. *See* Burke, J.R., *Curr. Opin. Drug Discov. Devel.*, Sep;6(5), 720-8, (2003).

[0005] In addition to inhibiting signaling cascades involved in the activation of NF-κB and AP-1, the glucocorticoid receptor has been shown to inhibit the activity of NF-κB and AP-1 via direct physical interactions. The glucocorticoid receptor (GR) is a member of the nuclear hormone receptor family of transcription factors, and a member of the steroid hormone family of transcription factors. Affinity labeling of the glucocorticoid receptor protein allowed the production of antibodies against the receptor which facilitated cloning the glucocorticoid receptors. For results in humans see Weinberger et al., *Science*, 228, 740-742 (1985); Weinberger et al., *Nature*, 318, 670-672 (1986) and for results in rats see Miesfeld, R., *Nature*, 312, 779-781 (1985).

[0006] Glucocorticoids which interact with GR have been used for over 50 years to treat inflammatory diseases. It has been clearly shown that glucocorticoids exert their anti-inflammatory activity via the inhibition by GR of the transcription factors NF-κB and AP-1. This inhibition is termed transrepression. It has been shown that the primary mechanism for inhibition of these transcription factors by GR is via a direct physical interaction. This interaction alters the transcription factor complex and inhibits the ability of NF-κB and AP-1 to stimulate transcription. *See* Jonat, C. et al., *Cell*, 62, 1189 (1990); Yang-Yen, H.F. et al, *Cell*, 62, 1205 (1990); Diamond, M.I. et al., *Science* 249, 1266 (1990); and Caldenhoven, E. et al., *Mol. Endocrinol.*, 9, 401 (1995). Other mechanisms such as sequestration of co-activators by GR have also been proposed. *See* Kamei, Y. et al., *Cell*, 85, 403 (1996); and Chakravarti, D. et al., *Nature*, 383, 99 (1996).

[0007] In addition to causing transrepression, the interaction of a glucocorticoid with GR can cause GR to induce transcription of certain genes. This induction of

transcription is termed transactivation. Transactivation requires dimerization of GR and binding to a glucocorticoid response element (GRE).

[0008] Recent studies using a transgenic GR dimerization defective mouse which cannot bind DNA have shown that the transactivation (DNA binding) activities of GR could be separated from the transrepressive (non-DNA binding) effect of GR. These studies also indicate that many of the side effects of glucocorticoid therapy are due to the ability of GR to induce transcription of various genes involved in metabolism, whereas, transrepression, which does not require DNA binding leads to suppression of inflammation. *See* Reichardt, H.M. et al., *Cell*, 93, 531 (1998) and Reichardt, H.M., *EMBO J.*, 20, 7168 (2001).

[0009] Compounds that modulate AP-1 and NF-κB activity would be useful in the treatment of inflammatory and immune diseases and disorders such as osteoarthritis, rheumatoid arthritis, multiple sclerosis, asthma, inflammatory bowel disease, transplant rejection and graft vs. host disease.

[0010] Also, with respect to the glucocorticoid receptor pathway, it is known that glucocorticoids are potent anti-inflammatory agents. However their systemic use is limited by side effects. Compounds that retain the anti-inflammatory efficacy of glucocorticoids while minimizing the side effects such as diabetes, osteoporosis and glaucoma would be of great benefit to a very large number of patients with inflammatory diseases.

[0011] Additionally concerning GR, the art is in need of compounds that antagonize transactivation. Such compounds may be useful in treating metabolic diseases associated with increased levels of glucocorticoid, such as diabetes, osteoporosis and glaucoma.

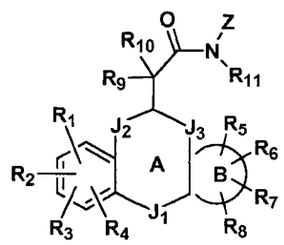
[0012] Additionally concerning GR, the art is in need of compounds that cause transactivation. Such compounds may be useful in treating metabolic diseases associated with a deficiency in glucocorticoid. Such diseases include Addison's disease.

DESCRIPTION OF THE INVENTION

[0013] The present invention relates to new non-steroidal compounds which are effective modulators of the glucocorticoid receptor, and/or AP-1, and/or NF-κB

activity and thus are useful in treating diseases such as inflammatory or immune associated diseases, and/or obesity and diabetes, and to a method for using such compounds to treat these and related diseases.

[0014] In accordance with one aspect of the invention, compounds are provided having the structure of formula I



I ,

an enantiomer, diastereomer, tautomer, or a pharmaceutically-acceptable salt thereof, wherein:

Z is selected from heterocyclo, heteroaryl and cyano;

A is selected from a 5- to 8- membered carbocyclic ring and a 5- to 8-membered heterocyclic ring;

the B ring is selected from a cycloalkyl, cycloalkenyl, aryl, heterocyclo ring, and heteroaryl ring, wherein the B ring is fused to the A ring, and the B ring is optionally substituted by one to four groups which are the same or different and are independently selected from R_5, R_6, R_7, and R_8;

J_1, J_2, and J_3 are the same or different and at each occurrence are independently $-A_1QA_2-$;

Q is independently at each occurrence selected from a bond, O, S, S(O), and $S(O)_2$;

A_1 and A_2 are the same or different and at each occurrence are independently selected from a bond, C_{1-3}alkylene, substituted C_{1-3}alkylene, C_{2-4}alkenylene, and substituted C_{2-4}alkenylene, provided that A_1 and A_2 are chosen so that ring A is a 5- to 8-membered carbocyclic ring or a 5- to 8-membered heterocyclic ring;

R_1, R_2, R_3, R_4, R_5, R_6, R_7, and R_8 are the same or different and at each occurrence are independently selected from (i) hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted

alkoxy, nitro, cyano, OR_{12}, $-NR_{12}R_{13}$, $-C(=O)R_{12}$, $-CO_2R_{12}$, $-C(=O)NR_{12}R_{13}$, $-OC(=O)NR_{12},R_{13}$, $-\underset{R_d}{N}C(=O)NR_{12}R_{13}$, $-OC(=O)R_{12}$, $-NR_{12}C(=O)R_{13}$, $-NR_{12}C(O)OR_{13}$, $-NR_{12}C(S)OR_{13}$, $S(O)_pR_{16}$, $NR_{12}SO_2R_{16}$, dialkylaminoalkoxy, alkoxyalkyloxyalkyloxy, $SO_2NR_{12}R_{13}$, cycloalkyl, cycloalkenyl, cycloalkynyl, heterocyclo, aryl, and heteroaryl; and/or (ii) where possible, each one of R_1-R_8 is taken together with any one of R_1-R_8 located on an adjacent atom to form a fused ring; and/or (iii) where possible any one of R_1-R_8 is taken together with any one of R_1-R_8 located on the same atom to form an oxo, alkenyl, substituted alkenyl, cycloalkyl, cycloalkenyl, or heterocyclo group;

R_9 and R_{10} are the same or different and at each occurrence are independently selected from (i) hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, nitro, cyano, OR_{14}, $NR_{14}R_{15}$, $C(=O)R_{14}$, CO_2R_{14}, $C(=O)NR_{14}R_{15}$, $-O-C(=O)R_{14}$, $NR_{14}C(=O)R_{15}$, $NR_{14}C(=O)OR_{15}$, $NR_{14}C(=S)OR_{15}$, $S(O)_pR_{17}$, $NR_{14}SO_2R_{17}$, $SO_2NR_{14}R_{15}$, cycloalkyl, cycloalkenyl, heterocyclo, aryl, and heteroaryl; or (ii) together with the atom to which the are attached, R_9 and R_{10} are taken together to form a carbonyl, alkenyl, substituted alkenyl, cycloalkyl, cycloalkenyl, or heterocyclo group;

R_{11} is selected from hydrogen, alkyl, substituted alkyl, C(=O)alkyl, CO_2(alkyl), SO_2alkyl, alkoxy, amino, substituted amino, aryl, heteroaryl, heterocyclo, and cycloalkyl;

R_{12}, R_{13}, R_{14}, and R_{15}, are the same or different and at each occurrence are independently selected from (i) hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclo; or (ii) where possible R_{12} is taken together with R_{13}, and/or where possible R_{14} is taken together with R_{15} to form a heteroaryl or heterocyclo ring;

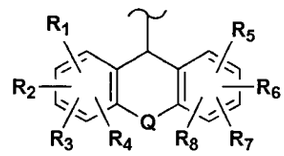
R_{16} and R_{17}, are the same or different and at each occurrence are independently selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclo;

R_d is H, alkyl or aryl; and

p is 0, 1 or 2,

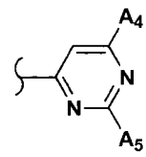
provided that

(1) where the tricyclic moiety in the formula I compound is



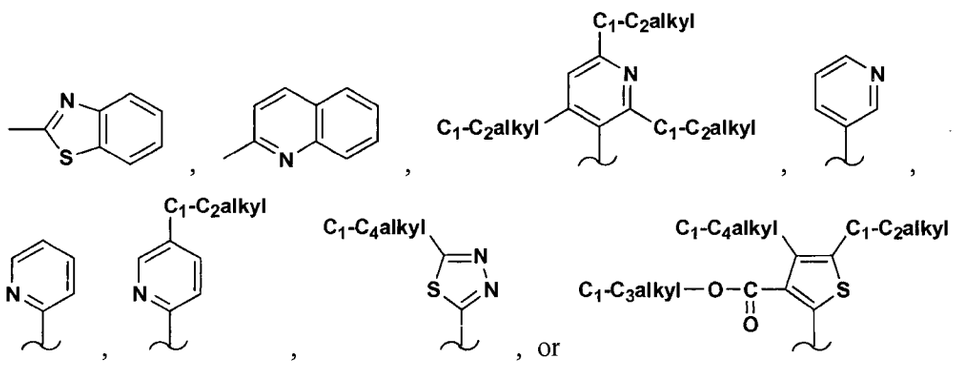
where Q is O and R_1 to R_8 are each H, then

(a) Z is other than



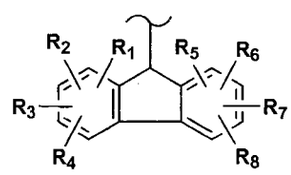
where A_4 and A_5 are the same or different and are independently H or C_1-C_2alkyl-; or

(b) Z is other than



, , , , , , , , or ,

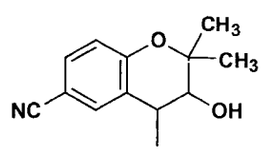
(2) where the tricyclic moiety is



where R_1 to R_8 are each H,

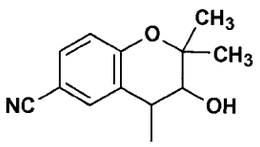
then

(a) Z is other than



, or

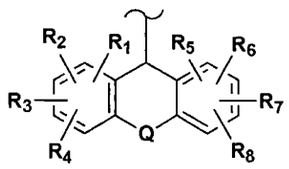
(b) where Z is



,

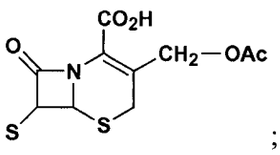
then R_{11} is other than a substituted C_1-C_2-alkylene;

(3) where the tricyclic moiety is



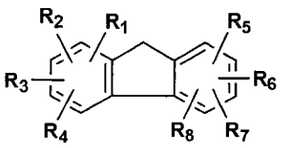
where Q is S or SO_2, and R_1 to R_8 are each H,

then Z is other than

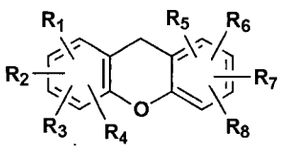


;

(4) where the tricyclic moiety is

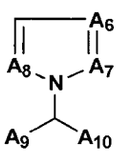


or



where R_1 to R_8 are each H,

then Z is other than



where A_6, A_7 and A_8 are independently N or CH,

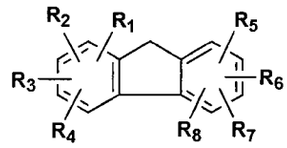
A_9 is $-(CH_2)_d-A_{11}$ where d is 0 to 4;

A_{11} is OH, CO_2H, 5-tetrazolyl, $-COO(C_1-C_4alkyl)_{n_a}$ or CN-;

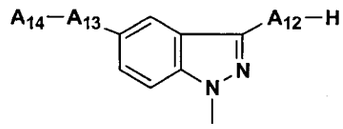
n_a is 0 to 4; and

A_{10} is C_4-C_7 straight chain alkyl;

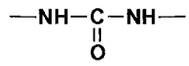
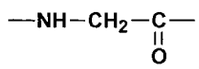
(5) where the tricyclic moiety is



then Z is other than



where A_{12} is O or S; and

A_{13} is O or an NH,  , , , or  ,

wherein the last 3 groups are joined to the aromatic ring through the N-atom;

A_{14} is H,

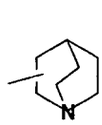
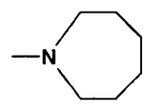
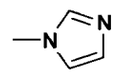
alkyl,

C_3-C_7 cycloalkyl,

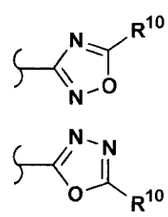
phenyl, naphthyl, anthranyl or fluorenyl optionally substituted, or

a quinolin-2-ylmethoxy or pyridin-ylmethoxy; or

Z is other than

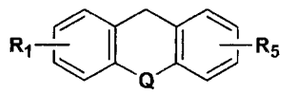
 ,  ,  , or  ; or

Z is other than



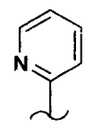
where R^{10} is a non-aromatic azacyclic or non-aromatic azabicyclic ring system;

(6) where the tricyclic moiety is



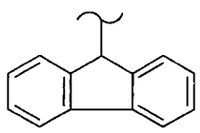
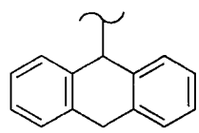
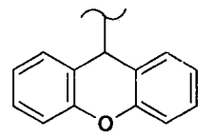
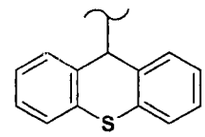
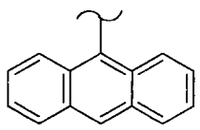
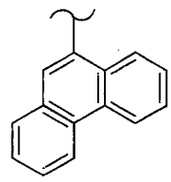
Q is -O-, -S-, -C(R^3R^4)-, -CH_2CH_2-, -CH=CH-CH_2-, -CH_2-CH=CH-, -CH_2-(C=O)-, -(C=O)-CH_2-, $CH_2CH_2CH_2$-, -CH=CH-, -O-CH_2-, -CH_2-O-, -O-CH_2-O-, -CH_2-O-CH_2-, -S-CH_2-, -CH_2-S-, -CH(R^5)CH_2-, -CH_2CH(R^5)-, -(C=O)-, or -(S=O)- wherein R^3 and R^4 independently are hydrogen or C_{1-7}-alkyl; and wherein R^5 is C_{1-7}-alkyl or phenyl;

then Z is other than

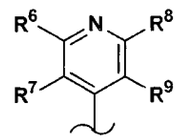


;

(7) where the tricyclic moiety is


,

,

,

,

or

,

then Z is other than



wherein:

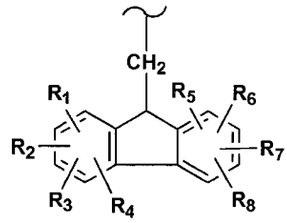
R^6 and R^7 are each independently selected from C_1-C_6alkyl, halo-C_1-C_6alkyl containing 1 to 5 halogen atoms, C_1-C_2alkoxy-C_1-C_6alkyl, nitro-C_1-C_6alkyl, cyano-C_1-C_6alkyl, C_1-C_2alkanoyl-C_1-C_6alkyl, C_1-C_2alkoxycarbonyl-C_1-C_6alkyl, C_1-C_2alkylthio-C_1-C_6alkyl, C_1-C_2alkanesulfinyl-C_1-C_6alkyl, C_1-C_2alkanesulfonyl-C_1-C_6alkyl, C_2-C_6alkenyl, halo-C_2-C_6alkenyl containing 1-5 halogen atoms,

C_2-C_6alkynyl, halo-C_2-C_6alkynyl containing 1-5 halogen atoms, C_3-C_7cycloalkyl and halogen; or

R^6 and R^7, taken together, form a saturated or unsaturated 5- to 7-membered carbocyclic or heterocyclic ring which may contain one or two hetero atoms selected from O and S; and

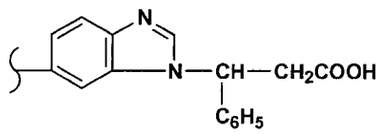
R^8 and R^9 are each independently selected from hydrogen, C_1-C_6alkyl and halogen;

(8) where the tricyclic moiety is



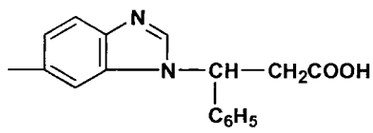
then

a) Z is other than



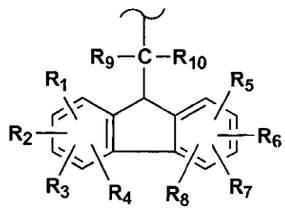
or a homolog thereof,

b) if Z is

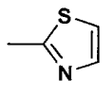


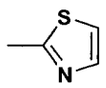
or a homolog thereof, then R_{11} is other than H; or

(9) where the tricyclic moiety is

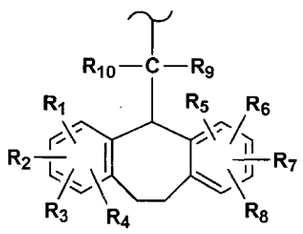


then

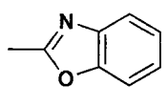
a) Z is other than substituted or unsubstituted  , or

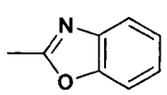
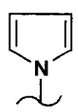
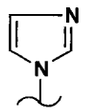
b) where Z is substituted or unsubstituted  , then at least one or R_9 and R_{10} is other than H and/or R_{11} is other than H;

(10) where the tricyclic moiety is

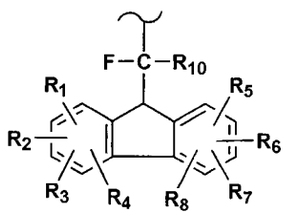


then

a) Z is other than  ,

b) where Z is  ,  ,  ,  , or  , then R_{11} is other than H and/or at least one of R_9 and R_{10} is other than H;

(11) where the tricyclic moiety is

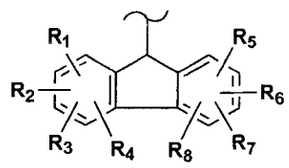


then

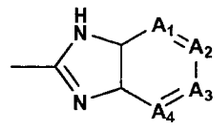
a) Z is other than heteroaryl, or

b) where Z is heteroaryl, then R_{11} is other than H and/or R_{10} is other than H; or

(12) where the tricyclic moiety is



then R_1, R_2, R_3, R_4, R_5, R_6, R_7 and R_8 is other than

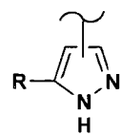


wherein A_1, A_2, A_3 and A_4 are selected from CR_a or N, where R_a is H or a substituent; or

(13) where the tricyclic moiety is

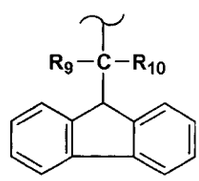


then Z is other than



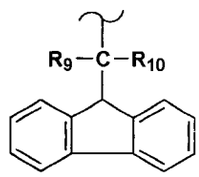
where R is C_3-C_6cycloalkyl optionally substituted by C_1-C_6alkyl or arylalkyl or a homolog thereof;

(14) where the tricyclic moiety is



and Z is heteroaryl containing or heterocyclyl containing an N atom in the ring, then the Z heteroaryl or heterocyclyl cannot be substituted with an R′A group where R′ is optionally substituted heterocyclic or phenyl and A is $(CH_2)_{0\text{-}2}(O)_{0 \text{ or } 1}$ or $(CR^3R^4)_{0 \text{ or } 1}NR^5(CO)_{0 \text{ or } 1}$ where R^3, R^4 = H or R^3 + R^4-imino and R^5 = H or alkyl;

(15) where the tricyclic moiety is

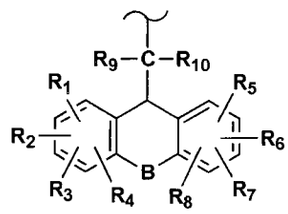


and Z is other than a 5-7 membered heterocyclic ring containing an N, O and/or S which heterocyclic ring is substituted by $-D-A-\overset{O}{\overset{\|}{C}}-R^1$ where D is $^{1-4}$Calkylene, O or S,

A is a 3 to 7 carbocyclic ring or a 5- to 7-membered heterocyclic ring containing N, O and/or S, and

R^1 is OH, alkoxy, or $NR^{10}R^{11}$ where R^{10} and R^{11} can be H or alkyl which Z and/or also may be optionally substituted by 1-3 group which can be C_{1-4}alkyl, C_{1-4}alkoxy, halo, trihalomethyl. CN, or NO_2; or

(16) where the tricyclic moiety is



where B is O or S, then

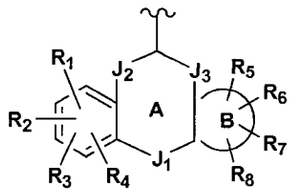
a) Z is other than optionally substituted dihydrofuryl or optionally substituted dihydrothienyl,

b) or if Z is optionally substituted dihydrofuryl or optionally substituted dihydrothienyl, then

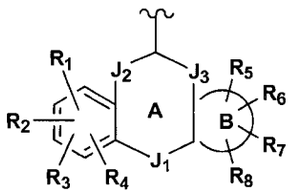
1) at least one of R_9 and/or R_{10} is other than H, or

2) R_{11} is other than H or lower alkyl.

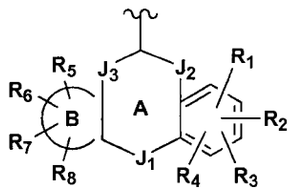
[0015] The tricyclic moiety



as used herein includes the moieties



and



[0016] Preferred B moieties are aryl and heteroaryl and includes phenyl, pyridinyl and pyrazinyl.

[0017] In the above moieties, it is preferred that

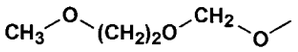
B is a phenyl, pyridinyl or pyrazinyl ring;

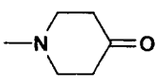
J_1 is O, S, SO, SO_2, a bond, CH_2, or CH_2CH_2; and

J_2 and J_3 are each a bond.

[0018] More preferably J_1 is O, S, SO, SO_2, or a bond, especially O, S, SO, or SO_2.

[0019] More preferably B is pyridinyl substituted with aryl or substituted aryl.

[0020] More preferably R_1, R_2, R_3 are each hydrogen, and R_4 is hydrogen, CF_3, CH_3O, $N(CH_3)_2CH_2CH_2O$-, OH,  ,

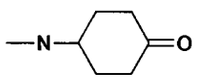
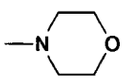
R_5, R_6, and R_7 are each hydrogen and R_8 is hydrogen, hydroxyl, CF_3, alkoxy, halogen, dialkylaminoalkoxy, alkyloxyalkyloxyalkyloxy, alkylamino, heterocyclo, pyridyl, arylalkylamino, alkoxyarylalkylamino, dialkylamino,  , alkoxyaryl, aryl, trifluoromethoxylaryl, carboxyaryl, haloalkyl, dialkylaminoaryl, naphthyl, alkylphenyl, CF_3aryl, alkylcarbonylaminoaryl, dialkylaryl, hydroxyaryl,

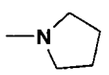
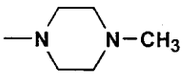
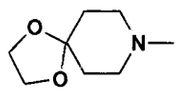
alkoxycarbonylaryl, alkylcarbonylaminoaryl, alkylsulfonylaminoaryl, arylaryl, alkylsulfonylaryl, aminoaryl, arylalkyloxyarylcyanoaryl, or alkylaryl.

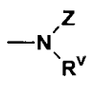
[0021] More preferably R_5, R_6, and R_7 are each hydrogen; and

R_8 is selected from hydrogen, Cl, $(CH_3)_2N(CH_2)_2O$-, $CH_3OCH_2CH_2OCH_2O$-, benzylamino, methoxybenzylamino, $N(CH_3)_2CH_2CH_2O$-, OH, CF_3, CH_3O-, dimethylamino, methoxyphenyl, phenyl, $CF_3OC_6H_4$-, CO_2H-C_6H_4, CN-C_6H_4, s-C_4H_9-C_6H_4-C_2H_5O-C_6H_4, s-C_4H_9-C_6H_4, -C_3H_7-C_6H_4-, n-C_4H_9-O-C_6H_4-, C_2H_5-C_6H_4-, t-C_4H_9-C_6H_4-, $CH_3COC_6H_4$-, $C_6H_5CH_2OC_6H_4$-, C_6H_5-C_6H_4-, C_6H_5-O-C_6H_4-, $CH_3SC_6H_4$-, $NH_2C_6H_4$-, CH_3-SO_2-NHC_6H_4-, F-C_6H_4, C_6H_5-, ClC_6H_4,

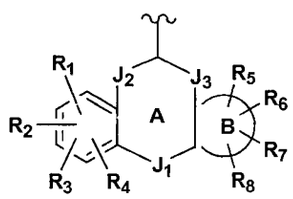
-diCH_3amino, naphthyl, $CH_3C_6H_4$, $CF_3C_6H_4$-, $CH_3CONHC_6H_4$-, $CH_3OC_6H_4$,  ,

di-$CH_3C_6H_3$-, HOC_6H_4-, $CH_3OCOC_6H_4$-,  ,  ,

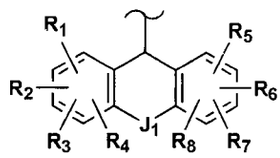
 ,  and  .

[0022] It is preferred that in the compounds of formula I of the invention where Z is heteroaryl or heterocyclo and the heteroaryl and/or heterocyclo is fused to an aryl group, the point of attachment of the fused group to the N atom of the  will be with the heteroaryl or heterocyclo portion and not the aryl portion.

[0023] In preferred embodiments, the moiety



(also referred to as the tricyclic moiety) is



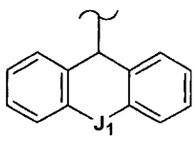
[0024] More preferred embodiments are those where J_1 is O, S, SO, SO_2, a bond, CH_2, or CH_2CH_2;

R_1 is selected from hydrogen, CF_3, alkoxy, halogen, hydroxyl and dialkylaminoalkoxy; and

R_5 is selected from hydrogen, CF_3, alkoxy, halogen, amino, dialkylamino, heterocyclo, aryl, carboxyaryl, alkoxyaryl, alkylaryl, heterocyclocarbonylaryl, alkoxy(halo)aryl, carboxy(halo)aryl, dialkylaminocarbonylaryl, alkylamino, hydroxyl, dialkylaminoalkoxy, arylalkylamino, alkoxyarylalkylamino, alkylheterocyclo, arylalkyl, heterocycloalkoxy, arylheterocyclo, arylalkyl(alkyl)amino, haloaryl, dialkylaminoaryl, haloaryl, alkoxyalkoxyalkoxyl, alkylcarbonylamino, heteroaryl, dialkylaryl, hydroxyaryl, alkoxycarbonylaryl, alkylcarbonylaminoaryl, alkylsulfonylaminoaryl, aryloxyaryl, alkylthioaryl, aminoaryl, alkylcarbonylaryl, arylalkoxyaryl, and cyanoaryl.

[0025] Also preferred are compounds of formula I

(1) where the tricyclic moiety is exclusive of



where J_1 is other than a bond, $-CH_2CH_2-$, or $-CH=CH-$; and

(2) where the tricyclic moiety ring B includes one, two or three hetero atoms selected from N, O, and S, preferably N.

[0026] Preferred compounds of the invention within the scope of formula I are those, including all enantiomers and diastereomers, or prodrug ester or pharmaceutically acceptable salts or hydrates, thereof, in which

Z is a 5- to 6-membered heteroaryl or heterocyclo group, each group substituted with one, two or three groups which are the same or different and are

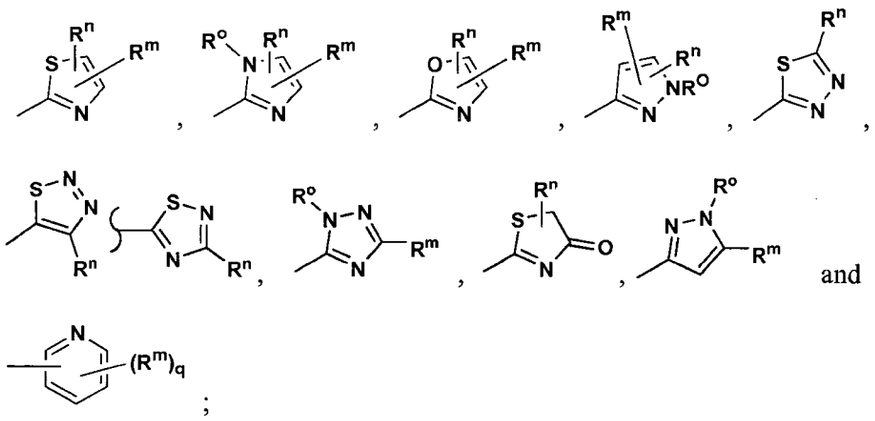
independently selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, nitro, cyano, OR^c, NR^aR^b, $C(=O)R^a$, CO_2R^a, $C(=O)NR^aR^b$, $-O-C(=O)R^a$, $NR^aC(=O)R^b$, $NR^aC(=O)OR^b$, $NR^aC(=S)OR^b$, $S(O)_pR^c$, $NR^aSO_2R^c$, $SO_2NR^aR^b$, cycloalkyl, cycloalkenyl, heterocyclo, aryl, and heteroaryl;

R^a and R^b are the same or different and at each occurrence are independently selected from (i) hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclo; or (ii) where possible together with the atoms to which they are attached R^a is taken together with R^b to form a heteroaryl or heterocyclo ring; and

R^c at each occurrence is independently selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclo.

[0027] More preferably, Z is selected from

Z is selected from:



;

R^m and R^n are the same or different and at each occurrence are independently selected from any of the heteroaryl substituents for Z set out above and are preferably selected from hydrogen, halogen, alkoxy, $-COR_1^a$, $-CO_2R_1^a$, $-C(O)N(R_1^a)(R_1^b)$, C_{1-6}alkyl, CF_3, substituted alkyl, aryl-NHC(O)-aryl, aryl, arylalkyl, CH_2OH, $-SR_1^a$, $S(O)_{1-2}R_1^c$, $N(R_1^a)(R_1^b)$, CH_2F, cyano, C_{3-6}cycloalkyl, and a 5 to-7-membered heteroaryl with a heteroatom selected from N, O or S;

R^o is hydrogen or C_{1-6}alkyl;

R_1^a and R_1^b are the same or different and at each occurrence are independently selected from hydrogen, alkyl, substituted alkyl, C(=O)alkyl, CO_2(alkyl), SO_2alkyl, alkenyl, substituted alkenyl, alkoxy, amino, substituted amino, aryl, heteroaryl, heterocyclo, and cycloalkyl, provided R_1^a and R_1^b are not both alkoxy, amino, or substituted amino;

or R_1^a and R_1^b, where possible can be taken together with the nitrogen to which they are attached to form a 5-, 6- or 7-membered heteroaryl or cycloheteroalkyl ring which contains 1, 2 or 3 hetero atoms which can be N, O, or S;

R_1^c is selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, amino, substituted amino, heteroaryl, heterocyclo, cycloalkyl, and aryl; and

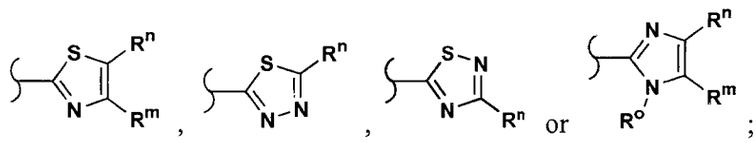
q is 1 or 2.

R_1^c is selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, amino, substituted amino, heteroaryl, heterocyclo, cycloalkyl, and aryl;

R^o is hydrogen or alkyl; and

q is 1 or 2.

[0028] Still, more preferably, Z is selected from



;

R^m and R^n are the same or different and at each occurrence are independently selected from hydrogen, -C(O)N(R_1^a)(R_1^b), C_{1-6}alkyl, CF_3, CH_2OH, -SR_1^a, N(R_1^a)(R_1^b), CH_2F, cyano, and C_{3-6}cycloalkyl;

R^o is hydrogen or C_{1-6}alkyl; and

R_1^a and R_1^b are the same or different and at each occurrence are independently selected from hydrogen, C_{1-6}alkyl, and C_{3-6}cycloalkyl.

[0029] In other preferred embodiments R^m is selected from hydrogen, C_1-C_4alkyl, phenyl, CO_2alkyl, naphthyl, quinolinyl, and -C(R^{18})(R^{19})-T wherein the naphthyl or

quinolinyl group is substituted by one or more substituents selected from the group consisting of hydrogen, amino, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, perfluoro substituted C_{1-4}alkyl (for example CF_3), cyano, nitro, -C(O)NHR^{22} (where R^{22} is phenyl which may optionally be substituted), and halogen;

R^n is selected from hydrogen, bromo, chloro, and CH_3;

T is selected from a cycloalkyl, cycloalkenyl, heterocyclo, aryl, and heteroaryl ring where each ring is substituted by 0-4 R^{20} and 0-1 R^{21};

R^{18} and R^{19} are the same or different and are independently at each occurrence selected from hydrogen, halogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, cyano, nitro, NR^{a}R^b, and CHO; or

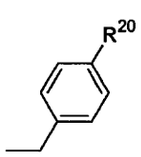
R^{18} and R^{19} combine to form =O or a double bond, wherein a carbon linked to the double bond is substituted by hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, amino, substituted amino, heteroaryl, heterocyclo, cycloalkyl, or aryl; and

R^{20} and R^{21} are the same or different and at each occurrence are independently selected from hydrogen, halogen, hydroxy, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, aryloxy, aryl, cycloalkyl, heteroaryl, heterocyclo, cyano, heteroarylaminocarboyl, heterocyclocarbonyl, cyanoalkyl, alkylaminoalkyl, hydroxyalkyl, hydroxyaryl, aryloxyalkyl, alkoxyalkyl, nitro, oxo, $NR_1{}^aR_1{}^b$, CHO, CO_2alkyl, $CONR_1{}^aR_1{}^b$, $CH_2NR_1{}^aR_1{}^b$, CO_2H, CH_2OH, $CH_2NHC(O)R_1{}^c$, $NHCOR_1{}^c$, $NHCONR_1{}^aR_1{}^b$, $NHSO_pR_1{}^c$, $-SO_2NR_1{}^aR_1{}^b$, $NR^aSO_2NR_1{}^aR_1{}^b$, and $NR^aSO_pR_1{}^c$; or

R^7 and R^8 located on adjacent atoms can be taken together to form an optionally substituted cycloalkyl, aryl, heteroaryl, or heterocyclo ring.

[0030] In a more preferred embodiment,

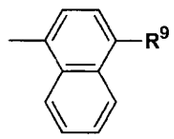
R^n is H;

R^m is 

;

R^{18} and R^{19} are the same or different and at each occurrence are independently selected from hydrogen, halogen, and hydroxy; or R^{18} and R^{19} combine to form =O; and

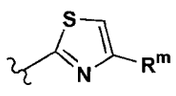
R^{20} is selected from C_{1-4}alkoxy, halogen, pyrimidine, isoxazole, pyrazole, and pyridine, where the C_{1-4}alkoxy, pyrimidine, isoxazole, pyrazole, or pyridine groups are substituted by hydrogen, morpholinyl, C_{1-4}alkoxy, and C_{1-4}alkyl;

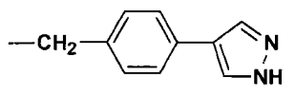
or R^m is selected from 

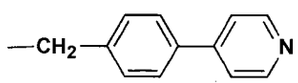
, and CO_2C_{1-4}alkyl; and

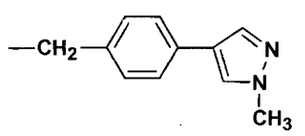
R^9 is selected from methyl, CF_3, fluoro, chloro, and bromo.

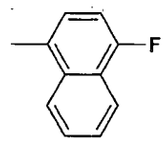
[0031] In still more preferred embodiments,

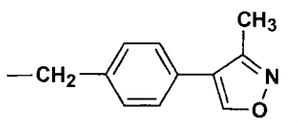
Z is 

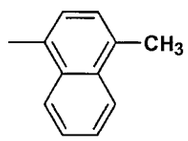
, where R^m is 

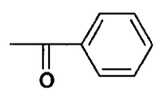
, 

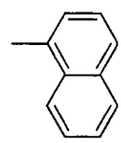
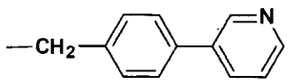
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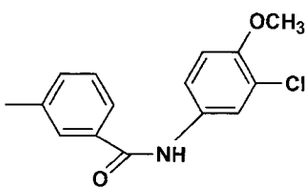
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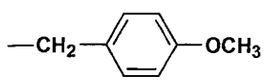
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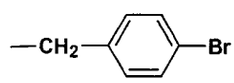
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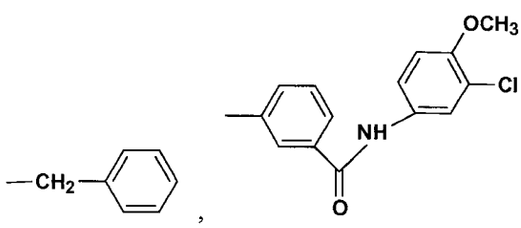
, 

, 
, 

, H, CH_3, $-CO_2C_2H_5$, $-CO_2CH_3$, 

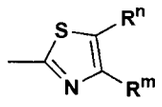
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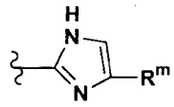
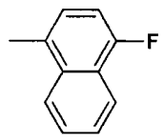
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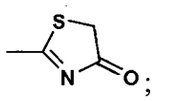
, 

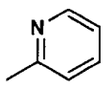
;

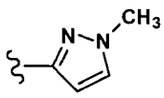
, where R^n is $S(CH_3)$, $S(O)(CH_3)$, $S(O)_2CH_3$, and CH_3;

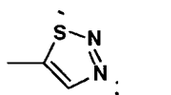
Z is  , where R^n is CH_3, R^m is CH_3;

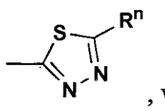
Z is  , where R^m is  or H;

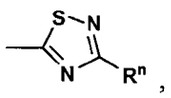
Z is  ;

Z is  ;

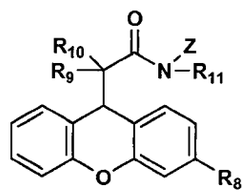
Z is  ;

Z is  ;

Z is  , where R^n is CH_3, H, CF_3, C(O)OEt, $C(O)NH_2$, C(O)NH(cyclopropyl), $C(O)NHCH_3$, C(O)NHEt, CH_2OH, S(methyl), $N(methyl)_2$, CH_2F, cyano, ethyl, or cyclopropyl; or

Z is  , where R^n is CH_3 or H.

[0032] Also preferred are compounds having the structure



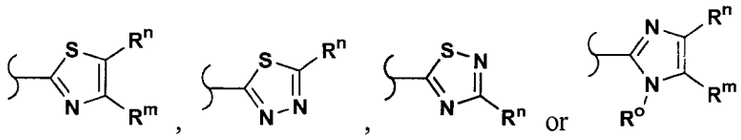
or an enantiomer, diastereomer, tautomer or a pharmaceutically acceptable salt thereof, wherein:

R_8 is hydroxy, cyano, $-C(=O)NR_{14}R_{15}$, $-CO_2R_{14}$, $-C(NH_2)=NOH$, $-NR_{14}C(=O)OR_{15}$, $-OC(O)NR_{14}R_{15}$, $-NHC(O)NR_{14}R_{15}$, or $-NHC(O)R_{15}$;

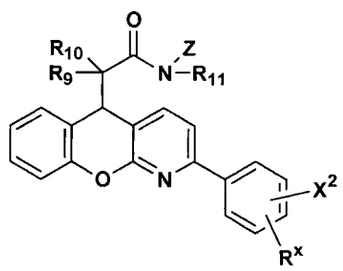
R_9 and R_{10} are the same or different and at each occurrence are independently selected from (i) hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, nitro, cyano, $-OR_{14}$, $-NR_{14}R_{15}$, $-C(=O)R_{14}$, $-CO_2R_{14}$, $-C(=O)NR_{14}R_{15}$, $-O-C(=O)R_{14}$, $-NR_{14}C(=O)R_{15}$, $-NR_{14}C(=O)OR_{15}$, $-NR_{14}C(=S)OR_{15}$, $-S(O)_pR_{17}$, $-NR_{14}SO_2R_{17}$, $-SO_2NR_{14}R_{15}$, cycloalkyl, cycloalkenyl, heterocyclo, aryl, and heteroaryl; or (ii) together with the atom to which the are attached, R_9 and R_{10} are taken together to form a carbonyl, alkenyl, substituted alkenyl, cycloalkyl, cycloalkenyl, or heterocyclo group;

R_{11} is selected from hydrogen, alkyl, substituted alkyl, C(=O)alkyl, CO_2(alkyl), SO_2alkyl, alkoxy, amino, substituted amino, aryl, heteroaryl, heterocyclo, and cycloalkyl; and

Z is a heteroaryl ring which is linked via a carbon atom to the N atom where Z is preferably

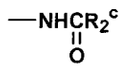
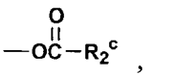
 and R^n, R^m, and R^o are as defined above.

[0033] In addition, preferred are compounds of the structure



or an enantiomer, diastereomer, or tautomer thereof, or a prodrug ester thereof, or a pharmaceutically acceptable salt thereof, wherein:

X^2 is halogen, alkoxy, H, or alkyl;

R^x is H, $C(O)NR_2{}^aR_2{}^b$, $OR_2{}^c$, $R_2{}^a$, COOH, CF_3,  ,  , $-NHSO_2R_2{}^c$, aryl, aryloxy, alkylthio, amino, acyl or cyano;

R_2^a and R_2^b are the same or different and at each occurrence are independently selected from hydrogen, alkyl, substituted alkyl, C(=O)alkyl, CO_2(alkyl), SO_2alkyl, hydrogen, alkenyl, substituted alkenyl, alkoxy, amino, substituted amino, aryl, heteroaryl, heterocyclo, and cycloalkyl;

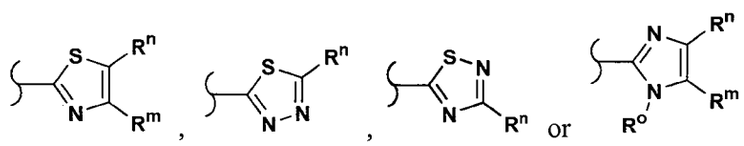
or R_2^a and R_2^b, where possible can be taken together with the nitrogen to which they are attached to form a 5-, 6- or 7-membered heteroaryl or cycloheteroalkyl ring which contains 1, 2 or 3 hetero atoms which can be N, O, or S;

R_2^c is selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, amino, substituted amino, heteroaryl, heterocyclo, cycloalkyl, and aryl;

R_9 and R_{10} are the same or different and at each occurrence are independently selected from (i) hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, nitro, cyano, OR_{14}, $NR_{14}R_{15}$, $C(=O)R_{14}$, CO_2R_{14}, $C(=O)NR_{14}R_{15}$, $-O-C(=O)R_{14}$, $NR_{14}C(=O)R_{15}$, $NR_{14}C(=O)OR_{15}$, $NR_{14}C(=S)OR_{15}$, $S(O)_pR_{17}$, $NR_{14}SO_2R_{17}$, $SO_2NR_{14}R_{15}$, cycloalkyl, cycloalkenyl, heterocyclo, aryl, and heteroaryl; or (ii) together with the atom to which they are attached, R_9 and R_{10} are taken together to form a carbonyl, alkenyl, substituted alkenyl, cycloalkyl, cycloalkenyl, or heterocyclo group; and

R_{11} is selected from hydrogen, alkyl, substituted alkyl, C(=O)alkyl, CO_2(alkyl), SO_2alkyl, alkoxy, amino, substituted amino, aryl, heteroaryl, heterocyclo, and cycloalkyl.

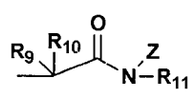
[0034] In a more preferred embodiment, Z is a heteroaryl ring which is linked via a carbon atom to the N atom, where Z is preferably



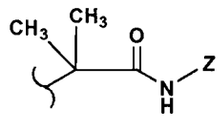
and R^n, R^m, and R^o are as defined above.

[0035] Also preferred are

(1) compounds of formula I where

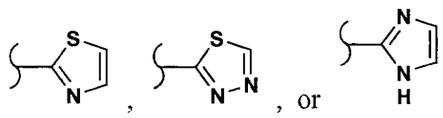


is

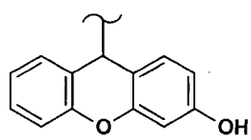


where

Z is

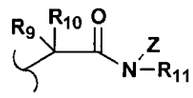


and the tricyclic moiety is

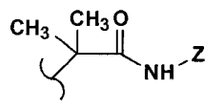


; and

(2) compounds of formula I wherein

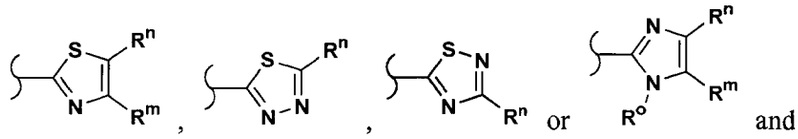


is



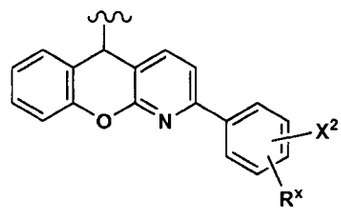
;

Z is

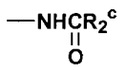
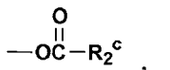


and R^n, R^m, and R^o are as defined above;

the tricyclic moiety is

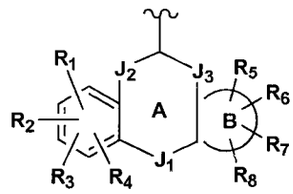


X^2 is halogen, alkoxy, H, or alkyl; and

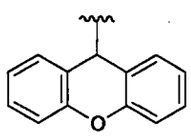
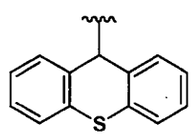
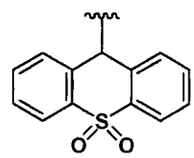
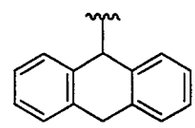
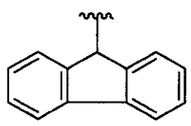
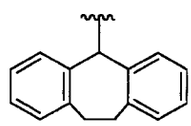
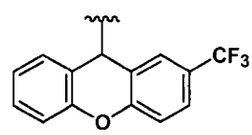
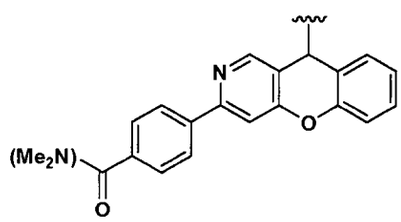
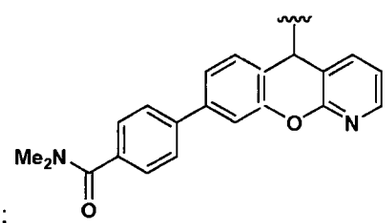
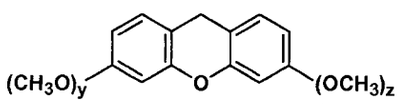
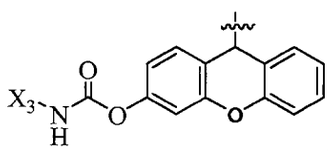
R^x is H, $C(O)NR_2^aR_2^b$, OR_2^c, R_2^a, COOH, CF_3,  ,  , $-NHSO_2R_2^c$, aryl, aryloxy, alkylthio, amino, acyl or cyano;

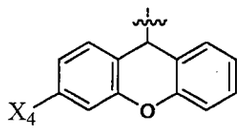
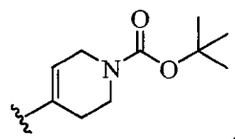
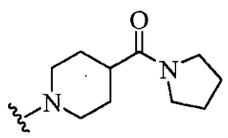
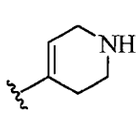
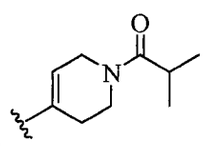
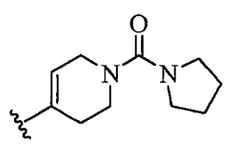
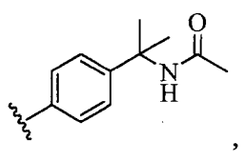
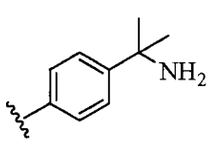
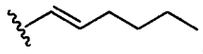
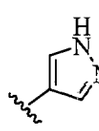
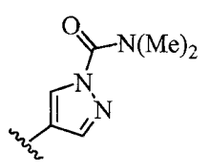
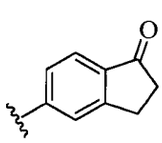
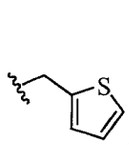
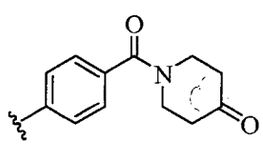
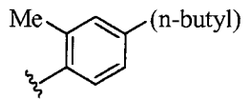
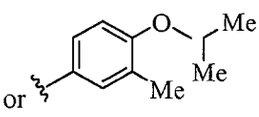
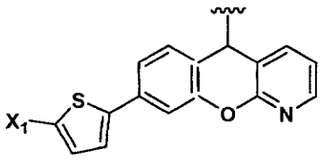
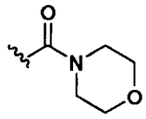
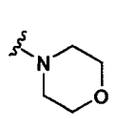
(where R_2^a, R_2^b and R_2^c are as defined hereinafter).

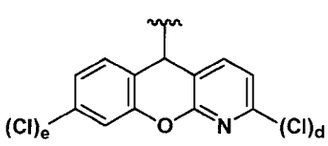
[0036] In other preferred embodiments,

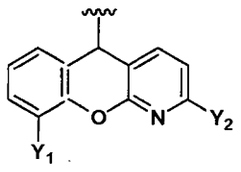


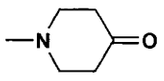
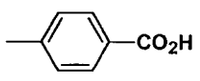
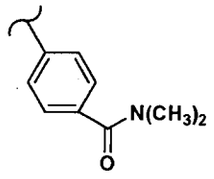
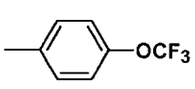
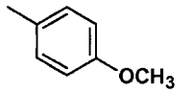
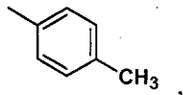
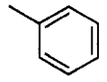
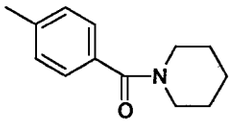
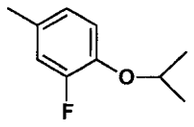
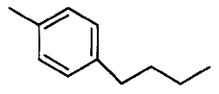
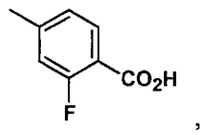
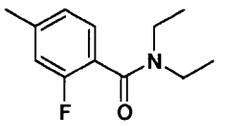
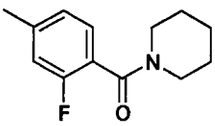
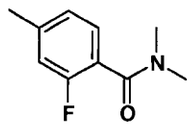
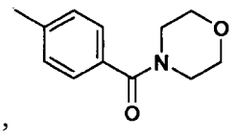
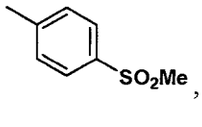
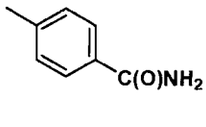
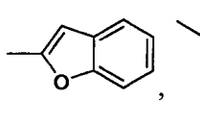
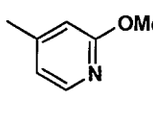
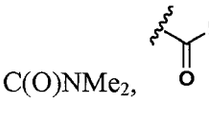
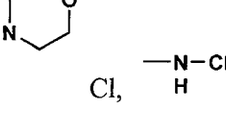
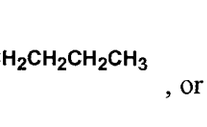
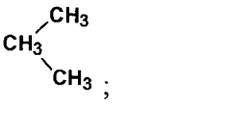
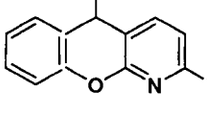
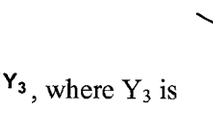
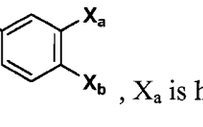
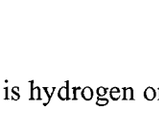
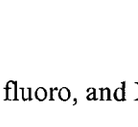
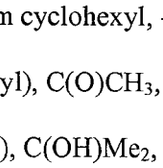
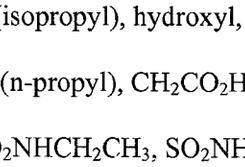
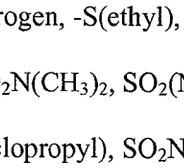
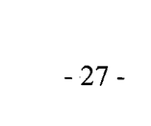
is

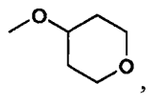

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, where z is 0 or 1 and y is 0 or 1;

, where X_3 is benzyl, $(CH_2)_3CH_3$, Ethyl, CH_2(2-furyl), cyclohexyl, $(CH_2)_7CH_3$, $(CH_2)_2$(phenyl), CH_2(2-thienyl), CH_2(4-fluorophenyl), tert-butyl, $CH(CH_3)$ethyl, $(CH_2)_2$(4-methoxyphenyl), 4-methoxyphenyl, or CH_2(cyclohexyl);

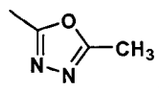

, where X_4 is NHC(O)O(cyclohexyl), NHC(O)O(methyl), -C≡C-$(CH_2)_2CH_3$, C(O)NHCH$_2$(phenyl), C(O)CH$_3$, -NHC(O)NH(CH_2)(O)N$(Me)_2$, -NHC(O)NH(CH_2)(N-pyrollidinyl),  ,  ,  ,  ,  ,  ,  ,  , -$(CH2)_5CH_3$,  ,  ,  ,  ,  ,  , 
;  , where X_1 is CO_2H,  , N$(Me)_2$,  , or C(O)CH$_3$;

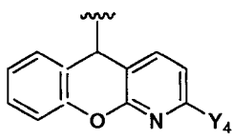
 , where d is 0 or 1 and e is 0 or 1;

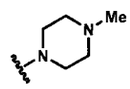

, where Y_1 is hydrogen or halogen; and Y_2 is

$-OCH_3$, $-N(CH_3)_2$,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , ,  , X_a is hydrogen or fluoro, and X_b is selected from cyclohexyl, -O(isopropyl), hydroxyl, hydrogen, -S(ethyl), SO_2(ethyl), SO_2(isopropyl), $C(O)CH_3$, -O(n-propyl), CH_2CO_2H, $SO_2N(CH_3)_2$, SO_2(N-morpholinyl), $C(OH)Me_2$, $SO_2NHCH_2CH_3$, SO_2NH(cyclopropyl), SO_2NH(isopropyl),

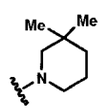
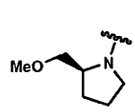
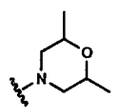
$CH2CO_2CH_3$, $CH(OH)CH_3$, $CH(OH)$(Isopropyl), $S(O)CH_3$,  ,

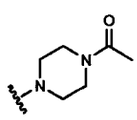
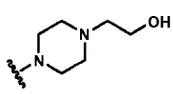
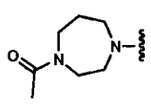
O(cyclohexyl), O(cyclopentyl), and  ;

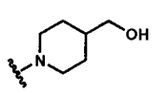
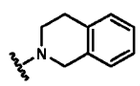
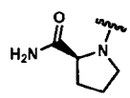
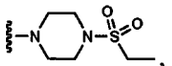
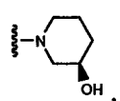
 , where Y_4 is NR_aR_b, NEt_2, piperidine, NMe_2, NMeEt, pyrrolidine,

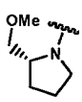
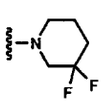
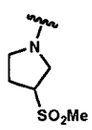
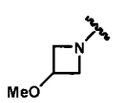
NHMe, NMe(*n*-Pr), NMe(Bn),  , morpholine, NMe(*i*-Pr), NEt_2, NMe_2,

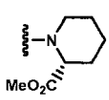
piperidine, NEt_2, NEt_2, piperidine, piperidine, piperidine, piperidine, $NMe(CH_2)_2CN$, 4-Me-,

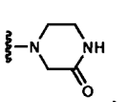
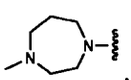
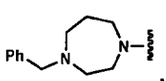
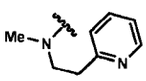
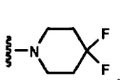
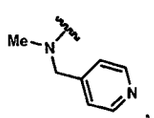
piperidine, 4-OH-piperidine, $NMe(CH_2)_2CH(CH_3)_2$,  ,  ,  ,

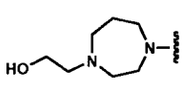
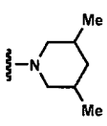
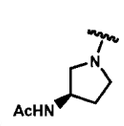
 ,  , $N(Me)(CH_2)_2Ph$,  , 4-Bn-piperidine,

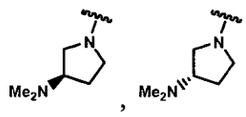
 ,  , 4-Ph-piperidine,  ,  ,  ,

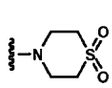
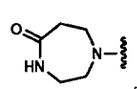
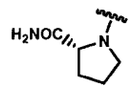
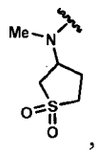
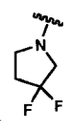
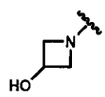
 , $NMe(CH_2)_2SO_2Me$,  ,  ,  , 4-(CF_3)-piperidine,

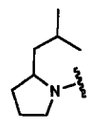
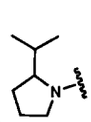
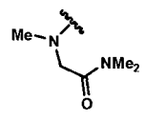
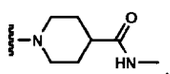
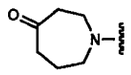
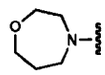
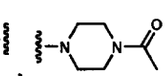
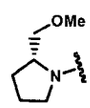
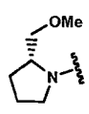
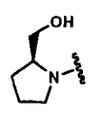
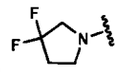
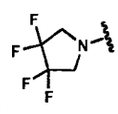
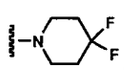
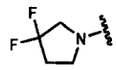
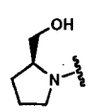
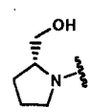
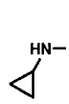
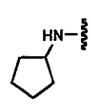
 , $NMe(n\text{-Bu})$, $NMeCH_2CO_2Me$, $NMe(CH_2)_2OH$, $NMe(CH_2)_2OMe$,

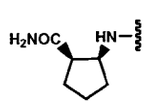
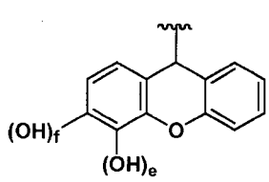
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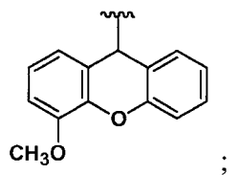
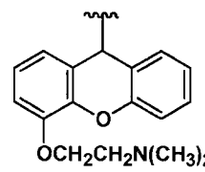
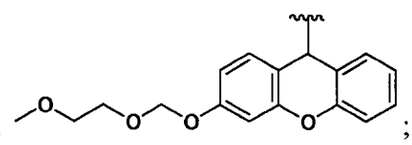
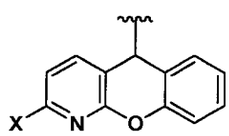
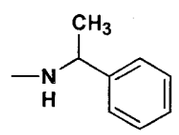
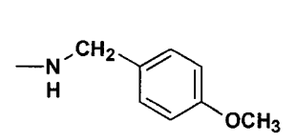
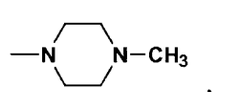
$NMe(CH_2)_2O(t\text{-Bu})$,  , $N((CH_2)_2OH)_2$,  ,  ,

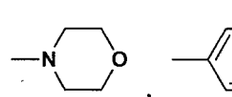


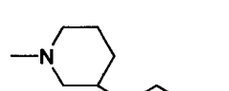
, 4-OMe-piperidine,







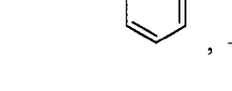



, $NEt(CH_2)_2OH$,





, $NMe(CH_2)_2CN$,
morpholinyl, NMe(*i*-Pr),



, NEtMe,

$NMe(CH_2)CO_2H$,


, pyrrolidine,

, NMe(*n*-Pr),

NMeEt, NMe(*n*-Pr), NMe_2, NHMe, NHBn,



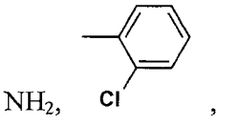
, NH*i*Pr,
$NH(CH_2)_2Ph$, $NH(CH_2)_2Ome$, $NH(CH_2)_2C(CH_3)_3$, $NH(CH_2)_2OH$, NH(*n*-Pr),
$NH(CH_2)_3OH$,

, or NHMe;

, where e is 0 or 1 and f is 0 or 1, provided that only one of e and f can be 1;

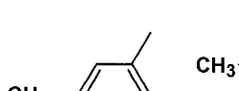










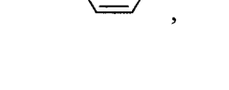


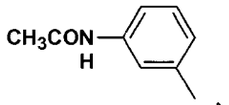


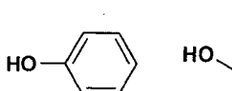


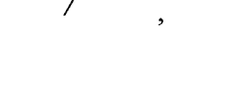


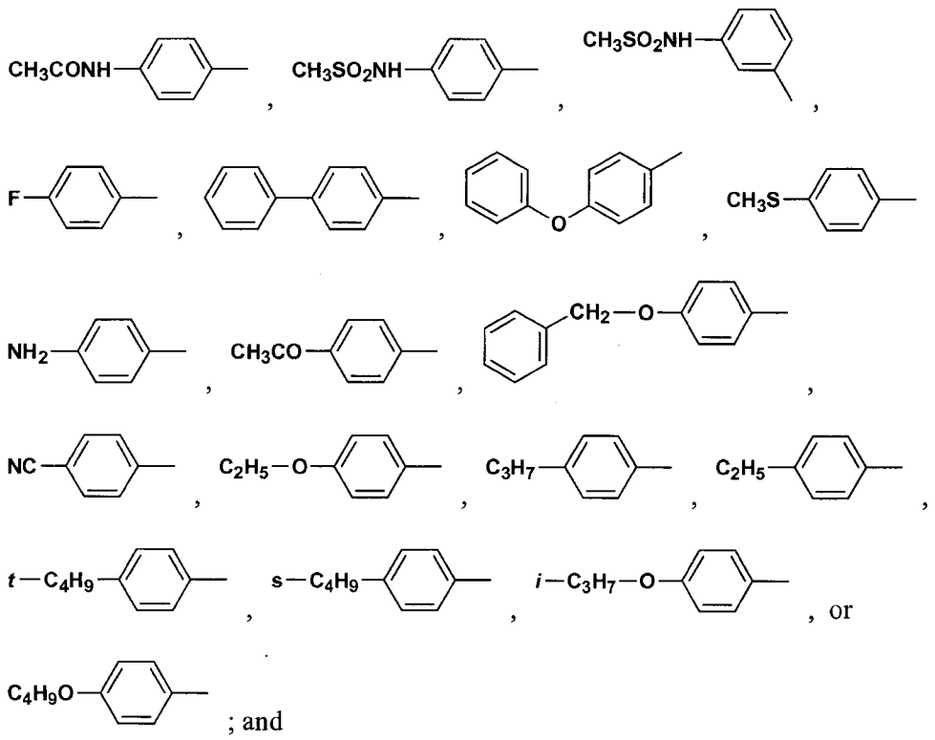
5 , $-N(CH_3)_2$,



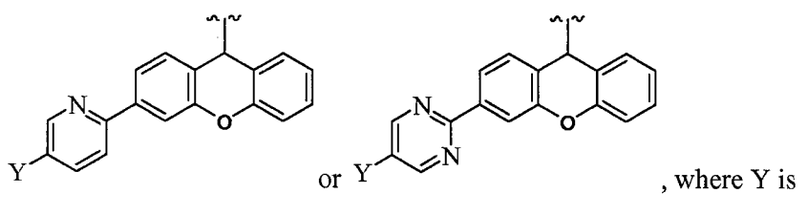








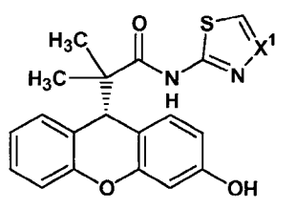
; and



, where Y is

$C_{1\text{-}6}$alkyl, C(O)N($C_{1\text{-}6}$alkyl)$_2$, COOH, and O$C_{1\text{-}6}$alkyl.

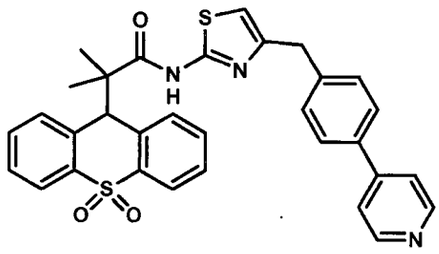
[0037] Most preferred are compounds of the structure

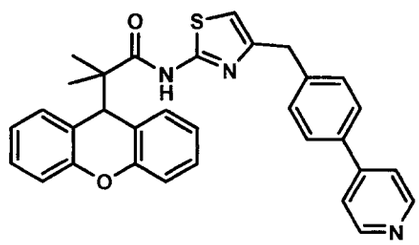


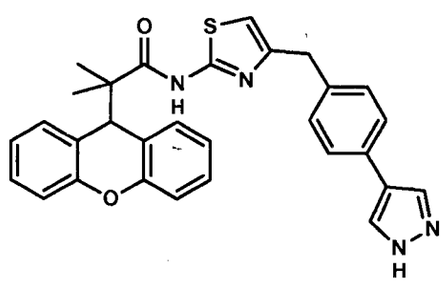
IC

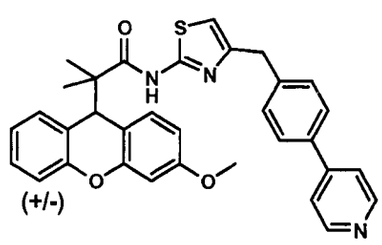
X^1 = CH, or

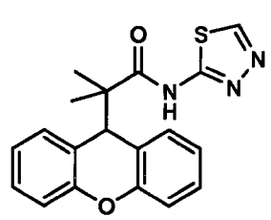
X^1 = N,

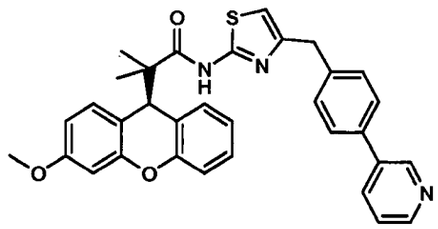

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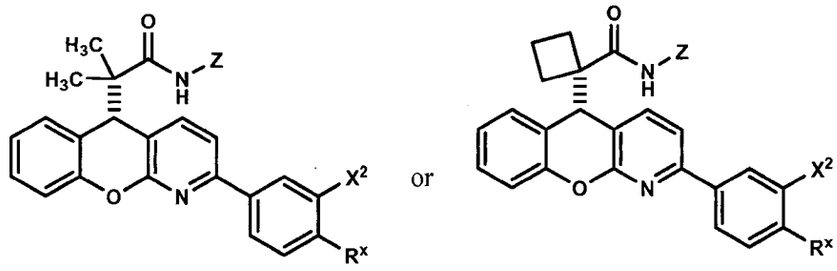

,


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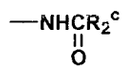
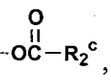


and compounds of the structure



wherein:

X^2 is H, halogen, or alkyl;

R^x is H, $C(O)NR_2^aR_2^b$, OR_2^a, R_2^a, COOH, CF_3,  ,  , $-NHSO_2R_2^c$, aryl, aryloxy, alkylthio, amino, acyl or cyano;

R_2^a is selected from hydrogen, alkyl, substituted alkyl, C(=O)alkyl, CO_2(alkyl), SO_2alkyl, hydrogen, alkenyl, substituted alkenyl, alkoxy, amino, substituted amino, aryl, heteroaryl, heterocyclo, and cycloalkyl;

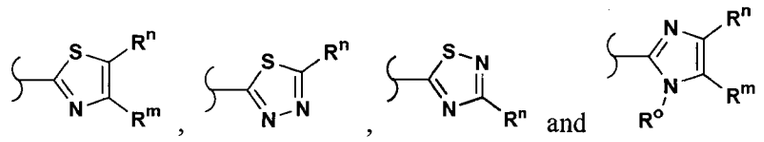
R_2^b is selected from alkyl, substituted alkyl, C(=O)alkyl, CO_2(alkyl), SO_2alkyl, hydrogen, alkenyl, substituted alkenyl, alkoxy, amino, substituted amino, aryl, heteroaryl, heterocyclo, and cycloalkyl;

or R_2^a and R_2^b are taken together with the nitrogen to which they are attached to form a 5-, 6- or 7-membered heteroaryl or cycloheteroalkyl ring which contains 1, 2 or 3 hetero atoms which can be N, O, or S; and

R_2^c is selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, amino, substituted amino, heteroaryl, heterocyclo, cycloalkyl, and aryl.

wherein R^a, R^b and R^c are as defined hereinafter, preferably $C(O)NR^aR^b$, alkoxy or alkyl.

[0038] Still, more preferably, Z is selected from



R^m and R^n are the same or different and at each occurrence are independently selected from hydrogen, -C(O)N(R_1^a)(R_1^b), C_{1-6}alkyl, CF_3, CH_2OH, -SR_1^a, N(R_1^a)(R_1^b), CH_2F, cyano, and C_{3-6}cycloalkyl;

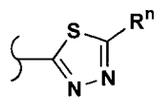
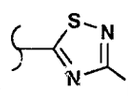
R^o is hydrogen or C_{1-6}alkyl; and

R_1^a and R_1^b are the same or different and at each occurrence are independently selected from hydrogen, C_{1-6}alkyl, and C_{3-6}cycloalkyl.

[0039] Most preferred is the S-enantiomer over the R-enantiomer.

[0040] Most preferred R^x is at the 4-position and R^x is tertiary amide (i.e., R^x = C(O)NR^aR^b), alkoxy, or alkyl.

[0041] More preferred is X^2 = F.

[0042] More preferred is where Z is  or  ; and R^n is CH_3, H, CF_3, C(O)OEt, $C(O)NH_2$, C(O)NH(cyclopropyl), $C(O)NHCH_3$, C(O)NHEt, CH_2OH, S(methyl), N(methyl)$_2$, CH_2F, cyano, ethyl, or cyclopropyl.

[0043] In another embodiment of the present invention, there is provided pharmaceutical compositions useful in treating endocrine disorders, rheumatic disorders, collagen diseases, dermatologic disease, allergic disease, ophthalmic disease, respiratory disease, hematologic disease, gastrointestinal disease, inflammatory disease, autoimmune disease, diabetes, obesity, and neoplastic disease, as well as other uses as described herein, which including a therapeutically effective amount (depending upon use) of a compound of formula (I) of the invention and a pharmaceutically acceptable carrier.

[0044] In still another embodiment, the present invention provides a method of treating endocrine disorders, rheumatic disorders, collagen diseases, dermatologic disease, allergic disease, ophthalmic disease, respiratory disease, hematologic disease, gastrointestinal disease, inflammatory disease, immune disease, metabolic disease (diabetes and/or obesity), and neoplastic disease. A disease associated with the expression product of a gene whose transcription is stimulated or repressed by

glucocorticoid receptors, or a disease associated with AP-1- and/or NF-κB-induced transcription, or a disease associated with AP-1 and/or NF-κB dependent gene expression, wherein the disease is associated with the expression of a gene under the regulatory control of AP-1 and/or NF-κB (particularly AP-1), including inflammatory and immune diseases and disorders as described hereinafter, which includes the step of administering a therapeutically effective amount of a compound of formula (I) of the invention to a patient.

[0045] Another embodiment of the present invention involves a method for treating a disease or disorder associated with the expression product of a gene whose transcription is stimulated or repressed by glucocorticoid receptors, or a method of treating a disease or disorder associated with AP-1- and/or NF-κB- (particularly AP-1-) induced transcription, or a method for treating a disease or disorder associated with AP-1 and/or NF-κB (particularly AP-1) dependent gene expression, wherein the disease is associated with the expression of a gene under the regulatory control of AP-1 and/or NF-κβ (particularly AP-1), such as inflammatory and immune disorders, cancer and tumor disorders, such as solid tumors, lymphomas and leukemia, and fungal infections such as mycosis fungoides.

[0046] The term "disease associated with GR transactivation," as used herein, refers to a disease associated with the transcription product of a gene whose transcription is transactivated by a GR. Such diseases include, but are not limited to: osteoporosis, diabetes, glaucoma, muscle loss, facial swelling, personality changes, hypertension, obesity, depression, and AIDS, the condition of wound healing, primary or secondary andrenocortical insufficiency, and Addison's disease.

[0047] The term "treat", "treating", or "treatment," in all grammatical forms, as used herein refers to the prevention, reduction, or amelioration, partial or complete alleviation, or cure of a disease, disorder, or condition, wherein prevention indicates treatment of a person at risk for developing such a disease, disorder or condition.

[0048] The terms "glucocorticoid receptor" and "GR," as used herein, refer either to a member of the nuclear hormone receptor ("NHR") family of transcription factors which bind glucocorticoids and either stimulate or repress transcription, or to GR-beta.

[0049] These terms, as used herein, refer to glucocorticoid receptor from any source, including but not limited to: human glucocorticoid receptor as disclosed in Weinberger, et al., *Science*, 228:740-742 (1985), and in Weinberger, et al., *Nature*, 318:670-672 (1986); rat glucocorticoid receptor as disclosed in Miesfeld, R., *Nature*, 312:779-781 (1985); mouse glucocortoid receptor as disclosed in Danielson, M. et al., *EMBO* J., 5:2513; sheep glucocorticoid receptor as disclosed in Yang, K. et al., *J. Mol. Endocrinol.*, 8:173-180 (1992); marmoset glucocortoid receptor as disclosed in Brandon, D.D. et al., *J. Mol. Endocrinol.* 7:89-96 (1991); and human GR-beta as disclosed in Hollenberg, S.M. et al., *Nature*, 318:635 (1985); Bamberger, C.M. et al., *J. Clin Invest.*, 95:2435 (1995).

[0050] The term, "disease or disorder associated with AP-1 and/or NF-κB" as used herein, refers to a disease associated with the expression product of a gene under the regulatory control of AP-1 and/or NF-κB. Such diseases include, but are not limited to: inflammatory and immune diseases and disorders; cancer and tumor disorders, such as solid tumors, lymphomas and leukemia; and fungal infections such as mycosis fungoides.

[0051] The term "inflammatory or immune associated diseases or disorders" is used herein to encompass any condition, disease, or disorder that has an inflammatory or immune component, including, but not limited to, each of the following conditions: transplant rejection (e.g., kidney, liver, heart, lung, pancreas (e.g., islet cells), bone marrow, cornea, small bowel, skin allografts, skin homografts (such as employed in burn treatment), heart valve xenografts, serum sickness, and graft vs. host disease, autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, Type I and Type II diabetes, juvenile diabetes, obesity, asthma, inflammatory bowel disease (such as Crohn's disease and ulcerative colitis), pyoderma gangrenum, lupus (systemic lupus erythematosis), myasthenia gravis, psoriasis, dermatitis, dermatomyositis; eczema, seborrhea, pulmonary inflammation, eye uveitis, hepatitis, Graves' disease, Hashimoto's thyroiditis, autoimmune thyroiditis, Behcet's or Sjorgen's syndrome (dry eyes/mouth), pernicious or immunohaemolytic anaemia, atherosclerosis, Addison's disease (autoimmune disease of the adrenal glands), idiopathic adrenal insufficiency, autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome), glomerulonephritis,

scleroderma, morphea, lichen planus, vitiligo (depigmentation of the skin), alopecia areata, autoimmune alopecia, autoimmune hypopituatarism, Guillain-Barre syndrome, and alveolitis; T-cell mediated hypersensitivity diseases, including contact hypersensitivity, delayed-type hypersensitivity, contact dermatitis (including that due to poison ivy), uticaria, skin allergies, respiratory allergies (hayfever, allergic rhinitis) and gluten-sensitive enteropathy (Celiac disease); inflammatory diseases such as osteoarthritis, acute pancreatitis, chronic pancreatitis, acute respiratory distress syndrome, Sezary's syndrome and vascular diseases which have an inflammatory and or a proliferatory component such as restenosis, stenosis and atherosclerosis. Inflammatory or immune associated diseases or disorders also includes, but is not limited to: endocrine disorders, rheumatic disorders, collagen diseases, dermatologic disease, allergic disease, ophthalmic disease, respiratory disease, hematologic disease, gastrointestinal disease, inflammatory disease, autoimmune disease, congenital adrenal hyperplasia, nonsuppurative thyroiditis, hypercalcemia associated with cancer, juvenile rheumatoid arthritis, Ankylosing spondylitis, acute and subacute bursitis, acute nonspecific tenosynovitis, acute gouty arthritis, post-traumatic osteoarthritis, synovitis of osteoarthritis, epicondylitis, acute rheumatic carditis, pemphigus, bullous dermatitis herpetiformis, severe erythema multiforme, exfoliative dermatitis, seborrheic dermatitis, seasonal or perennial allergic rhinitis, bronchial asthma, contact dermatitis, atopic dermatitis, drug hypersensitivity reactions, allergic conjunctivitis, keratitis, herpes zoster ophthalmicus, iritis and iridocyclitis, chorioretinitis, optic neuritis, symptomatic sarcoidosis, fulminating or disseminated pulmonary tuberculosis chemotherapy, idiopathic thrombocytopenic purpura in adults, secondary thrombocytopenia in adults, acquired (autoimmune) hemolytic anemia, leukemias and lymphomas in adults, acute leukemia of childhood, regional enteritis, autoimmune vasculitis, multiple sclerosis, chronic obstructive pulmonary disease, solid organ transplant rejection, sepsis. Preferred treatments include treatment of transplant rejection, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, asthma, inflammatory bowel disease, systemic lupus erythematosis, psoriasis and chronic pulmonary disease.

[0052] Accordingly, one embodiment of the present invention is a method of treating a disease or disorder selected from an endocrine disorder, rheumatic disorder, collagen disease, dermatologic disease, allergic disease, ophthalmic disease, respiratory disease, hematologic disease, gastrointestinal disease, inflammatory disease, immune disease, neoplastic disease and metabolic disease, which comprise administering to a patient in need of treatment, a therapeutically effective amount of a compound as defined in Claim 1.

[0053] In a preferable emobidment the disease or disorder is an inflammatory or autoimmune disease selected from transplant rejection of kidney, liver, heart, lung, pancreas, bone marrow, cornea, small bowel, skin allografts, skin homografts, heart valve xenograft, serum sickness, and graft vs. host disease, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, asthma, inflammatory bowel disease, Crohn's disease, ulcerative colitis, pyoderma gangrenum, systemic lupus erythematosis, myasthenia gravis, psoriasis, dermatitis, dermatomyositis; eczema, seborrhoea, pulmonary inflammation, eye uveitis, hepatitis, Graves' disease, Hashimoto's thyroiditis, autoimmune thyroiditis, Behcet's or Sjorgen's syndrome, pernicious or immunohaemolytic anaemia, atherosclerosis, Addison's disease, idiopathic adrenal insufficiency, autoimmune polyglandular disease, glomerulonephritis, scleroderma, morphea, lichen planus, viteligo, alopecia areata, autoimmune alopecia, autoimmune hypopituatarism, Guillain-Barre syndrome, and alveolitis; contact hypersensitivity, delayed-type hypersensitivity, contact dermatitis, uticaria,skin allergies, respiratory allergies, hayfever, allergic rhinitis and gluten-sensitive enteropathy, osteoarthritis, acute pancreatis, chronic pancreatitis, acute respiratory distress syndrome, Sezary's syndrome, restenosis, stenosis and artherosclerosis, congenital adrenal hyperplasia, nonsuppurative thyroiditis, hypercalcemia associated with cancer, juvenile rheumatoid arthritis, Ankylosing spondylitis, acute and subacute bursitis, acute nonspecific tenosynovitis, acute gouty arthritis, post-traumatic osteroarthritis, synovitis of osteoarthritis, epicondylitis, acute rheumatic carditis, pemphigus, bullous dermatitis herpetitformis, severe erythema multiforme, exfoliative dermatitis, psoriasis, seborrheic dermatitis, seasonal or perennial allergic rhinitis, bronchial asthma, contact dermatitis, atopic dermatitis, drug hypersensitivity reactions, allergic conjuncivitis, keratitis, herpes zoster ophthalmicus, iritis and iridocyclitis,

chorioretinitis, optic neuritis, symptomatic sarcoidosis, fulminating or disseminated pulmonary tuberculosis chemotherapy, idiopathic thrombocytopenic purpura in adults, secondary thrombocytopenia in adults, acquired (autoimmune) hemolytic anemia, leukemias and lymphomas in adults, acute leukemia of childhood, ulcerative colitis, regional enteritis, Crohn's disease, Sjogren's syndrome, autoimmune vasculitis, multiple sclerosis, myasthenia gravis, sepsis, and chronic obstructive pulmonary disease.

[0054] In an even more preferable embodiment, the disease or disorder is selected from transplant rejection, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, asthma, inflammatory bowel disease, systemic lupus, erythematosis, and psoriasis.

[0055] In addition, in accordance with the present invention a method of treating a disease associated with AP-1-induced and/or NF-κB-induced transcription (particularly AP-1-induced transcription) is provided wherein a compound of formula (I) of the invention is administered to a patient at risk of developing the disease in a therapeutically effective amount to induce NHR transrepression of the AP-1-induced and/or NF-κB-induced transcription (particularly AP-1-induced transcription), thereby treating the disease.

[0056] Other therapeutic agents, such as those described hereafter, may be employed with the compounds of the invention in the present methods. In the methods of the present invention, such other therapeutic agent(s) may be administered prior to, simultaneously with or following the administration of the compound(s) of the present invention.

[0057] In a particular embodiment, the compounds of the present invention are useful for the treatment of the aforementioned exemplary disorders irrespective of their etiology, for example, for the treatment of transplant rejection, rheumatoid arthritis, inflammatory bowel disease, and viral infections.

[0058] In still another embodiment, pharmaceutical combinations are contemplated comprising a compound as defined in Claim 1, an enantiomer, diastereomer, or tautomer thereof, or a prodrug ester thereof, or a pharmaceutically-acceptable salt thereof, and an immunosuppressant, an anticancer agent, an anti-viral agent, an anti-inflammatory agent, an anti-fungal agent, an anti-biotic, an anti-vascular hyperproliferation agent, an anti-depressant agent, a lipid-lowering agent, a

lipid modulating agent, an antidiabetic agent, an anti-obesity agent, an antihypertensive agent, a platelet aggregation inhibitor, and/or an antiosteoporosis agent, wherein the antidiabetic agent is 1, 2, 3 or more of a biguanide, a sulfonyl urea, a glucosidase inhibitor, a PPAR γ agonist, a PPAR α/γ dual agonist, an SGLT2 inhibitor, a DP4 inhibitor, an aP2 inhibitor, an insulin sensitizer, a glucagon-like peptide-1 (GLP-1), insulin and/or a meglitinide, wherein the anti-obesity agent is a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, a thyroid receptor agonist, an aP2 inhibitor and/or an anorectic agent, wherein the lipid lowering agent is an MTP inhibitor, an HMG CoA reductase inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, an upregulator of LDL receptor activity, a lipoxygenase inhibitor, or an ACAT inhibitor, wherein the antihypertensive agent is an ACE inhibitor, angiotensin II receptor antagonist, NEP/ACE inhibitor, calcium channel blocker and/or β-adrenergic blocker.

[0059] More preferred combinations are those wherein the antidiabetic agent is 1, 2, 3 or more of metformin, glyburide, glimepiride, glipyride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, Gl-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide, KAD1129, AR-HO39242, GW-409544, KRP297, AC2993, LY315902, P32/98 and/or NVP-DPP-728A, wherein the anti-obesity agent is orlistat, ATL-962, AJ9677, L750355, CP331648, sibutramine, topiramate, axokine, dexamphetamine, phentermine, phenylpropanolamine, and/or mazindol, wherein the lipid lowering agent is pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, itavastatin, visastatin, fenofibrate, gemfibrozil, clofibrate, avasimibe, TS-962, MD-700, cholestagel, niacin and/or LY295427, wherein the antihypertensive agent is an ACE inhibitor which is captopril, fosinopril, enalapril, lisinopril, quinapril, benazepril, fentiapril, ramipril or moexipril; an NEP/ACE inhibitor which is omapatrilat, [S[(R*,R*)]-hexahydro-6-[(2-mercapto-1-oxo-3-phenylpropyl)amino]-2,2-dimethyl-7-oxo-1H-azepine-1-acetic acid (gemopatrilat) or CGS 30440;

an angiotensin II receptor antagonist which is irbesartan, losartan or valsartan;

amlodipine besylate, prazosin HCl, verapamil, nifedipine, nadolol, propranolol, carvedilol, or clonidine HCl, wherein the platelet aggregation inhibitor is aspirin, clopidogrel, ticlopidine, dipyridamole or ifetroban;

the immunosuppressant is a cyclosporin, mycophenolate, interferon-beta, deoxyspergolin, FK-506 or Ant.-IL-2;

the anti-cancer agent is azathiprine, 5-fluorouracel, cyclophosphamide, cisplatin, methotrexate, thiotepa, or carboplatin;

the anti-viral agent is abacavir, aciclovir, ganciclovir, zidanocin, or vidarabine; and

the antiinflammatory drug is ibuprofen, celecoxib, rofecoxib, aspirin, naproxen, ketoprofen, diclofenac sodium, indomethacin, piroxicam, prednisone, dexamethasone, hydrocortisone, or triamcinolone diacetate.

[0060] The invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention also encompasses all combinations of alternative aspects and embodiments of the invention noted herein. It is understood that any and all embodiments may be taken in conjunction with any other embodiment to describe additional embodiments of the present invention. Furthermore, any elements of an embodiment are meant to be combined with any and all other elements from any of the embodiments to describe additional embodiments.

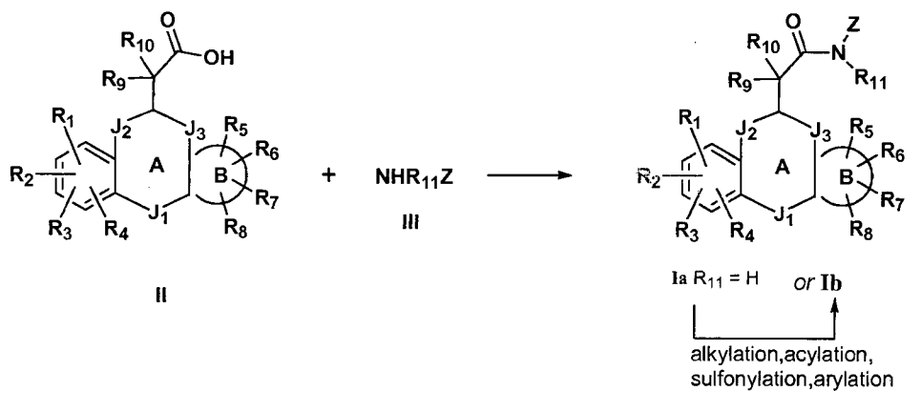
METHODS OF PREPARATION

[0061] The compounds of the present invention may be synthesized by many methods available to those skilled in the art of organic chemistry. General synthetic schemes for preparing compounds of the present invention are described below. These schemes are illustrative and are not meant to limit the possible techniques one skilled in the art may use to prepare the compounds disclosed herein. Different methods to prepare the compounds of the present invention will be evident to those skilled in the art. Additionally, the various steps in the synthesis may be performed in an alternate sequence in order to give the desired compound or compounds. Examples of compounds of the present invention prepared by methods described in the general schemes are given in the preparations and examples section set out hereinafter. Example compounds are typically prepared as racemic mixtures.

Preparation of homochiral examples may be carried out by techniques known to one skilled in the art. For example, homochiral compounds may be prepared by separation of racemic products by chiral phase preparative HPLC. Alternatively, the example compounds may be prepared by methods known to give enantiomerically enriched products. These include, but are not limited to, the incorporation of chiral auxiliary functionalities into racemic intermediates which serve to control the diastereoselectivity of transformations, providing enantio-enriched products upon cleavage of the chiral auxiliary.

SCHEME 1

Condensation of carboxylic acid II with amine III to form product I



[0062] Scheme 1 illustrates the preparation of title compounds of the invention (**I**) from intermediate carboxylic acids **II**. The amides **I** may be prepared from **II** by many of the myriad ways known to prepare carboxamides by the dehydrative condensation of carboxylic acids and amines. For example, condensation of acid **II** with amine ($NR_{11}Z$, **III,** where R_{11} = H, alkyl, cycloalkyl, alkoxy, dialkylamino, aryl or heteroaryl) may be effected by treatment of **II** with an activating reagent, such as a water-soluble carbodiimide (EDC), in the presence of an N-hydroxy triazole (HOAt or HOBt, or the like) and amine in the presence of base (preferably triethylamine, diisopropylethylamine, or the like) in an appropriate polar aprotic solvent (N,N-dimethylformamide, acetonitrile, dichloromethane, or the like). The carboxylic acid **II** may also be converted to an acid chloride by treatment with an appropriate chlorinating agent (thionyl chloride, oxalyl chloride, or the like). Similarly, **II** may be converted to an acyl fluoride upon exposure to a fluorinating agent (such as

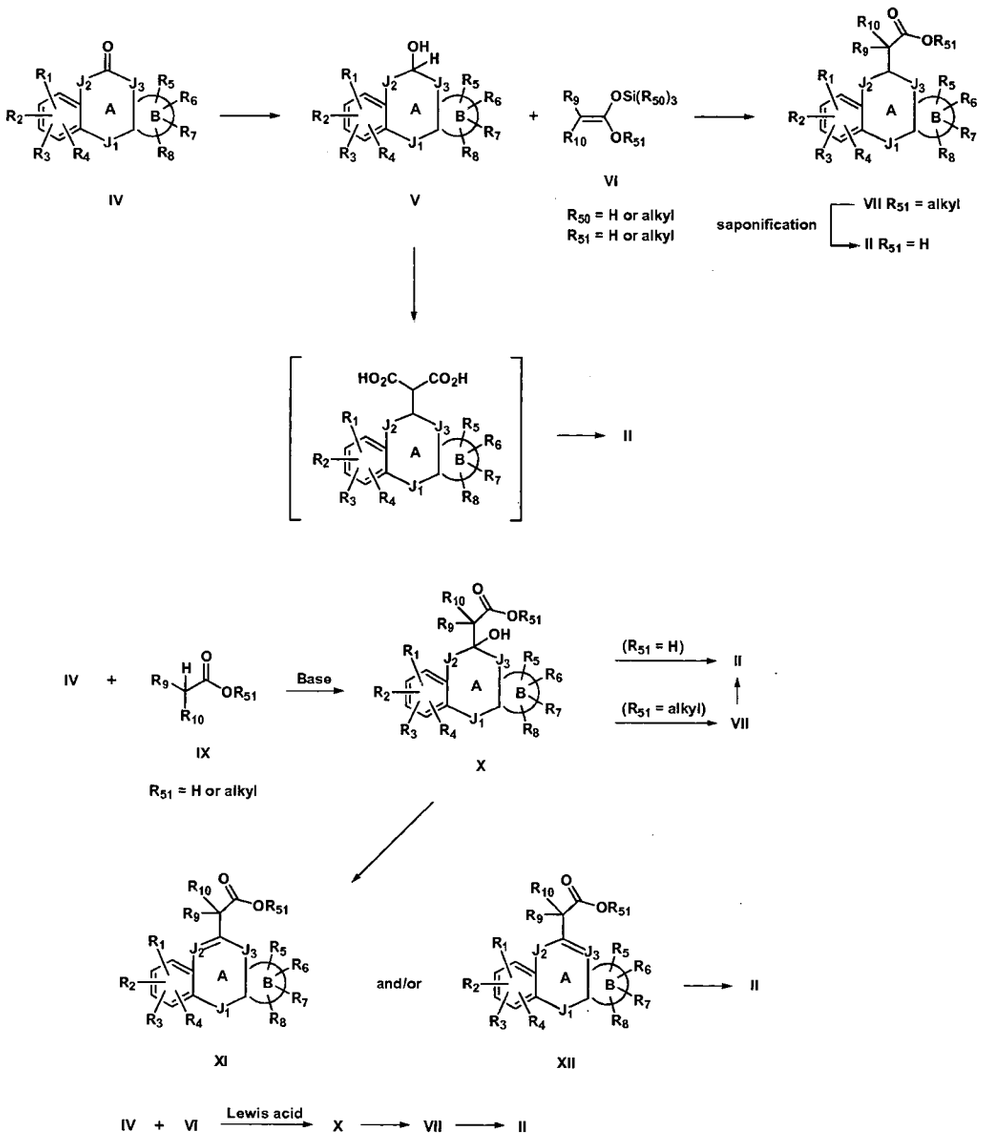
cyanuric fluoride). Condensation of the acyl halide (chloride or fluoride) with the amine **III** (typically carried out in the presence of a base such as pyridine or triethylamine in an aprotic solvent) may then provide the amide **Ia**. In cases where R_{11}= H (i.e., **III** = NH_2Z), the immediate product of condensation of **II** and **III** (**Ia**, R_{11}= H) may be converted to **Ib** (R_{11}= alkyl) by treatment of **Ia** with an alkylating agent (alkyl halide, alkyl sulfonate, or the like) in the presence of a base (cesium carbonate, sodium hydride, or the like). **Ia** (R_{11} = H) may be converted to **Ib** (R_{11} = C(O)alkyl, CO_2alkyl) by treatment with a strong base (sodium hydride, lithium diisopropyl amide, or the like) followed by acylation with an appropriate acylating reagent (an acid chloride, chloroformate, or the like). Similarly, sulfonylation may be effected by treatment with a base and sulfonyl halide to provide **Ib** (R_{11} = SO_2aryl or SO_2alkyl). Arylation of **Ia** to give **Ib** (R_{11} = aryl) may also be effected by palladium-catalyzed *N*-arylation of amides (see, for example, Yin, J.; Buchwald S. *Org. Lett.* **2000**, *2*, 1101-1104 and references cited therein) or the copper-promoted arylation of amides with aryl boronic acids or arylsiloxanes (see, for example, Lam, P. *et al.* *Synlett* **2000**, 674-676).

[0063] Scheme 2 illustrates various methods for the preparation of the intermediate carboxylic acid **II**. The intermediate ketone **IV** may be reduced to alcohol **V** by treatment with a reducing agent (typically a metal hydride such as sodium borohydride in methanol or lithium aluminum hydride in diethyl ether or THF). In one mode of preparation, the alcohol may be condensed with malonic acid to give, after decarboxylation of a putative intermediate dicarboxylic acid, the desired intermediate **II** (Jones *et al. J. Am. Chem. Soc.* **1948**, *70*, 2843; Beylin *et al.* *Tetrahedron Lett.* **1993**, *34*, 953-956.). The alcohol **V** may also be treated with a silyl ketene acetal, represented by **VI**. In cases where R_9 = R_{10} = R_{50} = R_{51} = Me, **VI** may be obtained from commercial sources. The condensation of **V** (J_2 = J_3 = bond) with **VI** to give ester **VII** generally requires the presence of a Lewis acid, such as boron trifluoride etherate, titanium tetrachloride, or the like and is best carried out in a polar, aprotic solvent such as dichloromethane. Saponification of ester **VII** to **II** may be carried out with sodium hydroxide or potassium hydroxide in water in the presence of co-solvents such as methanol, THF, and/or DMSO. In cases where R_9 =

R_{10} = alkyl, the hydrolysis of ester **VII** is best carried out at elevated temperature (generally 80 °C) for prolonged times (> 5h).

SCHEME 2

Preparation of carboxylic acids II from ketones IV



[0064] The ketone **IV** may also be condensed with an enolate derived from ester **IX** (R_{51} = alkyl), prepared by treatment of **IX** with an appropriate base (lithium diisopropyl amide, lithium or potassium hexamethyldisilizane or the like) at low temperature (-78 °C to 0 °C), to give ester **X**. An intermediate carboxylic acid **X** (R_{51}

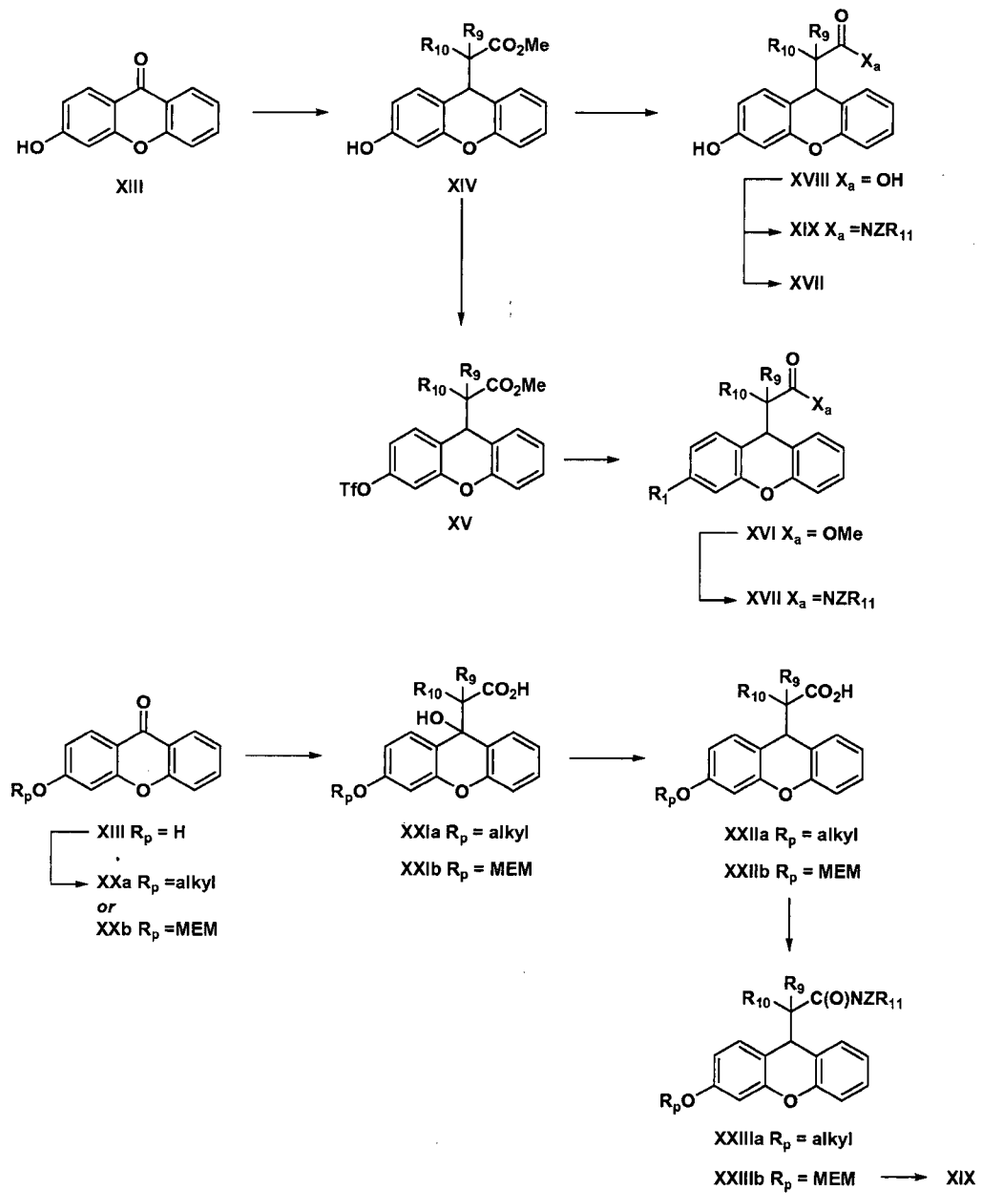
= H) may also be prepared by first treating a carboxylic acid **IX** (R_{50} = H) with at least two equivalents of a strong base (preferably lithium diisopropyl amide or lithium diethyl amide) to generate an enediolate dianion. Generation of the enediolate is preferably carried out at 0 °C to 55 °C. Condensation of the *in situ* prepared enediolate with ketone **IV** may then give the hydroxy acid **X** (R_{51} = H). In cases where one or both of J_2, J_3 = alkylene, the intermediate alcohol **X** may readily dehydrate to give the unsaturated intermediates **XI** and/or **XII**. The dehydration may occur spontaneously by exposure of **X** (J_2, J_3 = alkylene) to acidic conditions, such as aqueous acid or Lewis acid (boron trifluoride, titanium tetrachloride, or the like). The intermediate olefins **XI** and **XII** may be reduced to give ester **VII** (R_{51} = alkyl) under catalytic hydrogenation (typically palladium on carbon in the presence of hydrogen gas), which may be saponified as described above to prepare carboxylic acid **II**. Alternatively, in cases where olefins **XI** and **XII** are carboxylic acids (R_{51} = H), catalytic hydrogenation (typically palladium on carbon in the presence of hydrogen gas) may directly provide the carboxylic acid **II**. In cases where dehydration of alcohol **X** to **XI** and/or **XII** does not spontaneously occur, **X** (R_{51} = H) may be reduced to **II**. The reaction is preferably carried out with a silane (typically triethylsilane) in the presence of a protic acid (typically trifluoroacetic acid). The ester **X** (R_{51} = alkyl) may also be reduced to ester **VII** under the same conditions employed for conversion of **X** to **II**. Ester **VII** may be hydrolyzed to acid **II** under conditions described above.

[0065] The ketone **IV** may also be treated with silyl ketene acetal **VI** to provide the hydroxy ester **X** (R_{51} = alkyl). The condensation is best carried out in the presence of a Lewis acid (boron trifluoride etherate, or the like) in dichloromethane at 0 °C. Hydroxy ester **X** may be isolated, or, alternatively, *in situ* reduction to ester **VII** may be carried out. In cases where any one or more of R_1-R_4 = OH, addition of triethylsilane to the reaction mixture containing the unisolated hydroxy ester **X** may give the ester **VII**. Alternatively, addition of a strong protic acid (typically trifluoroacetic acid) and triethylsilane to the reaction mixture containing unisolated hydroxy ester **X** may provide ester **VII**. Conversion of ester **VII** to carboxylic acid **II** may then be carried out as described above.

[0066] The synthesis of hydroxylated xanthene-based examples and derivatives is described in Scheme 3. 3-Hydroxy-9*H*-xanthen-9-one **XIII** ("Sieber linker", Sieber P. *Tetrahedron Lett.*, **1987**, *28*, 6147-6150) may be converted to ester **XIV** by treatment with a silyl ketene acetal (e.g., (1-methoxy-2-methylprop-1-enyloxy)trimethylsilane, where $R_9 = R_{10} = Me$) in the presence of an appropriate Lewis acid (preferably boron trifluoride etherate) in dichloromethane at 0 °C. Subsequent addition of a reducing agent (preferably triethylsilane) may give the methyl ester **XIV**. The phenolic hydroxyl group of **XIV** may be derivatized by a number of different means. Treatment of **XIV** with a triflating reagent (triflic anhydride, $PhNTf_2$, or the like) in the presence of a suitable base (triethylamine, pyridine, or the like) may give an aryl triflate **XV** which may undergo metal-mediated cross-coupling reactions. For example, Suzuki coupling may be effected by treatment of **XV** with an aryl boronic acid or aryl boronate ester in the presence of a palladium catalyst (tetrakis triphenylphosphine palladium, or the like) and an aqueous base (potassium carbonate, sodium carbonate, potassium phosphate or the like) in an appropriate solvent or solvent combination(DMF, toluene/ethanol, 1,4-dioxane or the like) at elevated temperature (typically 100 °C) may provide an arylated intermediate methyl ester **XVI**. (R1 = aryl). The triflate may also undergo a variety of other metal-mediated cross-coupling reactions known to one skilled in the art (See, for example, de Meijere, A., & Diederich, F. (2004). *Metal-Catalyzed Cross-Coupling Reactions*. (2nd ed.): John Wiley & Sons). Saponification of the ester **XVI** under conditions described above for the preparation of **II** from **VII,** followed by condensation under the conditions described above for the preparation of **Ia** from **II** may give xanthene products **XVII**. The phenol ester **XIV** may also be hydrolyzed to carboxylic acid **XVIII** under conditions described above for the preparation of **VII** from **II**. Amide **XIX** may then be prepared as described above for the preparation of **Ia** from **II**. The amide **XVII** may also be prepared from amide **XIX** by conversion to a triflate derivative as described above for the preparation of **XV** from **XIV** followed by palladium-catalyzed cross-coupling as described above for the preparation of **XVI** from **XV**.

SCHEME 3

Preparation of phenolic xanthenes and their derivatives

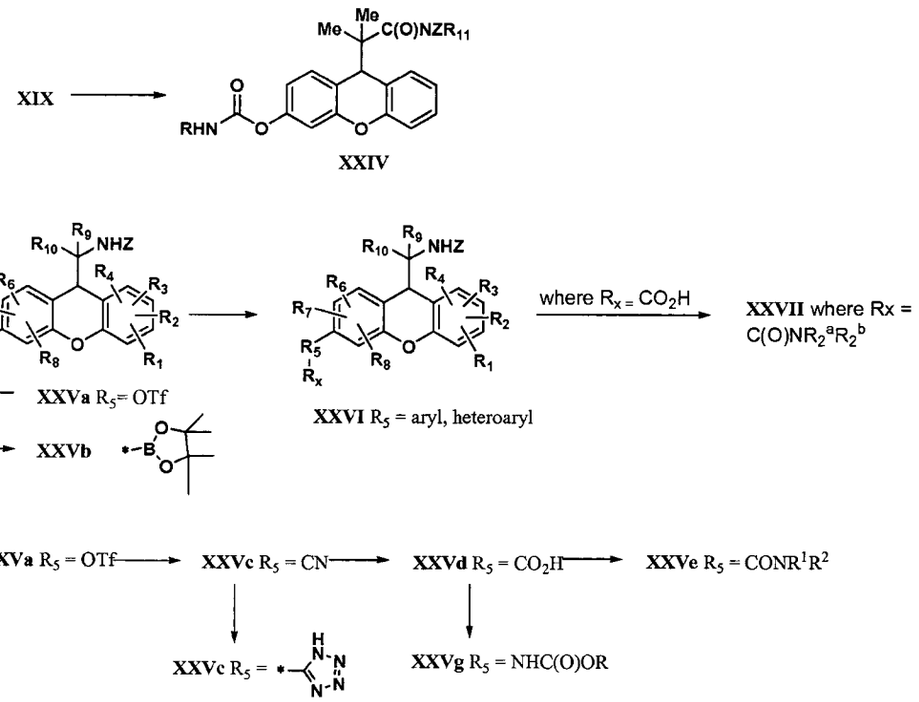


[0067] 3-Hydroxy-9*H*-xanthen-9-one ("Sieber linker") (**XIII**) may be converted to the corresponding alkyl ether **XXa** or (2-methoxyethoxy)methyl (MEM) ether **XXb** by treatment with an appropriate base (typically sodium hydride) in a polar aprotic solvent (typically DMF) in the presence of an alkyl halide (typically a primary halide such as iodomethane) or MEM-Cl. The hydroxy acids **XXIa** and **XXIb** may be prepared as described above for the preparation of **X** (R_{51} = H). Reduction as

described above for the preparation of **II** directly from **X** may then give **XXIIa** or **XXIIb**, which may be converted to **XXIIIa** or **XXIIIb** under the conditions described above for the preparation of **1a** from **II**. **XXIIIa** may be converted to phenol **XIX** by treatment with thiophenol or 2-aminothiophenol in the presence of a stoichiometric quantity of potassium carbonate in N-methyl-pyrrolidinone at high temperature (typically 200 °C – 205 °C in a microwave reactor) (see Chakraborti, et al. *J. Org. Chem.* **2002**, *67*, 6406-6414).

SCHEME 4

Preparation of substituted non-phenolic xanthene derivatives



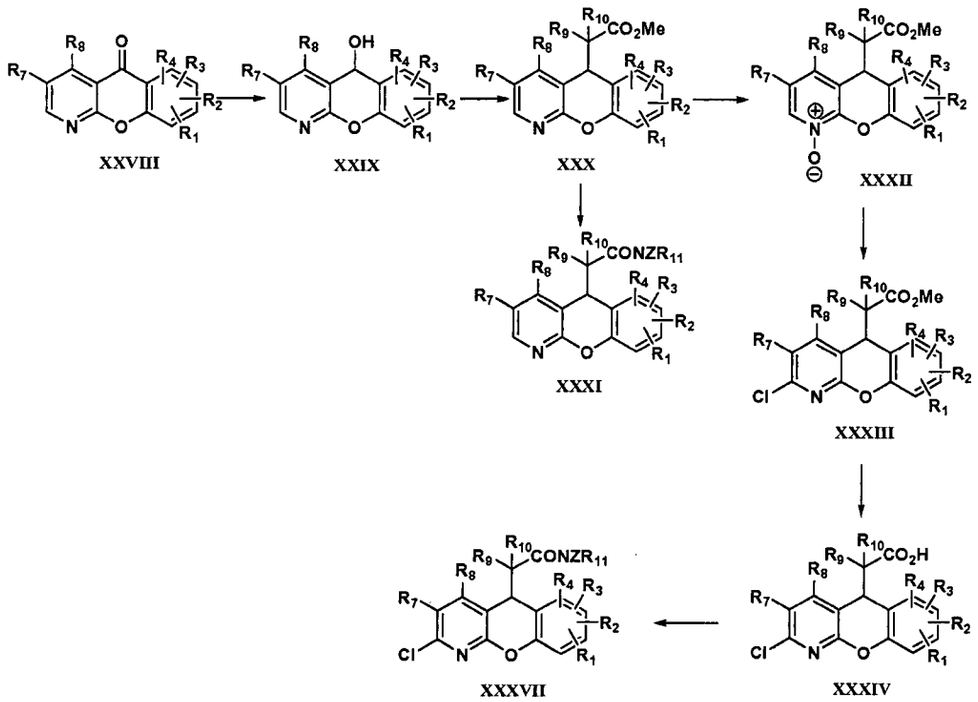
[0068] In one embodiment, example compounds represented by **XIX** may be converted to example compounds represented by **XXIV** (Scheme 4). Thus, treatment of **XIX** with an alkyl or aryl isocyanate in the presence of a non-nucleophilic base (preferably N,N-diisopropylethyl amine) in a polar, aprotic solvent (preferably 1,4-dioxane), preferably at ambient temperature may provide **XXIV**. Intermediate **XXV** , where R5 is triflate or nonoflate (ONf) may be converted to arylated xanthene **XXVI** by Suzuki coupling with an appropriate aryl boronate. For example, treatment of

XXV with any aryl boronic acid, aryl trifluoroborate salt, or aryl boronate (e.g., aryl pinacol boronate) in the presence of a palladium (0) catalyst (preferably tetrakistriphenylphosphine palladium (0)), and base (preferably, aqueous sodium carbonate, potassium carbonate, potassium phosphate, or the like) in a solvent system typically employed for Suzuki coupling reactions (such as toluene/ethanol, water/DMF, or the like) may provide **XXVI**. Alternatively, **XXV** may be converted to a boronate ester (for example, pinacol boronate **XXVb**) by treatment with a palladium catalyst (typically 1,1'-bis (diphenylphosphino)ferrocene-palladium (II) dichloride) in the presence of a boron source (preferably bis (pinacolato)diboron) in the presence of a base (preferably potassium acetate). Conversion of **XXVb** to **XXVI** may be carried out by cross-coupling with an aryl or heteroaryl halide under Suzuki conditions as described above for the conversion of **XXV** to **XXVI**. Where **XXVI** is appended with a carboxylic acid group, conversion to a carboxamide (**XXVII**) may be effected under any number of the typical conditions for dehydrative condensation of amines and carboxylic acids, for example as described for the conversion of **II** to **Ia**. The triflate (or nonflate) **XXVa** may also be converted to nitriles **XXVc** by methods for palladium-catalyzed cyanation of aryl halides (Sundmeier, M. *et al*, *Eur. J. Inorg. Chem.* **2003**, 3513). For example, treatment of **XXVa** with a cyanide source (typically zinc cyanide) in the presence of a palladium catalyst (typically tetrakis triphenylphosphine palladium (0)) in a polar solvent (typically DMF) at elevated temperature (typically 120 °C) provides nitriles **XXVc**. The nitriles **XXVc** may be hydrolyzed to provide carboxylic acids **XXVd** by treatment with sodium peroxide in water. Condensation of acids **XXVd** with primary or secondary amines (as described for conversion of II to Ia) may provide carboxamides **XXVe**. The nitriles **XXVc** may be converted to tetrazoles **XXVf** by condensation with a source of azide (preferably sodium azide) in the presence of an acid (preferably ammonium chloride or trimethylsilyl azide or tributyl tin oxide). The carboxylic acids **XXVd** may also be converted to carbamates **XXVg** by Curtius rearrangement. Thus, conversion of **XXVd** to an acyl azide (typically effected by exposure to diphenylphosphoryl azide), in the presence of a tertiary amine (typically triethylamine), with heating, followed by quenching with an alcohol, may give carbamates **XXVg**.

[0069] Azaxanthene-based examples may be prepared as illustrated in Scheme 5. 5*H*-Chromeno[2,3-b]pyridin-5-one **XXVIII** (commercially available or prepared in the manner described by Villani *et al., J. Med. Chem.* **1975**, *18*, 1) may be reduced to the corresponding alcohol **XXIX** upon treatment with sodium borohydride in anhydrous methanol as described by Bristol, *et al.* (*J. Med. Chem.*, **1981**, *24*, 1010-1013). Treatment of **XXIX** with the trimethyl silyl ketene acetal of methyl isobutyrate as described above for the preparation of **VII** from **V** may give the ester **XXX**. Hydrolysis of the ester as described above for the preparation of **II** from **VII**, followed by amidation as described for the preparation of **Ia** from **II** and **III** may provide the azaxanthene amides **XXXI**. Alternatively, oxidation of **XXX** may be effected under conditions for the preparation of pyridine N-oxides (preferably mCPBA in dichloromethane) to give the N-oxide **XXXII**, which may then be treated with an appropriate chlorinating reagent (preferably phosphorous oxychloride, $POCl_3$, in the absence of a co-solvent) to give the chloroazaxanthene **XXXIII**. Saponification of **XXXIII** to carboxylic acid **XXXIV** may be effected under conditions described above for the preparation of **VII** from **II**, preferably in the absence of DMSO. Condensation of **XXXIV** with an amine ($NHR_{12}R_{13}$) at elevated temperature (typically 130 °C) may provide **XXXVa** (Scheme 6, $R_5 = NR_{12}R_{13}$). Alternatively, Suzuki coupling of **XXXIV** with a suitable aryl boronic acid or aryl boronate as described above for the preparation of **XVI** from **XV** may provide **XXXVb**. **XXXVa** and **XXXVb** may be converted to **XXXVIa** or **XXXVIb**, respectively, following the conditions described above for the preparation of **Ia** from **II** and **III**. The carboxylic acid **XXXIV** may also be converted to amide **XXXVII** as described above for the preparation of **Ia** from **II** and **III**. Arylation as described above for the preparation of **XVI** from **XV** may provide **XXXVIb**. Any of the racemic intermediates **XXX** – **XXXVII** or example compounds may be separated into purified, single enantiomers by any of the various methods known to one skilled in the art.

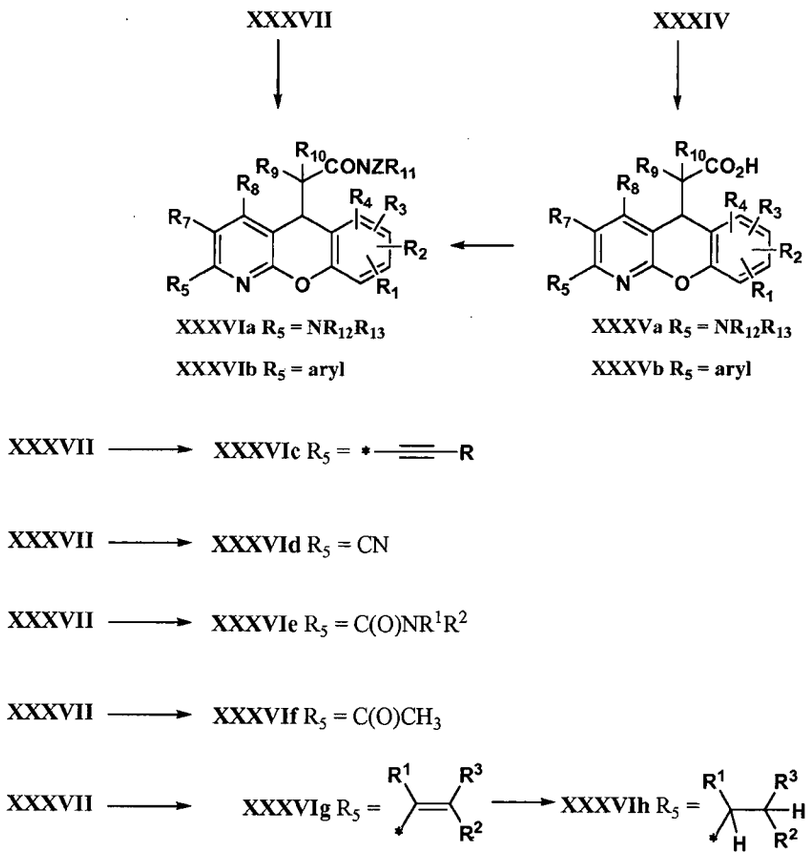
SCHEME 5

Preparation of 5*H*-chromeno[2,3-*b*]pyridines



SCHEME 6

Elaboration of 2-chloro-5*H*-chromeno[2,3-*b*]pyridines

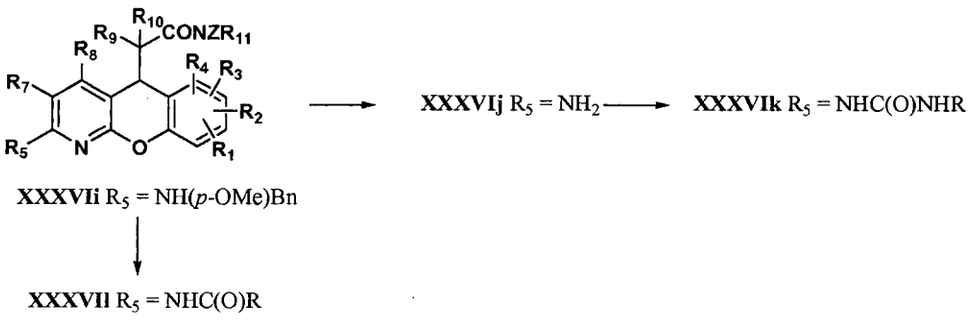


[0070] The chloride **XXXVII** (Scheme 6) may also undergo Sonagashira or Stevens-Castro cross-couplings with alkynes in the presence of a palladium catalyst (preferably bis (triphenylphosphine)-palladium (II(chloride) with catalytic cuprous iodide in the presence of a hindered secondary amine base (preferably diisopropylamine) to give alkynes **XXXVIc**. **XXXVII** may also be converted to nitriles **XXXVId**, as described for the preparation of **XXVc** from **XXVa**. **XXXVII** may also be converted to amides **XXXVIe** in a two-step procedure involving initial hydrolysis by hydroxide (typically potassium hydroxide) to give a carboxylic acid (R_5 = CO_2H) which may then be condensed with primary or secondary amines as described for the preparation of **Ia** from **II** to give carboxamides **XXVIe**. **XXXVII** may also be converted to ketones **XXXVIf** as described by Jean-Yves Legros *et al* (*Tetrahedron* **2001**, *57*, 2507). Treatment of **XXXVII** with alkenyl boronates (or

trifluoroborate salts) under conditions described for the preparation of **XXXVIb** from **XXXVII** may afford alkenyl example compounds (**XXXVIg**). Hydrogenation of **XXXVIg** may be effected with a palladium catalyst (preferably palladium on charcoal) under an atmosphere of hydrogen to afford corresponding alkyl compounds **XXXVIh**.

SCHEME 7

Preparation of amino-, urea-, and carbamoyl- substituted 5*H*-chromeno[2,3-*b*]pyridines



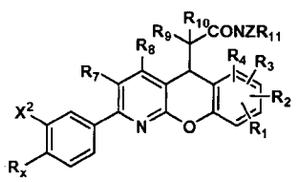
[0071] Amino-, urea-, and carbamoyl-substituted 5*H*-chromeno[2,3-*b*]pyridines may be prepared as shown in Scheme 7. Thus, heating a solution of *p*-methoxy benzylamino-substituted **XXXVIi** (prepared as described above for the preparation of **XXXVIa**) in trifluoroacetic acid (preferably at 50 °C) may provide amines **XXXVIj**. The amines **XXXVIj** may be converted to ureas **XXXVIk** by first treating with a carbonylating reagent (such as phenyl chloroformate) in the presence of a base (preferably pyridine) to afford carbamoylated intermediates (R5 = NHC(O)OPh) which, without isolation, may then be condensed with amines, with heating (typically at 100 °C). The amines **XXXVIi** may also be converted to amides **XXXVII** by acylation with an appropriate acylating reagent (acid halide, or other suitably activated carboxylic acid as described for the preparation of **Ia** from **II**), followed by cleavage of the *p*-methoxybenzyl group as described for the preparation of **XXXVIj** from **XXXVIi**.

[0072] 2-(*Para*-substituted phenyl)-5*H*-chromeno[2,3-*b*]pyridines may be further elaborated as depicted in Scheme 8. Phenols **XXXVIm** (R_x = OH) may be alkylated under Mitsunobu conditions (*Synthesis* 1, 1981). Thus treatment of **XXXVIm** with

an alcohol (R_yOH) in the presence of a phosphine (preferably, triphenylphosphine) and an alkyl diazodicarboxylate (preferably diisopropyl azodicarboxylate or diethylazodicarboxylate) in tetrahydrofuran may provide ethers **XXXVIn**. Thioethers (for example, **XXXVIo**, R_x = SMe) may be oxidized to sulfoxides or sulfones (**XXXVIp**) by treatment with any of a number of oxidants, including *m*-chloroperbenzoic acid. Carboxylic acids (**XXXVIq**) may be converted to benzamides (**XXXVIr**) using many of the myriad methods for the conversion of benzoic acids to benzamides. Preferably, treatment of **XXVIq** with activating reagent(s) (typically HOBt in the presence of a carbodiimide such as EDCI) in the presence of tertiary amine bases (typically triethylamine or diisopropylethylamine) and primary or secondary amines in a polar, aprotic solvent (typically acetonitrile or DMF) gives benzamides **XXXVIr**. Aldehyde **XXXVIs** may be converted to alcohol **XXXVIt** by reduction with an appropriate reducing agent (sodium borohydride, or the like) or by treatment with an organometallic nucleophile (alkyl or aryl lithium, Grignard reagent, or the like). Similarly, ketones **XXXVIv** may be condensed with organometallic nucleophiles to provide tertiary alcohols **XXXVIv**.

SCHEME 8

Elaboration of phenyl-substituted 5*H*-chromeno[2,3-*b*]pyridines



XXXVIm R_x = OH **XXXVIo** R_x = SMe **XXXVIq** R_x = CO_2H **XXXVIs** R_x = CHO **XXXVIu** R_x = C(O)Me

↓ ↓ ↓ ↓ ↓

XXXVIn R_x = OR_y **XXXVIp** R_x = $S(O)_nMe$ where n = 1,2 **XXXVIr** R_x = $C(O)NR_2{}^aR_2{}^b$ **XXXVIt** R_x = CH(OH)R **XXXVIv** R_x = $C(OH)R_2{}^aR_2{}^b$

[0073] Scheme 9 illustrates a number of classic methods for synthesizing reactive intermediates **XXXVIII – XLIII** which are then used to form heterocycles **XLIV** and **XLV** ($NHR_{11}Z$). Scheme 5, reaction (1) shows typical conditions for brominating alpha to a ketone. In this specific case, bromination occurs first at the benzylic position and then at the desired R8-substituted position. Using the procedure of Chi

et al (*Org. Lett.* **2003**, *5*, 411-414), dibromination followed by debromination with acetone yields the desired alpha-bromoketone **XXXVIII**.

[0074] Scheme 5, reaction (2) is the same transformation as reaction (1) but when the benzylic position is substituted with R^4 and R^5, bromination occurs selectively or exclusively at the desired position to give structure **XXXIX**.

[0075] Scheme 5, reaction (3) is a summary of the method of Takano (*Heterocycles* **1989**, *29*, 1861-1864; also see Zhao et *al Bioorg. Med. Chem. Lett.* **1998**, *6*, 2531-2539) which describes the use of cuprates to open epichlorohydrin to form chlorohydrins. It should be noted that Grignard reagents themselves open epoxides either in the presence or absence of copper salts (see, Mazzocchi et al *Synth Commun.* **1986**, 309-312; *Eur. J. Med. Chem.* **1979**, *14*, 165-170). Oxidation of the chlorohydrin using Dess-Martin periodinane or other suitable oxidant yields the desired chloromethylketone **XL**.

[0076] Another method of forming chloromethylketones is shown in Scheme 5 reaction (4). Lithiation of activated methyl groups using butyllithium followed by reaction with chloroacetylchloride (or ethyl chloroacetate, *Khim. Geterot. Soed.* **1986**, *6*, 802-809) directly provides the chloromethylketone **XLI** intermediate.

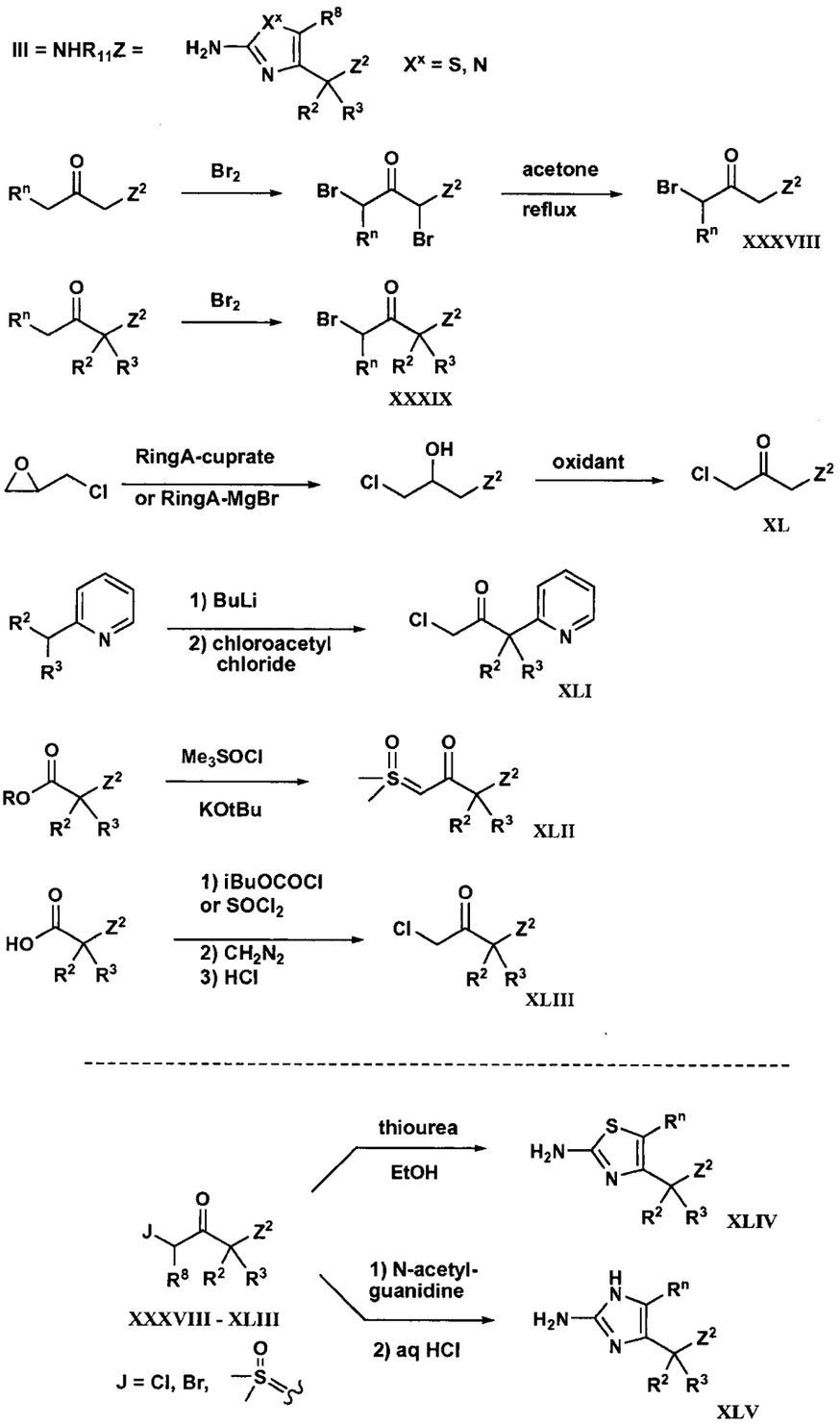
[0077] Scheme 5, reaction (5) shows the method of Nugent et al (*J. Org. Chem.* **2004**, *69*, 1629-1633) which uses dimethylsulfoxonium methylide to nucleophilically add to esters forming reactive β-keto sulfur ylides **XLII**.

[0078] Lastly, a widely used acid homologation procedure shown in Scheme 5 reaction (6) involves the conversion of a carboxylic acid to a mixed anhydride (or acid chloride) followed by treatment with diazomethane and then HCl to form the chloromethylketone **XLIII**.

[0079] Reactive intermediates **XXXVIII – XLIII** can be treated with thiourea with or without added acid to yield the desired substituted 2-aminothiazoles **XLIV**. Synthesis of substituted 2-aminoimidazoles **XLV** is best accomplished using the procedure of Little and Webber (*J. Org. Chem.* **1994**, *59*, 7299-7305) using N-acetylguanidine as the nucleophile followed by acid hydrolysis of the acetyl group.

SCHEME 9

Preparation of 2-aminothiazoles and 2-aminoimidazoles



[0080] Z^2 is a cycloalkyl, cycloalkenyl, cycloheteroalkyl, aryl, or heteroaryl ring;

R^2 and R^3 are independently at each occurrence hydrogen, halogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, cyano, nitro, NR^eR^f, or CHO;

or R^2 and R^3 combine to form =O or a double bond, wherein the double bond is substituted by hydrogen, aryl, alkyl, alkenyl, alkynyl, alkoxy, amino, substituted amino, alkoxyalkyl, alkylaminoalkyl, dialkylaminoalkyl, heteroaryl, cycloheteroalkyl, heteroarylalkyl, cycloheteroalkylalkyl, cycloalkyl, or cycloalkylalkyl;

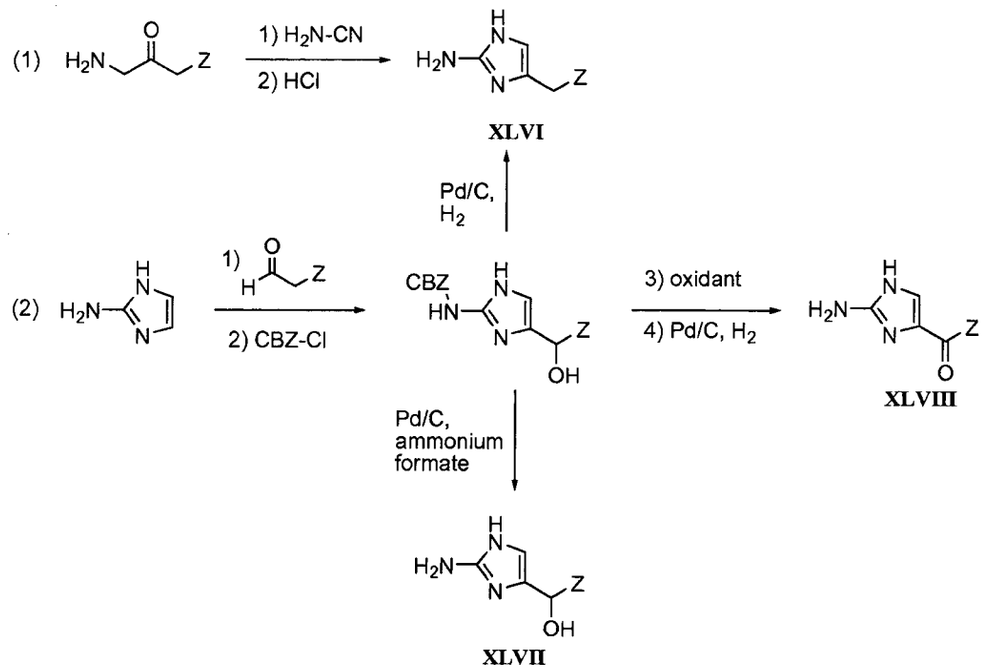
R^e and R^f are independently at each occurrence selected from hydrogen, aryl, alkyl, alkenyl, alkynyl, alkoxy, amino, substituted amino, alkoxyalkyl, alkylaminoalkyl, dialkylaminoalkyl, heteroaryl, cycloheteroalkyl, heteroarylalkyl, cycloheteroalkylalkyl, cycloalkyl, and cycloalkylalkyl, provided R^e and R^f are not both alkoxy or amino;

or R^e and R^f at each occurrence can be taken together with the nitrogen to which they are attached to form a 5-, 6- or 7-membered heteroaryl or cycloheteroalkyl ring which contains 1, 2 or 3 hetero atoms which can be N, O or S.

[0081] Two other syntheses of 2-aminoimidazoles are listed in Scheme 10 below. In Scheme 10, reaction (1), an aminomethylketone is condensed with cyanamide to form an intermediate guanidinomethylketone which undergoes dehydration upon treatment with HCl (see, Lancini and Lazzari, *J. Het. Chem.* **1966**, *3*, 152-154) to form compound **XLVI**. Aminomethyl ketones can be synthesized from the reactive intermediates XXXVIII-XLIII (Scheme 5) using standard procedures known to one skilled in the art.

SCHEME 10

Additional Syntheses of 2-aminoimidazoles



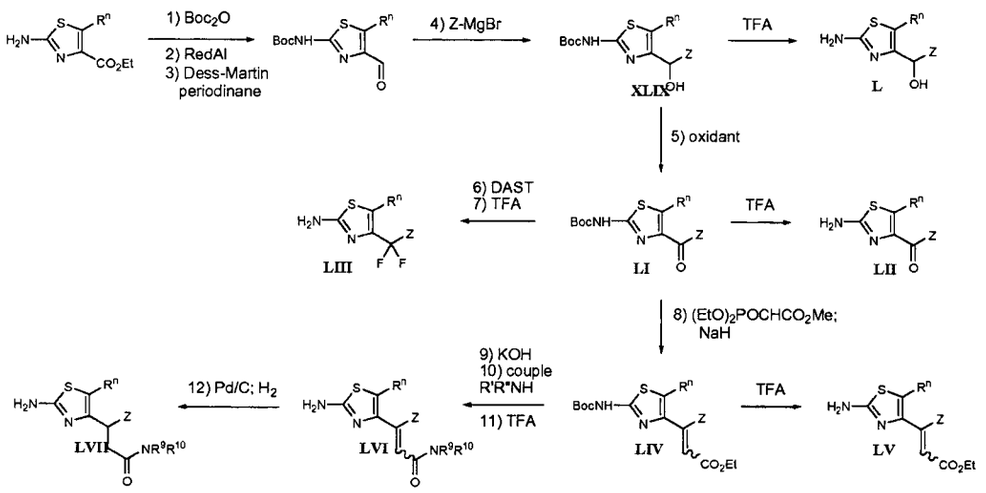
[0082] Scheme 10 (above) details the procedure of Horne et al (*Tetrahedron. Lett.* **1993**, *34*, 6981-6984) to make substituted 2-aminoimidazoles. Commercially available 2-aminoimidazole reacts with aldehydes to form hydroxyalkylaminoimidazoles which are conveniently protected in situ with a CBZ group in situ to facilitate purification. Catalytic hydrogenation of this intermediate under mild conditions first reduces the CBZ group to give the hydroxyalkylaminoimidazoles **XLVIII**. Prolonged hydrogenation under stronger conditions reduces the benzylic hydroxyl group to give compound **XLVI**. If the intermediate hydroxyalkylaminoimidazole is first oxidized (using Dess-Martin periodinane for example) and then treated with under mild hydrogenation conditions, the 2-amino-4-ketoimidazole compound **XLVIII** is formed.

[0083] Scheme 11 illustrates several other synthetic transformations to make substituted 2-aminothiazoles. Starting from commercially available 2-aminothiazole-4-carboxylic ester, the amino group was protected using Boc anhydride and the ester reduced with RedAl. Oxidation of the alcohol with Dess-Martin periodinane gives the aldehyde which can undergo reactions with organometallic reagents such as

Grignard reagents to give compound **XLIX.** TFA deprotection of **XLIX** gives **L** which is ready for coupling to different cores to make compounds of Formula I. Alternatively, oxidation of intermediate **XLIX** gives the keto compound **LI** that can be deprotected to give compound **LII**, fluoridated using (diethylamino) sulfur trifluoride (DAST) and deprotected to give compound **LIII**, or homologated using a Horner-Wadsworth-Emmons procedure to give the α,β-unsaturated ester **LIV**. Ester **LIV** can be deprotected with TFA to give compound **LV**, the ester converted using standard procedures to amide **LVI**, and lastly reduced to amide **LVII**.

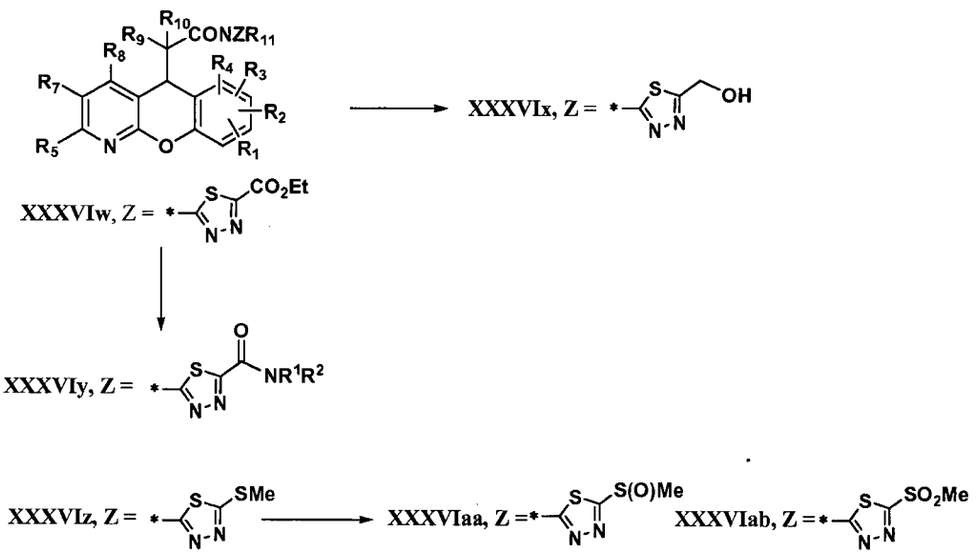
SCHEME 11

Additional Syntheses of 2-aminothiazoles



SCHEME 12

Synthesis and Elaboration of 1,3,4-thiadiazoles



[0084] Scheme 12 illustrates the preparation of some example compounds where group Z is a 5-substituted-1,3,4-thiadiazole. Thus, the ester **XXXVIw** may be reduced by the action of any number of reducing agents, such as sodium borohydride, to give alcohol **XXXVIx**. Alternatively, ester **XXXVIw** may be hydrolyzed to a carboxylic acid (typically employing aqueous sodium hydroxide in methanol) which may then undergo condensation with primary or secondary amines under standard conditions (such as described for the preparation of Ia from II) to provide carboxamides **XXXVIy**. Example compounds containing 5-alkylthio-1,3,4-thiadiazoles (**XXXVIz**) may be oxidized to sulfoxides (**XXXVIaa**) and/or sulfones (**XXVIab**) under the action of an appropriate oxidant, such as *m*-CPBA.

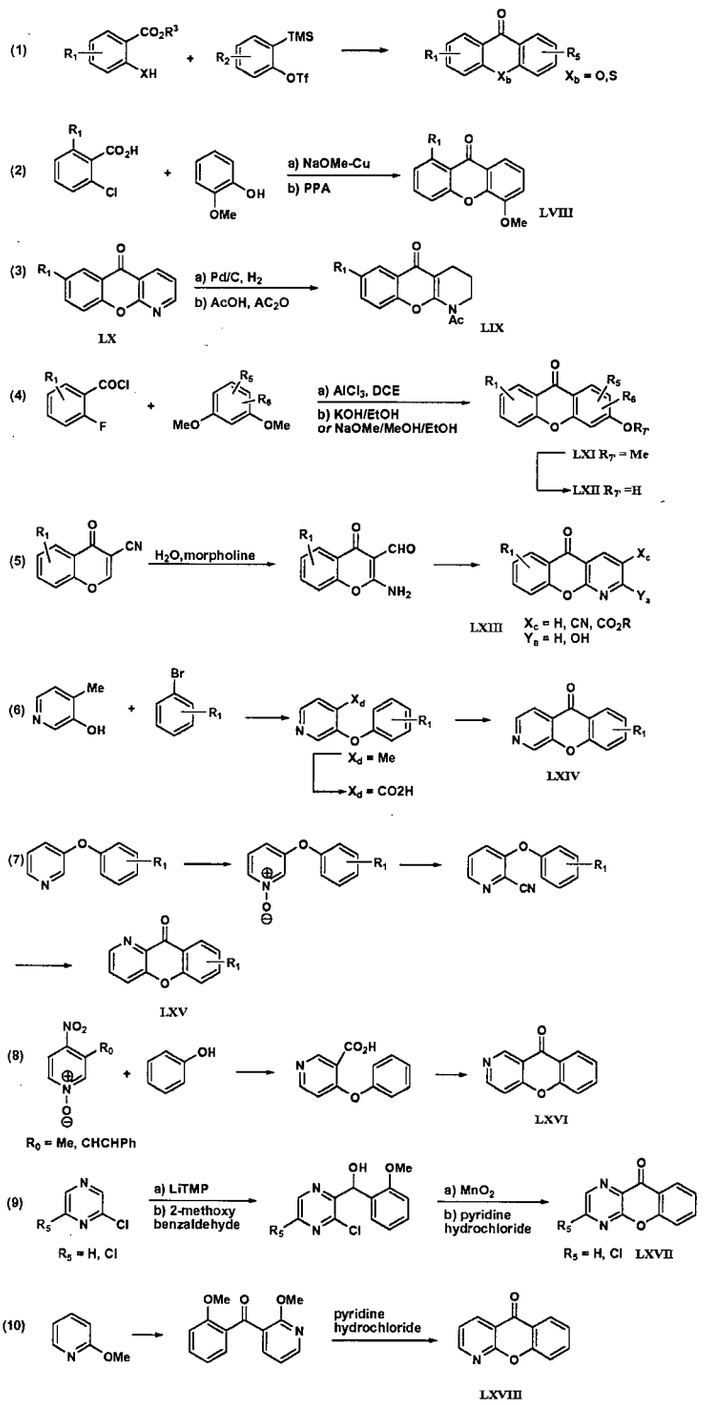
[0085] Scheme 13 illustrates just several syntheses of ketones IV which have been described in the literature. Scheme 13, reaction (1) shows the method of Zhao and Larock (Organic Letters 2005, 7, 4273-4275) for the one-pot synthesis of xanthones and thioxanthones by the tandem coupling-cyclization of arynes and salicylates. Scheme 13, reaction sequence (2) illustrates the preparation of xanthones **LVIII** by the Ullman condensation of o-halobenzoic acids and phenols followed by polyphosphoric acid-induced cyclication, as described by Galt et al. (J. Med. Chem. 1989, 32, 2357-2362). A variety of related methyl-, nitro-, carboxy-, and nitro-

substituted xanthones may be prepared by a similar method (Pickert et al. Arch. Pharm. Pharm. Med. Chem. 1998, 331, 177-192). Similar chemistry may be utilized for the preparation of variably substituted 9-oxo-9H-xanthene-4-acetic acids as per the procedures of Rewcastle et al. (J. Med. Chem. 1991, 34, 217-222 and J. Med. Chem. 1989, 32, 793). 4-Methoxyxanthone may be prepared by the two-step procedure described by Coelho et al. (Helv. Chim. Act. 2001, 84, 117-123). 1-Hydroxyxanthone may be prepared by the condensation of salicylic acid and resorcinol in the presence of zinc chloride (ibid). 2-Hydroxy and 3-hydroxyxanthone may be prepared following the methods described by Lin et al. (J. Pharm. Sci. 1993, 82, 11) and Quillinan et al. (J. Pharm. Sci. 1965, 54, 633). Scheme 13, reaction sequence (3) shows the synthesis of 5H-[1]benzopyrano[2,3-b]-1,2,3,4-tetrahydropyridin-5-ones **LIX** by the two step sequence reported by Pasutto et al. (Heterocycles 1985, 2293-2297). The starting benzopyranopyridin-5-ones **LX** may be obtained by the method of Villani et al. (J. Med. Chem. 1975, 18, 1-8). Scheme 13, reaction sequence (4) illustrates the method of Sato et al. (Chem. Pharm. Bull. 1990, 38, 1266-1277) which may be employed for the preparation of 3-methoxy and 3-hydroxy xanthones (**LXI** and **LXII**, respectively)by the Friedel-Crafts acylation of resorcinol dimethyl ethers with o-fluoro benzoyl chlorides followed by base-induced cyclization. 5H-[1]benzopyrano[2,3-b]pyridine-5-ones **LXIII** (Scheme 13, reaction sequence (5)) may also be prepared from 4-oxo-4H-1-benzopyran-3-carbonitriles following the procedures described by Nohara et al. (J. Med. Chem. 1985, 28, 559-567). The benzopyranopyridines **LXIV**, **LXV** and **LXVI** (isomers of benzopyranopyridin-5-ones **LX**) may be prepared by the methods of Villani et al. (J. Med. Chem. 1975, 18, 1-8, Scheme 8, reaction sequences (6 – 8)). Benzopyranopyridine **LXVI** may also be prepared from (4-fluoro-3-pyridyl)-2-methoxyphenylmethanone by the method of Marsais, et al. (J. Heterocycl. Chem. 1988, 25, 81-87) or from N,N-diethyl-2-(pyridine-4-yloxy)benzamide by the method of Familoni et al. (Syn. Lett. 1997, 9, 1081-1083). 10-Oxo-10H-[1]benzopyrano[2,3-b]pyrazines **LXVII** (Scheme 13, reaction sequence (9)) may be prepared by the sequence of reactions described by Turck et al. (Synthesis 1988, 11, 881-884 and J. Organometallic Chem. 1991, 412, 301-310). 4-Azaxanthone **LXVIII** may also be

prepared as shown in Scheme 8, reaction (10) (Trecourt, et al., J. Chem. Soc. Perkin Trans. 1990, 2409-2415).

SCHEME 13

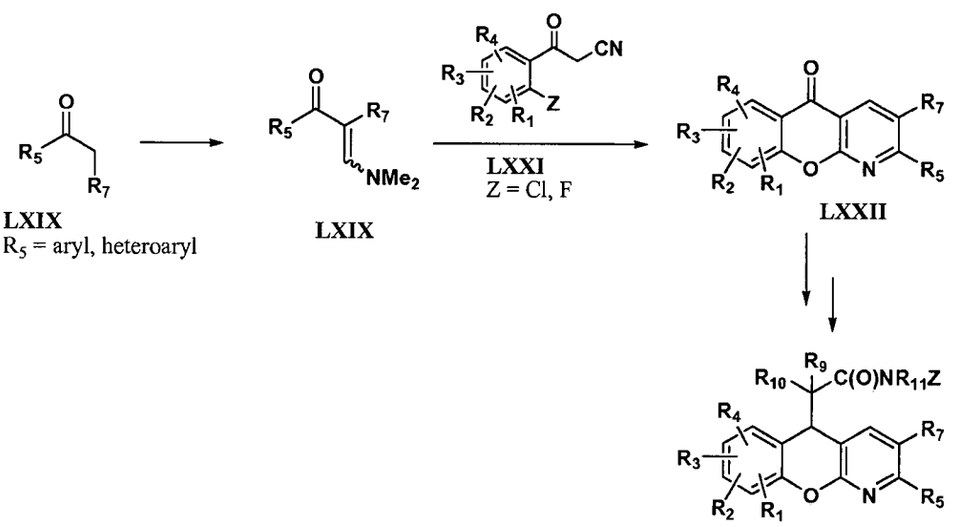
Preparation of ketones IV



[0086] An alternative synthesis of Example compounds **XXXVIa** is depicted in Scheme 14. Aryl (or heteroaryl) ketones **LXIX** may be converted to vinylogous amides (**LXX**) by treatment with DMF dimethyl acetal, typically by heating a mixture of the two at reflux overnight. Cyanoacetophenones (**LXXI**) may be purchased, or prepared as described in the literature (see, for example, Ridge, David N. *et al, J Med Chem* **1979**, 1385). Ketones **LXXII** may be prepared by condensation of **LXX** and **LXXI** in hot (typically 120 °C) solvent (typically DMF or DMA) under acidic conditions (typically acetic acid). The elaboration of intermediate **LXXII** to title compounds of the invention may then be carried out as depicted in Scheme 2 for the conversion of **IV** to **II**, and as depicted in Scheme 1, for the conversion of **II** to **Ia**.

SCHEME 14

Preparation and Elaboration of 2-aryl-5*H*-chromeno[2,3-*b*]pyridine-5-ones

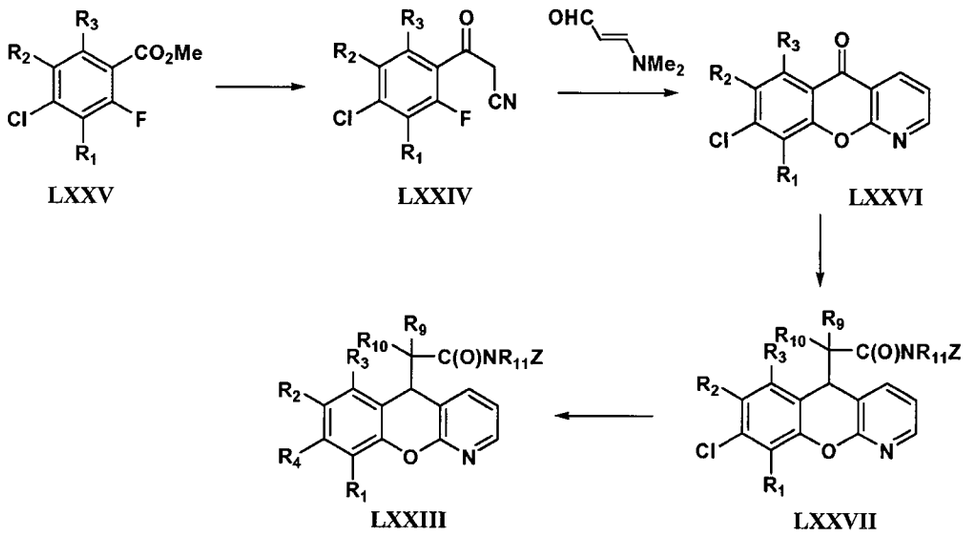


[0087] Another synthesis of compounds of the invention (**LXXIII**) is depicted in Scheme 15. *Para*-chloro-cyanoacetophenones **LXXIV** may be prepared as described for the preparation of **LXXI**. Alternatively, **LXXIV** may be prepared by treatment of alkyl –*p*-chlorobenzoates (**LXXV**) with the anion derived from treatment of acetonitrile with a strong base (preferably LDA). Condensation of **LXXIV** with (E)-3-dimethylamino)acrylaldehyde may be carried out as described for the conversion of **LXX** to **LXXII** (Scheme 14) to provide ketones **LXXVI**. **LXXVI** may be elaborated

to amides **LXXVII** as described for the conversion of **IV** to **II** (Scheme 2) and **II** to **Ia** (Scheme 1). Conversion of **LXXVII** to **LXXIII** may be then carried out as described for the preparation of **XXXVb** from **XXXIV**, employing a palladium catalyst/ligand useful for the cross-coupling arylation of aryl chlorides (see, for example, Littke, A.F.; *Angew. Chem. IEE* **2002**, 4176). The aryl chlorides **LXXVII** may also be converted to **LXXIII** by way of a boronate ester, as described for the conversion of **XXVa** to **XXVI** via **XXVb** (Scheme 4).

SCHEME 15

Preparation and Elaboration of 8-chloro-5*H*-chromeno[2,3]*b*-pyridine-5-ones



DEFINITIONS

[0088] The following are definitions of terms used in this specification and appended claims. The initial definition provided for a group or term herein applies to that group or term throughout the specification and claims, individually or as part of another group, unless otherwise indicated.

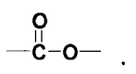
[0089] The term "alkyl" alone or as part of another group refers to straight or branched chain hydrocarbon groups having 1 to 12 carbon atoms, preferably 1 to 8 carbon atoms. Lower alkyl groups, that is, alkyl groups of 1 to 4 carbon atoms, are most preferred. When numbers appear in a subscript after the symbol "C", the subscript defines with more specificity the number of carbon atoms that a particular

group may contain. For example, "C_{1-6}alkyl" refers to straight and branched chain alkyl groups with one to six carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, and so forth. The subscript "0" refers to a bond. Thus, the term hydroxy(C_{0-2})alkyl or (C_{0-2})hydroxyalkyl includes hydroxy, hydroxymethyl and hydroxyethyl.

[0090] "Alkyl" includes "unsubstituted" and "substituted alkyl" where the alkyl may be substituted with any of the substituents for substituted alkyl set out below.

[0091] The term "substituted alkyl" refers to an alkyl group as defined above having one, two, or three substituents independently selected from the group consisting of halo (*e.g.*, trifluoromethyl), alkenyl, substituted alkenyl, alkynyl, nitro, cyano, oxo (=O), OR_a, SR_a, (=S), $-NR_aR_b$, $-N(alkyl)_3^+$, $-NR_aSO_2$, $-NR_aSO_2R_c$, $-SO_2R_c$, $-SO_2NR_aR_b$, $-SO_2NR_aC(=O)R_b$, SO_3H, $-PO(OH)_2$, $-C(=O)R_a$, $-CO_2R_a$, $-C(=O)NR_aR_b$, $-C(=O)(C_{1-4}alkylene)NR_aR_b$, $-C(=O)NR_a(SO_2)R_b$, $-CO_2(C_{1-4}alkylene)NR_aR_b$, $-NR_aC(=O)R_b$, $-NR_aCO_2R_b$, $-NR_a(C_{1-4}alkylene)CO_2R_b$, =N-OH, =N-O-alkyl, aryl, cycloalkyl, heterocyclo, and/or heteroaryl, wherein R_a and R_b are the same or different and are independently selected from hydrogen, alkyl, alkenyl, CO_2H, CO_2(alkyl), C_{3-7}cycloalkyl, phenyl, benzyl, phenylethyl, naphthyl, a four to seven membered heterocyclo, or a five to six membered heteroaryl, or when attached to the same nitrogen atom may join to form a heterocyclo or heteroaryl, and R_c is selected from same groups as R_a and R_b but is not hydrogen. Each group R_a and R_b when other than hydrogen, and each R_c group optionally has up to three further substituents attached at any available carbon or nitrogen atom of R_a, R_b, and/or R_c, said substituent(s) being the same or different and are independently selected from the group consisting of (C_{1-6})alkyl, (C_{2-6})alkenyl, hydroxy, halogen, cyano, nitro, CF_3, $O(C_{1-6}alkyl)$, OCF_3, C(=O)H, $C(=O)(C_{1-6}alkyl)$, CO_2H, $CO_2(C_{1-6}alkyl)$, $NHCO_2(C_{1-6}alkyl)$, $-S(C_{1-6}alkyl)$, $-NH_2$, $NH(C_{1-6}alkyl)$, $N(C_{1-6}alkyl)_2$, $N(CH_3)_3^+$, $SO_2(C_{1-6}alkyl)$, -NHC(=O)alkyl, $C(=O)(C_{1-4}alkylene)NH_2$, $C(=O)(C_{1-4}alkylene)NH(alkyl)$, $C(=O)(C_{1-4}alkylene)N(C_{1-4}alkyl)_2$, C_{3-7}cycloalkyl, phenyl, benzyl, phenylethyl, phenyloxy, benzyloxy, naphthyl, a four to seven membered heterocylo, or a five to six membered heteroaryl. When a substituted alkyl is substituted with an aryl, heterocyclo, cycloalkyl, or heteroaryl group, said ringed systems are as defined below

and thus may have zero, one, two, or three substituents, also as defined below and/or as defined for substituted alkyl.

[0092] One skilled in the field will understand that, when the designation "CO_2" is used herein, this is intended to refer to the group  .

[0093] When the term "alkyl" is used together with another group, such as in "arylalkyl", this conjunction defines with more specificity at least one of the substituents that the substituted alkyl will contain. For example, "arylalkyl" refers to a substituted alkyl group as defined above where at least one of the substituents is an aryl, such as benzyl. Thus, the term aryl(C_{0-4})alkyl includes a substituted lower alkyl having at least one aryl substituent and also includes an aryl directly bonded to another group, *i.e.*, aryl(C_0)alkyl.

[0094] The term "alkenyl" (which includes unsubstituted or substituted alkenyl) alone or as part of another group refers to straight or branched chain hydrocarbon groups having 2 to 12 carbon atoms and at least one double bond. Alkenyl groups of 2 to 6 carbon atoms and having one double bond are most preferred.

[0095] The term "alkynyl" (which includes unsubstituted or substituted alkynyl) alone or as part of another group refers to straight or branched chain hydrocarbon groups having 2 to 12 carbon atoms and at least one triple bond. Alkynyl groups of 2 to 6 carbon atoms and having one triple bond are most preferred.

[0096] The term "alkylene" (which includes unsubstituted or substituted alkylene) alone or as part of another group refers to bivalent straight or branched chain hydrocarbon groups having 1 to 12 carbon atoms, preferably 1 to 8 carbon atoms, *e.g.*, $\{-CH_2-\}_n$, wherein *n* is 1 to 12, preferably 1-8. Lower alkylene groups, that is, alkylene groups of 1 to 4 carbon atoms, are most preferred. The terms "alkenylene" and "alkynylene" refer to bivalent radicals of alkenyl and alkynyl groups, respectively, as defined above.

[0097] When reference is made to a substituted alkenyl, alkynyl, alkylene, alkenylene, or alkynylene group, these groups are substituted with one to three substituents as defined above for substituted alkyl groups.

[0098] The term "heteroalkylene" (which includes unsubstituted and "substituted heteroalkylene") alone or as part of another group is used herein to refer to saturated

and unsaturated bivalent straight or branched chain hydrocarbon groups having 2 to 12 carbon atoms, preferably 2 to 8 carbon atoms, wherein one or two carbon atoms in the straight chain are replaced by heteroatom(s) selected from –O–, –S–, –S(=O)–, $–SO_2–$, –NH–, and $–NHSO_2–$. Thus, the term "heteroalkylene" includes bivalent alkoxy, thioalkyl, and aminoalkyl groups, as defined below, as well as alkylene and alkenylene groups having a combination of heteroatoms in the alkyl chain. As an illustration, a "heteroalkylene" herein may comprise groups such as $–S-(CH_2)_{1-5}NH-CH_2-$, $–O-(CH_2)_{1-5}S(=O)-CH_2–$, $–NHSO_2-CH_2–$, $–CH_2-NH–$, and so forth. Preferably, a heteroalkylene does not have two adjacent atoms simultaneously selected from –O- and –S-. When a subscript is used with the term heteroalkylene, *e.g.*, as in C_{2-3}heteroalkylene, the subscript refers to the number of carbon atoms in the group in addition to heteroatoms. Thus, for example, a C_{1-2}heteroalkylene may include groups such as $–NH-CH_2-$, $-CH_2-NH-CH_2-$, $-CH_2-CH_2-NH-$, $-S-CH_2-$, $-CH_2-S-CH_2-$, $-O-CH_2-NH-CH_2-$, CH_2-O-CH_2 and so forth.

[0099] The term "substituted heteroalkylene" refers to a heteroalkylene group as defined above wherein at least one of the nitrogen or carbon atoms in the heteroalkylene chain is bonded to (or substituted with) a group other than hydrogen. Carbon atoms in the heteroalkylene chain may be substituted with a group selected from those recited above for substituted alkyl groups, or with a further alkyl or substituted alkyl group. Nitrogen atoms of the heteroalkylene chain may be substituted with a group selected from alkyl, alkenyl, alkynyl, cyano, or $A_1-Q-A_2-R_h$, wherein A_1 is a bond, C_{1-2}alkylene, or C_{2-3}alkenylene; Q is a bond, $-C(=O)-$, $-C(=O)NR_d-$, $-C(=S)NR_d-$, $-SO_2-$, $-SO_2NR_d-$, $–CO_2-$, or $–NR_dCO_2-$; A_2 is a bond, C_{1-3}alkylene, C_{2-3}alkenylene, $-C_{1-4}$alkylene-NR_d-, $-C_{1-4}$alkylene-$NR_dC(=O)-$, $-C_{1-4}$alkylene-S-, $-C_{1-4}$alkylene-SO_2-, or $-C_{1-4}$alkylene-O-, wherein said A_2 alkylene groups are branched or straight chain and optionally substituted as defined herein for substituted alkylene; R_h is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, heteroaryl, heterocyclo, or cycloalkyl; and R_d is selected from hydrogen, alkyl, and substituted alkyl, as defined herein, provided, however, that for a substituted heteroalkylene R_h is not hydrogen when A_1, Q and A_2 are each bonds. When R_h is aryl, heteroaryl, cycloalkyl, or heterocyclo, these rings are, in turn,

optionally substituted with one to three groups as defined below in the definitions for these terms.

[00100] The term "alkoxy" refers to an alkyl or substituted alkyl group as defined above having one or two oxygen atoms (-O-) in the alkyl chain. For example, the term "alkoxy" includes the groups -O-C_{1-12}alkyl, –(C_{1-6}alkylene)-O-C_{1-6}alkyl, –(C_{1-4}alkylene-O-C_{1-4}alkylene)-O-C_{1-4}alkyl, and so forth.

[00101] The term "thioalkyl" or "alkylthio" refers to an alkyl or substituted alkyl group as defined having one or two sulfur atoms in the alkyl chain. For example, the term "thioalkyl" or "alkylthio" includes the groups -S-C_{1-12}alkyl, –(S-C_{1-6}alkylene)-S-C_{1-6}alkyl, and so forth.

[00102] The terms "aminoalkyl" or "alkylamino" refer to an alkyl or substituted alkyl group as defined above having one or two nitrogen (-NR-) atoms in the alkyl chain. For example, the term "aminoalkyl" includes the groups -NR-C_{1-12}alkyl, –NR-C_{1-6}alkylene-NR-C_{1-6}alkyl, etc. (where R is preferably hydrogen but may include alkyl or substituted alkyl as defined above.) When a subscript is used with reference to an alkoxy, thioalkyl or aminoalkyl, the subscript refers to the number of carbon atoms that the group may contain in addition to heteroatoms. Thus, for example, monovalent C_{1-2}aminoalkyl includes the groups -CH_2-NH_2, -NH-CH_3, -$(CH_2)_2$-NH_2, -NH-CH_2-CH_3, -CH_2-NH_2- CH_3, and -N-$(CH_3)_2$. A lower aminoalkyl comprises an aminoalkyl having one to four carbon atoms. "Amino" refers to the group NH_2.

[00103] The alkoxy, thioalkyl, or aminoalkyl groups may be monovalent or bivalent. By "monovalent" it is meant that the group has a valency (*i.e.*, ability to combine with another group), of one, and by "bivalent" it is meant that the group has a valency of two. Thus, for example, a monovalent alkoxy includes groups such as -O-C_{1-12}alkyl, –C_{1-6}alkylene-O-C_{1-6}alkyl, –C_{1-4}alkylene-O-C_{1-4}alkylene-O-C_{1-4}alkyl, whereas a bivalent alkoxy includes groups such as -O-C_{1-12}alkylene-, –C_{1-6}alkylene-O-C_{1-6}alkylene-, –C_{1-4}alkylene-O-C_{1-4}alkylene-O-C_{1-4}alkylene-, and so forth.

[00104] It should be understood that the selections for alkoxy, thioalkyl, and aminoalkyl will be made by one skilled in the field to provide stable compounds. Thus, for example, in compounds of formula I, when R_5, R_6, R_7 or R_8 is attached to a nitrogen atom (N*) of ring B and is selected from an alkoxy or alkylthio group, the

alkoxy and alkylthio groups will have at least one carbon atom bonded directly to ring B (at N*), with the oxygen or sulfur atoms being at least one atom away from said nitrogen atom.

[00105] The term "acyl" alone or as part of another group refers to a carbonyl group linked to an organic radical, more particularly, the group $C(=O)R_e$, as well as the bivalent groups $-C(=O)-$ or $-C(=O)R_e-$, which are linked to organic radicals or a ring in compounds of formula I. The group R_e can be selected from alkyl, alkenyl, alkynyl, aminoalkyl, substituted alkyl, substituted alkenyl, or substituted alkynyl, as defined herein, or when appropriate, the corresponding bivalent group, *e.g.*, alkylene, alkenylene, etc. Accordingly, in compounds of formula I, when it is recited that R_1 to R_8 can be "acyl," this is intended to encompass a selection for R_1 to R_8 of $-C(=O)-$ and also the groups $-C(=O)R_e-$ or $-R_eC(=O)-$, wherein in this instance, the group R_e will be selected from bivalent groups, *e.g.*, alkylene, alkenylene, alkynylene, bivalent aminoalkyl, substituted alkylene, substituted alkenylene, or substituted alkynylene.

[00106] The term "alkoxycarbonyl" alone or as part of another group refers to a carboxy group ($-\overset{O}{\overset{\|}{C}}-O-$ or $-O-\overset{O}{\overset{\|}{C}}-$) linked to an organic radical (CO_2R_e), as well as the bivalent groups $-CO_2-$, $-CO_2R_e-$ which are linked to organic radicals in compounds of formula I, wherein R_e is as defined above for acyl. The organic radical to which the carboxy group is attached may be monovalent (*e.g.*, $-CO_2$-alkyl or $-OC(=O)$alkyl), or bivalent (*e.g.*, $-CO_2$-alkylene, $-OC(=O)$alkylene, etc.). Accordingly, "alkoxycarbonyl," is intended to encompass the groups $-CO_2R_e-$ or $-R_eCO_2-$, wherein in this instance, the group R_e will be selected from bivalent groups, *e.g.*, alkylene, alkenylene, alkynylene, bivalent aminoalkyl, substituted alkylene, substituted alkenylene, or substituted alkynylene.

[00107] The term "amide" or "amidyl" alone or as part of another group refers to the group $C(=O)NR_aR_b$ (or other R groups other than R_a or R_b linked to an N atom), wherein the groups R_a and R_b are defined as recited above in the definition for substituted alkyl groups.

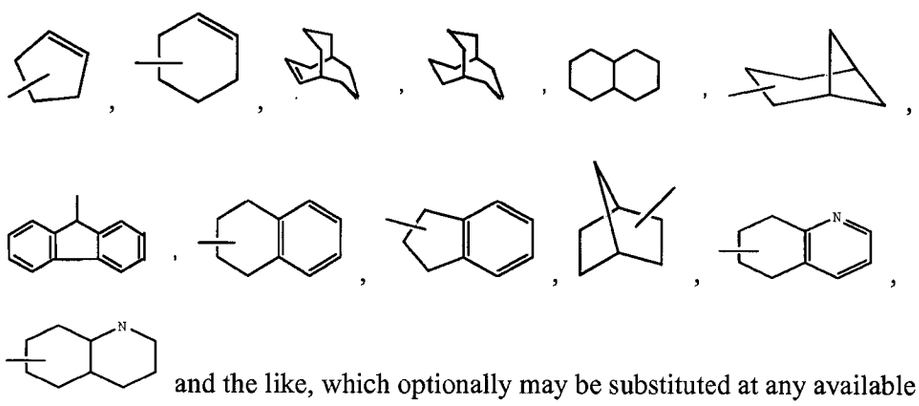
[00108] The term "sulfonyl" alone or as part of another group refers to a sulphoxide group linked to an organic radical in compounds of formula I, more particularly, the monovalent group $S(O)_{1-2}$-R_e, or the bivalent group -$S(O)_{1-2}$- linked

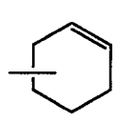
to organic radicals in compounds of formula I. Accordingly, in compounds of formula I, "sulfonyl," is intended to encompass $-S(=O)-$ or $-SO_2-$ as well as the groups $-S(=O)R_e-$, $-R_eS(=O)-$, $-SO_2R_e-$, or $-R_eSO_2-$, wherein in this instance, the group R_e will be selected from those recited above for acyl and alkoxycarbonyl groups.

[00109] The term "sulfonamidyl" alone or as part of another group refers to the group $-S(O)_2NR_aR_b$ (or other R groups other than R_a or R_b linked to an N atom), wherein R_a and R_b are as defined above for substituted alkyl groups. Additionally, the sulfonamidyl group may be bivalent, in which case one of the groups R_a and R_b will be a bond. Thus, in compounds of formula I, sulfonamidyl is intended to mean the group $-S(O)_2NR_a-$.

[00110] The term "cycloalkyl" alone or as part of another group refers to fully saturated and partially unsaturated hydrocarbon rings of 3 to 9, preferably 3 to 6 carbon atoms. Accordingly, the term "cycloalkyl" is intended to include a cycloalkenyl (e.g. cyclohexenyl) ring. The term "cycloalkyl" includes such rings having zero, one, two, or three substituents selected from the group consisting of halogen, trifluoromethyl, trifluoromethoxy, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, nitro, cyano, oxo (=O), OR_a, SR_a, (=S), $-NR_aR_b$, $-N(alkyl)_3^+$, $-NR_aSO_2$, $-NR_aSO_2R_c$, $-SO_2R_c$ $-SO_2NR_aR_b$, $-SO_2NR_aC(=O)R_b$, SO_3H, $-PO(OH)_2$, $-C(=O)R_a$, $-CO_2R_a$, $-C(=O)NR_aR_b$, $-C(=O)(C_{1-4}alkylene)NR_aR_b$, $-C(=O)NR_a(SO_2)R_b$, $-CO_2(C_{1-4}alkylene)NR_aR_b$, $-NR_aC(=O)R_b$, $-NR_aCO_2R_b$, $-NR_a(C_{1-4}alkylene)CO_2R_b$, =N-OH, =N-O-alkyl, aryl, cycloalkyl, heterocyclo, and/or heteroaryl, wherein R_a, R_b and R_c are as defined above for substituted alkyl groups, and are also in turn optionally substituted as recited above in the definition for substituted alkyl groups. The term "cycloalkyl" also includes such rings having a second ring fused thereto (*e.g.*, including benzo, heterocyclo, or heteroaryl rings) or having a carbon-carbon bridge of 3 to 4 carbon atoms. When a cycloalkyl is substituted with a further ring (or has a second ring fused thereto), said ring in turn is optionally substituted with one to two of (C_{1-4})alkyl, (C_{2-4})alkenyl, halogen, hydroxy, cyano, nitro, CF_3, $O(C_{1-4}alkyl)$, OCF_3, C(=O)H, $C(=O)(C_{1-4}alkyl)$, CO_2H, $CO_2(C_{1-4}alkyl)$, $NHCO_2(C_{1-4}alkyl)$, $-S(C_{1-4}alkyl)$, $-NH_2$, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)_2$, $N(C_{1-4}alkyl)_3^+$, $SO_2(C_{1-4}alkyl)$, $C(=O)(C_{1-4}alkylene)NH_2$, $C(=O)(C_{1-4}alkylene)NH(alkyl)$, and/or $C(=O)(C_{1-4}alkylene)N(C_{1-4}alkyl)_2$.

[00111] Accordingly, in compounds of formula (I), the term "cycloalkyl" includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, etc., as well as the following ring systems,



and the like, which optionally may be substituted at any available atoms of the ring(s). Preferred cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,  and  .

[00112] The term "halo" or "halogen" alone or as part of another group refers to chloro, bromo, fluoro and iodo.

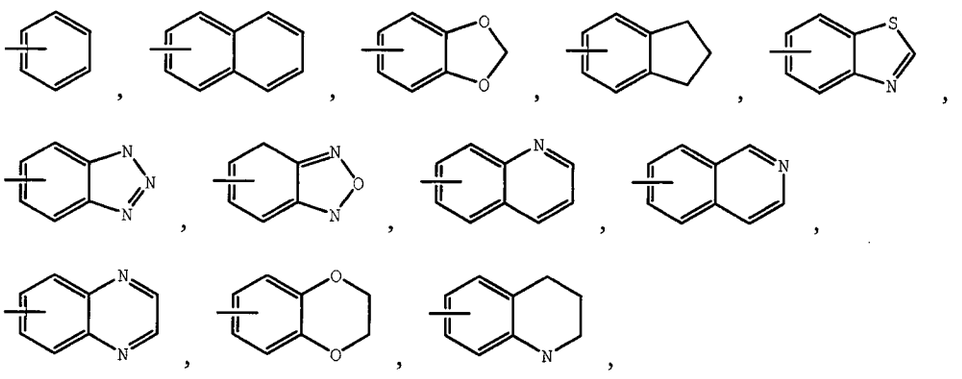
[00113] The term "haloalkyl" alone or as part of another group means a substituted alkyl having one or more halo substituents. For example, "haloalkyl" includes mono, bi, and trifluoromethyl.

[00114] The term "haloalkoxy" alone or as part of another group means an alkoxy group having one or more halo substituents. For example, "haloalkoxy" includes OCF_3.

[00115] The term "aryl" alone or as part of another group refers to phenyl, biphenyl, 1-naphthyl and 2-naphthyl. The term "aryl" includes such rings having zero, one, two or three substituents selected from the group consisting of halogen, trifluoromethyl, trifluoromethoxy, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, nitro, cyano, OR_a, SR_a, (=S), $-NR_aR_b$, $-N(alkyl)_3^+$, $-NR_aSO_2$, $-NR_aSO_2R_c$, $-SO_2R_c$ $-SO_2NR_aR_b$, $-SO_2NR_aC(=O)R_b$, SO_3H, $-PO(OH)_2$, $-C(=O)R_a$, $-CO_2R_a$, $-C(=O)NR_aR_b$, $-C(=O)(C_{1-4}alkylene)NR_aR_b$, $-C(=O)NR_a(SO_2)R_b$, $-CO_2(C_{1-4}alkylene)NR_aR_b$, $-NR_aC(=O)R_b$, $-NR_aCO_2R_b$, $-NR_a(C_{1-4}alkylene)CO_2R_b$, aryl, cycloalkyl, heterocyclo, and/or heteroaryl, wherein R_a, R_b and R_c are as defined

above for substituted alkyl groups, and are also in turn optionally substituted as recited above, or any of the substituents for alkyl set out hereinbefore. Additionally, two substituents attached to an aryl, particularly a phenyl group, may join to form a further ring such as a fused or spiro-ring, *e.g.*, cyclopentyl or cyclohexyl, or fused heterocyclo or heteroaryl. When an aryl is substituted with a further ring (or has a second ring fused thereto), said ring in turn is optionally substituted with one to four, preferably one or two of (C_{1-4})alkyl, (C_{2-4})alkenyl, halogen, hydroxy, cyano, nitro, CF_3, $O(C_{1-4}alkyl)$, OCF_3, C(=O)H, $C(=O)(C_{1-4}alkyl)$, CO_2H, $CO_2(C_{1-4}alkyl)$, $NHCO_2(C_{1-4}alkyl)$, $-S(C_{1-4}alkyl)$, $-NH_2$, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)_2$, $N(C_{1-4}alkyl)_3^+$, $C(=O)NH_2$, $SO_2(C_{1-4}alkyl)$, $C(=O)(C_{1-4}alkylene)NH_2$, $C(=O)(C_{1-4}alkylene)NH(alkyl)$, and/or $C(=O)(C_{1-4}alkylene)N(C_{1-4}alkyl)_2$.

[00116] Thus, examples of aryl groups include:



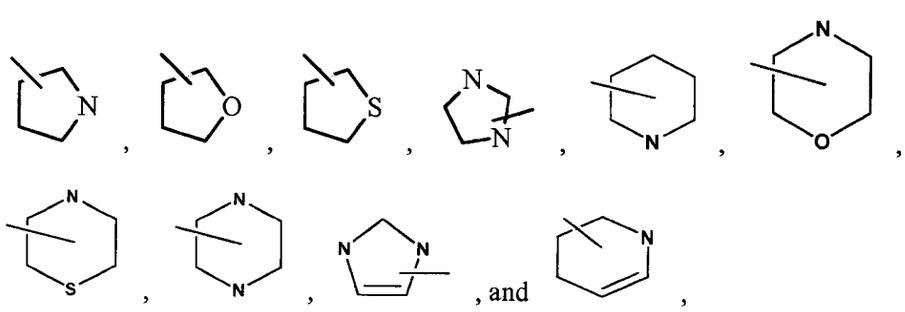
and the like, which optionally may be substituted at any available carbon or nitrogen atom. A preferred aryl group is optionally-substituted phenyl.

[00117] The terms "heterocyclo" or "heterocyclic" or "cycloheteroalkyl" alone or as part of another group refers to substituted and unsubstituted non-aromatic 3 to 7 membered monocyclic groups, 7 to 11 membered bicyclic groups, and 10 to 15 membered tricyclic groups, in which at least one of the rings has at least one heteroatom (O, S or N) (also referred to as cycloheteroalkyl or heterocycloalkyl). Each ring of the heterocyclo group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less, and further provided that the ring contains at least one carbon atom. The fused rings completing bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or

unsaturated. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. The heterocyclo group may be attached at any available nitrogen or carbon atom. The heterocyclo ring may contain zero, one, two or three substituents selected from the group consisting of halogen, trifluoromethyl, trifluoromethoxy, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, nitro, cyano, oxo (=O), OR_a, SR_a, (=S), $-NR_aR_b$, $-N(alkyl)_3^+$, $-NR_aSO_2$, $-NR_aSO_2R_c$, $-SO_2R_c$ $-SO_2NR_aR_b$, $-SO_2NR_aC(=O)R_b$, SO_3H, $-PO(OH)_2$, $-C(=O)R_a$, $-CO_2R_a$, $-C(=O)NR_aR_b$, $-C(=O)(C_{1-4}alkylene)NR_aR_b$, $-C(=O)NR_a(SO_2)R_b$, $-CO_2(C_{1-4}alkylene)NR_aR_b$, $-NR_aC(=O)R_b$, $-NR_aCO_2R_b$, $-NR_a(C_{1-4}alkylene)CO_2R_b$, =N-OH, =N-O-alkyl, aryl, cycloalkyl, heterocyclo, and/or heteroaryl, wherein R_a, R_b and R_c are as defined above for substituted alkyl groups, and are also in turn optionally substituted as recited above. When a heterocyclo is substituted with a further ring, said ring in turn is optionally substituted with one to two of (C_{1-4})alkyl, (C_{2-4})alkenyl, halogen, hydroxy, cyano, nitro, CF_3, $O(C_{1-4}alkyl)$, OCF_3, C(=O)H, $C(=O)(C_{1-4}alkyl)$, CO_2H, $CO_2(C_{1-4}alkyl)$, $NHCO_2(C_{1-4}alkyl)$, $-S(C_{1-4}alkyl)$, $-NH_2$, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)_2$, $N(C_{1-4}alkyl)_3^+$, $SO_2(C_{1-4}alkyl)$, $C(=O)(C_{1-4}alkylene)NH_2$, $C(=O)(C_{1-4}alkylene)NH(alkyl)$, and/or $C(=O)(C_{1-4}alkylene)N(C_{1-4}alkyl)_2$.

[00118] Exemplary monocyclic groups include azetidinyl, pyrrolidinyl, oxetanyl, imidazolinyl, oxazolidinyl, isoxazolinyl, thiazolidinyl, isothiazolidinyl, tetrahydrofuranyl, piperidyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, 4-piperidonyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl and the like. Exemplary bicyclic heterocyclo groups include quinuclidinyl.

[00119] Preferred heterocyclo groups in compounds of formula (I) include



which optionally may be substituted.

[00120] The term "heteroaryl" alone or as part of another group refers to substituted and unsubstituted aromatic 5 or 6 membered monocyclic groups, 9 or 10 membered bicyclic groups, and 11 to 14 membered tricyclic groups which have at least one heteroatom (O, S or N) in at least one of the rings. Each ring of the heteroaryl group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less and each ring has at least one carbon atom. The fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. Heteroaryl groups which are bicyclic or tricyclic must include at least one fully aromatic ring but the other fused ring or rings may be aromatic or non-aromatic. The heteroaryl group may be attached at any available nitrogen or carbon atom of any ring. The heteroaryl ring system may contain zero, one, two or three substituents selected from the group consisting of halogen, trifluoromethyl, trifluoromethoxy, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, nitro, cyano, OR_a, SR_a, (=S), $-NR_aR_b$, $-N(alkyl)_3^+$, $-NR_aSO_2$, $-NR_aSO_2R_c$, $-SO_2R_c$ $-SO_2NR_aR_b$, $-SO_2NR_aC(=O)R_b$, SO_3H, $-PO(OH)_2$, $-C(=O)R_a$, $-CO_2R_a$, $-C(=O)NR_aR_b$, $-C(=O)(C_{1-4}alkylene)NR_aR_b$, $-C(=O)NR_a(SO_2)R_b$, $-CO_2(C_{1-4}alkylene)NR_aR_b$, oxo(=O), $-NR_aC(=O)R_b$, $-NR_aCO_2R_b$, $-NR_a(C_{1-4}alkylene)CO_2R_b$, aryl, cycloalkyl, heterocyclo, and/or heteroaryl, wherein R_a, R_b and R_c are as defined above for substituted alkyl groups, and are also in turn optionally substituted as recited above. When a heteroaryl is substituted with a further ring, said ring in turn is optionally substituted with one to two of (C_{1-4})alkyl, (C_{2-4})alkenyl, halogen, hydroxy, cyano, nitro, CF_3, $O(C_{1-4}alkyl)$, OCF_3, C(=O)H, $C(=O)(C_{1-4}alkyl)$, CO_2H, $CO_2(C_{1-4}alkyl)$, $NHCO_2(C_{1-4}alkyl)$, $-S(C_{1-4}alkyl)$, $-NH_2$, $NH(C_{1-4}alkyl)$, $N(C_{1-4}alkyl)_2$, $N(C_{1-4}alkyl)_3^+$, $SO_2(C_{1-4}alkyl)$, $C(=O)(C_{1-4}alkylene)NH_2$, $C(=O)(C_{1-4}alkylene)NH(alkyl)$, and/or $C(=O)(C_{1-4}alkylene)N(C_{1-4}alkyl)_2$.

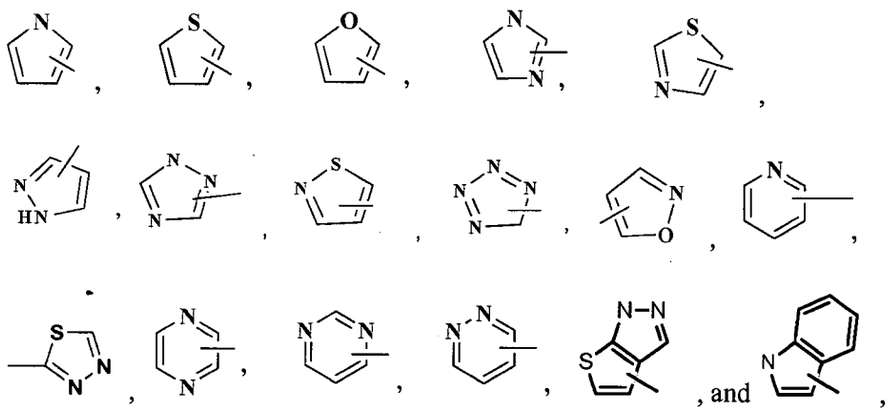
[00121] Exemplary monocyclic heteroaryl groups include pyrrolyl, pyrazolyl, pyrazolinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl,

furanyl, thienyl, oxadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl and the like.

[00122] Exemplary bicyclic heteroaryl groups include indolyl, benzothiazolyl, benzodioxolyl, benzoxazolyl, benzothienyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuranyl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridyl, dihydroisoindolyl, tetrahydroquinolinyl and the like.

[00123] Exemplary tricyclic heteroaryl groups include carbazolyl, benzidolyl, phenanthrollinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

[00124] In compounds of formula (I), preferred heteroaryl groups include



and the like, which optionally may be substituted at any available carbon or nitrogen atom.

[00125] Unless otherwise indicated, when reference is made to a specifically-named aryl (*e.g.*, phenyl), cycloalkyl (*e.g.*, cyclohexyl), heterocyclo (*e.g.*, pyrrolidinyl) or heteroaryl (*e.g.*, imidazolyl), unless otherwise specifically indicated the reference is intended to include rings having 0 to 3, preferably 0-2, substituents selected from those recited above for the aryl, cycloalkyl, heterocyclo and/or heteroaryl groups, as appropriate.

[00126] The term "heteroatoms" shall include oxygen, sulfur and nitrogen.

[00127] The term "carbocyclic" means a saturated or unsaturated monocyclic or bicyclic ring in which all atoms of all rings are carbon. Thus, the term includes cycloalkyl and aryl rings. The carbocyclic ring may be substituted in which case the substituents are selected from those recited above for cycloalkyl and aryl groups.

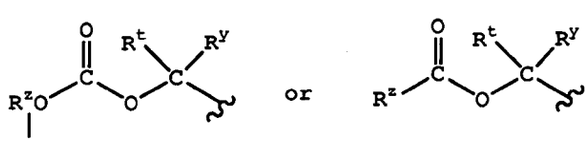
[00128] When the term "unsaturated" is used herein to refer to a ring or group, the ring or group may be fully unsaturated or partially unsaturated.

[00129] Throughout the specification, groups and substituents thereof may be chosen by one skilled in the field to provide stable moieties and compounds and compounds useful as pharmaceutically-acceptable compounds and/or intermediate compounds useful in making pharmaceutically-acceptable compounds.

[00130] The term "prodrug" denotes a compound which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of the formula (I), and/or a salt and/or solvate thereof. For example, compounds containing a carboxy group can form physiologically hydrolyzable esters which serve as prodrugs by being hydrolyzed in the body to yield formula (I) compounds *per se*. Such prodrugs are preferably administered orally since hydrolysis in many instances occurs principally under the influence of the digestive enzymes. Parenteral administration may be used where the ester *per se* is active, or in those instances where hydrolysis occurs in the blood. Examples of physiologically hydrolyzable esters of compounds of formula (I) include C_{1-6}alkylbenzyl, 4-methoxybenzyl, indanyl, phthalyl, methoxymethyl, C_{1-6}alkanoyloxy-C_{1-6}alkyl, *e.g.* acetoxymethyl, pivaloyloxymethyl or propionyloxymethyl, C_{1-6}alkoxycarbonyloxy-C_{1-6}alkyl, *e.g.* methoxycarbonyl-oxymethyl or ethoxycarbonyloxymethyl, glycyloxymethyl, phenylglycyloxymethyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)-methyl and other well known physiologically hydrolyzable esters used, for example, in the penicillin and cephalosporin arts. Such esters may be prepared by conventional techniques known in the art.

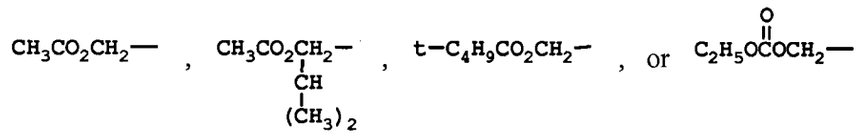
[00131] Prodrug ester examples include the following groups:

(1-alkanoyloxy)alkyl such as,

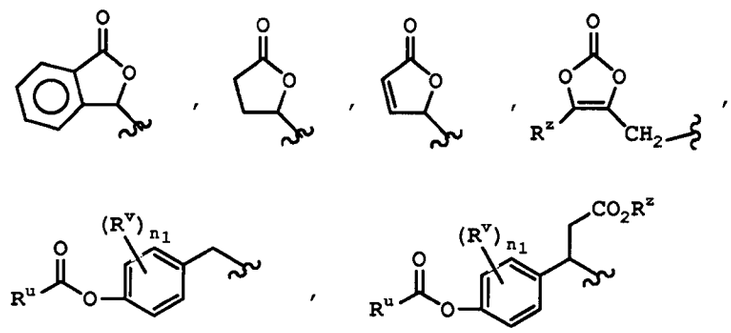


wherein R^z, R^t and R^y are H, alkyl, aryl or arylalkyl; however, R^zO cannot be HO.

[00132] Examples of such prodrug esters include



[00133] Other examples of suitable prodrug esters include



wherein R^z can be H, alkyl (such as methyl or t-butyl), arylalkyl (such as benzyl) or aryl (such as phenyl); R^v is H, alkyl, halogen or alkoxy, R^u is alkyl, aryl, arylalkyl or alkoxyl, and n_1 is 0, 1 or 2.

[00134] For further examples of prodrug derivatives, see:

a) *Design of Prodrugs*, edited by H. Bundgaard, (Elsevier, 1985) and *Methods in Enzymology*, Vol. 112, pp. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);

b) *A Textbook of Drug Design and Development*, edited by Krosgaard-Larsen and H. Bundgaard, Chapter 5, "Design and Application of Prodrugs," by H. Bundgaard, pp. 113-191 (1991); and

c) H. Bundgaard, *Advanced Drug Delivery Reviews*, Vol. 8, pp. 1-38 (1992).

[00135] The term "tautomer" refers to compounds of the formula (I) and salts thereof that may exist in their tautomeric form, in which hydrogen atoms are transposed to other parts of the molecules and the chemical bonds between the atoms of the molecules are consequently rearranged. It should be understood that the all tautomeric forms, insofar as they may exist, are included within the invention.

[00136] The terms pharmaceutically acceptable "salt" and "salts" refer to basic salts formed with inorganic and organic bases. Such salts include ammonium salts;

alkali metal salts, such as lithium, sodium and potassium salts (which are preferred); alkaline earth metal salts, such as calcium and magnesium salts; salts with organic bases, such as amine like salts (e.g., dicyclohexylamine salt, benzathine, N-methyl-D-glucamine, and hydrabamine salts); and salts with amino acids like arginine, lysine and the like; and zwitterions, the so-called "inner salts". Nontoxic, pharmaceutically acceptable salts are preferred, although other salts are also useful, e.g., in isolating or purifying the product.

[00137] The term pharmaceutically acceptable "salt" and "salts" also includes acid addition salts. These are formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid, phosphoric acid or a hydrohalic acid such as HCl or HBr, with strong organic carboxylic acids, such as alkanecarboxylic acids of 1 to 4 carbon atoms which are unsubstituted or substituted, for example, by halogen, for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, such as hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid, such as amino acids, (for example aspartic or glutamic acid or lysine or arginine), or benzoic acid, or with organic sulfonic acids, such as (C_1-C_4) alkyl or arylsulfonic acids which are unsubstituted or substituted, for example by halogen, for example methanesulfonic acid or p-toluenesulfonic acid.

[00138] All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present invention can have asymmetric centers at any of the carbon atoms including any one or the R substituents. Consequently, compounds of formula I can exist in enantiomeric or diastereomeric forms or in mixtures thereof. The processes for preparation can utilize racemates, enantiomers or diastereomers as starting materials. When diastereomeric or enantiomeric products are prepared, they can be separated by conventional methods for example, chromatographic or fractional crystallization.

[00139] The inventive compounds may be in the free or solvate (e.g. hydrate) form.

COMBINATIONS

[00140] Where desired, the compounds of structure I may be used in combination with one or more other types of therapeutic agents such as immunosuppressants, anticancer agents, anti-viral agents, anti-inflammatory agents, anti-fungal agents, antibiotics, anti-vascular hyperproliferation agents, anti-depressive agents, hypolipidemic agents or lipid-lowering agents or lipid modulating agents, antidiabetic agents, anti-obesity agents, antihypertensive agents, platelet aggregation inhibitors, and/or anti-osteoporosis agents, which may be administered orally in the same dosage form, in a separate oral dosage form or by injection.

[00141] The immunosuppressants which may be optionally employed in combination with compounds of formula I of the invention include cyclosporins, for example cyclosporin A, mycophenolate, interferon-beta, deoxyspergolin, FK-506 or Ant.-IL-2.

[00142] The anti-cancer agents which may be optionally employed in combination with compounds of formula I of the invention include azathiprine, 5-fluorouracil, cyclophosphamide, cisplatin, methotrexate, thiotepa, carboplatin, and the like.

[00143] The anti-viral agents which may be optionally employed in combination with compounds of formula I of the invention include abacavir, aciclovir, ganciclovir, zidanocin, vidarabine, and the like.

[00144] The anti-inflammatory agents which may be optionally employed in combination with compounds of formula I of the invention include non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, cox-2 inhibitors such as celecoxib, rofecoxib, aspirin, naproxen, ketoprofen, diclofenac sodium, indomethacin, piroxicam, steroids such as prednisone, dexamethasone, hydrocortisone, triamcinolone diacetate, gold compounds, such as gold sodium thiomalate, TNF-α inhibitors such as tenidap, anti-TNF antibodies or soluble TNF receptor, and rapamycin (sirolimus or Rapamune) or derivatives thereof, infliximab (Remicade® Centocor, Inc.). CTLA-4Ig, LEA29Y, antibodies such as anti-ICAM-3, anti-IL-2 receptor (Anti-Tac), anti-CD45RB, anti-CD2, anti-CD3 (OKT-3), anti-CD4, anti-CD80, anti-CD86, monoclonal antibody OKT3, agents blocking the interaction between CD40 and CD154 (a.k.a. "gp39"), such as antibodies specific for CD40 and/or CD154, fusion proteins such as etanercept, fusion proteins constructed from

CD40 and/or CD154gp39 (e.g. CD40Ig and CD8gp39), inhibitors, such as nuclear translocation inhibitors, of NF-kappa B function, such as deoxyspergualin (DSG).

[00145] The anti-fungal agents which may be optionally employed in combination with compounds of formula I of the invention include fluconazole, miconazole, amphotericin B, and the like.

[00146] The antibiotics which may be optionally employed in combination with compounds of formula I of the invention include penicillin, tetracycline, amoxicillin, ampicillin, erythromycin, doxycycline, vancomycin, minocycline, clindamycin or cefalexin.

[00147] The anti-vascular hyperproliferation agents which may be optionally employed with compounds of formula I of the invention include methotrexate, leflunomide, FK506 (tacrolimus, Prograf),

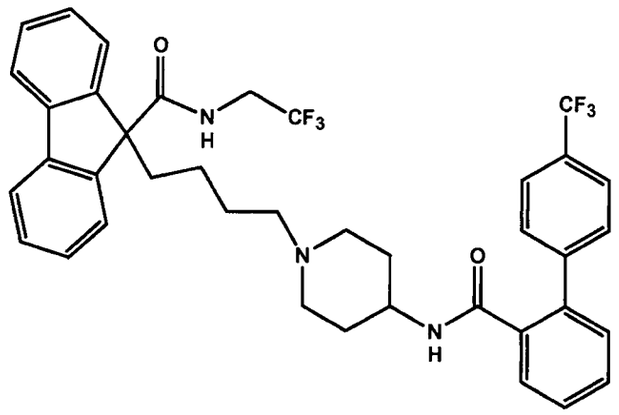
[00148] The hypolipidemic agent or lipid-lowering agent or lipid modulating agents which may be optionally employed in combination with the compounds of formula I of the invention may include 1,2,3 or more MTP inhibitors, HMG CoA reductase inhibitors, squalene synthetase inhibitors, fibric acid derivatives, ACAT inhibitors, lipoxygenase inhibitors, cholesterol absorption inhibitors, ileal Na^+/bile acid cotransporter inhibitors, upregulators of LDL receptor activity, bile acid sequestrants, and/or nicotinic acid and derivatives thereof.

[00149] MTP inhibitors employed herein include MTP inhibitors disclosed in U.S. Patent No. 5,595,872, U.S. Patent No. 5,739,135, U.S. Patent No. 5,712,279, U.S. Patent No. 5,760,246, U.S. Patent No. 5,827,875, U.S. Patent No. 5,885,983 and U.S. Application Serial No. 09/175,180 filed October 20, 1998, now U.S. Patent No. 5,962,440. Preferred are each of the preferred MTP inhibitors disclosed in each of the above patents and applications.

[00150] All of the above U.S. Patents and applications are incorporated herein by reference.

[00151] Most preferred MTP inhibitors to be employed in accordance with the present invention include preferred MTP inhibitors as set out in U.S. Patent Nos. 5,739,135 and 5,712,279, and U.S. Patent No. 5,760,246.

[00152] The most preferred MTP inhibitor is 9-[4-[4-[[2-(2,2,2-trifluoroethoxy)benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide



[00153] The hypolipidemic agent may be an HMG CoA reductase inhibitor which includes, but is not limited to, mevastatin and related compounds as disclosed in U.S. Patent No. 3,983,140, lovastatin (mevinolin) and related compounds as disclosed in U.S. Patent No. 4,231,938, pravastatin and related compounds such as disclosed in U.S. Patent No. 4,346,227, simvastatin and related compounds as disclosed in U.S. Patent Nos. 4,448,784 and 4,450,171. Other HMG CoA reductase inhibitors which may be employed herein include, but are not limited to, fluvastatin, disclosed in U.S. Patent No. 5,354,772, cerivastatin disclosed in U.S. Patent Nos. 5,006,530 and 5,177,080, atorvastatin disclosed in U.S. Patent Nos. 4,681,893, 5,273,995, 5,385,929 and 5,686,104, itavastatin (Nissan/Sankyo's nisvastatin (NK-104)) disclosed in U.S. Patent No. 5,011,930, Shionogi-Astra/Zeneca visastatin (ZD-4522) disclosed in U.S. Patent No. 5,260,440, and related statin compounds disclosed in U.S. Patent No. 5,753,675, pyrazole analogs of mevalonolactone derivatives as disclosed in U.S. Patent No. 4,613,610, indene analogs of mevalonolactone derivatives as disclosed in PCT application WO 86/03488, 6-[2-(substituted-pyrrol-1-yl)-alkyl)pyran-2-ones and derivatives thereof as disclosed in U.S. Patent No. 4,647,576, Searle's SC-45355 (a 3-substituted pentanedioic acid derivative) dichloroacetate, imidazole analogs of mevalonolactone as disclosed in PCT application WO 86/07054, 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives as disclosed in French Patent No. 2,596,393, 2,3-disubstituted pyrrole, furan and thiophene derivatives as disclosed in

European Patent Application No. 0221025, naphthyl analogs of mevalonolactone as disclosed in U.S. Patent No. 4,686,237, octahydronaphthalenes such as disclosed in U.S. Patent No. 4,499,289, keto analogs of mevinolin (lovastatin) as disclosed in European Patent Application No. 0142146 A2, and quinoline and pyridine derivatives disclosed in U.S. Patent No. 5,506,219 and 5,691,322.

[00154] In addition, phosphinic acid compounds useful in inhibiting HMG CoA reductase suitable for use herein are disclosed in GB 2205837.

[00155] The squalene synthetase inhibitors suitable for use herein include, but are not limited to, α-phosphono-sulfonates disclosed in U.S. Patent No. 5,712,396, those disclosed by Biller et al., *J. Med. Chem.*, Vol. 31, No. 10, pp. 1869-1871 (1988), including isoprenoid (phosphinyl-methyl)phosphonates as well as other known squalene synthetase inhibitors, for example, as disclosed in U.S. Patent No. 4,871,721 and 4,924,024 and in Biller, S.A., Neuenschwander, K., Ponpipom, M.M., and Poulter, C.D., *Current Pharmaceutical Design*, Vol. 2, pp. 1-40 (1996).

[00156] In addition, other squalene synthetase inhibitors suitable for use herein include the terpenoid pyrophosphates disclosed by P. Ortiz de Montellano et al., J. Med. Chem., 1977, *20*, 243-249, the farnesyl diphosphate analog A and presqualene pyrophosphate (PSQ-PP) analogs as disclosed by Corey and Volante, *J. Am. Chem. Soc.*, 98, 1291-1293 (1976), phosphinylphosphonates reported by McClard, R.W. et al., *J. Am. Chem. Soc.*, 1987, *109*, 5544 (1987), and cyclopropanes reported by Capson, T.L., PhD dissertation, Dept. Med. Chem. U. of Utah, Abstract, Table of Contents, pp. 16, 17, 40-43, 48-51, Summary (June, 1987).

[00157] Other hypolipidemic agents suitable for use herein include, but are not limited to, fibric acid derivatives, such as fenofibrate, gemfibrozil, clofibrate, bezafibrate, ciprofibrate, clinofibrate and the like, probucol, and related compounds as disclosed in U.S. Patent No. 3,674,836, probucol and gemfibrozil being preferred, bile acid sequestrants such as cholestyramine, colestipol and DEAE-Sephadex (Secholex®, Policexide®) and cholestagel (Sankyo/Geltex), as well as lipostabil (Rhone-Poulenc), Eisai E-5050 (an N-substituted ethanolamine derivative), imanixil (HOE-402), tetrahydrolipstatin (THL), istigmastanylphos-phorylcholine (SPC, Roche), aminocyclodextrin (Tanabe Seiyoku), Ajinomoto AJ-814 (azulene derivative), melinamide (Sumitomo), Sandoz 58-035, American Cyanamid CL-

277,082 and CL-283,546 (disubstituted urea derivatives), nicotinic acid (niacin), acipimox, acifran, neomycin, p-aminosalicylic acid, aspirin, poly(diallylmethylamine) derivatives such as disclosed in U.S. Patent No. 4,759,923, quaternary amine poly(diallyldimethylammonium chloride) and ionenes such as disclosed in U.S. Patent No. 4,027,009, and other known serum cholesterol lowering agents.

[00158] The hypolipidemic agent may be an ACAT inhibitor such as disclosed in, Drugs of the Future, 24, 9-15 (1999), (Avasimibe); "The ACAT inhibitor, Cl-1011 is effective in the prevention and regression of aortic fatty streak area in hamsters", Nicolosi et al., *Atherosclerosis* (Shannon, Irel). 137(1), 77-85 (1998), "The pharmacological profile of FCE 27677: a novel ACAT inhibitor with potent hypolipidemic activity mediated by selective suppression of the hepatic secretion of ApoB100-containing lipoprotein", Ghiselli, Giancarlo, *Cardiovasc. Drug Rev.* (1998), 16(1), 16-30; "RP 73163: a bioavailable alkylsulfinyl-diphenylimidazole ACAT inhibitor", Smith, C., et al, *Bioorg. Med. Chem. Lett.* 6(1), 47-50 (1996); "ACAT inhibitors: physiologic mechanisms for hypolipidemic and anti-atherosclerotic activities in experimental animals", Krause et al, Editor(s): Ruffolo, Robert R., Jr.; Hollinger, Mannfred A., *Inflammation: Mediators Pathways* 173-98 (1995), Publisher: CRC, Boca Raton, Fla.; "ACAT inhibitors: potential anti-atherosclerotic agents", Sliskovic et al, *Curr. Med. Chem.* 1(3), 204-25 1994); "Inhibitors of acyl-CoA:cholesterol O-acyl transferase (ACAT) as hypocholesterolemic agents. 6. The first water-soluble ACAT inhibitor with lipid-regulating activity. Inhibitors of acyl-CoA:cholesterol acyltransferase (ACAT). 7. Development of a series of substituted N-phenyl-N'-[(1-phenylcyclopentyl)methyl]ureas with enhanced hypocholesterolemic activity", Stout et al, *Chemtracts: Org. Chem.* 8(6), 359-62 (1995), or TS-962 (acetamide, N-[2,6-bis(1-methylethyl)phenyl]-2-(tetradecylthio)-) (Taisho Pharmaceutical Co. Ltd).

[00159] The hypolipidemic agent may be an upregulator of LD2 receptor activity such as MD-700 (1(3H)-isobenzofuranone, 3-(13-hydroxy-10-oxotetradecyl)-5,7-dimethoxy) (Taisho Pharmaceutical Co. Ltd) and LY295427 (cholestan -3-ol, 4-(2-propenyl)-, (3a, 4a, 5a)-) (Eli Lilly).

[00160] The hypolipidemic agent may be a cholesterol absorption inhibitor preferably Schering-Plough's ezetimibe (SCH58235) and SCH48461 as well as those disclosed in *Atherosclerosis* 115, 45-63 (1995) and *J. Med. Chem.* 41, 973 (1998).

[00161] The hypolipidemic agent may be an ileal Na^+/bile acid cotransporter inhibitor such as disclosed in *Drugs of the Future*, 24, 425-430 (1999).

[00162] The lipid-modulating agent may be a cholesteryl ester transfer protein (CETP) inhibitor such as Pfizer's CP 529,414 (torcetrapib) (WO/0038722 and EP 818448) and Pharmacia's SC-744 and SC-795.

[00163] The ATP citrate lyase inhibitor which may be employed in the combination of the invention may include, for example, those disclosed in U.S. Patent No. 5,447,954.

[00164] Preferred hypolipidemic agents are pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin, cerivastatin, itavastatin and visastatin and ZD-4522.

[00165] The above-mentioned U.S. patents are incorporated herein by reference. The amounts and dosages employed will be as indicated in the Physicians' Desk Reference and/or in the patents set out above.

[00166] The compounds of formula I of the invention will be employed in a weight ratio to the hypolipidemic agent (were present), within the range from about 500:1 to about 1:500, preferably from about 100:1 to about 1:100.

[00167] The dose administered must be carefully adjusted according to age, weight and condition of the patient, as well as the route of administration, dosage form and regimen and the desired result.

[00168] The dosages and formulations for the hypolipidemic agent will be as disclosed in the various patents and applications discussed above.

[00169] The dosages and formulations for the other hypolipidemic agent to be employed, where applicable, will be as set out in the latest edition of the Physicians' Desk Reference.

[00170] For oral administration, a satisfactory result may be obtained employing the MTP inhibitor in an amount within the range of from about 0.01 mg to about 500 mg and preferably from about 0.1 mg to about 100 mg, one to four times daily.

[00171] A preferred oral dosage form, such as tablets or capsules, will contain the MTP inhibitor in an amount of from about 1 to about 500 mg, preferably from about 2

to about 400 mg, and more preferably from about 5 to about 250 mg, one to four times daily.

[00172] For oral administration, a satisfactory result may be obtained employing an HMG CoA reductase inhibitor, for example, pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin or cerivastatin in dosages employed as indicated in the Physicians' Desk Reference, such as in an amount within the range of from about 1 to 2000 mg, and preferably from about 4 to about 200 mg.

[00173] The squalene synthetase inhibitor may be employed in dosages in an amount within the range of from about 10 mg to about 2000 mg and preferably from about 25 mg to about 200 mg.

[00174] A preferred oral dosage form, such as tablets or capsules, will contain the HMG CoA reductase inhibitor in an amount from about 0.1 to about 100 mg, preferably from about 0.5 to about 80 mg, and more preferably from about 1 to about 40 mg.

[00175] A preferred oral dosage form, such as tablets or capsules will contain the squalene synthetase inhibitor in an amount of from about 10 to about 500 mg, preferably from about 25 to about 200 mg.

[00176] The hypolipidemic agent may also be a lipoxygenase inhibitor including a 15-lipoxygenase (15-LO) inhibitor such as benzimidazole derivatives as disclosed in WO 97/12615, 15-LO inhibitors as disclosed in WO 97/12613, isothiazolones as disclosed in WO 96/38144, and 15-LO inhibitors as disclosed by Sendobry et al "Attenuation of diet-induced atherosclerosis in rabbits with a highly selective 15-lipoxygenase inhibitor lacking significant antioxidant properties", *Brit. J. Pharmacology* 120, 1199-1206 (1997), and Cornicelli et al, "15-Lipoxygenase and its Inhibition: A Novel Therapeutic Target for Vascular Disease", *Current Pharmaceutical Design*, 5, 11-20 (1999).

[00177] The compounds of formula I and the hypolipidemic agent may be employed together in the same oral dosage form or in separate oral dosage forms taken at the same time.

[00178] The compositions described above may be administered in the dosage forms as described above in single or divided doses of one to four times daily. It may

be advisable to start a patient on a low dose combination and work up gradually to a high dose combination.

[00179] The preferred hypolipidemic agent is pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin or cerivastatin as well as niacin and/or cholestagel.

[00180] The other antidiabetic agent which may be optionally employed in combination with the compound of formula I may be 1,2,3 or more antidiabetic agents or antihyperglycemic agents including insulin secretagogues or insulin sensitizers, or other antidiabetic agents preferably having a mechanism of action different from the compounds of formula I of the invention, which may include biguanides, sulfonyl ureas, glucosidase inhibitors, PPAR γ agonists, such as thiazolidinediones, aP2 inhibitors, dipeptidyl peptidase IV (DP4) inhibitors, SGLT2 inhibitors, and/or meglitinides, as well as insulin, and/or glucagon-like peptide-1 (GLP-1).

[00181] The other antidiabetic agent may be an oral antihyperglycemic agent preferably a biguanide such as metformin or phenformin or salts thereof, preferably metformin HCl.

[00182] Where the antidiabetic agent is a biguanide, the compounds of structure I will be employed in a weight ratio to biguanide within the range from about 0.001:1 to about 10:1, preferably from about 0.01:1 to about 5:1.

[00183] The other antidiabetic agent may also preferably be a sulfonyl urea such as glyburide (also known as glibenclamide), glimepiride (disclosed in U.S. Patent No. 4,379,785), glipizide, gliclazide or chlorpropamide, other known sulfonylureas or other antihyperglycemic agents which act on the ATP-dependent channel of the β-cells, with glyburide and glipizide being preferred, which may be administered in the same or in separate oral dosage forms.

[00184] The compounds of structure I will be employed in a weight ratio to the sulfonyl urea in the range from about 0.01:1 to about 100:1, preferably from about 0.02:1 to about 5:1.

[00185] The oral antidiabetic agent may also be a glucosidase inhibitor such as acarbose (disclosed in U.S. Patent No. 4,904,769) or miglitol (disclosed in U.S. Patent No. 4,639,436), which may be administered in the same or in a separate oral dosage forms.

[00186] The compounds of structure I will be employed in a weight ratio to the glucosidase inhibitor within the range from about 0.01:1 to about 100:1, preferably from about 0.05:1 to about 10:1.

[00187] The compounds of structure I may be employed in combination with a PPAR γ agonist such as a thiazolidinedione oral anti-diabetic agent or other insulin sensitizers (which has an insulin sensitivity effect in NIDDM patients) such as troglitazone (Warner-Lambert's Rezulin®, disclosed in U.S. Patent No. 4,572,912), rosiglitazone (SKB), pioglitazone (Takeda), Mitsubishi's MCC-555 (disclosed in U.S. Patent No. 5,594,016), Glaxo-Wellcome's GL-262570 (farglitazar), englitazone (CP-68722, Pfizer) or darglitazone (CP-86325, Pfizer, isaglitazone (MIT/J&J), JTT-501 (reglitazar) (JPNT/P&U), L-895645 (Merck), R-119702 (rivoglitazone) (Sankyo/WL), NN-2344 (balaglitazone) (Dr. Reddy/NN), or YM-440 ((Z)-1,4-bis-4-[(3,5-dioxo-1,2,4-oxadiazolidin-2-yl-methyl)]-phenoxybut-2-ene) (Yamanouchi), preferably rosiglitazone and pioglitazone.

[00188] The compounds of structure I will be employed in a weight ratio to the thiazolidinedione in an amount within the range from about 0.01:1 to about 100:1, preferably from about 0.05 to about 10:1.

[00189] The sulfonyl urea and thiazolidinedione in amounts of less than about 150 mg oral antidiabetic agent may be incorporated in a single tablet with the compounds of structure I.

[00190] The compounds of structure I may also be employed in combination with a antihyperglycemic agent such as insulin or with glucagon-like peptide-1 (GLP-1) such as GLP-1(1-36) amide, GLP-1(7-36) amide, GLP-1(7-37) (as disclosed in U.S. Patent No. 5,614,492 to Habener, the disclosure of which is incorporated herein by reference), as well as AC2993 (exenatide) (Amylin) and LY-315902 (8-37—glucagon-like peptide I (human), N-[3-(1H-imidazol-4-yl)-1-oxopropyl]-26-L-arginine-34-[N6-(1-oxooctyl)-L-lysine]-) (Lilly), which may be administered via injection, intranasal, inhalation or by transdermal or buccal devices.

[00191] Where present, metformin, the sulfonyl ureas, such as glyburide, glimepiride, glipyride, glipizide, chlorpropamide and gliclazide and the glucosidase inhibitors acarbose or miglitol or insulin (injectable, pulmonary, buccal, or oral) may

000131

be employed in formulations as described above and in amounts and dosing as indicated in the Physicians' Desk Reference (PDR).

[00192] Where present, metformin or salt thereof may be employed in amounts within the range from about 500 to about 2000 mg per day which may be administered in single or divided doses one to four times daily.

[00193] Where present, the thiazolidinedione anti-diabetic agent may be employed in amounts within the range from about 0.01 to about 2000 mg/day which may be administered in single or divided doses one to four times per day.

[00194] Where present insulin may be employed in formulations, amounts and dosing as indicated by the Physicians' Desk Reference.

[00195] Where present GLP-1 peptides may be administered in oral buccal formulations, by nasal administration or parenterally as described in U.S. Patent Nos. 5,346,701 (TheraTech), 5,614,492 and 5,631,224 which are incorporated herein by reference.

[00196] The other antidiabetic agent may also be a PPAR α/γ dual agonist such as AR-HO39242 (tesaglitazar) (Astra/Zeneca), GW-409544 (Glaxo-Wellcome), KRP297 (benzamide, 5-[(2,4-dioxo-5-thiazolidinyl)methyl]-2-methoxy-N-[[4-(trifluoromethyl)phenyl]methyl]- (Kyorin Merck) as well as those disclosed by Murakami et al, "A Novel Insulin Sensitizer Acts As a Coligand for Peroxisome Proliferation-Activated Receptor Alpha (PPAR alpha) and PPAR gamma. Effect on PPAR alpha Activation on Abnormal Lipid Metabolism in Liver of Zucker Fatty Rats", *Diabetes* 47, 1841-1847 (1998).

[00197] The antidiabetic agent may be an SGLT2 inhibitor such as disclosed in U.S. application Serial No. 09/679,027, filed October 4, 2000, employing dosages as set out therein. Preferred are the compounds designated as preferred in the above application.

[00198] The antidiabetic agent may be an aP2 inhibitor such as disclosed in U.S. application Serial No. 09/391,053, filed September 7, 1999, and in U.S. application Serial No. 09/519,079, filed March 6, 2000, employing dosages as set out herein. Preferred are the compounds designated as preferred in the above application.

[00199] The antidiabetic agent may be a DP4 inhibitor such as disclosed in U.S. application Serial No. 09/788,173 filed February 16, 2001, WO99/38501,

WO99/46272, WO99/67279 (PROBIODRUG), WO99/67278 (PROBIODRUG), WO99/61431 (PROBIODRUG), NVP-DPP728A (1-[[[2-[(5-cyanopyridin-2-yl)amino]ethyl]amino]acetyl]-2-cyano-(S)-pyrrolidine) (Novartis) (preferred) as disclosed by Hughes et al, *Biochemistry*, 38(36), 11597-11603, (1999), TSL-225 (tryptophyl-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (disclosed by Yamada et al, *Bioorg. & Med. Chem. Lett.* 8 1537-1540 (1998), 2-cyanopyrrolidides and 4-cyanopyrrolidides as disclosed by Ashworth et al, *Bioorg. & Med. Chem. Lett.*, Vol. 6, No. 22, pp 1163-1166 and 2745-2748 (1996) employing dosages as set out in the above references.

[00200] The meglitinide which may optionally be employed in combination with the compound of formula I of the invention may be repaglinide, nateglinide (Novartis) or KAD1229 (mitiglinide) (PF/Kissei), with repaglinide being preferred.

[00201] The compound of formula I will be employed in a weight ratio to the meglitinide, PPAR γ agonist, PPAR α/γ dual agonist, aP2 inhibitor, DP4 inhibitor or SGLT2 inhibitor within the range from about 0.01:1 to about 100:1, preferably from about 0.05 to about 10:1.

[00202] The other type of therapeutic agent which may be optionally employed with a compound of formula I may be 1, 2, 3 or more of an anti-obesity agent including a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, an aP2 inhibitor, a thyroid receptor agonist and/or an anorectic agent.

[00203] The beta 3 adrenergic agonist which may be optionally employed in combination with a compound of formula I may be AJ9677 (rafabegron) (Takeda/Dainippon), L750355 (benezenesulfonamide, N-[4-[2-[[(2S)-3-[(6-amino-3-pyridinyl)oxy]-2-hydroxypropyl]amino]ethyl]phenyl]-4-(1-methylethyl)-) (Merck), or CP331684 (4-[2-[[2-(6-aminopyridin-3-yl)-2(R)-hydroxyethyl]-amino]ethoxy]phenyl]acetic acid) (Pfizer) or other known beta 3 agonists as disclosed in U.S. Patent Nos. 5,541,204, 5,770,615, 5,491,134, 5,776,983 and 5,488,064, with AJ9677, L750,355 (benzenesulfonamide, N-[4-[2-[[(2S)-3-[(6-amino-3-pyridinyl)oxy]-2-hydroxypropyl]amino]ethyl]phenyl]-4-(1-methylethyl)-) and CP331684 being preferred.

[00204] The lipase inhibitor which may be optionally employed in combination with a compound of formula I may be orlistat or ATL-962 (Alizyme), with orlistat being preferred.

[00205] The serotonin (and dopamine) reuptake inhibitor which may be optionally employed in combination with a compound of formula I may be sibutramine, topiramate (Johnson & Johnson) or axokine (Regeneron), with sibutramine and topiramate being preferred.

[00206] The thyroid receptor agonist which may be optionally employed in combination with a compound of formula I may be a thyroid receptor ligand as disclosed in WO97/21993 (U. Cal SF), WO99/00353 (KaroBio), WO00/039077 (KaroBio), and U.S. Provisional Application 60/183,223 filed February 17, 2000, with compounds of the KaroBio applications and the above U.S. provisional application being preferred.

[00207] The anorectic agent which may be optionally employed in combination with a compound of formula I may be dexamphetamine, phentermine, phenylpropanolamine or mazindol, with dexamphetamine being preferred.

[00208] The various anti-obesity agents described above may be employed in the same dosage form with the compound of formula I or in different dosage forms, in dosages and regimens as generally known in the art or in the PDR.

[00209] The antihypertensive agents which may be employed in combination with the compound of formula I of the invention include ACE inhibitors, angiotensin II receptor antagonists, NEP/ACE inhibitors, as well as calcium channel blockers, β-adrenergic blockers and other types of antihypertensive agents including diuretics.

[00210] The angiotensin converting enzyme inhibitor which may be employed herein includes those containing a mercapto (-S-) moiety such as substituted proline derivatives, such as any of those disclosed in U.S. Pat. No. 4,046,889 to Ondetti et al mentioned above, with captopril, that is, 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline, being preferred, and mercaptoacyl derivatives of substituted prolines such as any of those disclosed in U.S. Pat. No. 4,316,906 with zofenopril being preferred.

[00211] Other examples of mercapto containing ACE inhibitors that may be employed herein include rentiapril (fentiapril, Santen) disclosed in Clin. Exp. Pharmacol. Physiol. 10:131 (1983); as well as pivopril and YS980.

[00212] Other examples of angiotensin converting enzyme inhibitors which may be employed herein include any of those disclosed in U.S. Pat. No. 4,374,829 mentioned above, with N-(1-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-proline, that is, enalapril, being preferred, any of the phosphonate substituted amino or imino acids or salts disclosed in U.S. Pat. No. 4,452,790 with (S)-1-[6-amino-2-[[hydroxy-(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl]-L-proline or (ceronapril) being preferred, phosphinylalkanoyl prolines disclosed in U.S. Pat. No. 4,168,267 mentioned above with fosinopril being preferred, any of the phosphinylalkanoyl substituted prolines disclosed in U.S. Pat. No. 4,337,201, and the phosphonamidates disclosed in U.S. Pat. No. 4,432,971 discussed above.

[00213] Other examples of ACE inhibitors that may be employed herein include Beecham's BRL 36,378 as disclosed in European Patent Application Nos. 80822 and 60668; Chugai's MC-838 disclosed in C.A. 102:72588v and *Jap. J. Pharmacol.* 40:373 (1986); Ciba-Geigy's CGS 14824 (3-([1-ethoxycarbonyl-3-phenyl-(1S)-propyl]amino)-2,3,4,5-tetrahydro-2-oxo-1-(3S)-benzazepine-1 acetic acid HCl) disclosed in U.K. Patent No. 2103614 and CGS 16,617 (3(S)-[[(1S)-5-amino-1-carboxypentyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-ethanoic acid) disclosed in U.S. Pat. No. 4,473,575; cetapril (alacepril, Dainippon) disclosed in Eur. Therap. Res. 39:671 (1986); 40:543 (1986); ramipril (Hoechst) disclosed in Euro. Patent No. 79-022 and *Curr. Ther. Res.* 40:74 (1986); Ru 44570 (Hoechst) disclosed in *Arzneimittelforschung* 34:1254 (1985), cilazapril (Hoffman-LaRoche) disclosed in *J. Cardiovasc. Pharmacol.* 9:39 (1987); R 31-2201 (Hoffman-LaRoche) disclosed in *FEBS Lett.* 165:201 (1984); lisinopril (Merck), indalapril (delapril) disclosed in U.S. Pat. No. 4,385,051; indolapril (Schering) disclosed in *J. Cardiovasc. Pharmacol.* 5:643, 655 (1983), spirapril (Schering) disclosed in *Acta. Pharmacol. Toxicol.* 59 (Supp. 5):173 (1986); perindopril (Servier) disclosed in *Eur. J. Clin. Pharmacol.* 31:519 (1987); quinapril (Warner-Lambert) disclosed in U.S. Pat. No. 4,344,949 and CI925 (Warner-Lambert) ([3S-[2[R(*)R(*)]]3R(*)]-2-[2-[[1-(ethoxy-carbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid HCl)disclosed in *Pharmacologist* 26:243, 266 (1984), WY-44221 (Wyeth) disclosed in *J. Med. Chem.* 26:394 (1983).

[00214] Preferred ACE inhibitors are captopril, fosinopril, enalapril, lisinopril, quinapril, benazepril, fentiapril, ramipril and moexipril.

[00215] NEP/ACE inhibitors may also be employed herein in that they possess neutral endopeptidase (NEP) inhibitory activity and angiotensin converting enzyme (ACE) inhibitory activity. Examples of NEP/ACE inhibitors suitable for use herein include those disclosed in U.S. Pat. Nos. 5,362,727, 5,366,973, 5,225,401, 4,722,810, 5,223,516, 4,749,688, U.S. Patent. No. 5,552,397, U.S. Pat. No. 5,504,080, U.S. Patent No. 5,612,359,U.S. Pat. No. 5,525,723, European Patent Application 0599444, 0481522, 0599444, 0595610, European Patent Application 0534363A2, 534396 and 534492, and European Patent Application 0629627A2.

[00216] Preferred are those NEP/ACE inhibitors and dosages thereof which are designated as preferred in the above patents/applications which U.S. patents are incorporated herein by reference; most preferred are omapatrilat ([S-(R*,R*)]-hexahydro-6-[(2-mercapto-1-oxo-3-phenylpropyl)amino]-2,2-dimethyl-7-oxo-1H-azepine-1-acetic acid (gemopatrilat)) and CGS 30440.

[00217] The angiotensin II receptor antagonist (also referred to herein as angiotensin II antagonist or AII antagonist) suitable for use herein includes, but is not limited to, irbesartan, losartan, valsartan, candesartan, telmisartan, tasosartan or eprosartan, with irbesartan, losartan or valsartan being preferred.

[00218] A preferred oral dosage form, such as tablets or capsules, will contain the ACE inhibitor or AII antagonist in an amount within the range from abut 0.1 to about 500 mg, preferably from about 5 to about 200 mg and more preferably from about 10 to about 150 mg.

[00219] For parenteral administration, the ACE inhibitor, angiotensin II antagonist or NEP/ACE inhibitor will be employed in an amount within the range from about 0.005 mg/kg to about 10 mg/kg and preferably from about 0.01 mg/kg to about 1 mg/kg.

[00220] Where a drug is to be administered intravenously, it will be formulated in conventional vehicles, such as distilled water, saline, Ringer's solution or other conventional carriers.

[00221] It will be appreciated that preferred dosages of ACE inhibitor and AII antagonist as well as other antihypertensives disclosed herein will be as set out in the latest edition of the Physicians' Desk Reference (PDR).

[00222] Other examples of preferred antihypertensive agents suitable for use herein include omapatrilat (Vanlev®) amlodipine besylate (Norvasc®), prazosin HCl (Minipress®), verapamil, nifedipine, nadolol, diltiazem, felodipine, nisoldipine, isradipine, nicardipine, atenolol, carvedilol, sotalol, terazosin, doxazosin, propranolol, and clonidine HCl (Catapres®).

[00223] Diuretics which may be employed in combination with compounds of formula I include hydrochlorothiazide, torasemide, furosemide, spironolactono, and indapamide.

[00224] Antiplatelet agents which may be employed in combination with compounds of formula I of the invention include aspirin, clopidogrel, ticlopidine, dipyridamole, abciximab, tirofiban, eptifibatide, anagrelide, and ifetroban, with clopidogrel and aspirin being preferred.

[00225] The antiplatelet drugs may be employed in amounts as indicated in the PDR. Ifetroban may be employed in amounts as set out in U.S. Patent No. 5,100,889.

[00226] Antiosteoporosis agents suitable for use herein in combination with the compounds of formula I of the invention include parathyroid hormone or bisphosphonates, such as MK-217 (alendronate) (Fosamax®).

[00227] Dosages employed for the above drugs will be as set out in the Physicians' Desk Reference.

PHARMACEUTICAL FORMULATIONS

[00228] The pharmaceutical composition of the invention includes a pharmaceutically acceptable carrier, adjuvant or vehicle that may be administered to a subject, together with a compound of the present invention, and which does not destroy the pharmacological activity thereof. Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of the present invention include, but are not limited to, the following: ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems ("SEDDS") such as d(-tocopherol polyethyleneglycol 1000 succinate), surfactants

used in pharmaceutical dosage forms such as Tweens or other similar polymeric delivery matrices, serum proteins such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat. Cyclodextrins such as α-, β- and γ-cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl-β-cyclodextrins, or other solubilized derivatives may also be used to enhance delivery of the modulators of the present invention.

[00229] The compositions of the present invention may contain other therapeutic agents as described below, and may be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (for example, excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques such as those well known in the art of pharmaceutical formulation.

[00230] The compounds of the invention may be administered by any suitable means, for example, orally, such as in the form of tablets, capsules, granules or powders; sublingually; buccally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal injection or infusion techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally such as by inhalation spray; topically, such as in the form of a cream or ointment; or rectally such as in the form of suppositories; in dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents. The compounds of the invention may, for example, be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved by the use of suitable pharmaceutical compositions including the compounds of the invention, or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or osmotic pumps. The compounds of the invention may also be administered liposomally.

[00231] Exemplary compositions for oral administration include suspensions which may contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which may contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The present compounds may also be delivered through the oral cavity by sublingual and/or buccal administration. Molded tablets, compressed tablets or freeze-dried tablets are exemplary forms which may be used. Exemplary compositions include those formulating the compound(s) of the invention with fast dissolving diluents such as mannitol, lactose, sucrose and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (Avicel) or polyethylene glycols (PEG). Such formulations may also include an excipient to aid mucosal adhesion such as hydroxy propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), maleic anhydride copolymer (e.g., Gantrez), and agents to control release such as polyacrylic copolymer (e.g., Carbopol 934). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

[00232] Exemplary compositions for nasal aerosol or inhalation administration include solutions in saline which may contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

[00233] Exemplary compositions for parenteral administration include injectable solutions or suspensions which may contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid. The term "parenteral" as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

[00234] Exemplary compositions for rectal administration include suppositories which may contain, for example, a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquefy and/or dissolve in the rectal cavity to release the drug.

[00235] Exemplary compositions for topical administration include a topical carrier such as Plastibase (mineral oil gelled with polyethylene).

[00236] The effective amount of a compound of the present invention may be determined by one of ordinary skill in the art, and includes exemplary dosage amounts for an adult human of from about 0.1 to 500 mg/kg of body weight of active compound per day, or between 5 and 2000 mg per day which may be administered in a single dose or in the form of individual divided doses, such as from 1 to 5 times per day. It will be understood that the specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition. Preferred subjects for treatment include animals, most preferably mammalian species such as humans, and domestic animals such as dogs, cats and the like.

[00237] A typical capsule for oral administration contains compounds of structure I (250 mg), lactose (75 mg) and magnesium stearate (15 mg). The mixture is passed through a 60 mesh sieve and packed into a No. 1 gelatin capsule.

[00238] A typical injectable preparation is produced by aseptically placing 250 mg of compounds of structure I into a vial, aseptically freeze-drying and sealing. For use, the contents of the vial are mixed with 2 mL of physiological saline, to produce an injectable preparation.

[00239] The compounds of the examples are inhibitors of AP-1 activity and/or compete with known ligands of the the glucorcorticoid receptor.

[00240] Identical and/or similar assays are described in copending provisional application No. 60/396,907, filed July 18, 2002 which is incorporated in its entirety herein by reference.

ASSAYS

GR Binding Assays

Glucocorticoid Receptor Binding Assay (I)[a]

[00241] In order to assess the affinity of test compounds for the human glucocorticoid receptor, a commercially available kit was used (Glucocorticoid Receptor Competitor Assay Kit, Invitrogen Part # 2893). Briefly, purified human recombinant full-length glucocorticoid receptor (2 nM) was mixed with fluorescently labeled glucocorticoid (1 nM Fluormone GS Red) in the presence or absence of test compound. After two hour incubation at room temperature in the dark, the fluorescence polarization (FP) of the samples was measured. The FP of a mixture of receptor, fluorescent probe (i.e. Fluormone GS Red) and 5μM dexamethasone represented background fluorescence or 100% inhibition, whereas, the FP of the mixture without dexamethasone (but in the presence of vehicle) was taken to be 100% binding. The percentage inhibition of test compounds were then compared to the sample with 5μM dexamethasone and expressed as % relative binding activity with dexamethasone being 100% and no inhibition is 0%. Test compounds were analyzed in the concentration range from 8.5E-05μM to 5μM.

Glucocorticoid Receptor Binding Assay (II)[b]

[00242] In order to measure the binding of compounds on the glucocorticoid receptor a commercially available kit was used (Glucocorticoid receptor competitor assay kit, PanVera Co., Madison, WI, P2816). Briefly, a cell lysate containing recombinantly expressed human full-length glucocorticoid receptor was mixed with a fluorescently labeled glucocorticoid (4nM FITC-dexamethasone) plus or minus test molecule. After one hour at room temperature, the fluorescence polarization (FP) of the samples were measured. The FP of a mixture of receptor, fluorescent probe (i.e. FITC-dexamethasone) and 1mM dexamethasone represented background fluorescence or 100% inhibition, whereas, the FP of the mixture without dexamethasone was taken to be 100% binding. The percentage inhibition of test molecules were then compared to the sample with 1mM dexamethasone and expressed as % relative binding activity with dexamethasone being 100% and no inhibition is 0%. Test molecules were analyzed in the concentration range from 0.1nM to 40 μM.

Cellular Transrepressional Assay

[00243] To measure the ability of test molecules to inhibit AP-1 induced transcriptional activity we utilized an A549 cell which was stably transfected with a plasmid containing 7x AP-1 DNA binding sites (pAP-1-Luc plasmid , Stratagene Co. La Jolla, CA) followed by the gene for luciferase. Cells were activated with 10ng/ml of phorbol myristic acid (PMA) plus or minus test molecules for 7 hours. After 7 hours a luciferase reagent was added to measure luciferase enzymatic activity in the cell. After a 10 minute incubation of luciferase reagent with cells, luminescence was measured in a TopCount luminescence counter. Repression of AP-1 activity was calculated as the percentage decrease in the signal induced by PMA alone. Test molecules were analyzed in the concentration range from 0.1nM to 40 μM. EC50s were determined by using standard curve fitting methods such as Excel fit (Microsoft Co.). An EC50 is the test molecule concentration at which there is a 50% repression of the maximal inhibition of transcription, i.e. a 50% reduction of AP-1 activity. In the absence of an EC50 the maximum % inihibition recorded is the inhibition of AP-1 at a compound concentration of 10micromolar.

[00244] Other reporters and cell lines also may be used in a cellular transrepressional assay. A similar assay is performed in which NF-κB activity is measured. A plasmid containing NF-κB DNA binding sites is used, such as pNF-kB-Luc, (Stratagene, LaJolla CA), and PMA or another stimulus, such as TNF-α or lipopolysaccharide, is used to activate the NF-κB pathway. NF-κB assays similar to that described in Yamamoto K., et al., *J. Biol. Chem.*, Dec 29, 270(52):31315-20 (1995) may be used.

[00245] The cellular transrepressional assays described above may be used to measure transrepression by any NHR. One of skill in the art will understand that assays may require the addition of components, such as a stimulus (e.g. PMA, lipopolysaccharide, TNF-α, etc) which will induce transcription mediated by AP-1 or NF-κB.

[00246] Additionally, AR mediated transrepression may be measured by the assay described in Palvimo. J.J. et al., *J. Biol. Chem.*, Sep 27, 271(39):24151-6 (1996), and PR mediated transrepression may be measured by the assay described in Kalkhoven E., et al. *J. Biol. Chem.*, Mar 15, 271(11):6217-24 (1996).

ABBREVIATIONS

[00247] The following abbreviations are employed in the following Preparations and Examples:

Ph = phenyl

Bn = benzyl

t-Bu = tertiary butyl

Me = methyl

Et = ethyl

TMS = trimethylsilyl

$TMSN_3$ = trimethylsilyl azide

TBS = *tert*-butyldimethylsilyl

FMOC = fluorenylmethoxycarbonyl

Boc = *tert*-butoxycarbonyl

Cbz = carbobenzyloxy or carbobenzoxy or benzyloxycarbonyl

THF = tetrahydrofuran

Et_2O = diethyl ether

hex = hexanes

EtOAc = ethyl acetate

DMF = dimethyl formamide

MeOH = methanol

EtOH = ethanol

i-PrOH = isopropanol

DMSO = dimethyl sulfoxide

DME = 1,2 dimethoxyethane

DCE = 1,2 dichloroethane

HMPA = hexamethyl phosphoric triamide

HOAc or AcOH = acetic acid

TFA = trifluoroacetic acid

TFAA = trifluoroacetic anhydride

$i\text{-}Pr_2NEt$ = diisopropylethylamine

Et_3N = triethylamine

NMM = N-methyl morpholine

DMAP = 4-dimethylaminopyridine

$NaBH_4$ = sodium borohydride

$NaBH(OAc)_3$ = sodium triacetoxyborohydride

DIBALH = diisobutyl aluminum hydride

LAH or $LiAlH_4$ = lithium aluminum hydride

n-BuLi = n-butyllithium

LDA = lithium diisopropylamide

Pd/C = palladium on carbon

PtO_2 = platinum oxide

KOH = potassium hydroxide

NaOH = sodium hydroxide

LiOH = lithium hydroxide

K_2CO_3 = potassium carbonate

$NaHCO_3$ = sodium bicarbonate

DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

EDC (or EDC.HCl) or EDCI (or EDCI.HCl) or EDAC = 3-ethyl-3'-(dimethylamino)propyl- carbodiimide hydrochloride (or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride)

HOBT or $HOBT.H_2O$ = 1-hydroxybenzotriazole hydrate

HOAT = 1-Hydroxy-7-azabenzotriazole

BOP reagent = benzotriazol-1-yloxy-tris (dimethylamino) phosphonium hexafluorophosphate

$NaN(TMS)_2$ = sodium hexamethyldisilazide or sodium bis(trimethylsilyl)amide

Ph_3P = triphenylphosphine

$Pd(OAc)_2$ = Palladium acetate

$(Ph_3P)_4Pd^o$ = tetrakis triphenylphosphine palladium

DEAD = diethyl azodicarboxylate

DIAD = diisopropyl azodicarboxylate

Cbz-Cl = benzyl chloroformate

CAN = ceric ammonium nitrate

SAX = Strong Anion Exchanger

SCX = Strong Cation Exchanger

Ar = argon

N_2 = nitrogen

min = minute(s)

h or hr = hour(s)

L = liter

mL = milliliter

μL = microliter

g = gram(s)

mg = milligram(s)

mol = moles

mmol = millimole(s)

meq = milliequivalent

RT = room temperature

sat or sat'd = saturated

aq. = aqueous

TLC = thin layer chromatography

HPLC = high performance liquid chromatography

Reverse phase HPLC = reverse phase high performance liquid chromatography, using a YMC ODS S5 column and a binary solvent A/solvent B eluents

Solvent A = 10% MeOH – 90% H_2O – 0.1% TFA

Solvent B = 90% MeOH – 10% H_2O – 0.1% TFA

LC/MS = high performance liquid chromatography/mass spectrometry

MS or Mass Spec = mass spectrometry

NMR = nuclear magnetic resonance

NMR spectral data: s = singlet; d = doublet; m = multiplet; br = broad; t = triplet

mp = melting point

EXAMPLES

[00248] The following Examples illustrate embodiments of the inventive compounds and starting materials, and are not intended to limit the scope of the claims.

PREPARATIONS

[00249] The preparations set out below are for the synthesis of reagents that were not obtained from commercial sources and were employed for the preparation of compounds of formula I of the invention. All chiral compounds in the tables and schemes are racemic unless specified otherwise.

[00250] Reverse-phase preparative high performance liquid chromatography ("HPLC") was performed with Shimadzu 8A liquid chromatographs using YMC S5 ODS columns (20 x 100, 20 x 250, or 30 x 250 millimeter ("mm")). Gradient elution was performed with methanol ("MeOH")/water mixtures in the presence of 0.1% trifluoroacetic acid ("TFA").

Analytical HPLC Method Employed in Characterization of Examples

[00251] Analytical HPLC was performed on Shimadzu LC10AS liquid chromatographs using the following methods:

Method A (Used in all cases, unless otherwise indicated):

Linear gradient of 0 to 100% solvent B over 4 minutes ("min"), with 1 minute ("min") hold at 100% B.

Ultraviolet ("UV") visualization at 220 nanometers ("nm")

Column: YMC S5 ODS Ballistic 4.6 x 50 mm

Flow rate: 4 milliliters ("mL")/min

Solvent A: 0.2% phosphoric acid, 90% water, 10% methanol

Solvent B: 0.2% phosphoric acid, 90% methanol, 10% water

Method B:

Column:	Phenomenex Luna C18(2), 4.6 x 50 mm x 5 um
Mobile Phase:	(A) 10:90 methanol:water; (B) 90:10 methanol:water
Buffer:	0.1% TFA
Gradient Range:	0-100% B
Gradient Time:	4 min
Flow Rate:	4 mL/min
Analysis Time:	5 min

Detection:

Detector 1:	UV at 220 nm
Detector 2:	MS (ESI+)
Detector 3:	ELSD

Method C:

Column:	Waters SunFire C18, 4.6 x 50 mm x 5 um
Mobile Phase:	(A) 10:90 methanol:water; (B) 90:10 methanol:water
Buffer:	0.1% TFA
Gradient Range:	0-100% B
Gradient Time:	4 min
Flow Rate:	4 mL/min
Analysis Time:	5 min

Detection:

Detector 1:	UV at 220 nm
Detector 2:	MS (ESI+)
Detector 3:	ELSD

Method D:

Linear gradient of 0 to 100% solvent B over 4 min, with 1 min hold at 100% B.

UV visualization at 220 nm

Column: YMC CombiScreen ODS-A S5 4.6 x 50 mm

Flow rate: 4 mL/min

Solvent A: 0.2% phosphoric acid, 90% water, 10% methanol

Solvent B: 0.2% phosphoric acid, 90% methanol, 10% water

Method E:

Linear gradient of 0 to 100% solvent B over 2 min, with 1 min hold at 100% B.

UV visualization at 254 nm

Column: YMC S5 ODS Ballistic 4.6 x 50 mm

Flow rate: 4 mL/min

Solvent A: 0.2% phosphoric acid, 90% water, 10% methanol

Solvent B: 0.2% phosphoric acid, 90% methanol, 10% water

Method F:

Linear gradient of 0 to 100% solvent B over 2 min, with 1 min hold at 100% B.

UV visualization at 254 nm

Column: Phenomenex Luna C18 4.6 x 30 mm

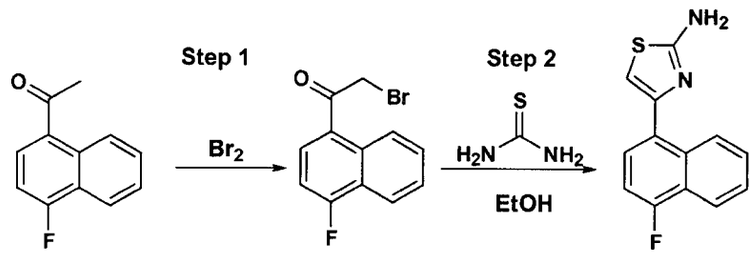
Flow rate: 5 mL/min

Solvent A: 0.1% TFA, 90% water, 10% methanol

Solvent B: 0.1% TFA, 90% methanol, 10% water

PREPARATION 1

4-(4-Fluoro-naphthalen-1-yl)-thiazol-2-ylamine



Step 1

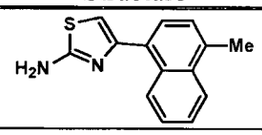
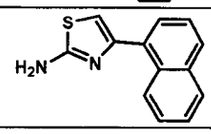
[00252] To a solution of 4'-fluoro-1'-acetonaphthone (28.69 millimoles ("mmol"), 5.4 grams ("g")) in 1,4-dioxane (18.0 mL) at 0 °C was added bromine (35.13 mmol, 5.61 g). After 3 hours ("h" or "hr") at room temperature ("rt") the reaction mixture was concentrated *in vacuo* to give 7.66 g (Yield ("Y"): 100%) of the product of step 1.

Step 2

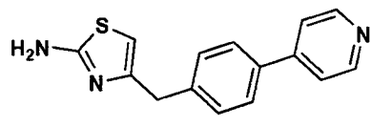
[00253] To a solution of the product of step 1 (28.69 mmol, 7.66 g) in ethyl alcohol ("EtOH") (20 mL) at room temperature was added thiourea (36.13 mmol, 2.75 g). After 1 hour at room temperature a precipitate formed. To the reaction

mixture was added water (100 mL) and the solid was collected by vacuum filtration. The solid was then washed with water (3 x 100 mL) and dichloromethane (3 x 100 mL), then dried *in vacuo* to give 5.5 g (Y: 75%) of the title compound. Mass Spectrometry ("MS") (E+) m/z: 245 (MH^+).

[00254] The following compounds were prepared in the same manner as the product of Preparation 1:

Preparation No.	Structure
2	
3	

PREPARATION 4



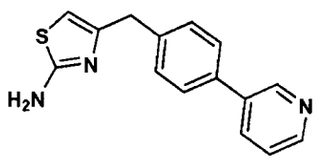
(a) To a solution of commercially available 4-bromophenylacetone (25 g, 117 mmol) in 30 mL of acetic acid and 15 mL of 48% HBr was added a solution of bromine (40 g, 217 mmol) in 50 mL of acetic acid. After 4 hr, acetone (150 mL) was added and the reaction mixture was stirred for 3 d. The reaction was concentrated by rotary evaporator, diluted with brine, and extracted 2 x DCM. The DCM extracts were dried over $MgSO_4$. The solution was filtered, concentrated by rotary evaporator, and chromatographed on SiO_2 using DCM to give 20.8 g (98%) of a dark oil 4a. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.49 (d, 2H), 7.12 (d, 2H), 3.94 (s, 2H), 3.92 (s, 2H).

(b) To a solution of 4a (116 mmol) in 200 mL of EtOH was added thiourea (9.0 g, 118 mmol) all at once. The reaction was heated at reflux for 4 hr. The reaction was concentrated by rotary evaporator and the crude residue was dissolved in EtOAc and extracted 3 x 1N HCl. The aqueous extracts were basified

with 1N NaOH and then extracted 2 x EtOAC. EtOAc extracts were dried over $MgSO_4$, and solid was triturated in 10% hexanes in EtOAc. Solid was collected and dried *in vacuo* to give 18 g (57%) of pure 6b. MS found: (M+H)+ = 270.

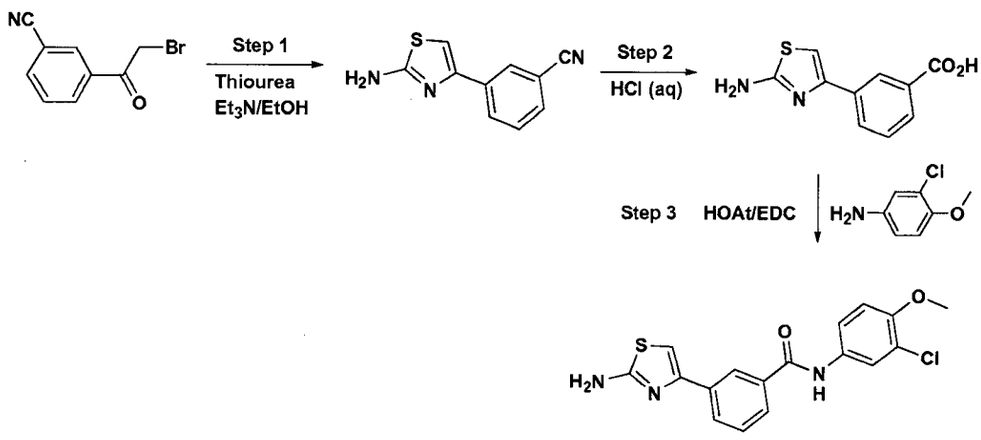
(c) Charged a flask with 4b (8.07 g, 30 mmol), 4-pyridineboronic acid (6.1 g, 50 mmol), tetrakis(triphenylphosphine)palladium(0) (3.5 g, 3.0 mmol), 30 mL of 2M K_2CO_3, and 200 mL of DMF. The reaction mixture was degassed by bubbling nitrogen through for 15 min then heated at 100 °C overnight. The reaction mixture was diluted in EtOAc and extracted 3 x 1N HCl. The aqueous extracts were basified with 1N NaOH and then allowed to stand in refrigerator for 2 hr. Solid was collected and dried *in vacuo* to give 5.4 g (68%) of pure 4c. MS found: (M+H)+ = 268.

PREPARATION 5



[00255] The title compound was prepared from intermediate bromide 4b in the same manner as 4c substituting 3-pyridylboronic acid for 4-pyridylboronic acid. MS (E-) m/z: 268 (M+H); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.80 (s, 1 H), 8.51 (dd, 1 H), 8.13 (dd, 1 H), 7.62 (d, 2 H), 7.53 (dd, 1 H), 7.40 (d, 2 H), 6.15 (s, 1 H), 3.89 (s, 2 H).

PREPARATION 6



Step 1

[00256] To a solution of 3-(2-bromoacetyl)benzonitrile (15.0 g, 66.6 mmol) (prepared in the manner described in Tanaka et al., J. Med. Chem. 1998, 41, 2390-2410), in EtOH (220 mL) was added triethylamine ("TEA") (9.3 mL, 66.6 mmol) and thiourea (6.6 g, 86.6 mmol) and the reaction was stirred at rt overnight. After 20 h, the reaction was concentrated *in vacuo* and the residue partitioned between water and EtOAc. The aqueous layer was washed with EtOAc (3x). The combined organic extracts were washed with saturated ("sat.") sodium bicarbonate ("$NaHCO_3$"), dried over $MgSO_4$, filtered, and concentrated by rotary evaporator. The resulting solid was recrystallized from EtOAc and hexane to give 7.78 g of pale yellow solid in a first batch and 1.87 g of a second batch (72% yield combined). MS found: (M+H)+ = 202. 1H-NMR (DMSO) δ 8.21 s (1H), 8.14 (dd, 1H), 7.72 (dd, 1H), 7.60 (app t, 1H), 7.27 (s, 1H), 7.19 (s, 2H).

Step 2

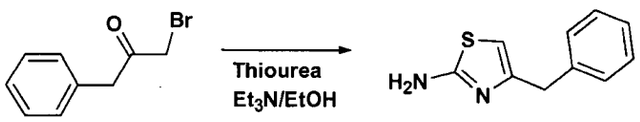
[00257] The product of Step 1 (6.73 g, 33.5 mmol) was suspended in 110 mL of conc HCl and refluxed while stirring for 4 hr. The homogeneous solution was cooled in an ice bath to form crystals which were filtered, washed with water and dried *in vacuo* to give 6.89 g of the desired product (94% yield). MS found: (M+H)+ = 221.

Step 3

[00258] To a solution of the product of Step 2 (6.89 g, 31.3 mmol) in DMF (100 mL) was added triethylamine (8.8 mL, 63 mmol), 1-hydroxy-7-azabenzotriazole ("HOAt") (4.26 g, 31.3 mmol), and 3-ethyl-3'-(dimethylamino)propyl- carbodiimide hydrochloride (or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) ("EDC") (6.0 g, 31.3 mmol). After stirring 25 min, a solution of 3-chloro-4-anisidine (5.92 g, 37.6 mmol) in 50 mL DMF and 8.8 mL triethylamine was added all at once at rt. After stirring for 24 h, the reaction was concentrated by rotary evaporator, extracted from a saturated sodium chloride solution ("brine") with EtOAc. The combined organics were dried over $MgSO_4$ to yield crude product. The crude product was concentrated *in vacuo*, dissolved in a minimum amount of EtOAc and triturated with hexane. The resulting solid was filtered and trituration was repeated twice to

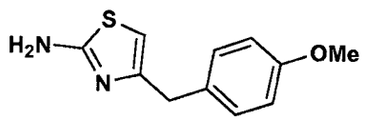
give a total of 5.7 g (51% yield) of pure product. MS found: (M+H)+ = 360. 1H-NMR (DMSO) δ 10.3 (s, 1H), 8.35 (s, 1H), 8.00 (d, 1H), 7.95 (d, 1H), 7.80 (d, 1H), 7.69 (d, 1H), 7.52 (t, 1H), 7.16 (m, 4H), 3.85 (s, 3H).

PREPARATION 7



[00259] To a solution of 1-bromo-3-phenyl-2-propanone (2.2 g, 10 mmol) (prepared in the manner described in Choi et al., Org. Lett. 2003, vol. 5, no. 4, 411-414), in EtOH (100 mL) was added thiourea (1.0 g, 13 mmol) and the reaction was stirred at reflux overnight. After 20 h, the reaction was concentrated *in vacuo* and partitioned between water and ethyl acetate ("EtOAc"). The aqueous layer was washed with EtOAC (3x). The combined organic extracts were dried over magnesium sulfate ("$MgSO_4$"), filtered, and concentrated by rotary evaporator. The resulting solid was purified by silica gel chromatography using 10% MeOH/EtOAc as the eluent to give 2.1 g of pale yellow solid (95% yield). MS found: (M+H)+ = 191. Proton nuclear magnetic resonance ("1H-NMR") in chloroform ("CDCl3") δ 7.2-7.35 m (5H), 6.01 (s, 1H), 4.8-5.3 (bs, 2H), 3.86 (s, 2H). NMR spectral data: s = singlet; d = doublet; m = multiplet; br = broad; t = triplet.

PREPARATION 8



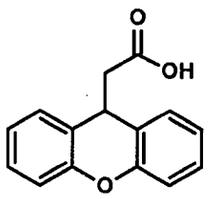
(a) Applying the method of Mazzocchi et al (Synth. Commun. 1986, 309-312) a cuprate was prepared from 4-methoxyphenylmagnesium bromide (20 mmol, 40 mL of 0.5 M THF solution) and CuBr (574 mg, 2.0 mmol) in 50 mL anhydrous ether. The cuprate was treated with epichlorohydrin (1.94 g, 21 mmol) and stirred at -40 C for 20 hr. The reaction was quenched with water, extracted 2 x Et_2O, and the ethereal extracts were dried over $MgSO_4$. The solution was filtered, concentrated by rotary evaporator, and chromatographed on SiO_2 using 25% EtOAc in hexanes to give

888 mg (22%) of the chlorohydrin 5a as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.18 (d, 2H), 6.88 (d, 2H), 4.0 (m, 1H), 3.82 (s, 3H), 3.65 (dd, 1H), 3.52 (dd, 1H), 2.83 (d, 2H).

(b) The intermediate alcohol 8a (888 mg, 4.44 mmol) was taken up in dichloromethane (40 mL) and treated with Dess-Martin periodinane (1.88 g, 4.44 mmol). The reaction was allowed to warm to rt and was complete by TLC monitoring after 4 hr. The reaction mixture was concentrated by rotary evaporation and the crude residue was purified on SiO_2 (dichloromethane as eluent) to give 762 mg (86% Y) of chloromethylketone 8b.

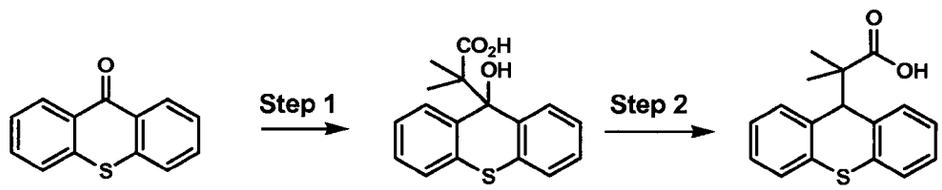
(c) This intermediate was taken up in 15 mL of EtOH and treated with a solution of thiourea (302 mg, 3.82 mmol) in 5 mL EtOH. The reaction was concentrated *in vacuo* and a solid formed on standing to give pure 8c, 208 mg (80%) as a yellow solid. MS found: (M+H)+ = 221.

PREPARATION 9



[00260] A mixture of 9-hydroxy xanthene (3.96 g, 20 mmol) and malonic acid (2.6 g, 25 mmol) in dry pyridine was stirred under nitrogen at 65 °C, turning homogeneous after 20 min at that temperature. After heating 2 h at 65 °C, the solution was warmed to 95 °C, and heated at that temperature for an additional 4.5 h. The solution was then poured into 1N aqueous HCl, giving an oil which solidified over 1 h. The solid was collected and washed with water, then partitioned between 1N aqueous NaOH and dichloromethane. The aqueous layer was acidified with concentrated HCl, then washed with ethyl acetate. The organic layer was dried (sodium sulfate) and concentrated to give the product (2.48 g, Y = 50%) as an off white/pale pink solid. MS (E-) m/z: 239 (M-H); LC retention time: 3.39 min.

PREPARATION 10



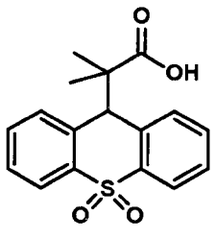
Step 1

[00261] To a solution of diisopropylamine (9.28 mL, 66.16 mmol) in dry THF (70 mL) at -30 °C was added n-butyl lithium (1.6 M in hexanes, 41.4 mL) dropwise. The resulting solution was warmed to 0 °C and a solution of isobutyric acid (3.06 mL, 33.1 mmol) in THF (10 mL) was then added dropwise. The mixture was heated at 55 °C for 1.5 h, then cooled to room temperature and added portionwise via canula to thioxanthen-9-one (5.0 g, 23.58 mmol) in THF (100 mL) at 0 °C. The ice bath was removed and the reaction mixture stirred at room temperature for 2 h, then partitioned between ethyl acetate and 1N HCl. The organic layer was washed with 1N aqueous NaOH. The basic aqueous layer was then acidified to pH 2 with the dropwise addition of concentrated HCl, then washed with ethyl acetate. The organic layer was dried (sodium sulfate) and concentrated to give the crude product (3.5 g), which was used directly in the next step without further purification. MS (E+) m/z: 301 (M+H); LC retention time: 3.44 min.

Step 2

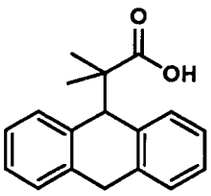
[00262] To a solution of the product of Step 1 (3.5 g, 11.7 mmol) in dichloromethane (40 mL) at 0 °C was added boron trifluoride etherate (2.6 mL, 20.4 mmol) followed by triethylsilane (3.4 mL, 21.3 mmol). The resulting solution was allowed to warm to room temperature over 1 h. After 2 h at room temperature, the reaction mixture was partitioned between dichloromethane and 1N aqueous NaOH. The aqueous layer was acidified to pH 2 with the dropwise addition of concentrated HCl, then washed with ethyl acetate. The organic layer was dried (sodium sulfate) and concentrated, then purified by flash column chromatography (silica, 1:1 ethyl acetate:hexanes, product Rf = 0.6) to give the product (0.7 g) as a pale yellow solid. LC retention time: 3.83 min.

PREPARATION 11



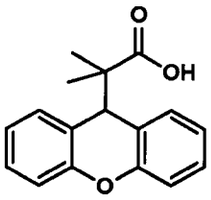
[00263] To a solution of the product of Preparation 9 (100 mg, 0.352 mmol) in glacial acetic acid (4 mL) at 0 °C was added hydrogen peroxide (4 mL). The solution was allowed to warm temperature, and stirred for 2 h. To the reaction mixture was added sodium tungstate dihydrate (30 mg, 0.10 mmol). After stirring another 12 h at ambient temperature, the reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed sequentially with a saturated solution of aqueous sodium sulfite and water, then dried over sodium sulfate and concentrated to give the product (95 mg, 85% yield) as a white solid. LC retention time: 2.69 min.

PREPARATION 12



[00264] The title compound was prepared in the same manner as the title compound of Preparation 10, replacing thioxanthen-9-one with anthrone.

PREPARATION 13

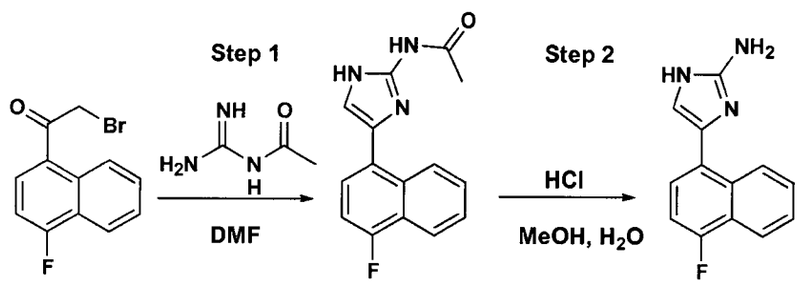


[00265] The title compound was prepared in the same manner as the title compound of Preparation 10, replacing thioxanthen-9-one with 9H–xanthen-9-one.

[00266] In alternative preparation of the title compound is as follows: To a solution of 9-hydroxy xanthene (250 mg, 1.26 mmol) in dichloromethane (11 mL) at °C under nitrogen was added titanium tetrachloride (1.0M in dichloromethane, 1.26 mL) dropwise to give a yellow, opaque mixture. After 5 min at 0 °C, methyl trimethylsilyl dimethylketene acetal (MTDKA) (0.64 mL, 3.15 mmol) was added dropwise, giving a brownish solution. After 30 min at 0 °C, water (3 mL) was added and the mixture was stirred for 10 min, turning yellow with the formation of a precipitate. The mixture was filtered over Celite, and the organic layer separated, then washed with saturated aqueous sodium bicarbonate, dried over sodium sulfate, and concentrated. Purification of the residue by flash column chromatography (5% ethyl acetate in hexanes) provided the title compound (178 mg). LC retention time: 3.89 min.

PREPARATION 14

4-[1-(4-Fluoro)naphthyl]aminoimidazole



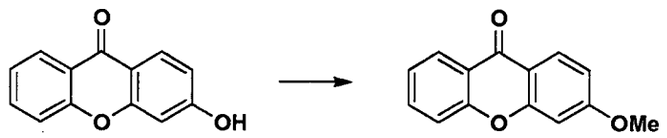
Step 1

[00267] To a solution of the product of Preparation 1, step 1 (18.73 mmol, 5.0 g) in DMF (15 mL) at room temperature was added 1-acetylguanidine (57.43 mmol, 5.80 g). After 5 hours at room temperature, the reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The organic phases were concentrated *in vacuo* and the residue chromatographed on silica gel (eluted with 5% methanol in dichloromethane) to give 2.0 g (Y: 39%) of the product of step 1. MS (E+) m/z: 270 (MH^+).

Step 2

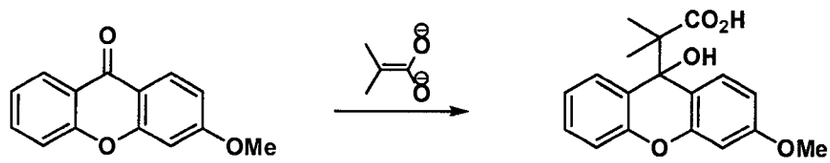
[00268] To a solution of the product of Step 1 (7.43 mmol, 2.0 g) in methanol (17 mL) was added water (8.5 mL) and 12 N HCl (12.0 mL). After 1 hour at reflux the reaction mixture was concentrated *in vacuo* to approximately 15 mL. The resulting solution was then purified and neutralized by cation exchange SPE to give 1.66 g (Y: 99%) of the title compound 2a. MS (E+) m/z: 228 (MH^+).

PREPARATION 15



Step 1

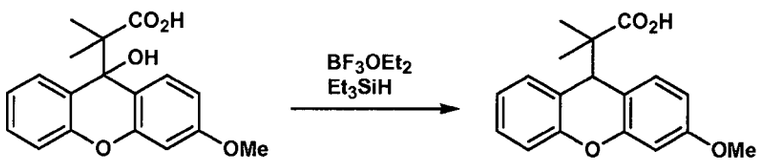
[00269] To a solution of 3-hydroxy-9-H-xanthenone ("Sieber linker") (20.4 g, 96.2 mmol) in DMF (475 mL) was added methyl iodide (18.0 mL, 287 mmol) followed by NaH (60% w/w in mineral oil, 7.68 g, 192 mmol). The mixture was allowed to stir at rt for 2.5 h, then partitioned between ethyl acetate (750 mL) and 1N HCl (300 mL). The aqueous layer was extracted again with 2 portions of ethyl acetate. The combined organic layer was washed sequentially with water (500 mL), saturated sodium bicarbonate, and brine, then dried over sodium sulfate and concentrated. The crude solid was re-crystallized from EtOH and a second crop of crystals was obtained by re-crystallization of the mother liquor to give 20.21 g (93% yield) of 15a as needles. MS m/z: 227 (M+H); LC retention time: 3.38 min.



Step 2

[00270] To a solution of diisopropyl amine (6.63 mL, 47.25 mmol) in dry THF (35 mL) at -30°C was added nBuLi (1.6 M/hexanes, 29.6 ml) dropwise. The solution was warmed to 0°C. A solution of isobutyric acid (2.19 mL, 23.63 mmol) in THF (10 mL) was then added dropwise. The solution was heated at 55°C for 1.5 h, then cooled to room temperature and added portionwise via canula to the ketone 15a (3.56

g, 15.75 mmol) in THF (30 mL) at 0°C. The solution was allowed to warm slowly to room temperature. After 2 h, LC indicated 70% completion. The reaction mixture was partitioned between ethyl acetate and 1N aq HCl. The organic layer was washed with 1N aq NaOH. The basic aqueous layer was acidified at 0°C with the dropwise addition of concentrated HCl until pH = 2. The acidic aqueous layer was washed with ethyl acetate, and the organic layer dried over sodium sulfate and concentrated to give the product alcohol (4.45 g, 90% yield). MS m/z: 297 (M-OH); LC retention time: 3.22 min.



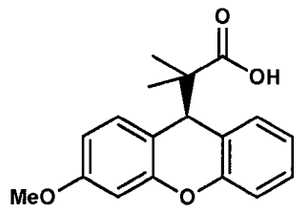
(+/-)

Step 3

[00271] To a solution of 15b (2.81 g, 8.95 mmol) in dichloromethane (35 mL) at 0 °C was added boron trifluoride diethyl etherate (2.27 mL, 17.9 mmol) followed by triethylsilane (2.86 mL, 17.9 mmol). The solution was allowed to warm to rt over 1 h. Reaction was complete after 2 h at rt as indicated by HPLC. Continuation of the reaction beyond 2 h led to a gradual increase in the production of a product derived from decarboxylation. The reaction mixture was partitioned between dichloromethane and 1N aq NaOH. The aqueous layer was acidified to pH 2 with the dropwise addition of conc. HCl, then washed with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated to give the product as a solid (1.81 g, 68% yield). MS m/z: 321 (M+Na); LC retention time: 3.64 min

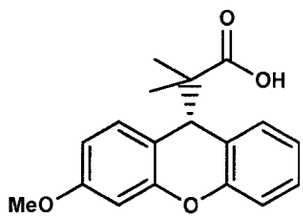
PREPARATION 16

[00272] The racemic carboxylic acid of Preparation 15 was resolved by chiral HPLC (Chiralpak AD, 1:1 ethanol:methanol, 0.05% TFA, isocratic) to provide the pure enantiomers 16a, 16b.



16a.

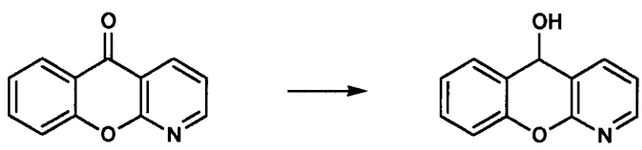
[00273] First to elute from preparative chiral HPLC. Analytical chiral HPLC (Chiralpak AD, 4.6 x 250 mm, 1:1 ethanol:methanol, isocratic, 0.5 mL/min) retention time = 6.41 min, >99.9% ee.



16b.

[00274] Second to elute from preparative chiral HPLC. Analytical chiral HPLC (Chiralpak AD, 4.6 x 250 mm, 1:1 ethanol:methanol, isocratic, 0.5 mL/min) retention time = 10.3 min, >99% ee. X-ray crystallographic analysis of the salt derived from 16b and (R)(+)-alpha-methylbenzylamine proved 16b to be the R enantiomer.

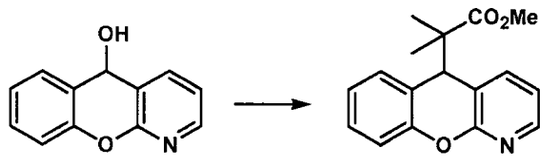
PREPARATION 17



Step 1

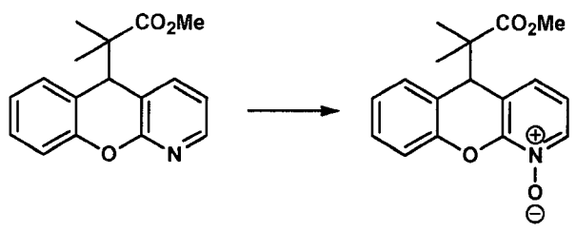
[00275] To a suspension of 1-azaxanthone (purchased or prepared by the method of Villani et al,. J. Med. Chem. 1975, 18, 1-8.) (18.5 g, 94 mmol) in MeOH (650 mL) at 0 °C was added sodium borohydride (4.26 g, 113 mmo) portionwise over 10 min. The reaction mixture was allowed to warm to room temperature, and stirred 15 h. HPLC analysis of the reaction mixture indicated two peaks, one corresponding to the alcohol, the other corresponding to 9-methoxy-1-azaxanthene which is presumably

generated under the conditions of LC analysis. The pale yellow solution was then concentrated to one third volume and poured into cold brine (500 mL). This mixture was washed with choloroform (2 x 300 mL). The combined organic layers were dried over sodium sulfate and concentrated to give a yellowish solid 17a (17.80 g, 95% yield) which was used directly in the next step with no further purification. MS (E+) m/z: 200 (M+H); LC retention time: 2.01 min., 2.46 min.



Step 2

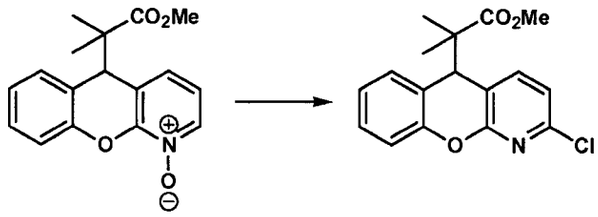
[00276] To a suspension of 17a (17.80 g, 89 mmol) in dichloromethane (475 mL) at 0°C was added titanium tetrachloride (1.0 M in dichloromethane, 89 mL) dropwise. The resulting tan-colored suspension stirred 10 min at 0 C (mechanical stirring recommended) before adding (1-methoxy-2-methylprop-1-enyloxy)trimethylsilane (36 mL, 173 mmol) to the mixture dropwise. The resulting dark, homogeneous solution was allowed to stir 1 h at 0°C, then quenched with the addition of saturated aqueous sodium bicarbonate, giving gas evolution and formation of a white precipitate. The mixture was filtered over celite, and the resulting organic layer of the filtrate separated, dried over sodium sulfate, and concentrated to give a solid (17b) (22.3 g, 89% yield) which was used directly in the next step with no further purification. MS (E+) m/z: 284 (M+H); LC retention time: 3.04 min.



Step 3

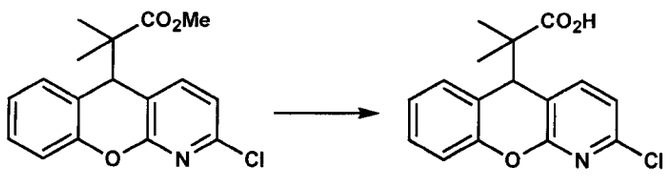
[00277] To a solution of 17b (21.2 g, 74.9 mmol) in dichloromethane at room temperature was added mCPBA (containing 30% m-chlorobenzoic acid) (53 g). After 2 h, the reaction mixture was washed sequentially with 10% aqueous sodium

sulfite (500 mL),1N aqueous NaOH (200 mL), and water (200 mL). The organic layer was dried over sodium sulfate, and concentrated to provide the title compound (17c) as an amorphous solid (21.63 g, 97% yield) which was used directly in the next step with no further purification. MS (E+) m/z: 300 (M+H); LC retention time: 2.25 min.



Step 4

[00278] A solution of 17c (21.15 g, 71.0 mmol) in phosphorous oxychloride (150 mL) was heated for 30 min at 90°C. The solvent was then removed by vacuum bulb-to-bulb distillation. The residual solid was dissolved in dichloromethane (250 mL) and transferred portionwise to a 1L beaker containing ice (3/4 full). Solid sodium carbonate was added portionwise with vigorous stirring (gas evolved) to the resulting slurry until it reached pH 6. The resulting emulsion was allowed to sit overnight in a separatory funnel. The organic layer was removed, dried (sodium sulfate), and concentrated to give the crude solid 17d 17.37g (77% crude yield). This solid may be recrystallized to high purity from methanol or taken directly into the next step with no further purifcation. MS (E+) m/z: 318 (M+H); LC retention time: 3.37 min.

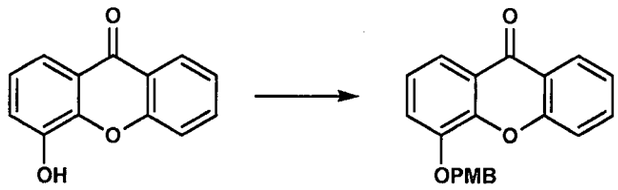


Step 5

[00279] To a solution of 17d (16.08 g, 50.7 mmol) in THF (240 mL) and methanol (400 mL) was added a solution of KOH (28.46 g, 507 mmol) in water (320 mL). The resulting solution was heated at reflux (65°C) 10 h, then concentrated under reduced pressure to about 2/3 volume. The resulting solution was acidified to pH 5 with the dropwise addition of 12N HCl, then washed with ethyl acetate (2 x 300 mL). The

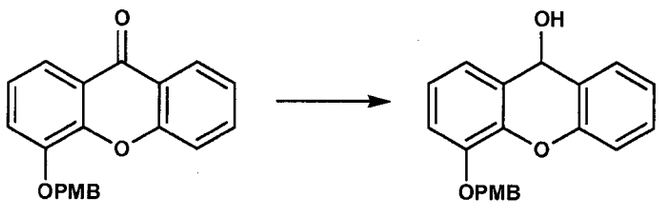
combined organic layers were dried (sodium sulfate) and concentrated. The crude carboxylic acid (12.6 g) was dissolved in warm ethyl acetate (600 mL) and treated with benzylamine (9.2 mL, 48 mmol). The solution was allowed to gradually cool to room temperature, and allowed to sit for 3 h. The precipitate was collected and washed (diethyl ether), then partitioned between ethyl acetate (350 mL) and 1N aqueous HCl (200 mL). The organic layer was dried over magnesium sulfate and concentrated to provide 17e as a solid (8.53 g, 43% yield for two steps). MS (E+) m/z: 304 (M+H); LC retention time: 3.19 min.

PREPARATION 18



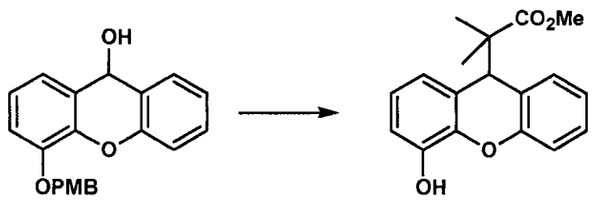
Step 1

[00280] To a solution of 4-hydroxy-9H-9-xanthenone (Maybridge) (512 mg, 2.42 mmol) and 4-methoxy benzyl chloride (0.393 mL, 2.90 mmol) in DMF (15 mL) was added sodium hydride (60 w% in mineral oil, 145 mg, 3.63 mmol), giving a dark red color and gas evolution. After 3 h at room temperature, the reaction mixture was partitioned between ethyl acetate and 1N aqueous HCl. The organic layer was washed sequentially with water, saturated aqueous sodium bicarbonate and brine, then dried over sodium sulfate and concentrated. The crude residue was purified by flash column chromatography (silica, 30% acetone in hexanes) to give the product 18a (420 mg). MS (E+) m/z: 333 (M+H).



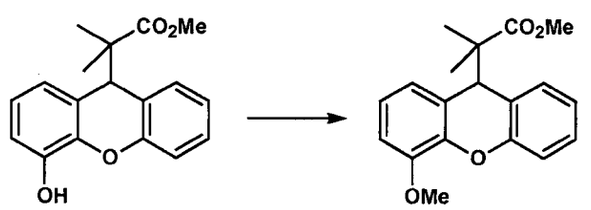
Step 2

[00281] A solution of 18a (197 mg, 0.59 mmol) in THF (6 mL) at 0°C under nitrogen was treated with lithium aluminum hydride (1.0M in diethyl ether, 0.59 mL). After 30 min at 0°C, water (approx. 2 mL) was added dropwise to the mixture. After stirring for 5 min at 0°C, the mixture was filtered over a pad of Celite and sodium sulfate, then concentrated to give the 18b (183 mg, 93%). MS (E+) m/z: 317 (M-OH); LC retention time: 3.88 min.



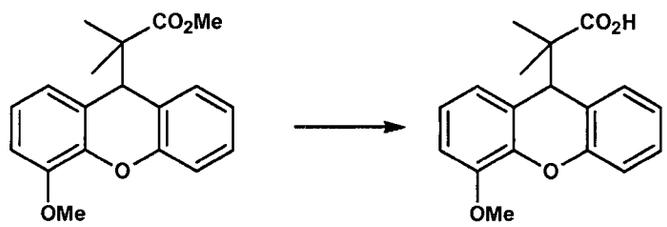
Step 3

[00282] To a solution of 18b (181 mg, 0.54 mmol) in dichloromethane (5 mL) at 0°C was added titanium tetrachloride (1.0M in dichloromethane, 0.54 mL) dropwise to give a deep, dark red solution, which became opaque over the course of 10 min at 0°C. (1-methoxy-2-methylprop-1-enyloxy)trimethylsilane (0.219 mL, 1.08 mmol) was then added dropwise, giving a clear, dark red solution. After 20 min at 0°C, the reaction was quenched with the addition of water (1 mL), turning the mixture colorless, with the formation of a precipitate. The mixture was filtered over celite. The organic layer was separated and washed with saturated aqueous sodium bicarbonate, dried over sodium sulfate, and concentrated. The residue was purified by flash column chromatography (silica, 10 – 20% ethyl acetate in hexanes) to give the product 18c as the third eluting fraction (110 mg, 68%). MS (E-) m/z: 297 (M-H); LC retention time: 3.29 min.



Step 4

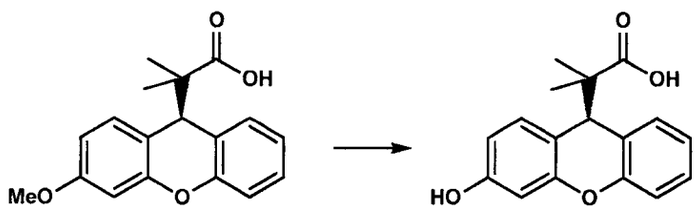
[00283] A mixture of 18c (32 mg, 0.11 mmol), methyl iodide (0.014 mL, 0.22 mmol) and cesium carbonate (42 mg, 0.13 mmol) in DMF (1 mL) was heated at 60°C for 6 h. The reaction mixture was then partitioned between ethyl acetate and water. The organic layer was washed sequentially with water, saturated aqueous sodium bicarbonate, and brine, then dried over sodium sulfate and concentrated. The intermediate 18d (28 mg, 82%) was used in the next step with no further purification. MS (ES+) m/z: 335 (M+Na); LC retention time: 3.57 min.



Step 5

[00284] The intermediate 18e was obtained from 18d in the same manner described above for the preparation of the title compound of 17e from 17d. MS (ES-) m/z: 297 (M-H); LC retention time: 3.29 min.

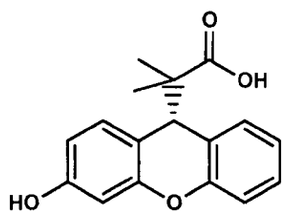
PREPARATION 19



[00285] The product of Preparation 16a (600 mg, 2.01 mmol) was divided evenly into 3 microwave reaction vessels. To each reaction vessel was added 1-methyl-2-pyrrolidinone (4 mL), 2-aminothiophenol (92 mg, 0.74 mmol) and potassium carbonate (102 mg, 0.74 mmol). Each mixture was heated by microwave at 205°C for 1.5 h. The reaction mixtures were combined and partitioned between ethyl acetate and water. The organic layer was extracted with 1N aqueous sodium hydroxide. The combined aqueous layers were acidified approximately to pH 2.0, then extracted with ethyl acetate (3x). The combined organic layers were washed with 1N aqueous HCl,

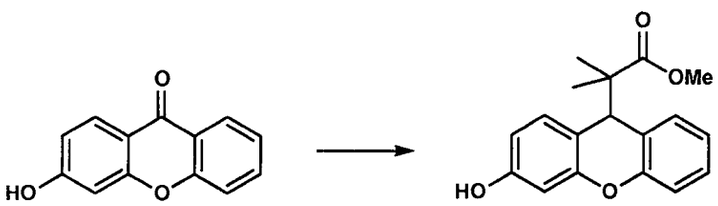
then dried over sodium sulfate and concentrated. Purification of the residue by preparative HPLC provided the product as an amorphous solid (400 mg, 70%). MS (ES-) m/z: 283 (M-H); LC retention time: 3.16 min.

PREPARATION 20



[00286] The title compound was prepared from the product of Preparation 16b following the procedure described above for the preparation of the title compound of Preparation 19. MS (ES-) m/z: 283 (M-H); LC retention time: 3.16 min.

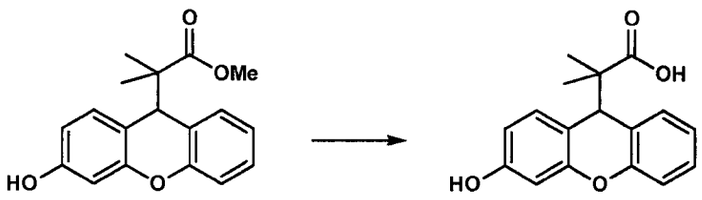
PREPARATION 21



Step 1

[00287] To a suspension of 3-hydroxy-9-H-xanthenone ("Sieber linker") (1.0 g, 4.72 mmol) in dichloromethane (10 mL) at 0°C under nitrogen was added boron trifluoride etherate (1.8 mL, 14.15 mmol) dropwise over 10 min. After stirring 10 min at 0°C, 1-methoxy-2-methylprop-1-enyloxy)trimethylsilane (2.88 mL, 14.15 mmol) was added dropwise to the suspension, giving a clear dark brown solution during the addition, which was stirred another 2 h at 0°C. Another portion of boron trifluoride etherate (1.8 mL, 14.15 mmol) was then added to the reaction mixture, followed by triethylsilane (2.26 mL, 14.15 mmol). The reaction mixture was allowed to warm slowly to room temperature, and stirred 15 h. A saturated aqueous solution of sodium bicarbonate was added to the reaction mixture, which was then extracted with dichloromethane. The organic phase was washed with another portion of saturated sodium bicarbonate, then dried over sodium sulfate and concentrated. The

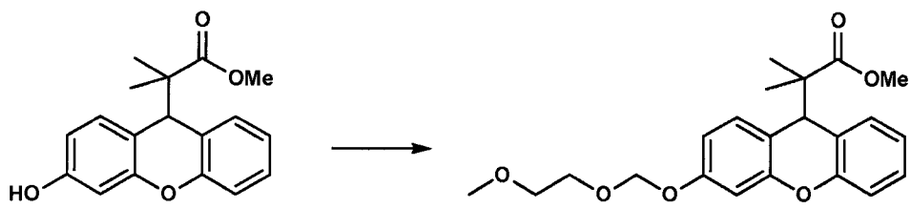
crude material was purified by passing through a short column of silica gel (30 – 50% ethyl acetate in hexanes) to give the product 21a (1.2g, 85% yield) as a pale yellow solid. MS (ES-) m/z: 297 (M-H); LC retention time: 3.42 min.



Step 2

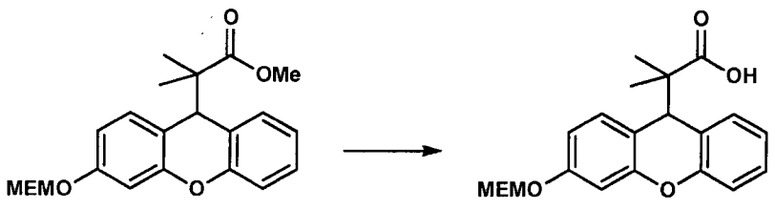
[00288] A suspension of 21a (133 mg, 0.45 mmol) in methanol (1 mL), water (2 mL), DMSO (1 mL) and 4N aqueous KOH (1.13 mL) was heated at 100°C for 3 h. The reaction mixture was then partitioned between ethyl acetate and 1N HCl. The organic layer was dried over sodium sulfate, and concentrated to give the product 21b (124 mg, 97% yield). LC retention time: 3.15 min.

PREPARATION 22



Step 1

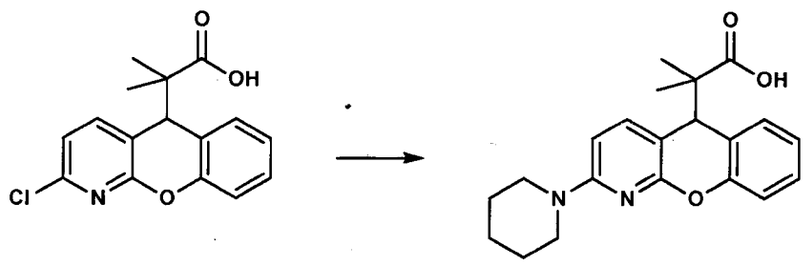
[00289] To a solution of 21a (490 mg, 1.64 mmol) in THF (15 mL) at 0°C was added 2-methoxyethoxymethyl (MEM) chloride (0.282 mL, 2.47 mmol), followed by sodium hydride (60% w/w in mineral oil, 85 mg). After 1.3 h, the reaction mixture was partitioned between ethyl acetate and 1N HCl. The organic layer was washed sequentially with saturated aqueous sodium bicarbonate and brine, then dried over sodium sulfate and concentrated to give 667 mg (ca. 99%) of the crude product 22a as an oil which was taken directly into the next step with no further purification. LC retention time: 3.83 min.



Step 2

[00290] A mixture of crude 22a (ca. 1.64 mmol) in methanol (4 mL), DMSO (3.5 mL), and 4N KOH (4.1 mL) was stirred at 100°C for 3 h, then partitioned between ethyl acetate and 1N HCl. The organic layer was dried over sodium sulfate and concentrated. Flash column chromatography (silica, 50 – 60% ethyl acetate in hexanes) provided the product 22b (428 mg, 70% for two steps) as a pale yellow oil. LC retention time: 3.61 min.

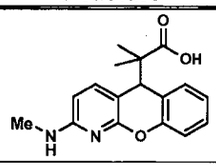
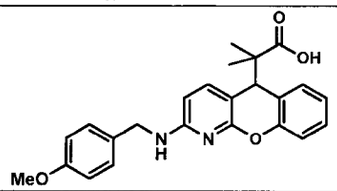
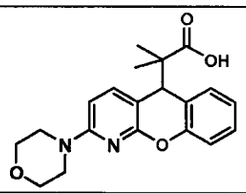
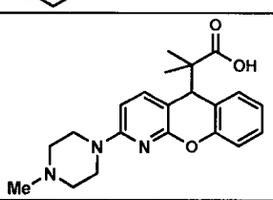
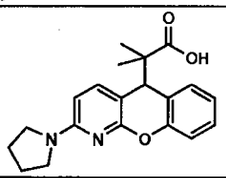
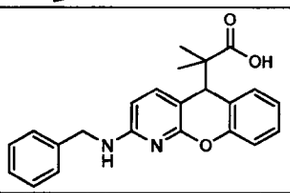
PREPARATION 23



[00291] A solution of the product of Preparation 17e (1.0g, 3.30 mmol) in piperidine (15 mL) in a sealed tube was hated at 150°C for 4 h. Most of the piperidine was then removed *in vacuo* to obtain a solid, which was suspended in a 1:1 solution of diethyl ether in hexanes. This suspension was washed with a 1N sodium hydroxide solution. The aqueous layer was washed twice with 1:1 diethyl ether in hexanes, then acidified to pH 3.0 with the dropwise addition of concentrated HCl and extracted with ethyl acetate. The aqueous layer was washed twice with ethyl acetate. The combined ethyl acetate layers were dried over sodium sulfate and concentrated to give a yellow solid (1.10 g, 95% yield). MS (ES+) m/z: 353 (M+H); LC retention time: 3.71 min.

PREPARATIONS 24 TO 29

[00292] The following compounds were prepared in the same manner as the product of Preparation 23.

Preparation No.	Structure
24	
25	
26	
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PREPARATION 30

[00293] The product of Preparation 17 (17e) was resolved into pure enantiomers by chiral supercritical fluid chromatography (SFC).

Preparative Conditions A:

Column:	Chiralcel OJ 250 X 30 mm ID; 10 um
Temperature:	Ambient
Mobil Phase:	CO2/ MeOH/TFA = 85:15:0.1
Flow rate:	65 mL/min
Injection volume:	1.2mL
UV Detection:	220 nm

Preparative Conditions B:

Column:	Chiralpak AD-H (3 x25cm, 5μm)
BPR Pressure:	100 bars
Temperature:	35°C
Mobil Phase:	CO2/MeOH = 88:12
Flow rate:	150mL/min
UV Detection:	220 nm
Injection Program:	Stacked Injection (4.20 min/per cycle)
Injection Volume:	2.20mL
Sample Preparation:	20,000mg/450mL MeOH = 46.7mg/mL

Analytical Conditions:

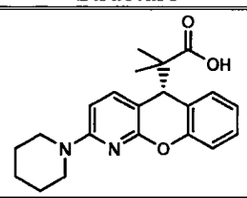
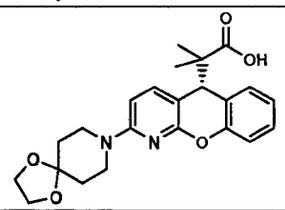
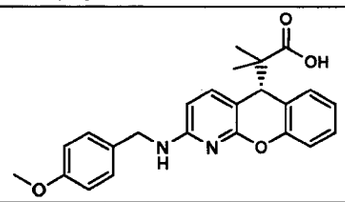
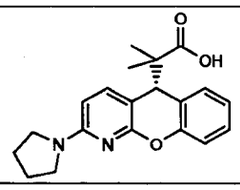
Column:	Chiralpak OJ 250 X 4.6 mm ID; 10 um
Temperature:	Ambient
Mobil Phase:	Hex/IPA/TFA = 80:20:0.1
Flow rate:	1.0 mL/min
Injection volume:	3~15 μl
UV Detection:	290 nm
Retention Time (min):	RT_1: 5.349 RT2: 8.231

[00294] The first peak to elute under the preparative (SFC) conditions (Preparative Conditions A) described above also eluted first under the aforementioned analytical chiral LC conditions. A sample of the first-eluting material (30a) was co-crystallized with (R)-(+)-alpha-methylbenzylamine. An X-ray crystal structure determination of the crystalline material thus obtained proved 30a to be of the 'R ' absolute

stereochemistry. The second-eluting enantiomer (30b) of "Preparative Conditions A" was thus deduced to be of the 'S' absolute stereochemistry. The SFC separation conditions for 17e were further optimized as described above ("Preparative Conditions B"), in which case the 'S' enantiomer (30b) eluted first, while the 'R' enantiomer (30a) eluted second (confirmed by comparison of chromatographs of homochiral compounds obtained from both preparative methods (A and B) under the analytical conditions described above.

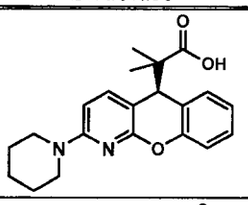
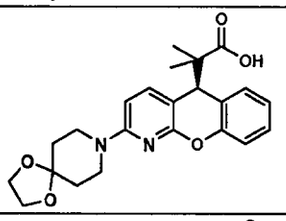
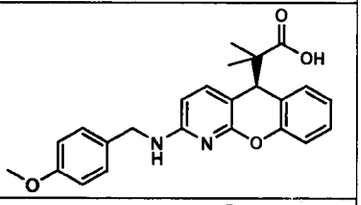
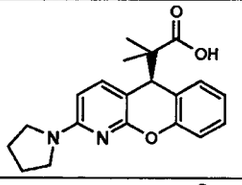
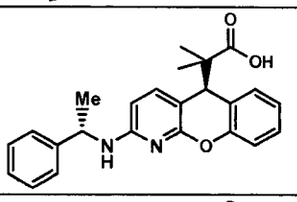
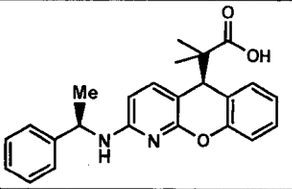
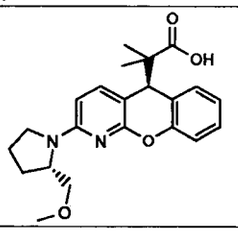
PREPARATIONS 31 TO 34

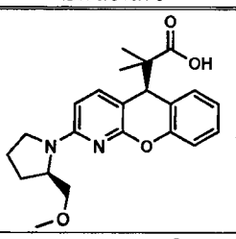
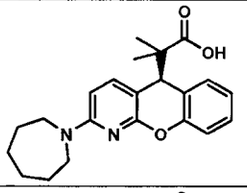
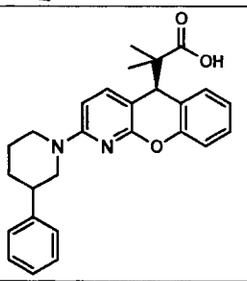
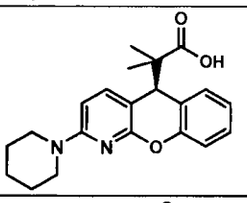
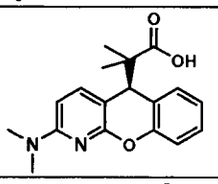
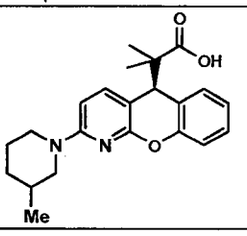
[00295] The following compounds were prepared from 30a in the same manner described above for the preparation of the title compounds of Preparations 23 to 29.

Preparation No.	Structure
31	
32	
33	
34	

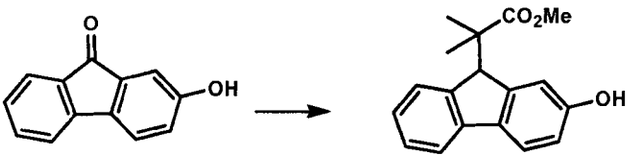
PREPARATIONS 35 TO 47

[00296] The following compounds were prepared from 30b in the same manner described above for the preparation of the title compounds of Preparations 23 to 29.

Preparation No.	Structure
35	
36	
37	
38	
39	
40	
41	

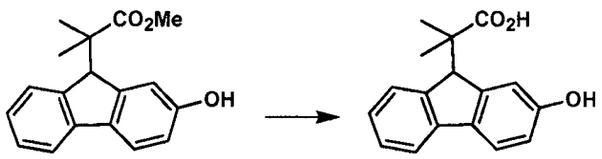
Preparation No.	Structure
42	
43	
44	
45	
46	
47	

PREPARATION 48



Step 1

[00297] To a rust-red colored suspension of 2-hydroxyfluorenone (303 mg, 1.54 mmol) in dichloromethane at 0 °C was added boron trifluoride etherate (0.392 mL, 3.09 mmol) dropwise, giving a brownish suspension. After 10 min at 0°C, 1-methoxy-2-methylprop-1-enyloxy)trimethylsilane (0.627 mL, 3.09 mmol) was added dropwise, giving a tan, clar solution. After 80 min at 0°C, trifluoroacetic acid (1.1 mL) was added, followed by triethylsilane (0.494 mL, 3.09 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. Saturated aqueous sodium bicarbonate was added slowly to the reaction mixture with stirring. The organic layer was removed, dried over sodium sulfate, and concentrated to give 48a (452 mg, 99%) as a foam. The crude material was used directly in the next step with no further purification. MS (E+) m/z: 305 (M+Na); LC retention time: 3.55 min.

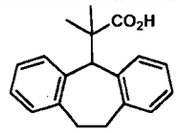


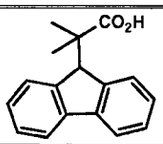
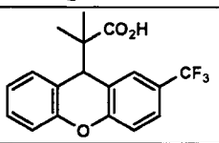
Step 2

[00298] The product (48b) was obtained in the manner described above for the preparation of 22b. MS (E+) m/z: 286 ($M+H_2O$); MS (E-) m/z: 267 (M-H); LC retention time: 3.32 min.

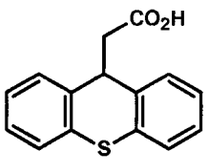
PREPARATIONS 49 TO 51

[00299] The following compounds were prepared in the manner described for the preparation of the title compound of Preparation 10, replacing thioxanthen-9-one with either dibenzosuberone, 9-fluorenone, or 2-trifluoromethylxanthen-9-one.

Preparation No.	Structure
49	

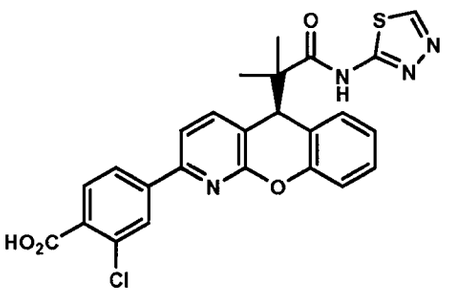
Preparation No.	Structure
50	
51	

PREPARATION 52



[00300] The title compound was prepared in the manner described above for the preparation of the title compound of Preparation 9, as described by Jones et al. (J. Am. Chem. Soc., 1948, 70, 2843).

PREPARATION 53



Step 1

[00301] To a soln. of (S)-2-(2-chloro-5*H*-chromeno[2,3-b]pyridin-5-yl)-2-methylpropanoic acid (30b, 10 g, 32.9 mmol) in acetonitrile (200 ml) was added triethylamine (22.94 ml, 165 mmol), O-(7-AZABENZOTRIAZOL-1-YL)-N,N,N',N'-TETRAMETHYLURONIUM PF6 (HATU) (16.27 g, 42.8 mmol) and 1,3,4-thiadiazol-2-amine (9.99 g, 99 mmol). The resulted mixture was heated at 80 °C for 12 h. The reaction mixture was then concentrated in vacuum and the residue was partitioned between EtOAc and 1N HCl. The obtained organic layer was washed with

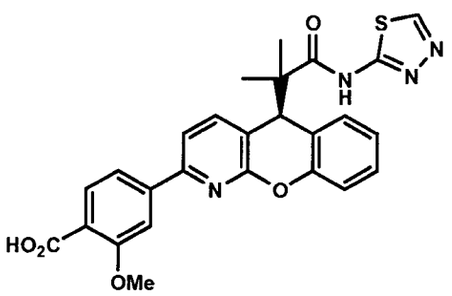
saturated $NaHCO_3$, brine, then dried (Na_2SO_4) and concentrated to give a solid. The solid was dissolved in EtOH (400 mL) with gentle warming. Added 1N HCl (~ 200 mL) portionwise. The solid was collected and washed with water, dried on vacuum pump overnight to give 10g (79%) of (S)-2-(2-chloro-5H-chromeno[2,3-b]pyridin-5-yl)-2-methyl-N-(1,3,4-thiadiazol-2-yl)propanamide (53a). MS (E+) m/z: 387 (M+H); LC retention time: 3.12 min.

Step 2

[00302] To a soln. of (S)-2-(2-chloro-5H-chromeno[2,3-b]pyridin-5-yl)-2-methyl-N-(1,3,4-thiadiazol-2-yl)propanamide (53a) (1 g, 2.58 mmol) in DMF (40 mL) was added 4-borono-2-chlorobenzoic acid (1.036 g, 5.17 mmol) (crude from 68106-008) and Potassium Orthophosphate (5.17 mL, 10.34 mmol). Bubbled argon through for 10 min. and then palladium tetrakis-(triphenylphosphine) (0.209 g, 0.181 mmol) was added. Kept bubbling argon for another 5 min., The reaction vessel was sealed and heated to 90°C for 4 h. Filtration, then washed with EtOAc. 1N HCl was added to pH ~ 2.0, and then extracted with EtOAc (3x). The combined organic layers were washed with base (1N NaOH, 3x), and then the base soln was acidified to Ph ~ 2.0, extracted with EtOAc (3x), dried (Na_2SO_4), concentrated.

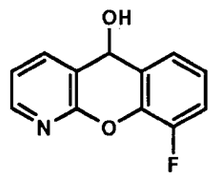
[00303] Repurified by above same sequence, i.e. dissolved in EtOAc, washed with 1N NaOH, and then acidified to PH ~ 2.0, extracted with EtOAc, dried (Na_2SO_4), and concentrated. MS (E+) m/z: 507 (M+H); LC retention time: 3.51 min.

PREPARATION 54



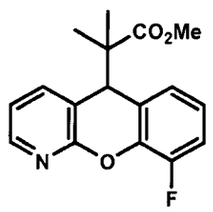
[00304] The title compound was prepared from the product of 53a in the same manner as described above for the preparation of the title compound of Preparation 53. MS (E+) m/z: 503.2 (M+H); LC retention time: 3.30 min.

PREPARATION 55



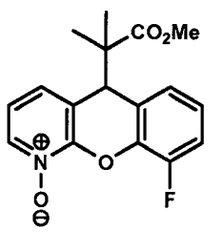
Step 1

[00305] The title compound (55a) was prepared from 9-fluoro-5*H*-chromeno[2,3-*b*]pyridine-5-one in the same manner as described above for the preparation of the title compound of Preparation 17a. 9-Fluoro-5*H*-chromeno[2,3-*b*]pyridine-5-one was prepared following the method of Villani *et al.* (J. Med. Chem. 1975, 18, 1-8), substituting phenol with 2-fluorophenol.



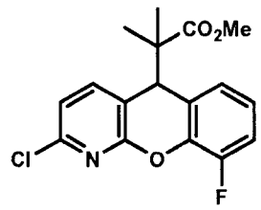
Step 2

[00306] The title compound (55b) was prepared from 55a in the same manner described above for the preparation of 17b from 17a. MS (E+) m/z: 302 (M+H); LC retention time: 2.96 min.



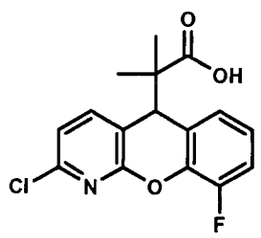
Step 3

[00307] The title compound (55c) was prepared from 55b in the same manner described above for the preparation of 17c from 17b. MS (E+) m/z: 318 (M+H); LC retention time: 2.13 min.



Step 4

[00308] The title compound (55d) was prepared from 55c in the same manner described above for the preparation of 17d from 17c. MS (E+) m/z: 336 (M+H); LC retention time: 3.26 min.



Step 5

[00309] The title compound (55e) was prepared from 55d in the same manner as described above for the preparation of the title compound of Preparation 17e from 17d. MS (E+) m/z: 322 (M+H); LC retention time: 3.11 min.

PREPARATION 56

[00310] The product of Preparation 55 (55e) was resolved into pure enantiomers (56a and 56b) by chiral supercritical fluid chromatography (SFC).

Preparative Conditions :

Preparative Column:	Chiralcel OJ-H (3×25cm, 5μm)
BPR pressure:	100 bars
Temperature:	35 °C
Flow rate:	70 mL/min
Mobile Phase:	CO_2/[IPA:ACN 1:1 w 0.1%TFA] (90/10)
Detector Wavelength:	212 nm
Separation Program:	Sequence injection

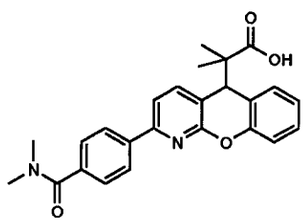
Injection:	0.25mL / (100.0 mg/mL) with cycle time 7.5 minutes
Sample preparation:	2g / 20 mL ACN/MeOH (1:1 v/v)

Analytical Conditions:

Analytical Column:	Chiralcel OJ-H (0.46×25cm, 5μm)
BPR pressure:	100 bars
Temperature:	35 °C
Flow rate:	2.0 mL/min
Mobile Phase:	CO_2/[IPA:ACN 1:1 w 0.1%TFA] (90/10)
Detector Wavelength:	212 nm
Retention Time (min):	RT_1: 7.43 RT2: 8.81

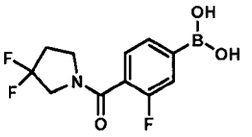
[00311] The first compound to elute under the preparative conditions (56a) also eluted with earlier retention time under the analytical conditions described above.

PREPARATION 57



[00312] A DMF (50 mL) solution of 17e (10367, page 107, Preparation 17) (1.45 g, 4.77 mmol), 4-(N,N-dimethylaminocarbonyl)phenyl boronic acid (Combi-Blocks Inc., 1.35 g, 1.5 eq), $Pd(Ph_3P)_4$ (0.67 g, 0.12 eq) and a 2 M solution of K_3PO_4 (12 mL, 5 eq) was degassed by vacuum-N_2 refill cycle twice then heated at 100 °C under N_2 for 5 h. After cooling to room temperature, the crude material was poured into 1 N HCl and extracted with ethyl acetate. The ethyl acetate phase was washed with water and brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated to give the expected product as a white needle crystal (1.59 g, 80% yield). MS (ES+) m/z: 417 (M+H); LC retention time: 3.79 min (Analytical HPLC Method D).

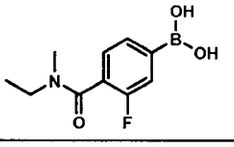
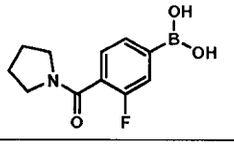
PREPARATION 58

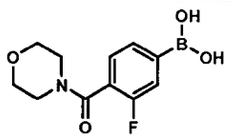
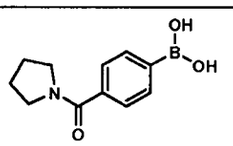
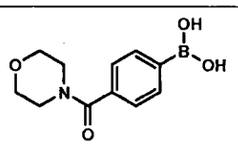


[00313] A DMF (6 mL) solution of 4-borono-2-fluorobenzoic acid (Combi-Bocks Inc., 1 g, 5.44 mmol), 3,3-difluoropyrrolidine hydrochloride salt (Matrix Scientific, 1 g, 1.3 eq), DIPEA (2.85 mL, 3 eq) and HATU (2.163 g, 1 eq) was stirred at room temperature for 1 h. The crude material was poured into 1 N HCl (16 mL) and extracted with ethyl acetate (40 mL). The aqueous phase was neutralized to pH 7 with solid NaOH then K_2CO_3, and extracted with ethyl acetate. The combined ethyl acetate extracts were dried over $MgSO_4$ and concentrated to give a thick brown oil. After addition of approximately equal volume of water, white needle crystals slowly precipitated out. The solid was collected by filtration and washed with small amount of ether to give the expected product (0.7811 g). The filtrate was purified by preparative reverse-phase HPLC (using Shimadzu 10A liquid chromatographs and Waters Sunfire S10 30 x 250 mm column) to give additional 0.5632 g of the expected product. Total yield was 1.3443 g (91%). MS (ES+) m/z: 274 (M+H); LC retention time: 2.68 min (Analytical HPLC Method D).

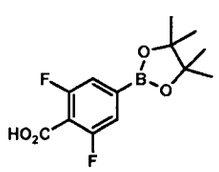
PREPARATIONS 59 TO 63

[00314] Using procedure analogous to Preparation 58, the following intermediates were prepared by couplings between commercially available amines and boronic acids.

Preparation No.	Structure
59	
60	

Preparation No.	Structure
61	
62	
63	

PREPARATION 64

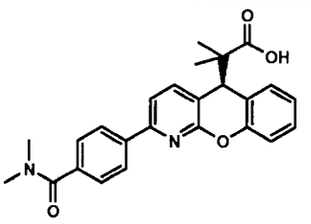
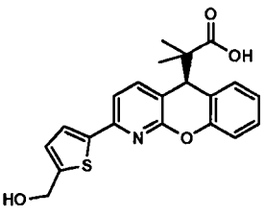
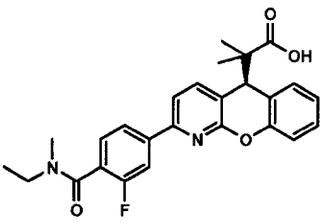
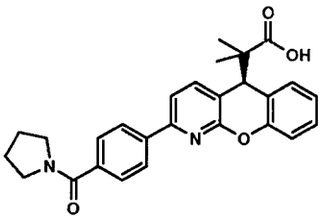
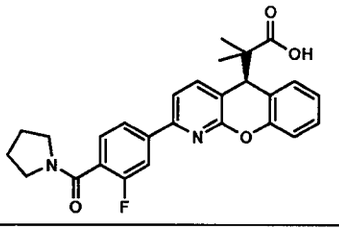
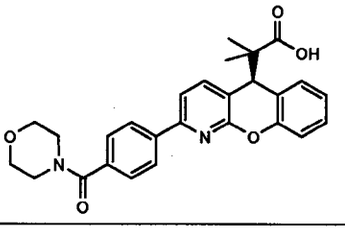


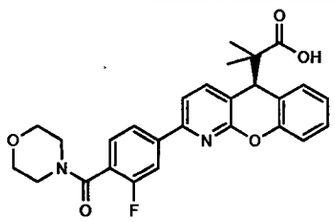
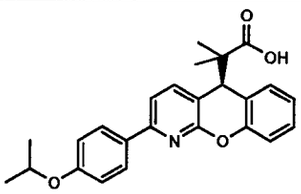
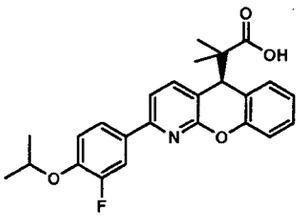
[00315] A dioxane (16.5 mL) solution of 4-bromo-2,6-difluorobenzoic acid (0.4 g, 1.6 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.5 g, 2.0 mmol), $PdCl_2$(dppf) (0.12 g, 0.17 mmol) and potassium acetate (0.49 g, 4.9 mmol) was placed in a sealed vial and degassed by vacuum-N_2 refill cycle twice. The mixture was heated to 80 °C for 21 h, cooled to room temperature and filtered through a short bed of silica gel. The filtrate was concentrated and purified by flash column chromatography (ISCO 12 g silica gel cartridge, 20-100% ethyl acetate-hexanes) to give the expected product as a brown oil (0.11 g, 19%). MS (ES-) m/z: 283 (M-H); LC retention time: 1.48 min (Analytical HPLC Method D).

PREPARATIONS 65 TO 73

[00316] Following procedure analogous to Preparation 57, the following intermediates were prepared by Suzuki couplings between boronic acids (commercially available or prepared in preparations 58-63 and 30b.

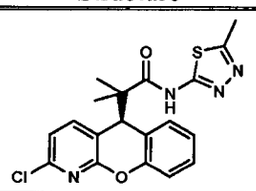
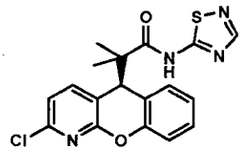
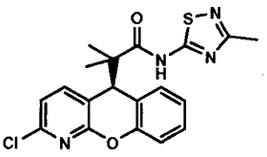
Preparation No.	Structure

Preparation No.	Structure
65	
66	
67	
68	
69	
70	

Preparation No.	Structure
71	
72	
73	

PREPARATIONS 74 TO 76

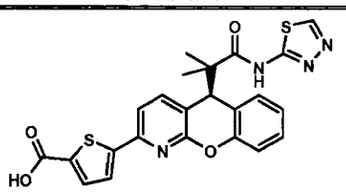
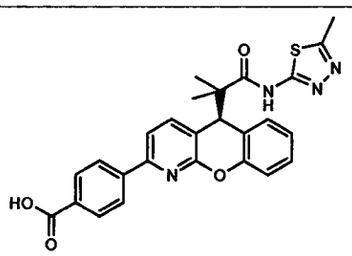
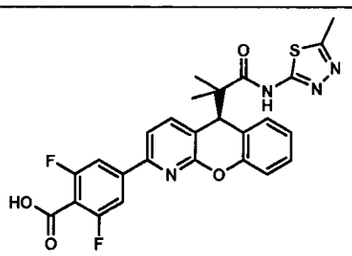
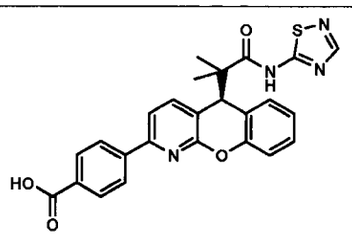
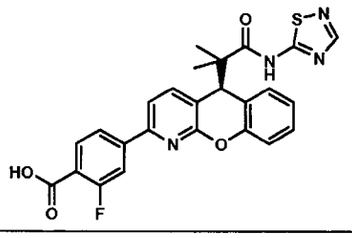
[00317] Following procedures analagous to the product of the first step of Preparation 53 (53a), the following intermediates were prepared by reaction between commercially available amino azoles and the 'S' enantiomer of Preparation (30b).

Preparation No.	Structure
74	
75	
76	

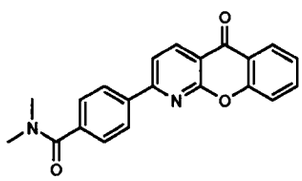
- 000182

PREPARATIONS 77 TO 81

[00318] Following procedure analogous to Preparation 57, the following intermediates were prepared by Suzuki couplings between boronic acids (commercially available or prepared in Preparations 58 to 64) and intermediates from Preparations 53a, 58 to 64.

Preparation No.	Structure
77	
78	
79	
80	
81	

PREPARATION 82



Step 1

[00319] A mixture of 4-acetylbenzoic acid (10.0 g, 60.9 mmol), 40% aqueous solution of dimethylamine (8.24 g, 73.1 mmol), EDC (14.0 g, 73.1 mmol), HOBT (11.2 g, 73.1 mmol) and DIEA (21.3 mL, 122 mmol) in CH_3CN (150 mL) was stirred at room temperature for 15 h and concentrated. The residue was dissolved in ethyl acetate (600 mL), washed with water (2x80 mL), brine (80 mL), dried ($MgSO_4$) and concentrated to provide 4-acetyl-N,N-dimethylbenzamide (9.80 g, 84%). MS (E+) m/z: 191 (M+H); HPLC retention time: 0.88 min (Analytical HPLC Method F).

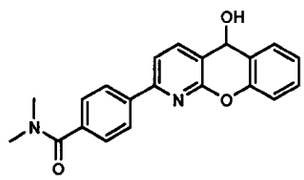
Step 2

[00320] A mixture of 4-acetyl-N,N-dimethylbenzamide (9.80 g, 51.2 mmol) and DMF dimethyl acetal (60 mL) was heated to reflux for 15 h, cooled to room temperature and concentrated. The residue was recrystallized from ethyl acetate to give (E)-4-(3-(dimethylamino)acryloyl)-N,N-dimethylbenzamide as a brown solid (8.80 g, 70%). MS (E+) m/z: 247 (M+H).

Step 3

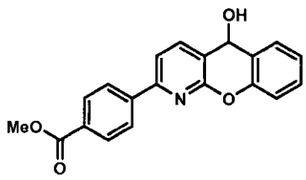
[00321] A mixture of (E)-4-(3-(dimethylamino)acryloyl)-N,N-dimethylbenzamide (4.0 g, 16.3 mmol), 3-(2-fluorophenyl)-3-oxopropanenitrile (3.44 g, 21.1 mmol) and acetic acid (4.65 mL, 81.0 mmol) in DMF (40 mL) was heated to 120 °C. After 48 h at 120 °C, the mixture was cooled to room temperature, diluted with ethyl acetate (600 mL), washed with saturated $NaHCO_3$ (80 mL), water (80 mL) and brine (80 mL), dried ($MgSO_4$) and concentrated. The residue was treated with MeOH and filtered to provide the expected product as brown solid (2.70 g, 48%). MS (E+) m/z: 345 (M+H); HPLC retention time: 1.67 min (Analytical HPLC Method F).

PREPARATION 83



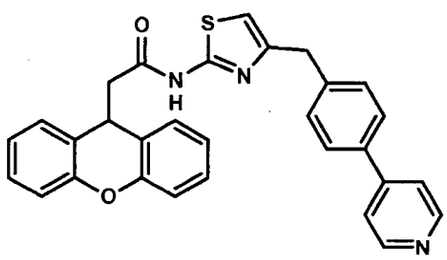
[00322] Sodium borohydride (1.48 g, 39.2 mmol) was added to a solution of the product from Preparation 82 (2.70 g, 7.84 mmol) in MeOH (160 mL) and dichloromethane (40 mL) at 0 °C. After 2 h at this temperature, the mixture was quenched with saturated $NaHCO_3$ (40 mL). The organic solvents were evaporated *in vacuo*. The aqueous residue was extracted with dichloromethane (3 x 100 mL). The combined organic extracts were washed with water (30 mL), brine (30 mL), dried ($MgSO_4$) and concentrated to provide the expected product (1.80 g, 66%). MS (ES+) m/z: 347 (M+H).

PREPARATION 84



[00323] Following procedure of Steps 2 and 3 of Preparation 82, and Preparation 83, the title compound was prepared from methyl 4-acetylbenzoate. MS (ES+) m/z: 334 (M+H).

EXAMPLE 1

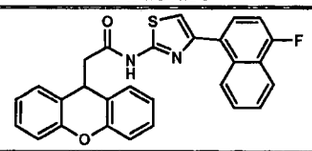
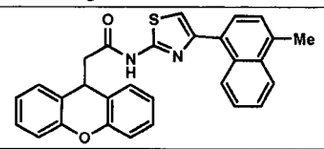
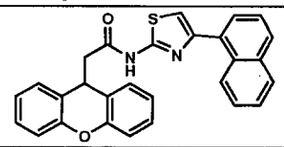


[00324] To a solution of the product of Preparation 9 (34 mg, 0.14 mmol) in DMF (1.2 mL) was sequentially added triethylamine (0.049 mL, 0.35 mmol), HOAt (23

mg, 0.17 mmol), EDC (33 mg, 0.17 mmol), and the product of Preparation 4 (42 mg, 0.16 mmol). The resulting mixture was heated at 85°C for 16h, filtered through a 0.45 micron syringe-tip filter, and purified by preparative HPLC. The product (30 mg, Y = 35%) was obtained as a white solid, TFA salt. MS (E+) m/z: 490 (M+H); LC retention time: 3.24 min.

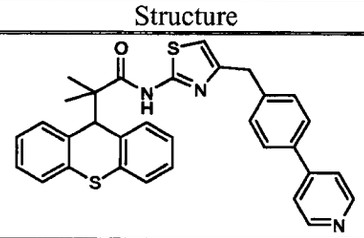
EXAMPLES 2 TO 4

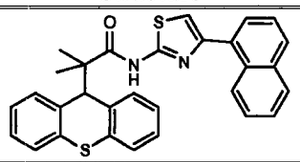
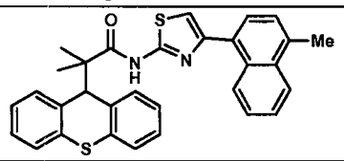
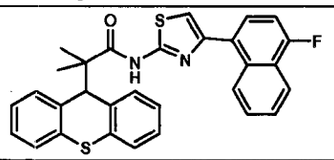
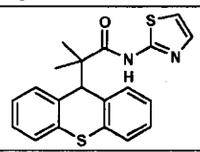
[00325] The following Examples 2 to 4 were prepared in the same manner as described for the preparation of the title compound of Example 1 using amines of Preparations 1 to 3.

Example No.	Structure	Rt (min)	M/z $(MH)^+$
2		3.872	467
3		3.935	463
4		3.785	449.00

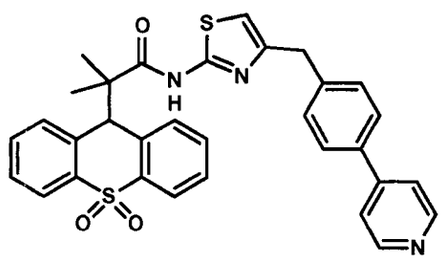
EXAMPLES 5 TO 9

[00326] The following Examples 5 to 9 were prepared in the same manner as described for the preparation of the title compound of Example 1 using the carboxylic acid product of Preparation 10 and amines of Preparations 1 to 4 and 2-aminothiazole.

Example No.	Structure	Rt (min)	M/z $(MH)^+$
5		3.48	534

Example No.	Structure	Rt (min)	M/z $(MH)^+$
6		3.25	493
7		3.88	507
8		3.37	511
9		3.87	365

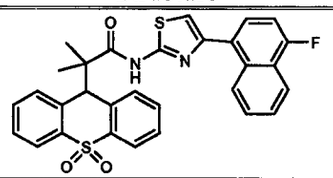
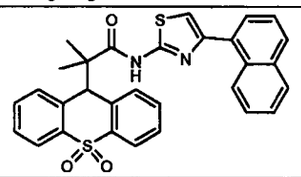
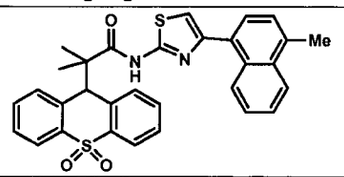
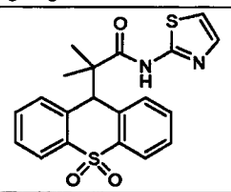
EXAMPLE 10



[00327] To a solution of the product of Preparation 11 (90 mg, 0.29 mmol) in acetonitrile (4 mL) were added HOAt (46 mg, 0.34 mmol) and EDC (66 mg, 0.34 mmol). The resulting solution was stirred at room temperature for 1 h, then treated with triethylamine (0.1 mL) and the product of Preparation 4 (84 mg, 0.31 mmol) and heated in a sealed pressure vessel at 140°C for 1.5 h. The solution was then concentrated and purified by HPLC. The product thus obtained was lyophilized from water/acetonitrile to give the title compound (45 mg) as a white solid TFA salt. MS (E+) m/z: 566 (M+H); LC retention time: 2.89 min.

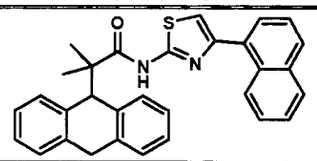
EXAMPLES 11 TO 14

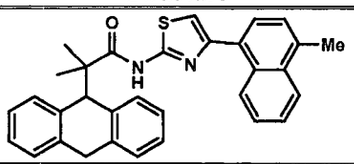
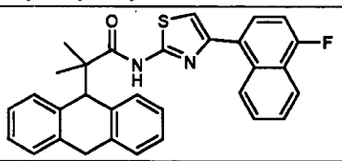
[00328] The following Examples 11 to 14 were prepared in the same manner as described for the preparation of the title compound of Example 10 using amines of Preparations 1 to 3 or 2-aminothiazole.

Example No.	Structure	Rt (min)	M/z $(MH)^+$
11		3.592	543
12		3.512	525
13		3.68	539
14		3.04	399

EXAMPLES 15 TO 17

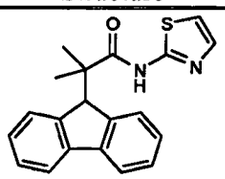
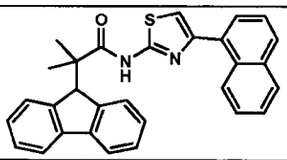
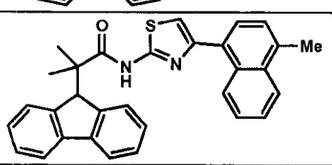
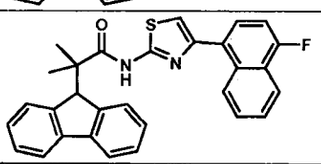
[00329] The following Examples 15 to 17 were prepared in the same manner as described for the preparation of the title compound of Example 10 using the product of Preparation 12 and amines of Preparations 1 to 3.

Example No.	Structure	Rt (min)	M/z $(MH)^+$
15		3.18	475

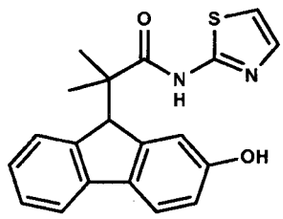
Example No.	Structure	Rt (min)	M/z $(MH)^+$
16		3.42	489
17		3.31	493

EXAMPLES 18 TO 21

[00330] The following Examples 18 to 21 were prepared in the same manner as described for the preparation of the title compound of Example 18 using the product of Preparation 50 amines of Preparations 1 to 3 or 2-aminothiazole.

Example No.	Structure	Rt (min)	M/z $(MH)^+$
18		4.11	335
19		3.18	461
20		3.41	475
21		3.30	479

EXAMPLE 22

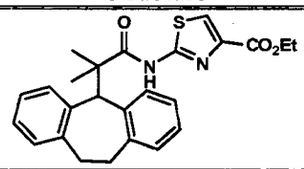
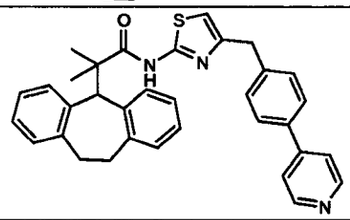
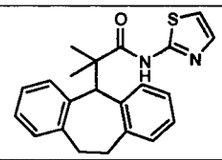


(+/-)

[00331] The title compound was prepared in the manner described for the preparation of the title compound of Example 10, using the product of Preparation 48b. MS (E+) m/z: 351 (M+H); LC retention time: 3.33 min.

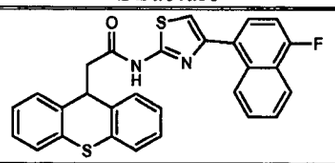
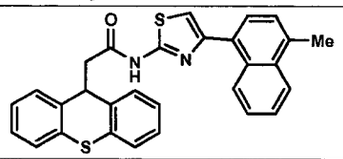
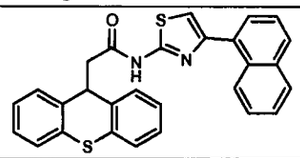
EXAMPLES 23 TO 25

[00332] The following Examples 23 to 25 were prepared in the same manner as described for the preparation of the title compound of Example 10 using the product of Preparation 49 and either the amine of Preparations 2 or 4, or 2-aminothiazole.

Example No.	Structure	Rt (min)	M/z $(MH)^+$
23		4.213	435.16
24		3.527	530.16
25		3.937	363.25

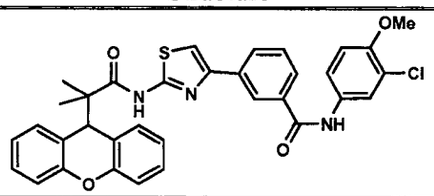
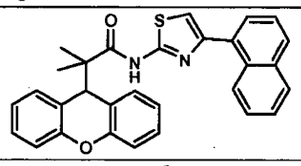
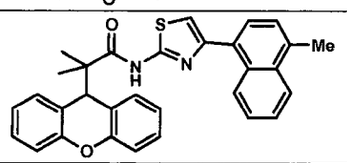
EXAMPLES 26 TO 28

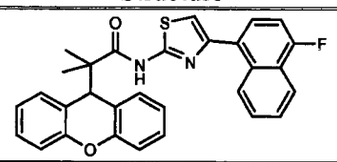
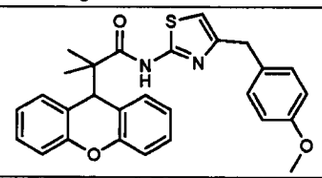
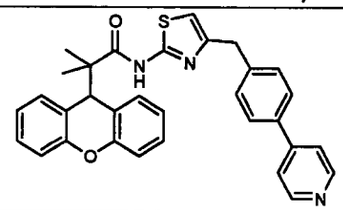
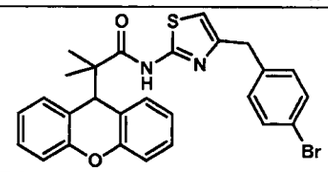
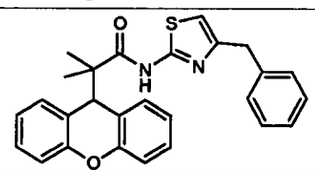
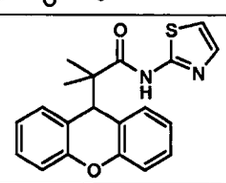
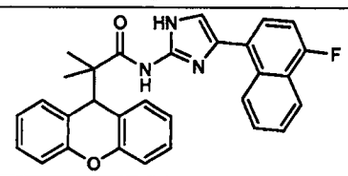
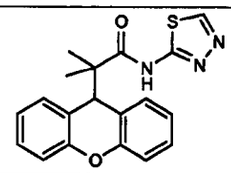
[00333] The following Examples 26 to 28 were prepared in the same manner as described for the preparation of the title compound of Example 10 using the product of Preparation 52 and amines of Preparations 1 to 3.

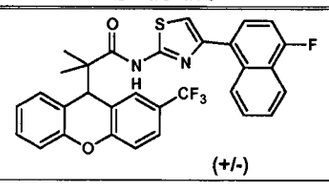
Example No.	Structure	Rt (min)	M/z $(MH)^+$
26		3.885	483
27		3.945	479
28		3.822	465

EXAMPLES 29 TO 40

[00334] The following Examples 29 to 40were prepared in the same manner as described for the preparation of the title compound of Example 10 using the carboxylic acids of Preparation 13 or Preparation 51 and either commercially available amines or amines of Preparations 1 to 7, 4b, or 14.

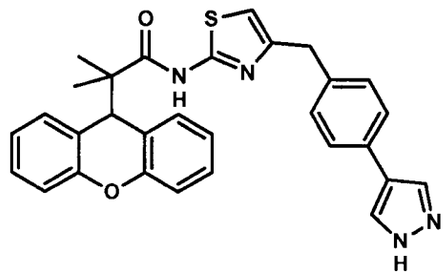
Example No.	Structure	Rt (min)	M/z $(MH)^+$
29		3.825	610.06
30		3.13	477
31		3.39	491

Example No.	Structure	Rt (min)	M/z $(MH)^+$
32		3.28	495
33		4.22	471
34		3.37	518
35		5.34	521
36		4.44	441
37		4.14	351
38		3.87	478
39		3.53	*

Example No.	Structure	Rt (min)	M/z $(MH)^+$
40		4.65	563

*observed m/e 350 (negative ion electrospray)

EXAMPLE 41

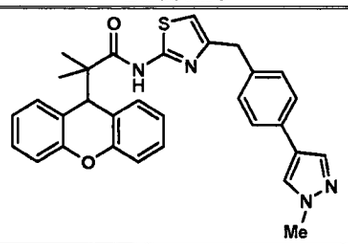
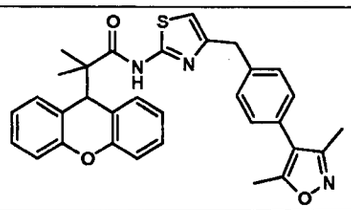


[00335] The title compound of Example 35 (25 mg, 0.048 mmol) and 4,4,5,5-tetramethyl-2-[1H-pyrazol-4-yl]-1,3,2-dioxaborolane (19 mg, 0.098 mmol) were dissolved in DMF (2 mL) in a microwave reaction vessel. Aqueous potassium phosphate (2.0M, 0.1 mL) was added and the mixture was purged with nitrogen gas for 5 min. Tetrakis (triphenylphosphine) palladium (21 mg, 0.018 mmol) was then added to the mixture which was heated in a Smith microwave reactor at 150°C for 30 min. The reaction mixture was then filtered over Celite, washing with ethyl acetate. The filtrate was partitioned between ethyl acetate and water, and the organic layer removed, dried over sodium sulfate, and concentrated. Purification of the crude material by preparative HPLC provided the title compound (18 mg, 75% yield). MS (E+) m/z: 507 (M+H); LC retention time: 4.66 min.

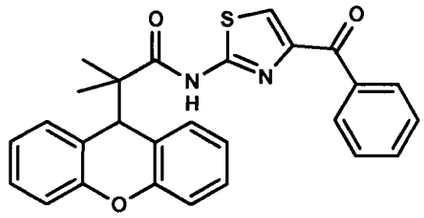
EXAMPLES 42 TO 43

[00336] The following Examples 42 and 43 were prepared in the same manner as the title compound of Example 41using commercially available boronates or boronic acids.

Example No.	Structure	Rt (min)	M/z $(MH)^+$

Example No.	Structure	Rt (min)	M/z $(MH)^+$
42		4.80	521
43		4.68	536

EXAMPLE 44



(a) To a solution of commercially available 1-phenyl-1,2-propanedione (3.3 g, 27.3 mmol) in 30 mL of was added a solution of bromine (34.7 g, 217 mmol) in 5 mL of $CHCl_3$ dropwise. The reaction was heated at reflux for 12 hr. The reaction was diluted with water and extracted 2 x $CHCl_3$. The $CHCl_3$ extracts were dried over $MgSO_4$, filtered, and concentrated by rotary evaporator to give 5.0 g (100%) of a dark solid 45a. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.03 (d, 2H), 7.68 (t, 1H), 7.53 (dd, 2H), 4.4 (s, 2H).

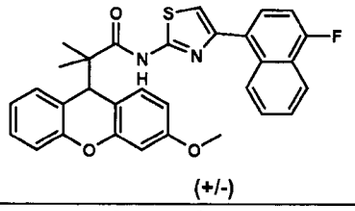
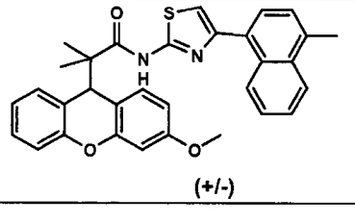
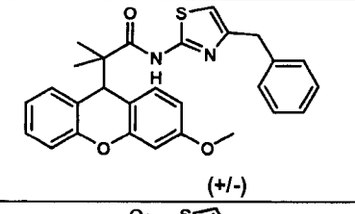
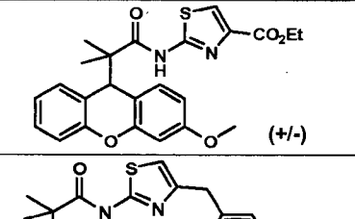
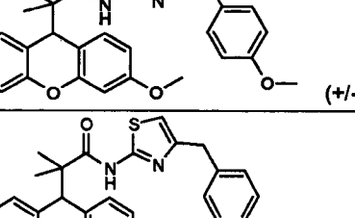
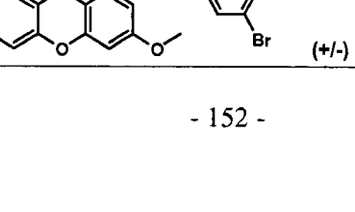
(b) To a solution of 45a (1.5 g, 6.6 mmol) in 25 mL of EtOH was added thiourea (0.55 g, 7.2 mmol) all at once. The reaction was heated at reflux for 4 hr. The reaction was diluted with water and extracted 2 x EtOAC. The EtOAc extracts were dried over $MgSO_4$, filtered, and concentrated by rotary evaporator to give 1.28 g (89%) of 46b. MS found: (M+H)+ = 205.

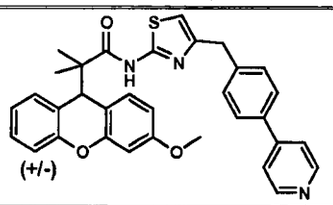
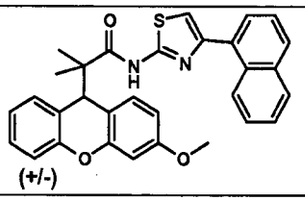
(c) The title compound was prepared in the same manner as described for the preparation of the title compound of Example 10 using the carboxylic acid of

Preparation 12 and the amine of 45b. MS (E+) m/z: 455 (M+H); LC retention time: 4.79 min.

EXAMPLES 45 TO 52

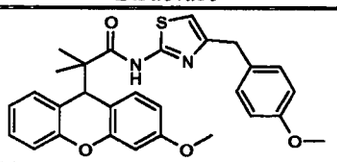
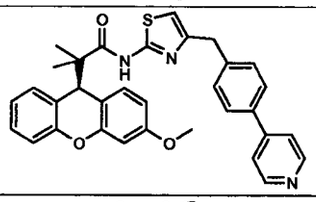
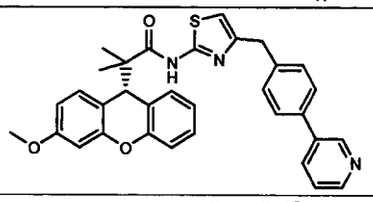
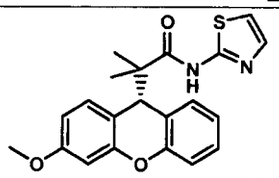
[00337] The following Examples 45 to 52 were prepared in the same manner as described for the preparation of the title compound of Example 10 using the carboxylic acid of Preparation 15 and either commercially available amines or amines of Preparations 1 to 4, 7, 8, or 4b.

Example No.	Structure	Rt (min)	M/z $(MH)^+$
45	 (+/-)	4.57	525
46	 (+/-)	4.70	521
47	 (+/-)	4.25	472
48	 (+/-)	4.02	453
49	 (+/-)	4.22	501
50	 (+/-)	4.59	549, 551

Example No.	Structure	Rt (min)	M/z $(MH)^+$
51		3.60	548
52		4.43	507

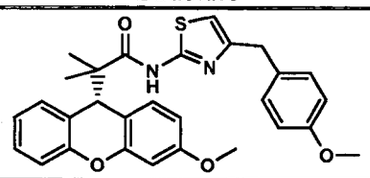
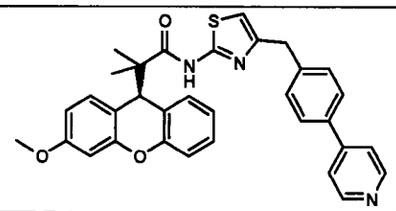
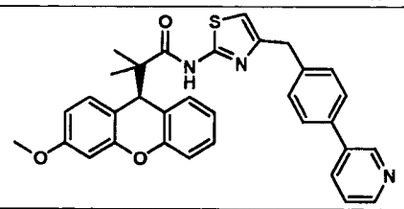
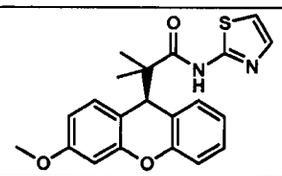
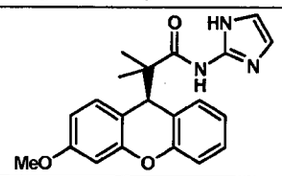
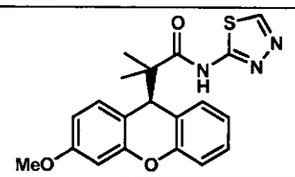
EXAMPLES 53 TO 56

[00338] The following Examples 53 to 56 were prepared from the R-enantiomer carboxylic acid of Preparation 16 and 2-amino thiazole or amines of Preparations 8, 4, and 5 in the same manner as described for the preparation of the title compounds of Examples 45 to 52.

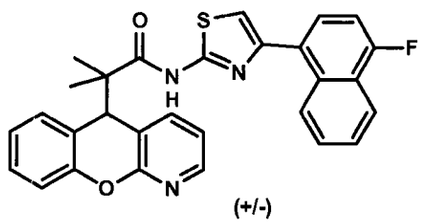
Example No.	Structure	Rt (min)	M/z $(MH)^+$
53		4.23	501
54		3.60	548
55		3.83	548.3
56		3.82	381

EXAMPLES 57 TO 62

[00339] The following Examples 57 to 62 were prepared from the S-enantiomer carboxylic acid of Preparation 16 and amines of Preparations 4, 5, and 8 or commercially available amines in the same manner as described for the preparation of the title compounds of Examples 45 to 52.

Example No.	Structure	Rt (min)	M/z $(MH)^+$
57		4.23	501
58		3.59	548
59		3.83	548
60		3.81	381
61		2.79	364
62		3.58	382

EXAMPLE 63



Step 1

[00340] To a solution of the product of Preparation 17b (1.0 g, 3.72 mmol) in methanol (30 mL) and THF (15 mL) was added a 4N aqueous solution of potassium hydroxide (9.3 mL). The resulting mixture was heated at 80°C for 16 h, then acidified to about pH 2.0 with the dropwise addition of concentrated HCl. The mixture was extracted with ethyl acetate. The organic layer removed, dried over sodium sulfate, then concentrated to give the carboxylic acid 65a as a solid (990 mg, 99%). MS (E+) m/z: 270 (M+H); LC retention time: 2.84 min.

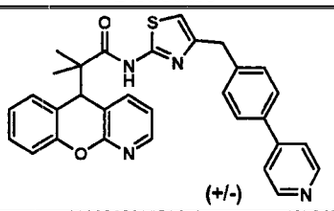
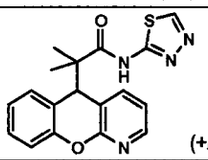
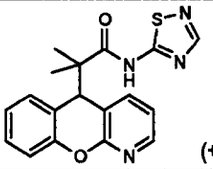
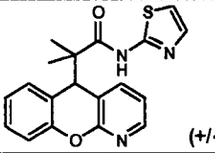
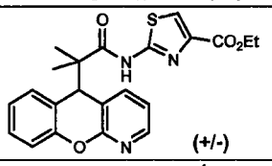
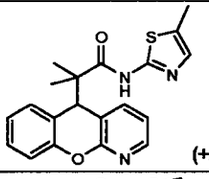
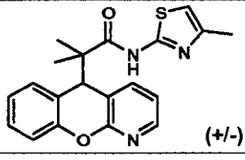
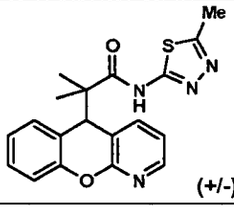
Step 2

[00341] A mixture of the product of Step 1 (20 mg, 0.052 mmol), triethylamine (0.022 mL, 0.16 mmol), HOBT hydrate (8.4 mg, 0.062 mmol) and EDC (12.0 mg, 0.062 mmol) in acetonitrile (0.6 mL) was heated for 4 h at 80 °C. Purification by preparative HPLC provided the product, which was lyopholized to give a colorless solid. MS (E+) m/z: 496 (M+H); LC retention time: 4.17 min.

EXAMPLES 64 TO 71

[00342] The following Examples 64 to 71 were prepared either in the manner described above for the preparation of the title compound of Example 63 or in the manner described for the preparation of the title compounds of Examples 45 to 52 using the carboxylic acid of Example 63, Step 1, and either commercially available amines or amines prepared as described in the Preparations section.

Example No.	Structure	Rt (min)	M/z $(MH)^+$

Example No.	Structure	Rt (min)	M/z $(MH)^+$
64	 (+/-)	2.99	519
65	 (+/-)	2.81	353
66	 (+/-)	3.07	353
67	 (+/-)	3.11	352
68	 (+/-)	3.50	424
69	 (+/-)	3.30	366
70	 (+/-)	3.26	366
71	 (+/-)	3.02	367

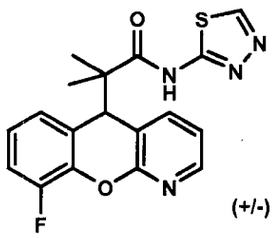
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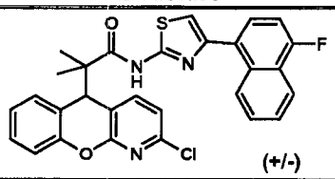
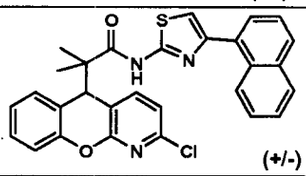
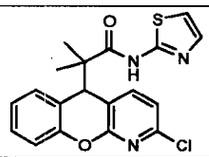
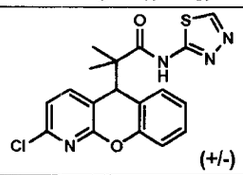
EXAMPLE 72



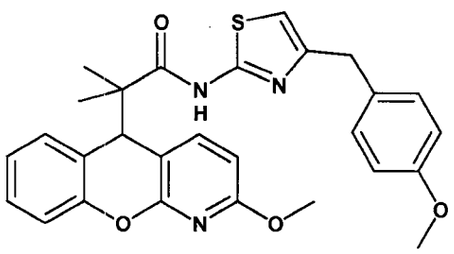
[00343] The title compound was prepared from the title compound of Preparation 55b in the same manner described above for the preparation of Examples 63 to 71. MS (E+) m/z: 371 (M+H); LC retention time: 2.51 min.

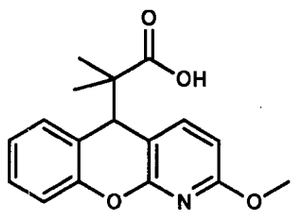
EXAMPLES 73 TO 76

[00344] The following Examples 73 to 76 were prepared in the same manner described for the preparation of the title compounds of Examples 45 to 52 from the product of Preparation 17e and amines obtained from commercial sources or the preparations described above.

Example No.	Structure	Rt (min)	M/z $(MH)^+$
73		4.31	530
74		4.23	512
75		3.48	386
76		3.37	387

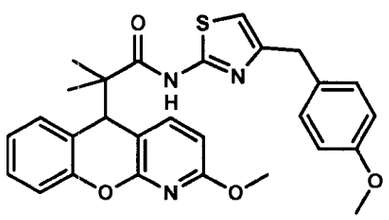
EXAMPLE 77





Step 1

[00345] A mixture of the title compound of Preparation 17e (150 mg, 0.50 mmol) in methanol (3 mL) and sodium methoxide in methanol (25% w/w, 1.23 mL) was heated by microwave at 140°C for 40 min, then acidified with the addition of concentrated HCl. The resulting suspension was partitioned between dichloromethane and water, and the organic layer removed, dried over sodium sulfate, and concentrated to give the product of Step 1 (120 mg, 80%), which was used in the next step with no further purification. LC retention time: 3.23 min.

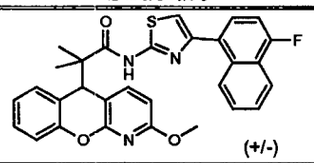
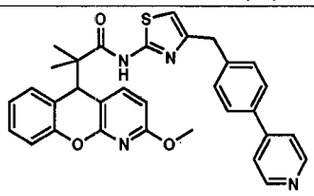
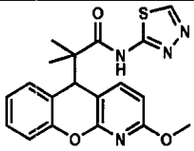


Step 2

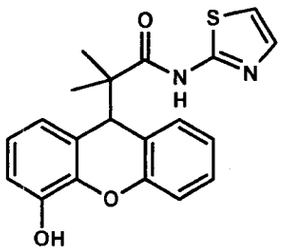
[00346] The title compound was prepared from the product of Step 1 and the amine of Preparation 8 in the same manner described for the preparation of the title compounds of 47 to 54. MS (E+) m/z: 502 (M+H); LC retention time: 4.06 min.

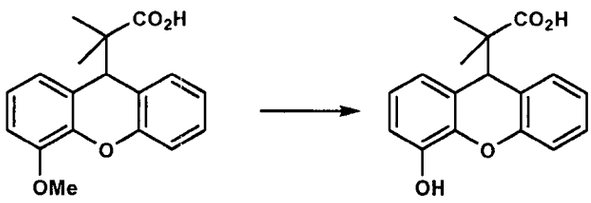
EXAMPLES 78 TO 80

[00347] The following Examples 78 to 80 were prepared in the manner described above for the preparation of the title compound of Example 77, replacing the amines of Preparation 1 and Preparation 4 for the amine of Preparation 8 or 2-amino-1,3,4-thiadiazole.

Example No.	Structure	Rt (min)	M/z $(MH)^+$
78		4.29	526
79		3.20	549
80		3.16	383

EXAMPLE 81

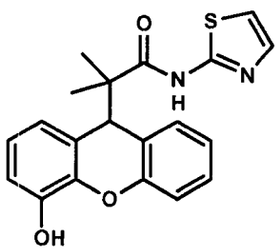




80a

Step 1

[00348] A mixture of the acid 18e (50 mg, 0.17 mmol), thiophenol (0.019 mL, 0.18 mmol), and potassium carbonate (25 mg, 0.18 mmol) in 1-methyl-2-pyrrolidinone (NMP) (1.5 mL) was heated by microwave at 205°C for 70 min. Another portion of thiophenol (0.01 mL) and potassium carbonate (12 mg) was added, and the mixture was heated by microwave another 30 min at 205°C. The reaction mixture was then partitioned between ethyl acetate and 0.5N HCl. The organic layer was removed and dried over sodium sulfate, concentrated, and purified by preparative HPLC to give the product of Step 1 (80a) as an amorphous solid (32 mg, 66%). MS (ES-) m/z: 283 (M-H); LC retention time: 3.02 min.



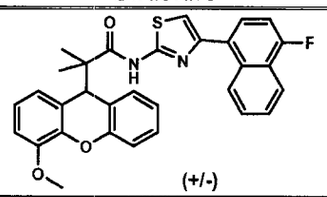
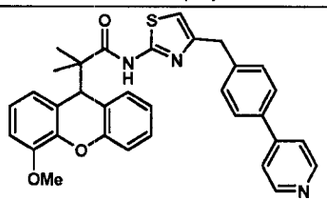
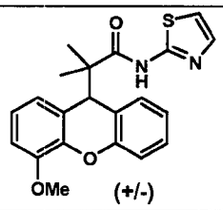
Step 2

[00349] A solution of the product of Step 1 (19 mg, 0.07 mmol), triethylamine (0.024 mL, 0.175 mmol), and HOAt (11 mg, 0.08 mmol) in acetonitrile (1 mL) was stirred at 65°C for 35 min. 2-Aminothiazole (8 mg, 0.077 mmol) was then added to the reaction mixture, which was heated at 140 °C for 1 h. Purification of the reaction mixture by preparative HPLC gave the title compound (11 mg). MS (ES+) m/z: 367 (M+H); LC retention time: 3.26 min.

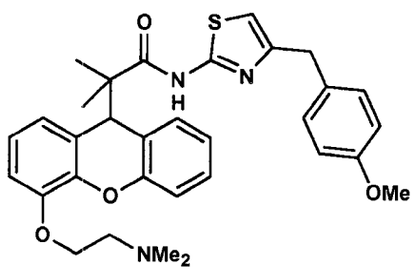
EXAMPLES 82 TO 84

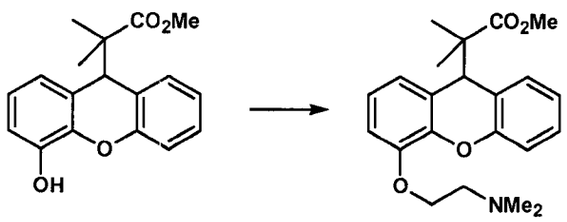
[00350] The following Examples 82 to 84 were prepared from 18e in the same manner described above for the preparations of the title compounds of Examples 76, 79 and 81.

Example No.	Structure	Rt (min)	M/z $(MH)^+$

Example No.	Structure	Rt (min)	M/z $(MH)^+$
82	 (+/-)	4.35	525
83	 (+/-)	3.38	548
84	 (+/-)	3.50	NA

EXAMPLE 85

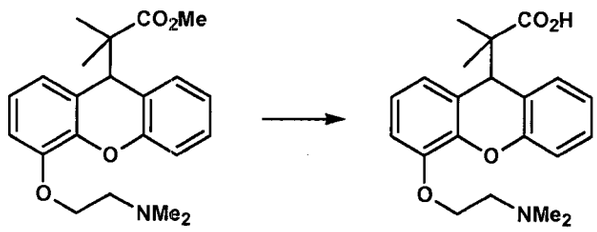




Step 1

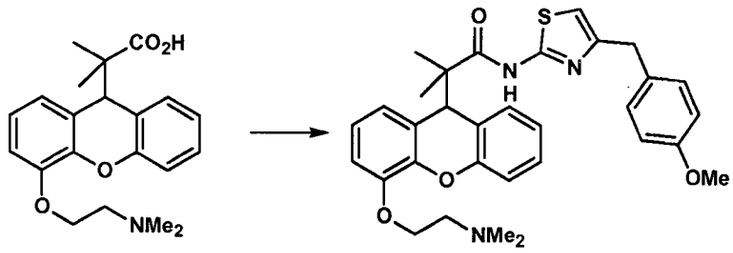
[00351] To a solution of the title compound of Preparation 18c (32 mg, 0.11 mmol) in DMF (1.1 mL) was added 2-(dimethylamino)ethyl chloride hydrochloride (17 mg, 0.12 mmol), followed by sodium hydride (60 %w/w in mineral oil, 9mg). The mixture was heated at 80 C for 35 min. The solvent was then removed *in vacuo*, and

the crude material used directly in the next step with no further purification. MS (ES+) m/z: 370 (M+H); LC retention time: 2.54 min.



Step 2

[00352] A mixture of the product of Step 1 (0.11 mmol), methanol (2 mL), THF (1 mL), and 4N aqueous KOH (1.1 mL) was heated at 80 C for 14 h. The reaction mixture was then acidified with concentrated HCl, then concentrated and purified by preparative HPLC to give the product of Step 2 (12 mg). MS (ES+) m/z: 356 (M+H); LC retention time: 2.33 min.



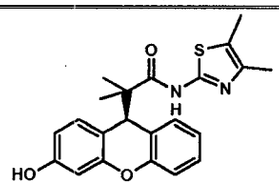
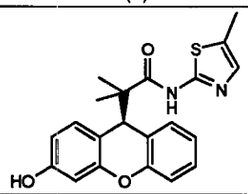
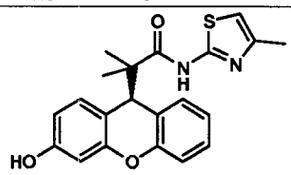
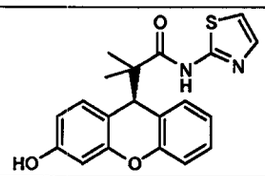
Step 3

[00353] The title compound was prepared from the product of Step 2 in the same manner as described for the preparation of the title compound of Example 57. MS (ES+) m/z: 558 (M+H); LC retention time: 3.27 min.

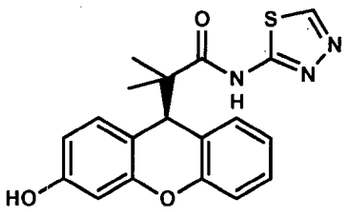
EXAMPLES 86 TO 89

[00354] The following Examples 86 to 89 were prepared from the title compound of Preparation 19 and commercially available amines in the same manner as described above for the preparation of the title compound of Example 81.

Example No.	Structure	Rt (min)	M/z $(MH)^+$

Example No.	Structure	Rt (min)	M/z $(MH)^+$
86	 (S)	3.59	395
87		3.47	379
88		3.45	379
89		3.33	365

EXAMPLE 90

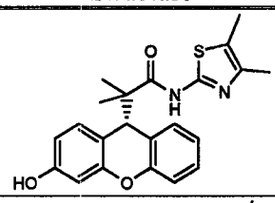
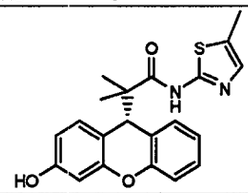
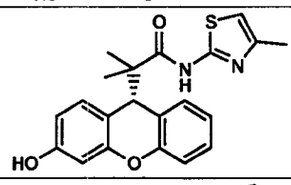
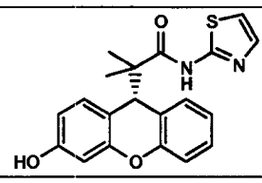


[00355] To a solution of the product of Preparation 19 (30 mg, 0.11 mmol) in dichloromethane (0.5 mL) were added sequentially pyridine (0.019 mL, 0.23 mmol), 4-dimethylaminopyridine (1 mg, catalytic), and chlorotrimethylsilane (0.029 mL, 0.23 mmol). After 4.5 h at room temperature, N,N-dimethylformamide (0.01 mL) followed by oxalyl chloride (0.01 mL, 0.11 mmol) were added to the reaction mixture. After an additional 1.5 h at room temperature, pyridine (0.044 mL, 0.55 mmol) was added to the reaction mixture, followed by 2-amino-1,3,4-thiadiazole (12 mg, 0.12 mmol). The reaction was allowed to sit at room temperature 10 min, then concentrated and purified by preparative thin layer chromatography (0.5 mm silica,

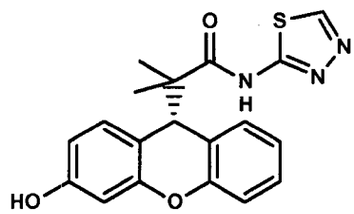
100 cm x 200 cm, 7% methanol in dichloromethane) to give the title compound (15 mg, 37%) as a colorless solid. MS (ES+) m/z: 368 (M+H); LC retention time: 3.10 min.

EXAMPLES 91 TO 94

[00356] The following Examples 90 to 93 were prepared from the title compound of Preparation 20 and commercially available amines in the same manner as described above for the preparation of the title compounds of Example 85 to 88.

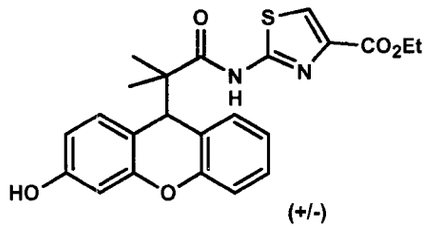
Example No.	Structure	Rt (min)	M/z $(MH)^+$
91		3.60	395
92		3.46	379
93		3.45	379
94		3.33	365

EXAMPLE 95



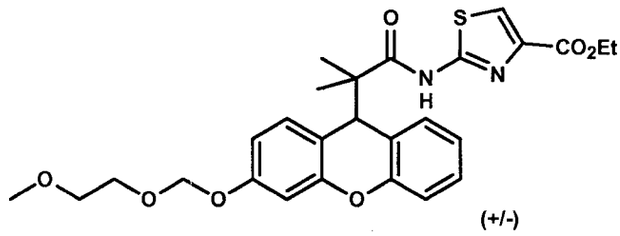
[00357] The title compound was prepared from the product of Preparation 20 in the same manner described above for the preparation of the title compound of Example 90. MS (ES+) m/z: 368 (M+H); LC retention time: 3.10 min.

EXAMPLE 96



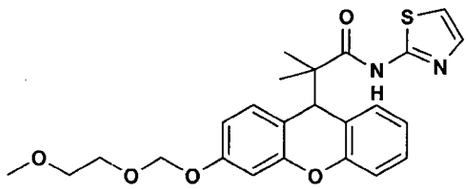
[00358] The title compound was prepared from the product of Preparation 21b in the same manner described above for the preparation of the title compound of Example 81, Step 1, substituting ethyl 2-aminothiazole-4-carboxylate for 2-aminothiazole. MS (ES+) m/z: 439 (M+H); LC retention time: 3.65 min.

EXAMPLE 97



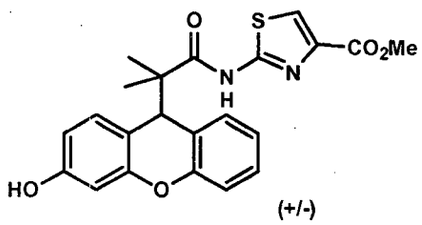
[00359] A mixture of the product of Preparation 22b (109 mg, 0.29 mmol), triethylamine (0.101 mL, 0.73 mmol), EDC (67 mg, 0.35 mmol), and HOAt (48 mg, 0.35 mmol) in acetonitrile (3.0 mL) stirred 12 h at room temperature. Ethyl 2-aminothiazole-4-carboxylate (55 mg, 0.32 mmol) was added to the mixture, which was heated in a sealed tube at 140°C for 1.5 h. The reaction mixture was concentrated *in vacuo* and the residue partitioned between ethyl acetate (30 mL) and 1N HCl (20 mL). The organic layer was washed sequentially with saturated aqueous sodium bicarbonate and brine, then dried over sodium sulfate and concentrated. Flash column chromatography (silica, 50% ethyl acetate in hexanes) provided the title compound (94 mg, 62% yield) as a foam. MS (ES+) m/z: 527 (M+H); LC retention time: 4.00 min.

EXAMPLE 98



[00360] The title compound was prepared from the product of Preparation 22b in the same manner as described above for the preparation of the title compound of Example 97, substituting 2-amino thiazole for ethyl 2-aminothiazole-4-carboxylate. MS (ES+) m/z: 455 (M+H); LC retention time: 3.68 min.

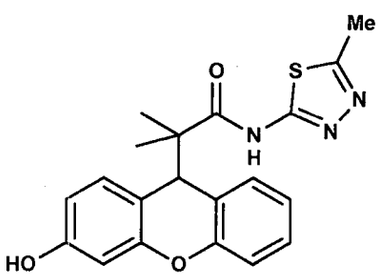
EXAMPLE 99

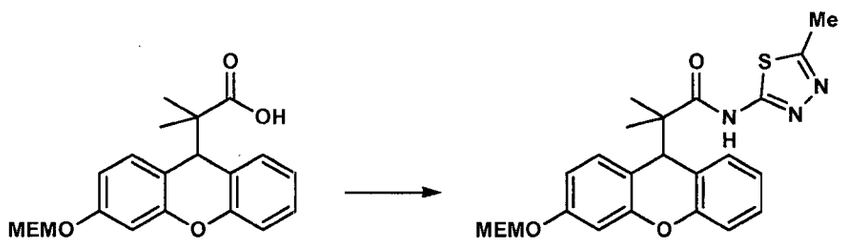


(+/-)

[00361] To a solution of the title compound of Example 97 (42 mg, 0.08 mmol) in dry methanol (0.8 mL) was added camphor sulfonic acid (5.5 mg, 0.024 mmol). The solution was heated at 70°C for 24 h, then concentrated *in vacuo*. The residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic layer was washed with brine, dried over sodium sulfate, then concentrated to give a sticky solid (22 mg, 65% yield). MS (ES+) m/z: 425 (M+H); LC retention time: 3.47 min.

EXAMPLE 100

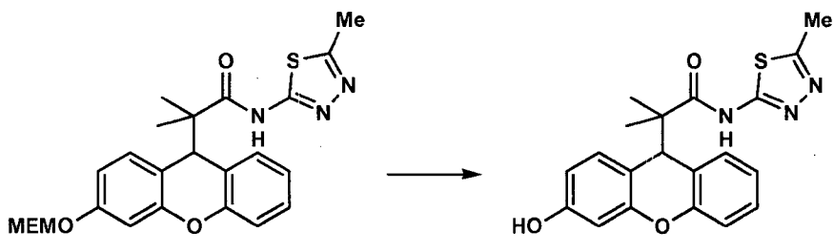




(MEMO = methoxyethoxymethoxy)

Step 1

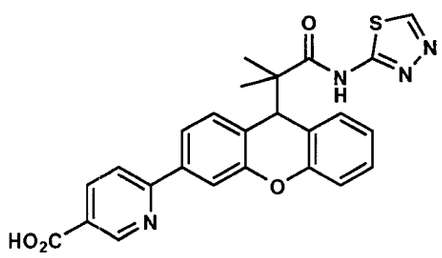
[00362] The product 100a was prepared in the same manner as described above for the preparation of the title compound of Example 97, substituting 5-methyl-2-amino-1,3,4-thiadiazole for ethyl 2-aminothiazole-4-carboxylate. MS (ES+) m/z: 470 (M+H); LC retention time: 3.82 min.

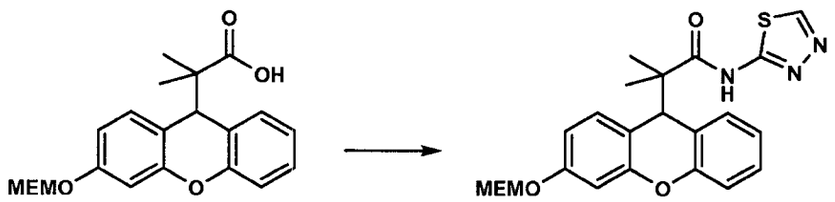


Step 2

[00363] The title compound was prepared in the same manner as described above for the preparation of the title compound of Example 99. MS (ES+) m/z: 382 (M+H); LC retention time: 3.32 min.

EXAMPLE 101

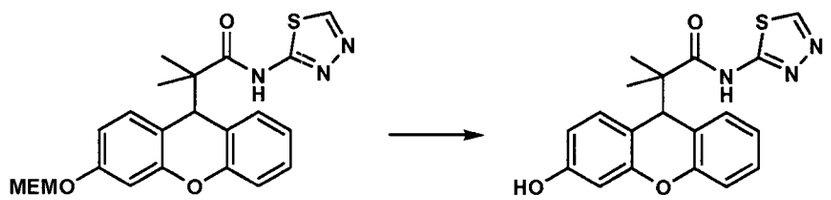




(MEMO = methoxyethoxymethoxy)

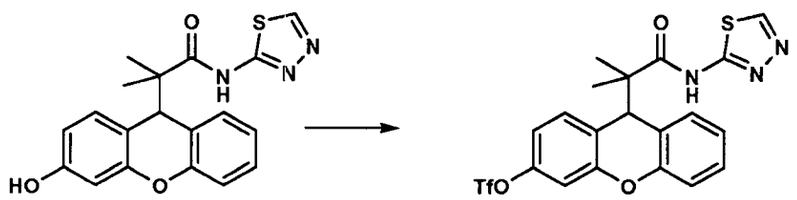
Step 1

[00364] The product of Step 1 was prepared in the manner described above for the preparation of the product of Step 1 of Example 100.



Step 2

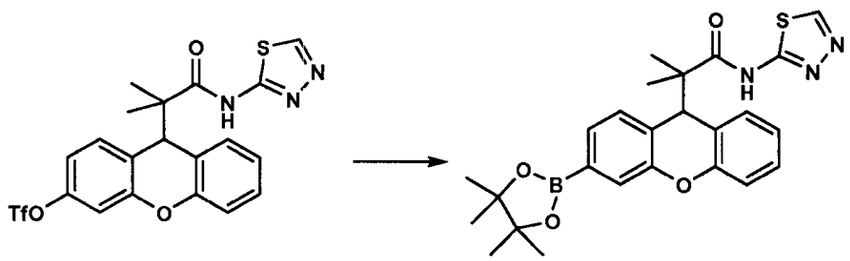
[00365] The product of Step 2 was prepared in the manner described above for the preparation of the product of Step 2 of Example 100.



Step 3

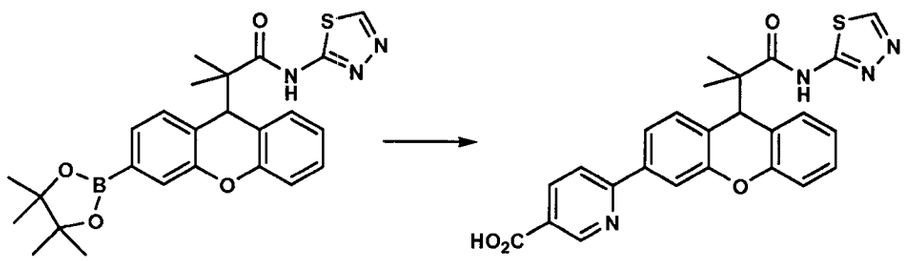
[00366] To a solution of the product of Step 2 (200 mg, 0.545 mmol) in dichloromethane (5 mL) at 0 °C under nitrogen was added triethylamine (0.182 mL, 1.31 mmol) followed by 1,1,1-trifluoro-*N*-phenyl-*N*-(trifluoromethylsulfonyl)methanesulfonamide (292 mg, 0.817 mmol). The reaction mixture was allowed to stir at 0 °C for 2.5 h, then partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried over sodium sulfate and concentrated. Purification by flash column chromatography (40 g silica, 50% ethyl acetate in hexanes) afforded the product of

Step 3 (150 mg, Y = 55%) as a white solid. MS (ES+) m/z: 500 (M+H); LC retention time: 3.99 min.



Step 4

[00367] To a solution of the product of Step 3 (160 mg, 0.32 mmol) in 1,4-dioxane (3 mL) were sequentially added 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (24 mg, 0.03 mmol), bis(pinacolato)diboron (120 mg, 0.47 mmol), and potassium acetate (96 mg, 0.98 mmol). A stream of nitrogen gas was blown through the reaction mixture for 15 min, which was then heated at 80 °C for 5 h. The reaction mixture was concentrated *in vacuo*, and the residue purified by flash column chromatography (12 g silica, 20% to 50% ethyl acetate in hexanes) to provide the product of Step 4 (120 mg, Y = 79%) as a yellow oil. MS (ES+) m/z: 478 (M+H); LC retention time: 4.07 min.

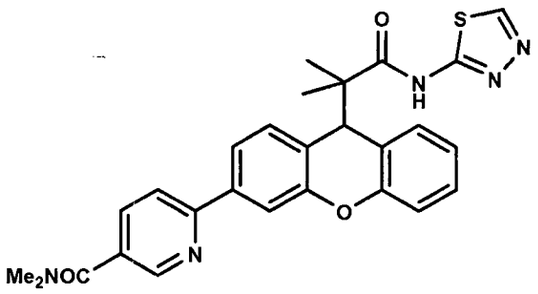


Step 5

[00368] To a solution of 6-chloronicotinic acid (7.4 mg, 0.047 mmol) in DMF (1 mL) was added the product of Step 4 (15 mg, 0.031 mmol), followed by aqueous potassium phosphate (2.0 M, 0.1 mL) and tetrakis(triphenylphophine)palladium(0) (10 mg, 0.009 mmol). A stream of nitrogen gas was bubbled through the mixture for 15 min, which was then heated at 100 °C for 2 h. The reaction mixture was purified by preparative HPLC to give the title compound as a TFA salt which was lyophilized

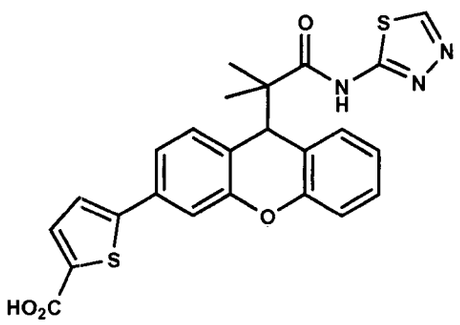
from acetonitrile/water to give a white powder (3.1 mg, Y =21%). MS (ES+) m/z: 473 (M+H); LC retention time: 3.55 min.

EXAMPLE 102



[00369] A mixture of the title compound of Example 101 (10 mg, 0.021 mmol), HOBT monohydrate (4.3 mg, 0.032 mmol), EDCI (6.12 mg, 0.032 mmol), triethylamine (0.1 mL) and dimethylamine hydrochloride (3.43 mg, 0.042 mmol) in acetonitrile (1 mL) was heated at 80 °C for 12 h. The reaction mixture was then purified by preparative HPLC to give the title compound, which was lyophilized from acetonitrile/water to give a white powder (4 mg, Y = 38%). MS (ES+) m/z: 500 (M+H); LC retention time: 3.26 min.

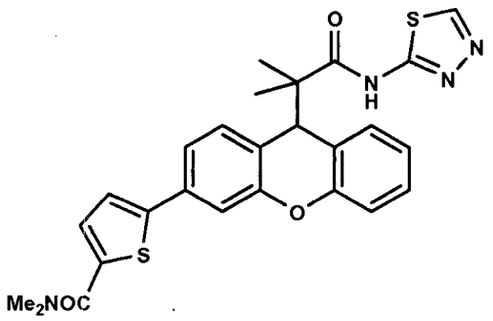
EXAMPLE 103



[00370] To a solution of the product of Example 101, Step 4 (45 mg, 0.094 mmol) and 5-bromothiophene-2-carboxylic acid (38 mg, 0.188 mmol) in DMF (9 mL) and water (0.1 mL) were added tetrakis(triphenylphophine)palladium(0) (10 mg, 0.009 mmol) and barium hydroxide hexahydrate (89 mg, 0.28 mmol). Nitrogen gas was bubbled through the mixture for 10 min, which was then heated at 100 °C for 14 h.

Purification by preparative HPLC provided the title compound (3 mg, Y = 7%) as a white powder. MS (ES+) m/z: 478 (M+H); LC retention time: 3.75min.

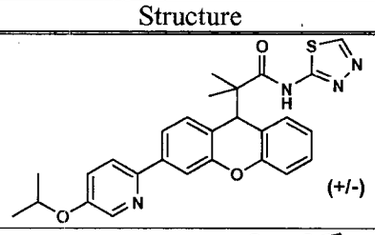
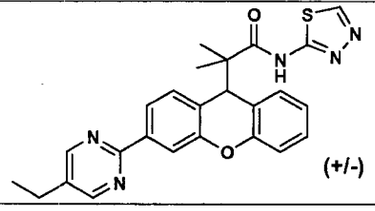
EXAMPLE 104

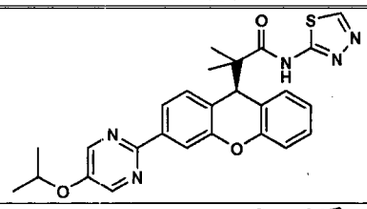
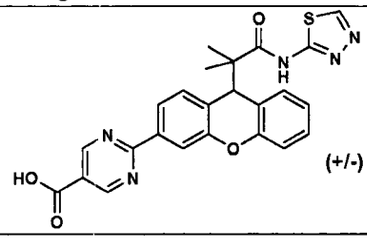


[00371] The title compound was prepared from the title compound of Example 103 in the manner described for the preparation of the title compound of Example 102 from Example 101. MS (ES+) m/z: 505 (M+H); LC retention time: 3.62 min.

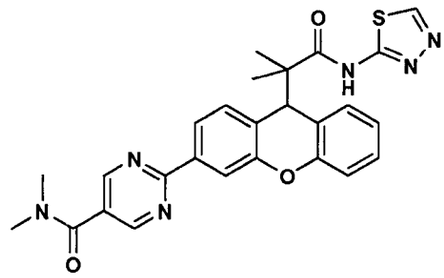
EXAMPLES 105 TO 108

[00372] The following Examples 105 to 108 were prepared in the same manner described above for the preparation of the title compound of Example 103 using the product of Example 101, step 4 or the title compound of Example 90 and commercially available halides in place of bromothiophene-2-carboxylic acid.

Example No.	Structure	Rt (min)	M/z $(MH)^+$
105		3.71	487
106		3.85	458

Example No.	Structure	Rt (min)	M/z $(MH)^+$
107		3.74	487
108		3.75	474

EXAMPLE 109

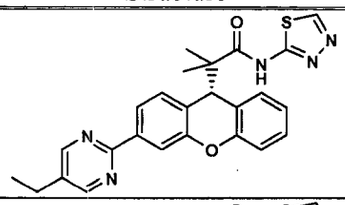
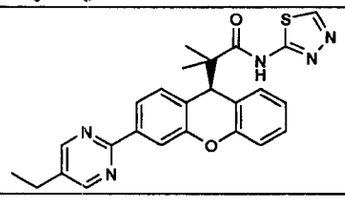


[00373] The title compound was prepared from the title compound of Example 108 in the same manner described above for the preparation of the title compound of Example 104 from the title compound of Example 103. MS (ES+) m/z: 501 (M+H); LC retention time: 3.42 min.

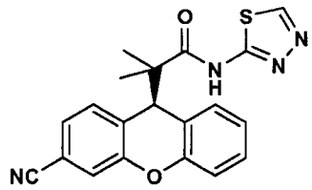
EXAMPLES 110 TO 111

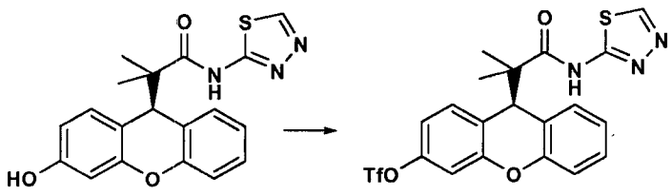
[00374] The following Examples 110 to 111 were prepared in the same manner described above for the preparation of the title compound of Example 106 using the title compounds of Example 95 and Example 90.

Example No.	Structure	Rt (min)	M/z $(MH)^+$

Example No.	Structure	Rt (min)	M/z $(MH)^+$
110		3.92	458
111		3.92	458

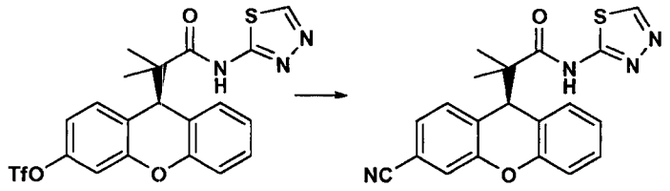
EXAMPLE 112





Step 1

[00375] The product of Step 1 was prepared from the title compound of Example 90 in the same manner as described above for the preparation of the product of Step 3 of Example 101.

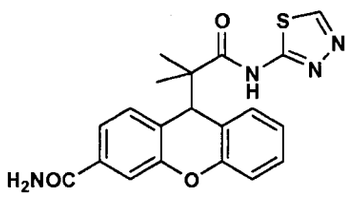


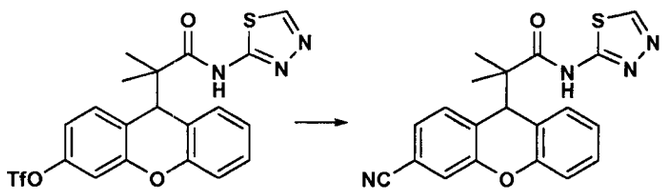
Step 2

[00376] A solution of the product of Step 1 (25 mg, 0.05 mmol) in DMF (0.3 mL) was degassed by passing through a nitrogen stream for 5 min. Zinc cyanide (12 mg,

0.1 mmol) and tetrakis(triphenylphophine)palladium(0) (12 mg, 0.05 mmol) were then added and the mixture was degassed for another 5 min, then heated at 120 °C for 2 h in a sealed vial. The mixture was filtered through a syringe-tip filter (0.45 micron, PTFE), then purified by preparative HPLC to give the product as a white solid. MS (ES+) m/z: 375; LC retention time: 3.40 min.

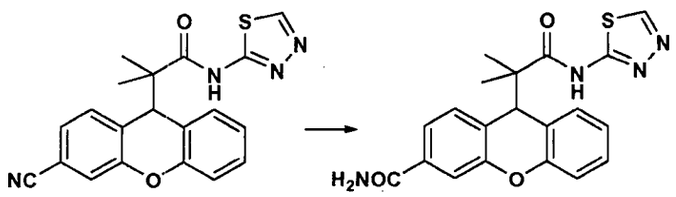
EXAMPLE 113





Step 1

[00377] The product of Step 1 was obtained from the product of Step 3 of Example 101 in the same manner described above for the preparation of the title compound of Example 112. MS (ES+) m/z: 375; LC retention time: 3.40 min.

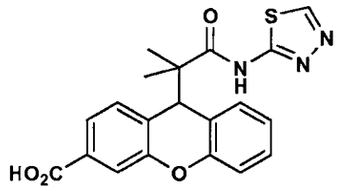


Step 2

[00378] To a suspension of the product of Step 1 (10 mg, 0.0266 mmol) in water (2 mL) was added sodium peroxide (12 mg, 0.16 mmol). The mixture was heated at 70 °C for 1h, then acidified to pH ~5 with the dropwise addition of 6 N HCl and purified by preparative HPLC. The material thus obtained was lyophilized from

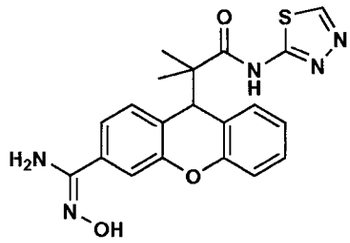
acetonitrile/water to give the title compound as a white powder, TFA salt (4 mg, Y = 29%). MS (ES+) m/z: 395 (M+H); LC retention time: 2.89 min.

EXAMPLE 114



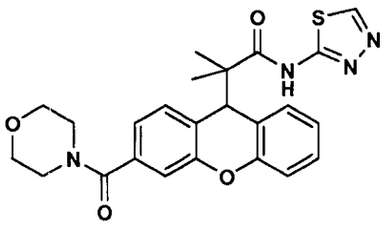
[00379] To a suspension of the product of Step 1 of Example 113 (10 mg, 0.027 mmol) in water (2 mL) was added sodium peroxide (30 mg, 0.38 mmol). The mixture was heated at 100 °C 16 h. Another portion of sodium peroxide (30 mg, 0.38 mmol) was then added and the mixture was heated at 100 °C for another 3 h, then purified by preparative HPLC to give the title compound as a white powder (3 mg, Y = 28%). MS (ES+) m/z: 396 (M+H); LC retention time: 3.36 min.

EXAMPLE 115



[00380] A mixture of the product of Example 113, step 1 (40 mg, 0.106 mmol), hydroxylamine hydrochloride (30 mg, 0.426 mmol) and potassium carbonate (59 mg, 0.426 mmol) in ethanol (5 mL) and water (1 mL) was heated to reflux overnight. Preparative HPLC afforded the product (28 mg, Y = 65%). MS (ES+) m/z: 410 (M+H); LC retention time: 2.29 min.

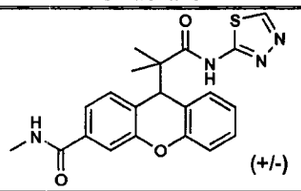
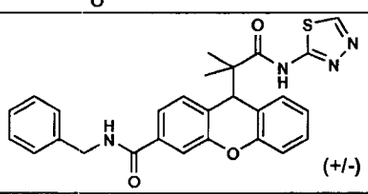
EXAMPLE 116



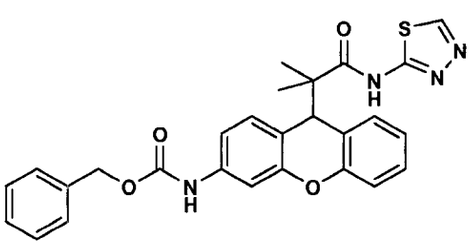
[00381] A solution of the title compound of Example 114 (5 mg, 0.013 mmol) in acetonitrile (2 mL) was treated with HOBT monohydrate (3 mg, 0.019 mmol), EDCI (4 mg, 0.019 mmol), pyridine (0.1 mL) and morpholine (0.003 mL, 0.025 mmol). The resulting solution was heated at 60 °C for 14 h, then purified by preparative HPLC to give the title compound (4.7 mg, Y = 78%) as a white solid. MS (ES+) m/z: 465 (M+H); LC retention time: 3.07 min.

EXAMPLES 117 TO 118

[00382] The following Examples 117 to 118 were prepared in the same manner described above for the preparation of the title compound of Example 116.

Example No.	Structure	Rt (min)	M/z $(MH)^+$
117		2.96	409
118		3.49	485

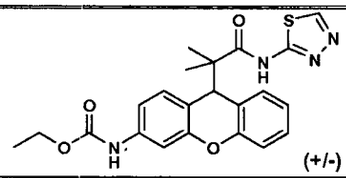
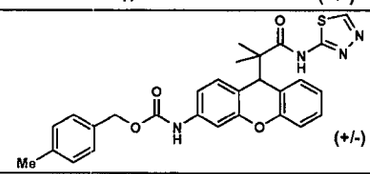
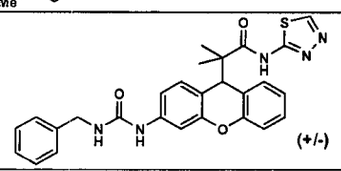
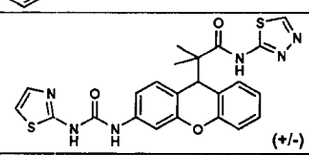
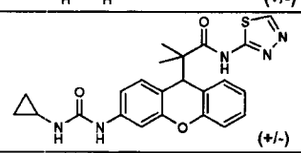
EXAMPLE 119

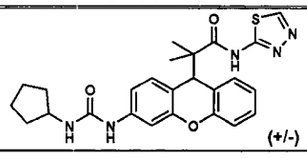


[00383] To a solution of the title compound of Example 114 (25 mg, 0.06 mmol) in toluene (3 mL) were added triethylamine (0.025 mL, 0.18 mmol) and diphenyl phosphoryl azide (0.026 mL, 0.12 mmol). The resulting solution was refluxed for 30 min, then cooled to room temperature. Benzyl alcohol (0.019 mL, 0.18 mmol) was then added to the reaction mixture, was refluxed for another 5 h. The solvent was removed *in vacuo* and the resulting residue purified by preparative HPLC to afford the product, which was lyophilized from acetonitrile/water to give the title compound (19 mg, Y = 43%) as a white powder. MS (ES+) m/z: 501 (M+H); LC retention time: 3.79 min.

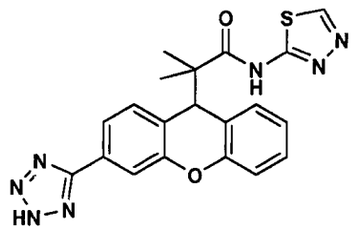
EXAMPLES 120 TO 125

[00384] The following Examples 120 to 125 were prepared in the same manner described above for the preparation of the title compound of Example 119, substituting benzyl alcohol with commercially available alcohols and amines.

Example No.	Structure	Rt (min)	M/z $(MH)^+$
120		3.71	487
121		2.92	515
122		3.49	500
123		3.47	493
124		3.17	450

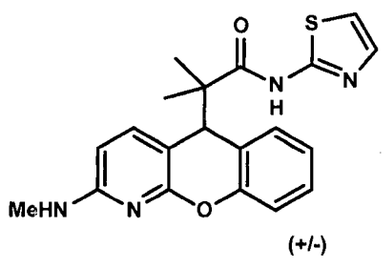
Example No.	Structure	Rt (min)	M/z $(MH)^+$
125		3.51	478

EXAMPLE 126



[00385] To a solution of the product of Example 113, step 1 (10 mg, 0.027 mmol) in DMF (1 mL) was added sodium azide (18 mg, 0.27 mmol) and ammonium chloride (53.5 mg, 0.27 mmol). The mixture was heated at 120 °C for 6 h. After cooling, the mixture was purified by preparative HPLC to give the product which was lyophilized from acetonitrile/water to afford the title compound (6 mg, Y = 53%) as a white powder. MS (ES+) m/z: 420 (M+H); LC retention time: 3.14 min.

EXAMPLE 127

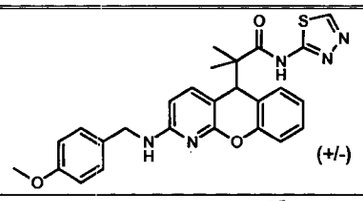
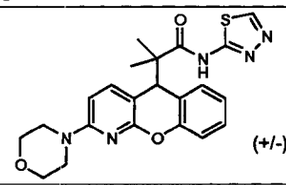


[00386] The title compound was prepared from the product of Preparation 24 in the same manner described above for the preparation of the title compound of Example 67. MS (ES+) m/z: 381 (M+H); LC retention time: 3.07 min.

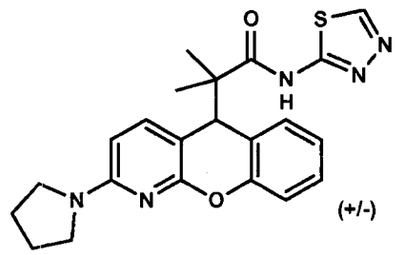
EXAMPLES 128 TO 129

[00387] The following Examples 128 to 129 were prepared in the same manner described above for the preparation of the title compound of Example 127 using

compounds of Preparations 25 and 26 and 2-amino-1,3,4-thiadiazole in place of 2-aminothiazole.

Example No.	Structure	Rt (min)	M/z $(MH)^+$
128		3.55	488
129		3.19	438

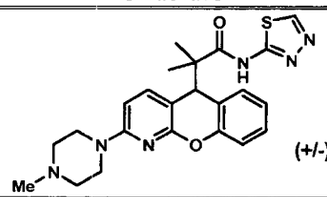
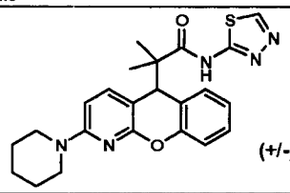
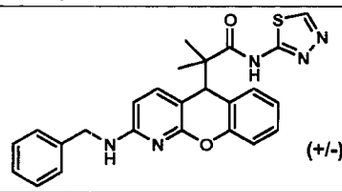
EXAMPLE 130



[00388] To a solution of the product of Preparation 28 (100 mg, 0.297 mmol) in acetonitrile (3.0 mL) was added O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluoro phosphate (HATU) (226 mg, 0.594 mmol), followed by triethylamine (0.2 mL) and 2-amino-1,3,4-thiadiazole (60 mg, 0.594 mmol). The solution was heated at 80°C for 16 h, then concentrated *in vacuo* and purified by preparative HPLC to give the product as a solid (120 mg, 76%). MS (ES+) m/z: 422 (M+H); LC retention time: 3.38 min.

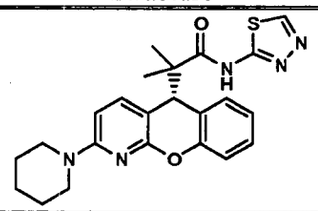
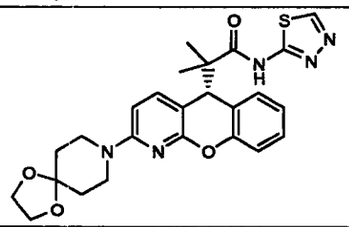
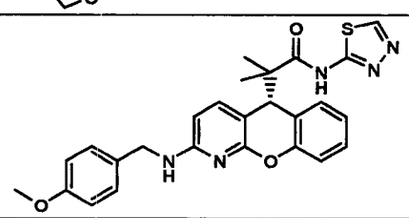
EXAMPLE 131 TO 133

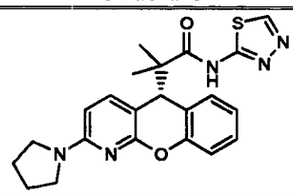
[00389] The following Examples 131 to 133 were prepared from the compounds of Preparations 23, 27 and 29 in the manner described above for the preparation of the title compound of Example 130.

Example No.	Structure	Rt (min)	M/z $(MH)^+$
131		2.20	451
132		3.70	4.36
133		3.51	456

EXAMPLES 134 TO 137

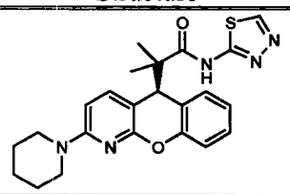
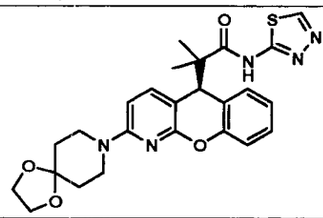
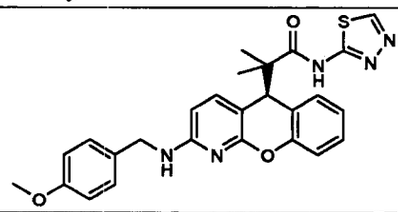
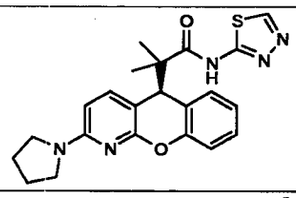
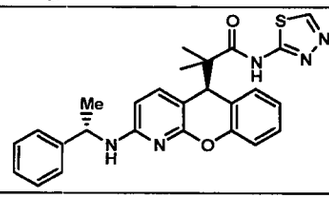
[00390] The following Examples 134 to 137 were prepared from the compounds of Preparations 31 to 34 in the manner described above for the preparation of the title compounds of Examples 130 to 133.

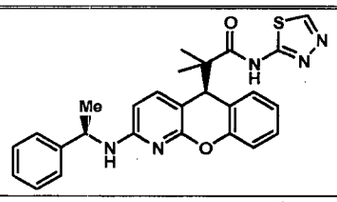
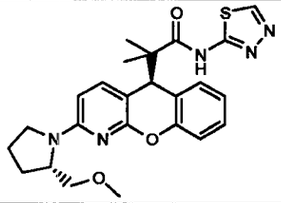
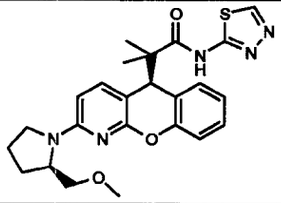
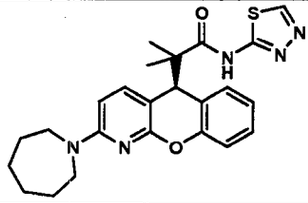
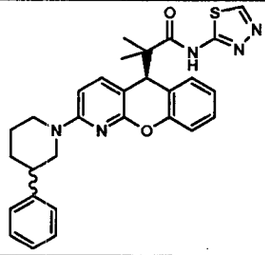
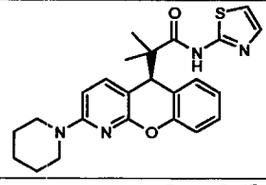
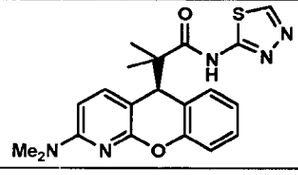
Example No.	Structure	Rt (min)	M/z $(MH)^+$
134		3.70	436
135		3.42	494
136		3.51	488

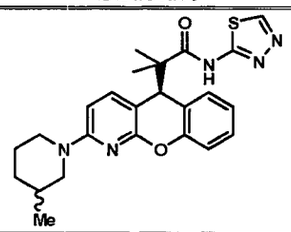
Example No.	Structure	Rt (min)	M/z $(MH)^+$
137		3.41	422

EXAMPLES 138 TO 150

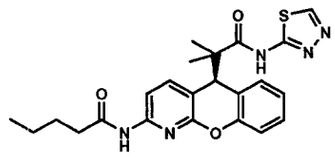
[00391] The following Examples 138 to 150 were prepared from the compounds of Preparations 35 to 47 in the manner described above for the preparation of the title compounds of Examples 130 to 137.

Example No.	Structure	Rt (min)	M/z $(MH)^+$
138		3.73	436
139		3.43	494
140		3.51	488
141		3.41	422
142		3.60	470

Example No.	Structure	Rt (min)	M/z $(MH)^+$
143		3.60	472
144		3.52	466
145		3.50	466
146		3.83	450, 448
147		4.15	512
148		3.86	435, 433
149		3.22	394, 396

Example No.	Structure	Rt (min)	M/z $(MH)^+$
150		3.92	448, 450

EXAMPLE 151



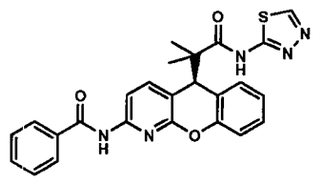
Step 1

[00392] To a solution of the title compound of Example 140 (20 mg, 0.04 mmol) in DMF (0.4 mL) were added triethylamine (0.028 mL, 0.2 mmol) and butyryl chloride (0.042 mL, 0.4 mmol), followed by *N,N*-dimethylaminopyridine (5 mg, 0.04 mmol). The mixture was heated at 80 °C for 30 min, then partitioned between ethyl acetate and 1N aqueous HCl. The organic layer was washed with saturated aqueous sodium bicarbonate and brine, then dried over sodium sulfate and concentrated. MS (ES+) m/z: 558 (M+H); LC retention time: 3.62 min. The crude material (140a) was used directly in the next step with no further purification.

Step 2

[00393] The product of Step 1 (140a) was dissolved in TFA (1 mL) and heated at 50 °C for 12 h. The solvent was removed *in vacuo*, and the residue purified by preparative HPLC to give the product (7 mg, 40% yield for two steps) as an off-white solid. MS (ES+) m/z: 438 (M+H); LC retention time: 3.24 min.

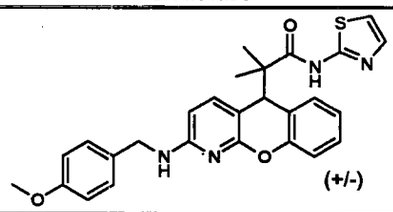
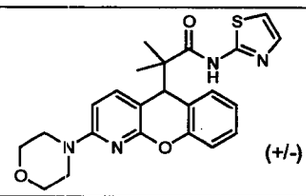
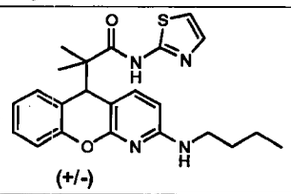
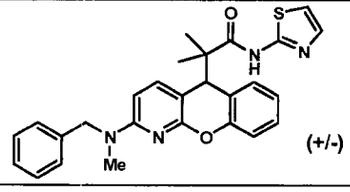
EXAMPLE 152

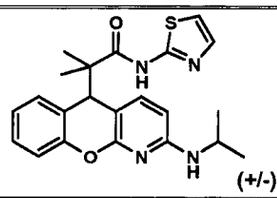


[00394] The title compound was prepared from the title compound of Example 140 in a similar manner as described above for the preparation of the title compound of Example 151. MS (ES+) m/z: 472 (M+H); LC retention time: 3.48 min.

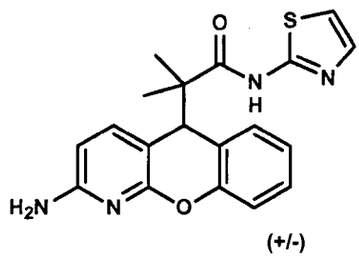
EXAMPLES 153 TO 157

[00395] The following Examples 153to 157 were prepared in the same manner described above for the preparations of the title compounds of Preparations 23 to 29, using the title compound of Example 75 in place of the product of Preparation 17e.

Example No.	Structure	Rt (min)	M/z $(MH)^+$
153		3.70	487
154		3.39	435
155		4.00	423
156		4.39	471

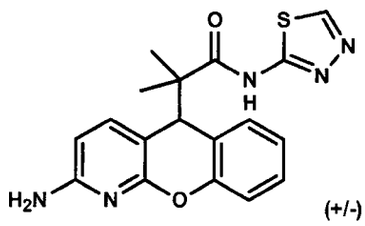
Example No.	Structure	Rt (min)	M/z $(MH)^+$
157		3.47	409

EXAMPLE 158



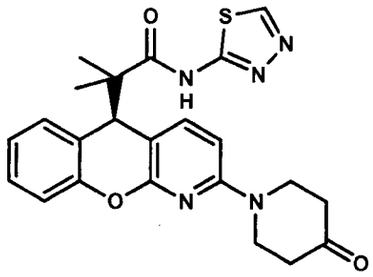
[00396] A solution of the title compound of Example 153 (10 mg, 0.021 mmol) in trifluoroacetic acid (1 mL) was heated at 50°C for 0.5 h. The solvent was removed *in vacuo* and the residue purified by preparative HPLC to give the product (8.5 mg, 86%) as a solid. MS (ES+) m/z: 365; LC retention time: 2.79 min.

EXAMPLE 159



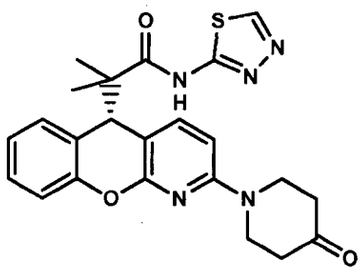
[00397] The title compound was prepared from the title compound of Example 128 in the manner described above for the preparation of the title compound of Example 158. MS (ES+) m/z: 368 (M+H); LC retention time: 2.50 min.

EXAMPLE 160



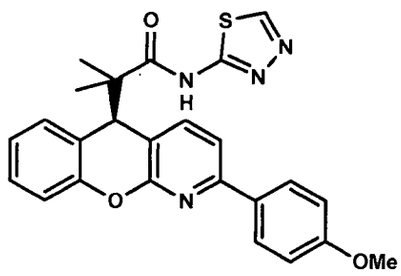
[00398] A solution of the title compound of Example 135 (11 mg, 0.022 mmol) in THF (0.6 mL) and 1N HCl (0.5 mL) was stirred at room temperature for 15 h. The product (2 mg, 20%) was isolated by preparative HPLC. MS (ES+) m/z: 464 (M+MeOH-OH);LC retention time: 3.10 min.

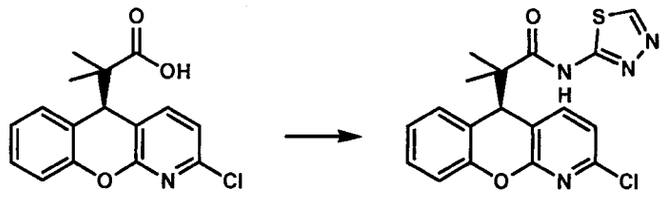
EXAMPLE 161



[00399] The title compound was prepared from the title compound of Example 139 in the manner described above for the preparation of the title compound of Example 160. MS (ES+) m/z: 464 (M+MeOH-OH);LC retention time: 3.10 min.

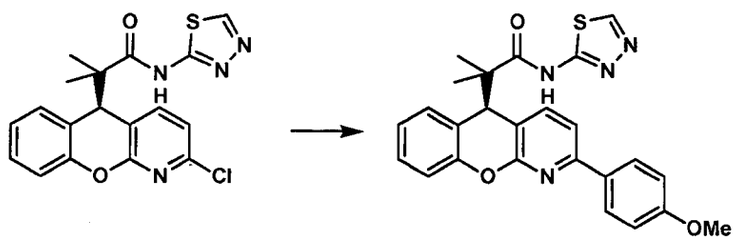
EXAMPLE 162





Step 1

[00400] The product of Step 1 (162a) was prepared from the R isomer of Preparation 30 (30a) in the same manner described above for the preparation of the title compound of Example 76.

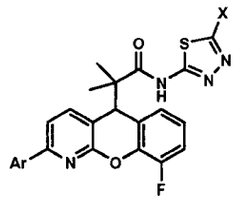


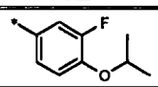
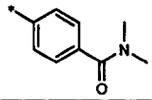
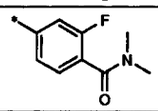
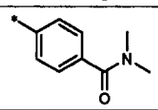
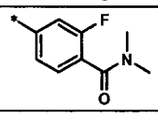
Step 2

[00401] 4-Methoxyphenyl boronic acid (24 mg, 0.156 mmol) and 134a (30 mg, 0.078 mmol) were combined in a microwave reaction vessel and taken up in DMF (1 mL) and 2M aqueous potassium phosphate (0.2 mL). Nitrogen gas was bubbled through the solution for 5 min, at which point tetrakis(triphenylphosphine)palladium(0) (10 mg, 0.009 mmol) was added. The mixture was heated by microwave for 30 min at 100 °C, then purified by preparative HPLC to give the title compound (21.2 mg, 60%) as a white solid. MS (ES+) m/z: 459 (M+H); LC retention time: 3.65 min.

EXAMPLES 163 TO 167

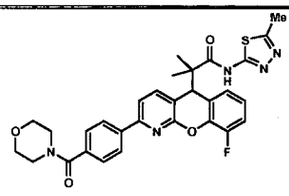
[00402] The following Examples 163 to 167 were prepared from the title compound of Preparation 55e in the same manner as the preparation of the title compound of Example 162, using 2-amino-1,3,4-thiadiazole or 2-amino-5-methyl-1,3,4-thiadiazole in the first step and commercially available boronic acids in place of 4-methoxyphenyl boronic acid in the second step.

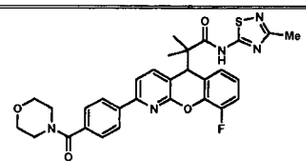
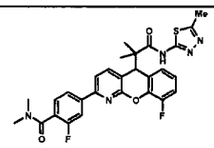
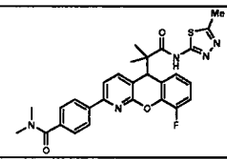


Example No.	X	Ar	Rt (min)	M/z $(MH)^+$
163	H		3.90	523
164	H		3.20	518
165	H		3.25	536
166	Me		3.31	532
167	Me		3.40	550

EXAMPLES 163[a] TO 166[a]

[00403] The following Examples 163[a] to 166[a] were prepared from the title compound of Preparation 56a in the same manner as the preparation of the title compound of Example 162, using 2-amino-1,3,4-thiadiazole or 2-amino-5-methyl-1,3,4-thiadiazole or 5-amino-3-methyl-1,2,4-thiadiazole in the first step and commercially available boronic acids in place of 4-methoxyphenyl boronic acid in the second step.

Example No.	Structure	Rt (min)	M/z $(MH)^+$
163[a]		3.31	574

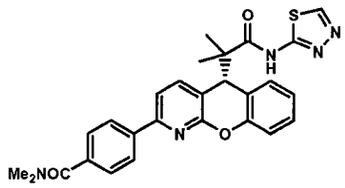
Example No.	Structure	Rt (min)	M/z $(MH)^+$
164[a]		3.40	574
165[a]		3.38	550
166[a]		3.33	532

[00404] 163[a]: ^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.25 (d, *J*=13.85 Hz, 6 H) 2.77 (s, 3 H) 3.44 - 3.93 (m, 8 H) 4.65 (s, 1 H) 6.91 (d, *J*=7.81 Hz, 1 H) 7.00 - 7.07 (m, 1 H) 7.11 - 7.18 (m, 1 H) 7.53 (d, *J*=8.06 Hz, 2 H) 7.59 (d, *J*=7.81 Hz, 1 H) 7.70 (d, *J*=7.81 Hz, 1 H) 8.11 (d, *J*=8.31 Hz, 2 H)

[00405] 164[a]: ^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.24 (d, *J*=6.04 Hz, 6 H) 2.59 (s, 3 H) 3.42 - 3.93 (m, 8 H) 4.62 (s, 1 H) 6.89 (d, *J*=7.81 Hz, 1 H) 6.99 - 7.06 (m, 1 H) 7.12 - 7.18 (m, 1 H) 7.50 - 7.64 (m, 4 H) 8.11 (d, *J*=8.31 Hz, 2 H)

[00406] 165[a]: ^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.25 (d, *J*=12.59 Hz, 6 H) 2.78 (s, 3 H) 3.00 (d, *J*=1.26 Hz, 3 H) 3.19 (s, 3 H) 4.70 (s, 1 H) 6.94 (d, *J*=7.81 Hz, 1 H) 7.00 - 7.07 (m, 1 H) 7.11 - 7.18 (m, 1 H) 7.51 (t, *J*=7.30 Hz, 1 H) 7.57 (d, *J*=7.81 Hz, 1 H) 7.74 (d, *J*=7.81 Hz, 1 H) 7.88 (d, *J*=9.57 Hz, 2 H)

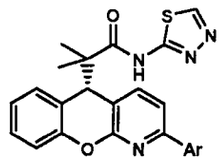
EXAMPLE 168

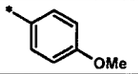
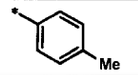
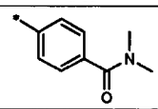
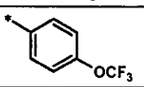
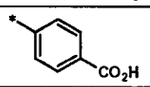
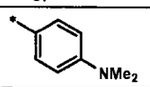


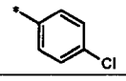
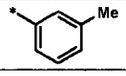
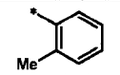
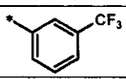
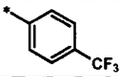
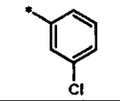
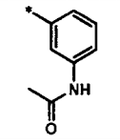
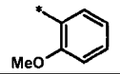
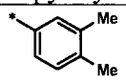
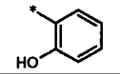
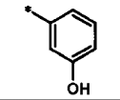
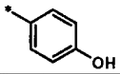
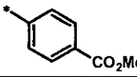
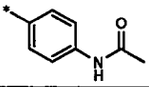
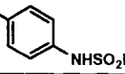
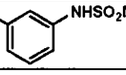
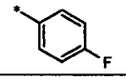
[00407] The title compound was prepared from the title compound of Example 162 Step 1 (162a) in the manner described above for the preparation of the title compounds of Example 162. MS (ES+) m/z: 500 (M+H); LC retention time: 3.22 min.

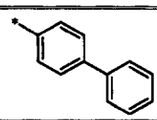
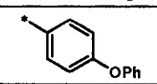
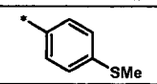
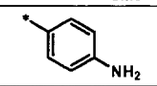
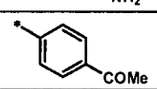
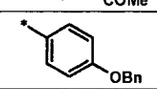
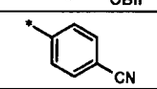
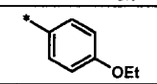
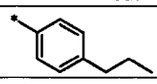
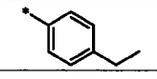
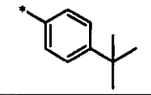
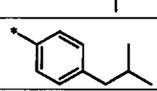
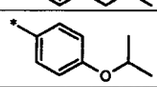
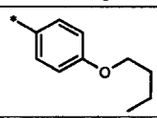
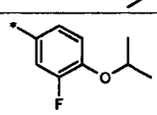
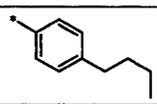
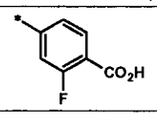
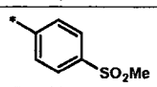
EXAMPLES 169 TO 237

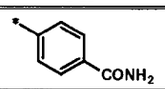
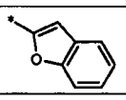
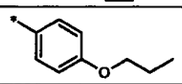
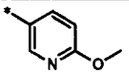
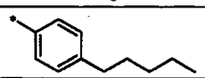
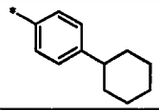
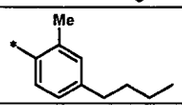
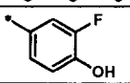
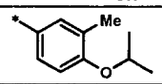
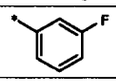
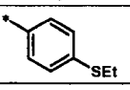
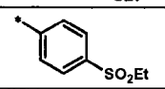
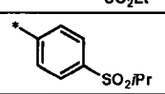
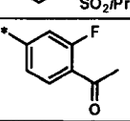
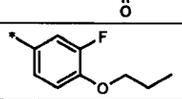
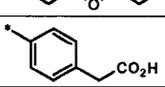
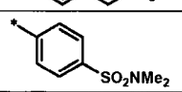
[00408] The following Examples 169 to 237 were prepared from the product of Preparation 53a in the manner described above for the preparation of the title compound of Example 162 from 162a, using commercially available boronic acids.

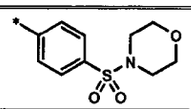
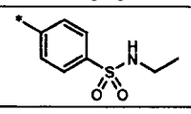
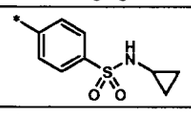
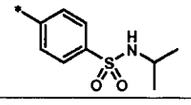
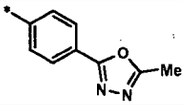


Example No.	Ar	Rt (min)	Obs. MS Ion
169		3.65	459
170		3.81	443
171	Ph	3.06	429
172		3.22	500
173		4.03	513
174		3.42	473
175		3.65*	463
176		3.03*	472

Example No.	Ar	Rt (min)	Obs. MS Ion
177	1-naphthyl	3.84**	479
178		3.96**	463
179		3.84**	443
180		3.67**	443
181		4.02**	497
182		4.00**	497
183		3.98**	463
184		3.33**	486
185		3.60**	459
186	2-naphthyl	4.02**	479
187	3-pyridyl	2.41**	430
188		3.97**	457
189		3.84**	445
190		3.35**	445
191		3.31**	445
192		3.73**	487
193		3.30**	486
194		3.23**	522
195		3.25**	522
196		3.72**	447

Example No.	Ar	Rt (min)	Obs. MS Ion
197		4.11**	505
198		4.08**	521
199		3.85**	475
200		2.69**	444
201		3.51**	471
202		4.06**	535
203		3.52**	454
204		3.81**	473
205		4.11**	471
206		3.94**	457
207		4.15**	485
208		4.22**	485
209		3.89**	487
210		4.12**	501
211		3.92	505
212		4.28	485
213		3.43	491
214		3.16	507

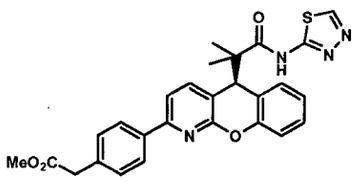
Example No.	Ar	Rt (min)	Obs. MS Ion
215		3.06	472
216		3.94	469
217		4.02	487
218		3.50	460
219		2.38	430
220		4.44	499
221		4.47	511
222		4.28	499
223		3.35	463
224		4.12	501
225		3.72	447
226		4.01	489
227		3.26	521
228		3.39	535
229		3.63	489
230		4.01	505
231		3.33	487
232		3.34	536

Example No.	Ar	Rt (min)	Obs. MS Ion
233		3.35	578
234		3.27	536
235		3.31	548
236		3.40	550
237		3.46	511

* Analytical HPLC Method B

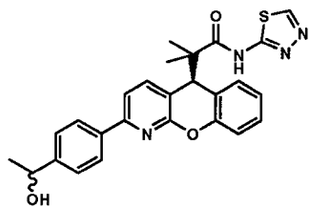
**Analytical HPLC Method C

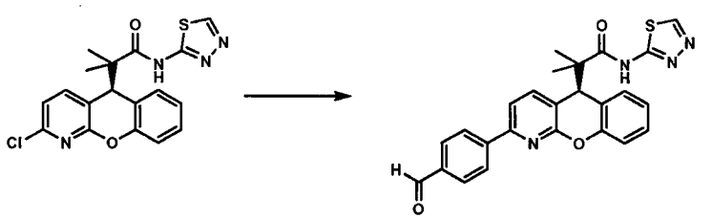
EXAMPLE 238



[00409] To a solution of the title compound of Example 231 (11 mg, 0.023 mmol) in benzene (0.3 mL) and methanol (0.3 mL) at room temperature was added trimethylsilyl diazomethane (0.037 mL, 0.2 mmol). The reaction mixture was allowed to sit at room temperature for 30 min, then quenched with the addition of 2 drops of glacial acetic acid. The reaction mixture was concentrated, and purified by preparative TLC (0.5 mm silica, 100 cm x 100 cm, 40% ethyl acetate in hexanes). The lower of the two bands was isolated, giving the title compound (6 mg, Y = 52%) as a colorless solid. MS (ES+) m/z: 501; LC retention time: 3.50 min. ^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.23 (s, 3 H) 1.25 (s, 3 H) 3.67 (s, 2 H) 3.69 (s, 3 H) 4.71 (s, 1 H) 6.99 – 7.05 (m, 1 H) 7.19 (d, *J*=7.63 Hz, 1 H) 7.28 – 7.33 (m, 2 H) 7.37 (d, *J*=8.14 Hz, 2 H) 7.48 (d, *J*=8.14 Hz, 1 H) 7.67 (d, *J*=7.63 Hz, 1 H) 7.98 (d, *J*=8.14 Hz, 2 H) 8.88 (s, 1 H).

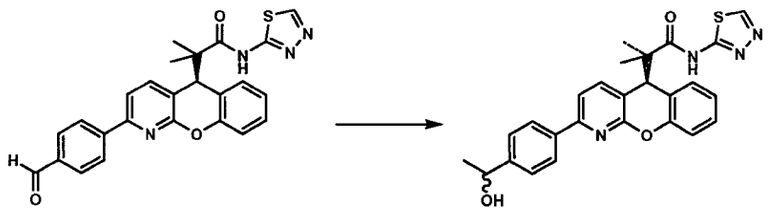
EXAMPLE 239





Step 1

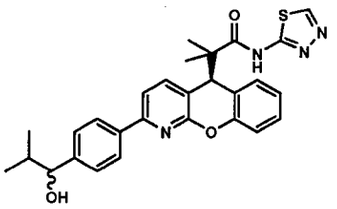
[00410] The product of Step 1 was prepared in the manner described above for the preparation of the title compounds of Examples 169 to 237. MS (ES+) m/z: 457; LC retention time: 3.44 min.



Step 2

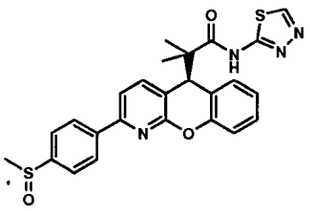
[00411] To a solution of the product of Step 1 (20 mg, 0.044 mmol) in THF (1 mL) was added methylmagnesium bromide (3M in diethyl ether, 0.04 mL) dropwise. The reaction mixture was stirred at room temperature for 1 h, then quenched with the addition of methanol, concentrated, and purified by preparative HPLC to afford the title compound as a mixture of co-eluting diastereoisomers (16 mg, Y = 77%). MS (ES+) m/z: 473; LC retention time: 3.34 min.

EXAMPLE 239



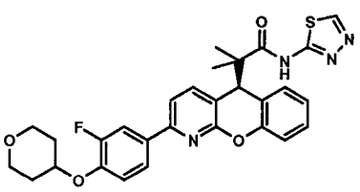
[00412] The title compound was obtained from the product of Step 1 of Example 239 in the manner described for the preparation of the title compound of Example 239. MS (ES+) m/z: 501; LC retention time: 3.65 min.

EXAMPLE 241



[00413] To a solution of the title compound of Example 199 (20 mg, 0.042 mmol) in dichloromethane (1 mL) at 0 °C was added *m*-chloroperbenzoic acid (containing ~30% 3-chlorobenzoic acid, 10 mg, 0.042 mmol). After 5 min at 0 °C, the solvent was removed and exchanged with methanol. This solution was purified by preparative HPLC to provide the product, which was lyophilized from acetonitrile/water to give the title compound (10 mg, Y = 39%) as a white powder. MS (ES+) m/z: 491; LC retention time: 3.08 min.

EXAMPLE 242

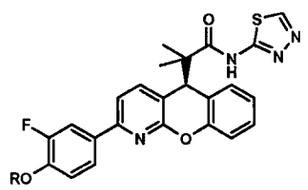


[00414] The title compound of Example 223 (21 mg, 0.045 mmol) was azeotroped to dryness from toluene, then dissolved in THF (0.5 mL). To this solution were sequentially added tetrahydro-4*H*-pyran-4-ol (0.0065 mL, 0.068 mmol), triphenyl phosphine (18 mg, 0.068 mmol), and diisopropyldiazodicarboxylate (DIAD) (0.013

mL, 0.068 mmol). The reaction mixture was allowed to stir at room temperature for 3h 20min, then concentrated and purified by preparative TLC (silica, 0.5 mm, 100 cm x 100 cm, 50% ethyl acetate in hexanes) to give the title compound (11 mg, Y = 45%) as a white powder. MS (ES+) m/z: 547; LC retention time: 3.69 min. ^{1}H NMR (500 MHz, Solvent) δ ppm 1.09 (s, 3 H) 1.17 (s, 3 H) 1.68 – 1.75 (m, 1 H) 1.76 – 1.83 (m, 1 H) 2.04 – 2.20 (m, 2 H) 3.39 – 3.49 (m, 2 H) 3.96 (dd, *J*=11.68, 3.71 Hz, 1 H) 4.04 (dd, *J*=11.68, 3.71 Hz, 1 H) 4.48 (s, 1 H) 4.77 – 4.86 (m, 1 H) 7.00 – 7.05 (m, 2 H) 7.14 (d, *J*=7.15 Hz, 1 H) 7.24 – 7.26 (m, 3 H) 7.29 (d, *J*=7.70 Hz, 1 H) 7.43 (d, *J*=8.25 Hz, 1 H) 7.64 – 7.68 (m, 1 H) 7.82 (dd, *J*=11.96, 2.06 Hz, 1 H) 8.33 (s, 1 H).

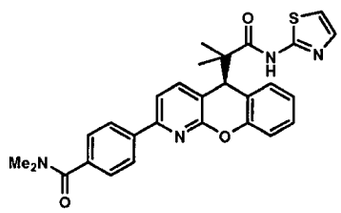
EXAMPLES 243 TO 244

[00415] The following Examples 243 to 244 were prepared in the manner described above for the preparation of the title compound of Example 242.



Example No.	R	Rt (min)	Obs. MS Ion
243	cyclohexyl	4.20	545
244	cyclopentyl	4.13	531

EXAMPLE 245



Step 1

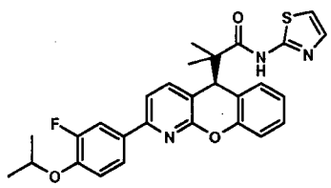
[00416] A stream of nitrogen gas was bubbled through mixture of the title compound of Preparation 30b (40 mg, 0.13 mmol), 4-(dimethylcarbamoyl)phenylboronic acid (50 mg, 0.26 mmol), potassium phosphate

(2.0 M, 0.36 mL) and tetrakis(triphenylphosphine)palladium(0) (15 mg, 0.014 mmol) for 10 min. The mixture was then heated at 100 °C for 2 h, then filtered through a syringe-tip filter (0.45 micron, PTFE), and purified by preparative HPLC to give the product (245a, (*S*)-2-(2-(4-(dimethylcarbamoyl)phenyl)-5*H*-chromeno[2,3-*b*]pyridine-5-yl)-2-methylpropanoic acid, 43 mg, 79% yield) as a white powder. MS (ES+) m/z: 417; LC retention time: 3.29 min.

Step 2

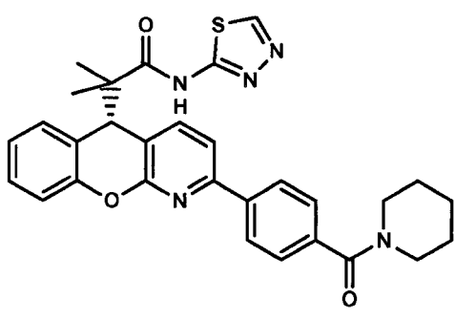
[00417] The title compound (245b) was prepared from 245a in a similar manner as described above for the preparation of Examples 73 to 76. MS (ES+) m/z: 499; LC retention time: 3.42 min.

EXAMPLE 246



[00418] The title compound was prepared in the manner described above for the preparation of the title compound of Example 246. MS (ES+) m/z: 504; LC retention time: 4.07 min. ^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.15 (s, 3 H) 1.17 (s, 3 H) 1.38 (d, *J*=6.10 Hz, 6 H) 4.57 (s, 1 H) 4.58 – 4.66 (m, 1 H) 7.17 (d, *J*=7.12 Hz, 1 H) 7.26 – 7.32 (m, 2 H) 7.37 (d, *J*=8.14 Hz, 1 H) 7.40 (d, *J*=3.56 Hz, 1 H) 7.58 (d, *J*=8.14 Hz, 1 H) 7.72 (d, *J*=9.66 Hz, 1 H) 7.77 (dd, *J*=12.46, 2.29 Hz, 1 H).

EXAMPLE 247

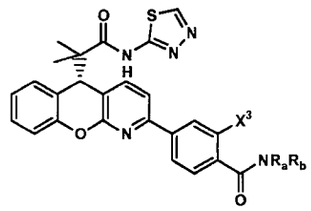


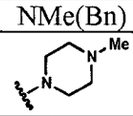
[00419] A solution of the title compound of Example 174 (31 mg, 0.066 mmol), triethylamine (0.028 mL, 0.20 mmol), HOBT monohydrate (12 mg, 0.086 mmol), EDC (16 mg, 0.086 mmol) and piperidine (0.013 mL, 0.132 mmol) in acetonitrile (0.5 mL) was heated for 12 h at 45°C. Purification by preparative HPLC gave the title compound (15 mg, 35%), which was lyophilized from acetonitrile/water to give an amorphous, white solid. MS (ES+) m/z: 540; LC retention time: 3.57 min.

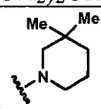
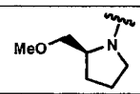
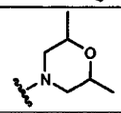
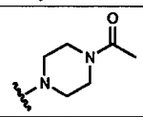
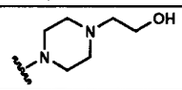
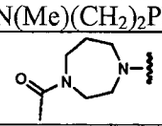
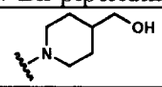
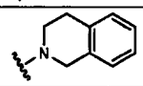
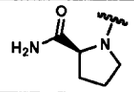
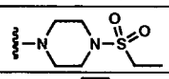
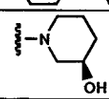
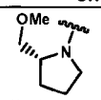
[00420] ^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.24 (s, 3 H) 1.26 (s, 3 H) 1.52 (s, 2 H) 1.68 (s, 4 H) 3.35 (s, 2 H) 3.73 (s, 2 H) 4.71 (s, 1 H) 6.98 - 7.10 (m, 1 H) 7.19 (d, *J*=7.12 Hz, 1 H) 7.30 (d, *J*=2.54 Hz, 2 H) 7.49 (t, *J*=8.39 Hz, 3 H) 7.69 (d, *J*=7.63 Hz, 1 H) 8.04 (d, *J*=8.14 Hz, 2 H) 8.88 (s, 1 H)

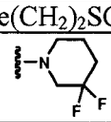
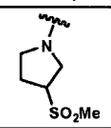
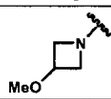
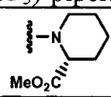
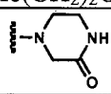
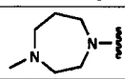
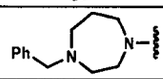
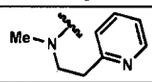
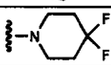
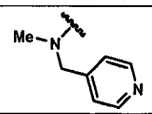
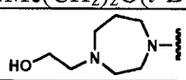
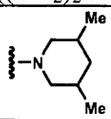
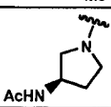
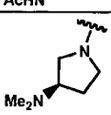
EXAMPLES 248 TO 361

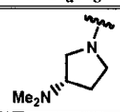
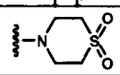
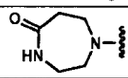
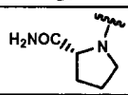
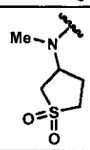
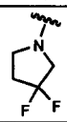
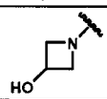
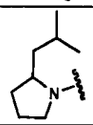
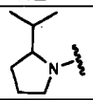
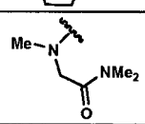
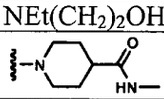
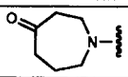
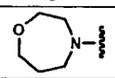
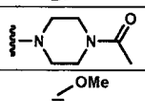
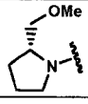
[00421] The following Examples 248 to 362 were prepared from the title compounds of Examples 174 and 213, and Preparations 53 and 54 in a manner similar to that described for the preparation of the title compound of Example 247.

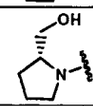
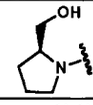
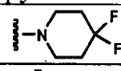
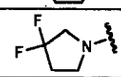
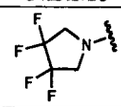
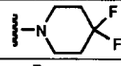
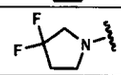
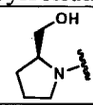
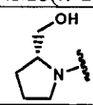


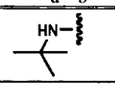
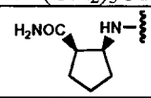
Example No.	NR_aR_b	X^3	Rt (min)	M/z $(MH)^+$
248	NEt_2	H	3.66	542
249	piperidine	F	3.66	558
250	NMe_2	F	3.30	518
251	NMeEt	H	3.38*	514
252	pyrrolidine	H	3.42*	526
253	NHMe	F	3.16	504
254	NMe(*n*-Pr)	H	3.53*	528
255	NMe(Bn)	H	3.73*	576
256		H	2.66*	555
257	morpholine	H	3.21*	542
258	NMe(*i*-Pr)	H	3.50*	528
259	NEt2	F	3.56	546
260	NMe2	Cl	3.41	534

Example No.	NR_aR_b	X^3	Rt (min)	M/z $(MH)^+$
261	piperidine	H	3.57	540
262	NEt_2	Ome	3.51	558
263	NEt_2	Cl	3.67	562
264	piperidine	Cl	3.58	575
265	piperidine	Ome	3.58	570
266	piperidine	F	3.66	558
267	$NMe(CH_2)_2CN$	H	3.08*	539
268	4-Me-piperidine	H	3.73*	554
269	4-OH-piperidine	H	3.11*	556
270	$NMe(CH_2)_2CH(CH_3)_2$	H	3.80*	556
271		H	3.81*	568
272		H	3.49*	570
273		H	3.49*	570
274		H	3.04*	583
275		H	3.30*	584
276	$N(Me)(CH_2)_2Ph$	H	3.75*	590
277		H	3.05*	597
278	4-Bn-piperidine	H	4.04*	630
279		H	3.19*	570
280		H	3.80*	588
281	4-Ph-piperidine	H	3.92*	616
282		H	3.03*	569
283		H	3.19*	633
284		H	3.17*	556
285		H	3.48*	570

Example No.	NR_aR_b	X^3	Rt (min)	M/z $(MH)^+$
286	$NMe(CH_2)_2SO_2Me$	H	3.03*	592
287		H	3.49*	576
288		H	3.00*	604
289		H	3.30*	542
290	4-(CF_3)-piperidine	H	3.71*	608
291		H	3.59*	598
292	NMe(*n*-Bu)	H	3.67*	542
293	$NMeCH_2CO_2Me$	H	3.22*	558
294	$NMe(CH_2)_2OH$	H	3.02*	530
295	$NMe(CH_2)_2OMe$	H	3.27*	544
296		H	2.91*	555
297		H	2.56*	569
298		H	2.80*	645
299		H	2.67*	591
300		H	3.53*	576
301		H	2.66*	577
302	$NMe(CH_2)_2O(t\text{-}Bu)$	H	3.70*	586
303		H	2.58*	599
304	$N((CH_2)_2OH)_2$	H	2.90*	560
305		H	3.90*	568
306		H	3.05*	583
307		H	2.58*	569

Example No.	NR_aR_b	X^3	Rt (min)	M/z $(MH)^+$
308		H	2.58*	570
309	4-OMe-piperidine	H	3.39*	570
310		H	2.99*	590
311		H	2.95*	569
312		H	3.03*	569
313		H	3.04*	604
314		H	3.46*	562
315		H	3.08*	528
316		H	3.23*	551
317		H	3.94*	582
318		H	3.83*	568
319		H	3.03*	571
320	$NEt(CH_2)_2OH$	H	3.16*	544
321		H	3.08*	597
322		H	3.14*	568
323		H	3.23*	556
324		F	3.12	601
325		F	3.58	588

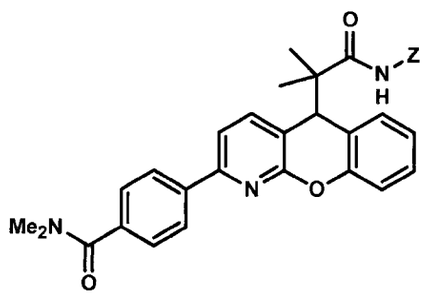
Example No.	NR_aR_b	X^3	Rt (min)	M/z $(MH)^+$
326	$NMe(CH_2)_2CN$	F	3.14	557
327	morpholine	F	3.27	560
328	morpholine	Cl	3.39	576
329	NMe(*i*-Pr)	F	3.57	546
330		Cl	3.70	604
331		H	3.25	556
332		H	3.25	556
333	pyrrolidine	F	3.44	544
334		F	3.61	594
335		F	3.51	580
336	NEtMe	F	3.47	532
337		F	3.69	616
338	$NMe(CH_2)CO_2H$	H	3.06	544
339		Cl	3.69	610
340		Cl	3.59	596
341	pyrrolidine	Cl	3.57	560
342		F	3.30	574
343	NMe(*n*-Pr)	F	3.60	546
344		F	3.30	574
345	NMeEt	Cl	3.49	548
346	NMe(*n*-Pr)	Cl	3.69	562
347	NMe_2	Ome	3.24	530
348	NHMe	H	3.17	486
349	NHBn	H	XX*	XX
350		H	3.35*	512
351		H	3.43*	540

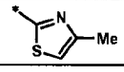
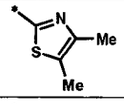
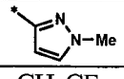
Example No.	NR_aR_b	X^3	Rt (min)	M/z $(MH)^+$
352		H	3.61*	528
353	NH*i*Pr	H	3.41*	514
354	$NH(CH_2)_2Ph$	H	3.74*	576
355	$NH(CH_2)_2Ome$	H	3.26*	530
356	$NH(CH_2)_2C(CH_3)_3$	H	3.70*	542
357	$NH(CH_2)_2OH$	H	3.06*	516
358	NH(*n*-Pr)	H	3.45*	514
359	$NH(CH_2)_3OH$	H	3.15*	530
360		H	3.36*	583
361	NHMe	OMe	3.30	516

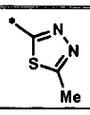
* Analytical HPLC Method B

EXAMPLES 362 TO 368

[00422] The following compounds 362 to 368 were prepared from the title compound of Preparation 57 in the same manner as described for the preparation of the title compound of Preparation 53a.

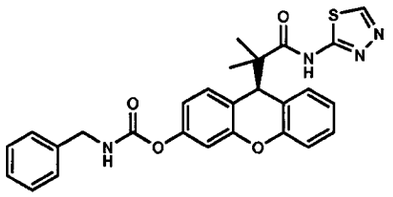


Example No.	Z	Rt (min)	M/z $(MH)^+$
362	*t*-Bu	2.47*	472
363		2.41*	513
364		2.45*	513
365		2.59*	527
366		1.98*	496
367	CH_2CF_3	2.29*	498

Example No.	Z	Rt (min)	M/z $(MH)^+$
378		2.07*	514

* Analytical HPLC Method B

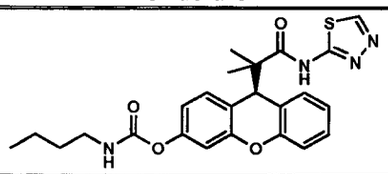
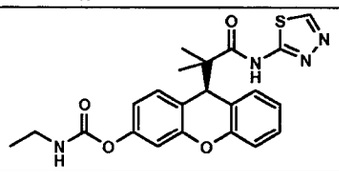
EXAMPLE 369

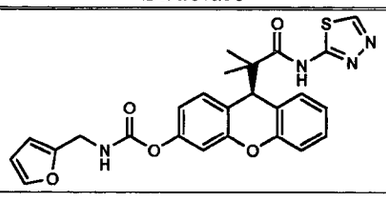


[00423] To a solution of the product of Example 90 (20 mg, 0.054 mmol) in dioxane (1 mL) was added diisopropylethyl amine (0.028 mL, 0.163 mmol) and (isocyanatomethyl)benzene (6.8 μL, 0.054 mmol), respectively. The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was purified by prep-HPLC to yield pure (*S*)-9-(1-(1,3,4-thiadiazole-2ylamino)-2-methyl-1-oxopropan-2-yl)-9H-xanthen-3-yl benzylcarbamate (17 mg, 62% yield): MS (E+) m/z: 501 $(M+H)^+$; LC retention time: 3.54 min.

EXAMPLES 370 TO 372

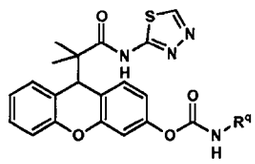
[00424] The following Examples 370 to 372 were prepared in the manner described above for the preparation of the title compound of Example 369.

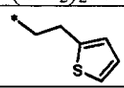
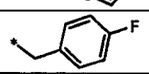
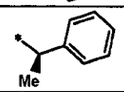
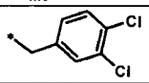
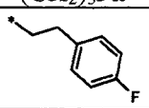
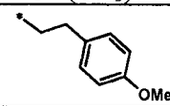
Example No.	Structure	Rt (min)	m/z $(M+H)^+$
370		3.61	467
371		3.27	439

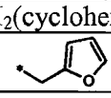
Example No.	Structure	Rt (min)	m/z $(M+H)^+$
372		3.36	491

EXAMPLES 373 TO 393

[00425] The following compounds 373 to 393 were prepared fro the product of Step 2 of Example 101 (101b) in the manner described above for the preparation of the title compounds of Examples 370 to 372, using commercially available amines.

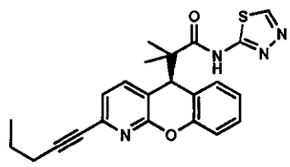


Example No.	R^q	Rt (min)	M/z $(MH)^+$
373	cyclohexyl	2.69*	493
374	*n*-octyl	3.31*	523
375	$(CH_2)_2Ph$	2.61*	515
376		2.59*	521
377		2.55*	519
378		2.63*	515
379		2.87*	569
380	$(CH_2)_3Ph$	2.74*	529
381		2.61*	533
382	*t*-Bu	2.57*	467
383	$CH(CH_3)Et$	2.51*	467
384		2.57*	545
385	Cyclohexyl	3.90	493
386	Me	3.23	425
387	Et	3.26	439

Example No.	R^q	Rt (min)	M/z $(MH)^+$
388	*n*-Bu	3.61	467
389	CH_2Ph	3.60	501
390	(*p*-OMe)Ph	3.56	517
391	(*p*-OMe)$PhCH_2$	2.54*	531
392	CH_2(cyclohexyl)	2.92*	507
393		2.36*	491

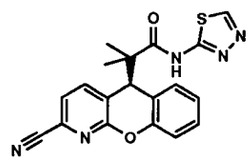
* Analytical HPLC Method B

EXAMPLE 394



[00426] A mixture of the title compound of Preparation 53a (42 mg, 0.11 mmol), bis (triphenylphosphine)-palladium(II) chloride (7.6 mg, 0.011 mmol) and cuprous iodide (2.1 mg, 0.011 mmol) in diisopropyl amine (0.39 mL) and DMF (0.49 mL) was purged with a stream of nitrogen for 30 min. 1-Pentyne (0.012 mL, 0.12 mmol) was then added dropwise via syringe. The mixture was heated with stirring under nitrogen at 80 °C for 3 h 20 min, then purified by preparative HPLC, to give an oil which was lyophilized from acetonitrile/water to give an off-white solid (4.4 mg, 10% Y). MS (ES+) m/z: 420 (M+H); LC retention time: 3.63 min.

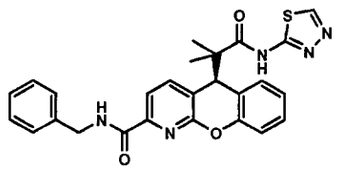
EXAMPLE 395

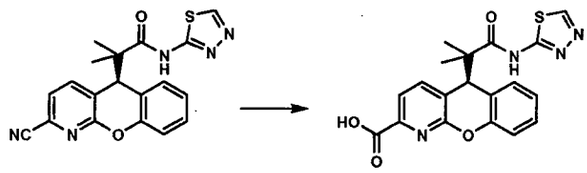


[00427] A stream of nitrogen gas was bubbled through a mixture of the product of Preparation 53a (50 mg, 0.13 mmol), Zn $(CN)_2$ (31 mg, 0.26 mmol), and tetrakis(triphenylphosphine)palladium(0) (30 mg, 0.026 mmol) in DMF (1 mL) for 10 min. The mixture was heated at 100 °C for 2.5 h, then filtered through a syringe-tip filter (0.45 micron, PTFE) and purified by preparative HPLC, giving material which contained residual triphenylphosphine oxide. The semipurified material was further

purified by flash column chromatography (12 g silica, 60% ethyl acetate in hexanes to 70% ethyl acetate in hexanes) to give the title compound (21 mg, Y = 43%) as a white powder. MS (ES+) m/z: 378 (M+H); LC retention time: 2.90 min. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.12 (s, 3 H) 1.15 (s, 3 H) 4.66 (s, 1 H) 7.14 (t, *J*=7.38 Hz, 1 H) 7.21 – 7.28 (m, 2 H) 7.37 (t, *J*=8.65 Hz, 1 H) 7.62 (d, *J*=7.63 Hz, 1 H) 7.83 (d, *J*=7.63 Hz, 1 H) 9.09 (s, 1 H)

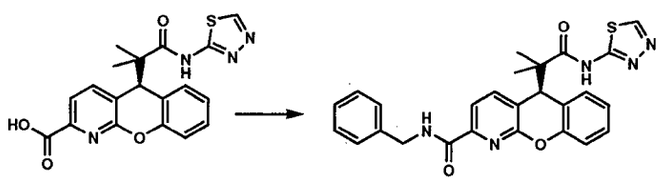
EXAMPLE 396





Step 1

[00428] A suspension of the title compound of Example 395 (8 mg, 0.021 mmol) in 1,4-dioxane (0.20 mL) and aqueous KOH (4N, 0.053 mL) was heated at 80 °C for 4.5 h. The reaction mixture was then partitioned between ethyl acetate and 1N aqueous HCl. The organic layer was dried over sodium sulfate and concentrated to give the product (398a) as a white solid (7 mg, Y = 84%). MS (ES+) m/z: 397 (M+H); LC retention time: 2.75 min.

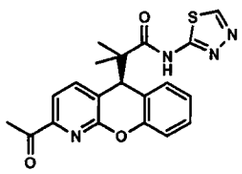


Step 2

[00429] To a soln of the product of Step 1 (396a) (10 mg, 0.025 mmol) in acetonitrile (1 mL) was added benzylamine (2.70 mg, 0.025 mmol), diisopropylethyl amine (0.013 mL, 0.076 mmol) and 1-(3-(dimethylamino)propyl)-3-ethyl-

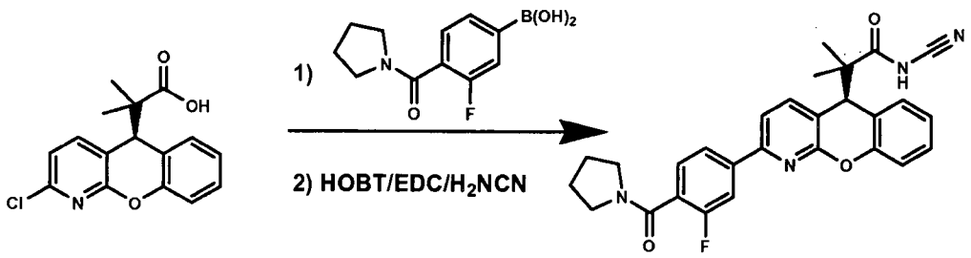
carbodiimide hydrochloride (7.25 mg, 0.038 mmol) and 1-hydroxybenzotriazole (5.79 mg, 0.038 mmol) . The resulted mixture was heated to 50°C for 2h with stirring, then purified by preparative HPLC to give the desired product, which was lyophilized from acetonitrile/water to afford the title compound (12.25 mg, Y = 86%) as a white solid. MS (ES+) m/z: 486 (M+H); LC retention time: 3.47 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.16 (d, J = 5.54 Hz, 6 H) 4.51 – 4.66 (m, 2 H) 4.68 (s, 1 H) 6.98 – 7.04 (m, 1 H) 7.11 – 7.34 (m, 8 H) 7.74 (d, J = 7.81 Hz, 1 H) 7.94 (d, J = 7.81 Hz, 1 H) 8.15 (t, J = 6.04 Hz, 1 H) 8.80 (s, 1 H).

EXAMPLE 397



[00430] See Jean-Yves Legros *et al. Tetrahedron*, **2001**, *57*, 2507. To a solution of the product of the first step of Preparation 53 (53a) (30 mg, 0.078 mmol) in toluene (1 mL) was added triphenylphosphine (2.03 mg, 0.008 mmol) and $Pd(dba)_2$ (7.10 mg, 0.008 mmol). The resulting mixture was stirred at room temperature under argon (bubbling) for 15 min. Tributyl(1-ethoxyvinyl)stannane (28.0 mg, 0.078 mmol) was added and the resulting mixture was stirred at 110°C for 3 h, then cooled to room temperature. Three drops of 1M HCl was added, and stirring was continued for 10 min at room temperature. The solvent was removed *in vacuo*, and the residue suspended in methanol, then filtered through a syringe-tip filter (0.45 micron, PTFE) and purified by preparative HPLC to afford the product which was lyophilized from acetonitrle/water to afford the title compound as a TFA salt. (22 mg, Y = 72%). MS (ES+) m/z: 395 (M+H); LC retention time: 4.60 min. ^{1}H NMR (400 MHz, chloroform-D) δ ppm 1.16 (s, 6 H) 2.67 (s, 3 H) 4.72 (s, 1 H) 6.97 - 7.03 (m, 1 H) 7.13 - 7.17 (m, 1 H) 7.23 - 7.28 (m, 2 H) 7.73 (s, 2 H) 8.82 (s, 1 H).

EXAMPLE 398



Step 1

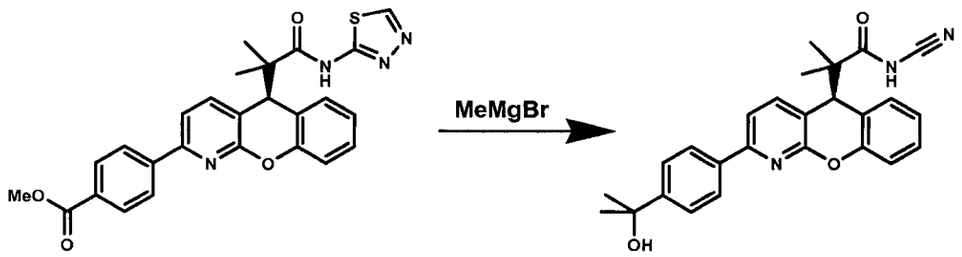
[00431] A mixture of the product of Preparation 30b (800 mg, 2.6 mmol), 3-fluoro-4-(pyrrolidine-1-carbonyl)phenylboronic acid (1.7 g, 7.2 mmol), 2 M aqueous solution of potassium phosphate (9 mL, 18 mmol), and DMF (24 mL) was bubbled with nitrogen for 5 min before tetrakis(triphenylphosphine)palladium(0) (300 mg, 0.26 mmol) was added. The mixture was bubbled with nitrogen for an additional 5 min. The reaction mixture was stirred at 90°C under nitrogen for 3 hr before concentrated *in vacuo*. The residue was mixed with water (50 mL), washed with 1:1 ethyl acetate/heptane mixture (30 mL). The organic mixture was extracted with water (3 x 15 mL). The combined aqueous solutions were decolorized with active charcoal, neutralized to pH = 6-7 with 6N aqueous HCl solution (4 mL) and then 10% aqueous citric acid solution. Ethyl acetate (15 mL) was added and the mixture was stirred for 1 hr. The solid formed was filtered, washed with water (3 x 2 mL) and ethyl acetate (2 x 1 mL), and dried to give the product (1.1 g, Y = 88 %) as a white solid. MS (E+) m/z: 461 (M+H); LC retention time: 3.41 min.

Step 2

[00432] To a stirred mixture of the product of Step 1 (398a) (33 mg, 0.072 mmol), HOBT hydrate (22 mg, 0.14 mmol), anhydrous acetonitrile (1 ml), and N,N-diisopropylethylamine (0.13 ml, 0.72 mmol) was added EDC (41 mg, 0.22 mmol) at RT under nitrogen. The mixture was stirred at RT over night before concentrated. The residue was partitioned between dichloromethane (1 mL) and water (2 mL). The aqueous layer was separated and extracted with methylene chloride (2 x 1 mL). The combined organic solutions were dried (Na_2SO_4). Silica gel flash chromatography (20=>100% ethyl acetate in hexanes) gave the HOBT ester, which was dissolved in

THF (2 mL). The obtained solution and 2 N aqueous NaOH (0.11 ml, 0.22 mmol) were added dropwise to a vigorously stirred cyanamide (20 mg, 0.48 mmol) solution in water (2.5 ml) simultaneously at 0°C. The reaction mixture was then stirred at RT for 1.5 h and concentrated *in vacuo* to remove THF. The aqueous residue was washed with diethyl ether (3 mL), neutralized with 6N aqueous HCl (0.036 mL), and extracted with ethyl acetate (3 x 1 mL). The combined ethyl acetate extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification using reverse phase HPLC (YMC S5 20 x 100 mm, 10 min. run, solvent A: 10% MeOH: 90% H_2O: 0.1% TFA, solvent B: 90% MeOH, 10% H_2O, 0.1% TFA) gave the title product (20 mg, Y = 47 %) as a TFA salt. MS (E+) m/z: 485 (M+H); LC retention time: 3.22 min. ^{1}H NMR (400 MHz, MeOD) δ ppm 7.91 - 8.01 (m, 2 H) 7.79 - 7.86 (m, 2 H) 7.54 (t, *J*=7.43 Hz, 1 H) 7.41 (td, *J*=7.70, 1.50 Hz, 1 H) 7.26 - 7.33 (m, 2 H) 7.23 (td, *J*=7.37, 1.13 Hz, 1 H) 4.46 (s, 1 H) 3.63 (t, *J*=6.92 Hz, 2 H) 3.39 (t, *J*=6.55 Hz, 2 H) 1.99 - 2.06 (m, 2 H) 1.91 - 1.98 (m, 2 H) 1.06 (s, 3 H) 1.04 (s, 3 H).

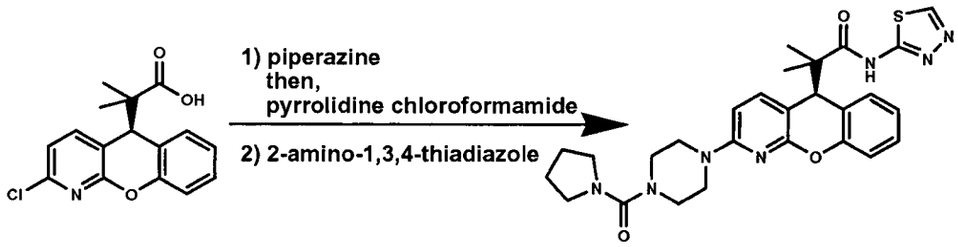
EXAMPLE 399



[00433] To a clear solution of the title compound of Example 192 (TFA salt, 13 mg, 0.022 mmol) in anhydrous THF (1 mL) was added methylmagnesium bromide solution (3 M in diethyl ether, 0.25 mL, 0.75 mmol) dropwise at -78°C under nitrogen. The mixture was stirred at the same temperature for 20 min before ethyl acetate (0.2 mL) was added to quench the reaction at -78°C. After the reaction mixture was stirred at RT for 10 min, acetic acid (0.06 mL) was added. Concentration *in vacuo* and purification using reverse phase HPLC (YMC S5 20 x 100 mm, 10 min. run, solvent A: 10% MeOH: 90% H_2O: 0.1% TFA, solvent B: 90% MeOH, 10% H_2O, 0.1% TFA) gave the title compound (TFA salt, 4.5 mg, Y = 32%) as a white solid. MS (E+) m/z: 428 (M+H); LC retention time: 3.18 min. ^{1}H NMR (400 MHz,

MeOD) δ ppm 8.00 (dt, *J*=8.60, 2.00 Hz, 2 H) 7.80 (d, *J*=8.00 Hz, 1 H) 7.73 (d, *J*=8.00 Hz, 1 H) 7.62 (dt, *J*=8.60, 2.00 Hz, 2 H) 7.38 - 7.43 (m, 1 H) 7.28 - 7.33 (m, 2 H) 7.22 (td, *J*=7.40, 1.20 Hz, 1 H) 4.44 (s, 1 H) 1.58 (s, 6 H) 1.06 (s, 3 H) 1.05 (s, 3 H).

EXAMPLE 400



Step 1

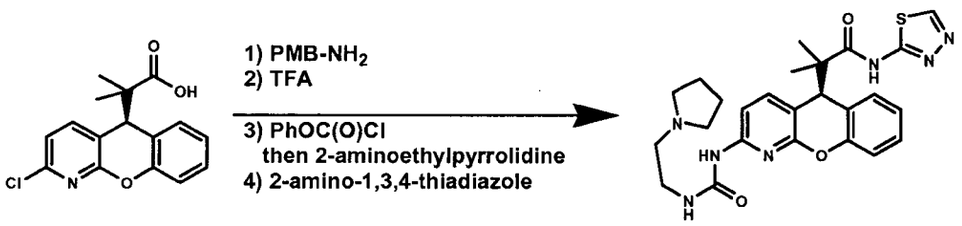
[00434] A mixture of the product of Preparation 30b (14 mg, 0.046 mmol) and piperazine (140 mg, 1.6 mmol) in a sealed tube was heated at 150°C under nitrogen for 30 min. Most of the piperidine was then removed at 160°C by passing nitrogen stream through the mixture to obtain a solid, which was dissolved anhydrous dichloromethane (1 mL). 1-pyrrolidinecarbonyl chloride (0.1 mL, 0.9 mmol) was added dropwise, followed by N, N-diisopropylethylamine (0.25 mL). The mixture was stirred at RT for 2 h, quenched with aqueous sodium hydroxide solution (1 M, 1 mL), concentrated *in vacuo*, and purified using reverse phase HPLC (YMC S5 20 x 100 mm, 10 min. run, solvent A: 10% MeOH: 90% H_2O: 0.1% TFA, solvent B: 90% MeOH, 10% H_2O, 0.1% TFA) gave the product (TFA salt, 20 mg, Y = 77%) as a white solid. MS (E+) m/z: 451 (M+H); LC retention time: 3.32 min.

Step 2

[00435] A mixture of the product of Step 1 (400a) (20 mg, 0.052 mmol), 2-amino-1,3,4-thiadiazole (18 mg, 0.18 mmol), HOBT hydrate (14 mg, 0.09 mmol), diisopropylethylamine (0.093 mL, 0.53 mmol), and EDC (27 mg, 0.14 mmol) in anhydrous acetonitrile (1.0 mL) was heated for 3 h at 80 °C. Purification using reverse phase HPLC (YMC S5 20 x 100 mm, 10 min. run, solvent A: 10% MeOH:

90% H_2O: 0.1% TFA, solvent B: 90% MeOH, 10% H_2O, 0.1% TFA) gave the title product (TFA salt, 12 mg, Y = 50%) as a white solid. MS (E+) m/z: 534 (M+H); LC retention time: 3.26 min. ^{1}H NMR (400 MHz, MeOD) δ ppm 9.09 (s, 1 H) 7.38 (d, *J*=8.56 Hz, 1 H) 7.27 - 7.33 (m, 1 H) 7.16 (dd, *J*=8.18, 1.13 Hz, 2 H) 7.04 (td, *J*=7.50, 1.30 Hz, 1 H) 6.52 (d, *J*=8.56 Hz, 1 H) 4.43 (s, 1 H) 3.54 - 3.59 (m, 4 H) 3.38 - 3.44 (m, 8 H) 1.85 - 1.90 (m, 4 H) 1.12 (s, 3 H) 1.10 (s, 3 H).

EXAMPLE 401



Step 1

[00436] A mixture of the product of Preparation 30b (50 mg, 0.17 mmol) and (4-methoxyphenyl)methanamine (0.4 mL) was stirred at 150°C under nitrogen for 26 hr. The mixture was concentrated *in vacuo*, and purified by preparative HPLC. The product (60 mg, Y = 62%) was obtained as a solid, TFA salt. MS (E+) m/z: 405 (M+H); LC retention time: 3.34 min.

Step 2

[00437] A mixture of the product of Step 1 (23 mg, 0.044 mmol), dichloromethane (0.5 mL), and TFA (0.5 mL) was stirred at room temperature for 3 hr before concentrating *in vacuo*. The residue was mixed with ethyl acetate (0.5 mL) and saturated aqueous sodium bicarbonate solution (0.5 mL). Solid potassium carbonate was added to make the mixture basic. The aqueous solution was separated, neutralized with 10% aqueous citric acid solution, and extracted with ethyl acetate (3 x 0.5 mL). The combined ethyl acetate extracts were dried (Na_2SO_4) and concentrated to gave an oil. MS (E+) m/z: 285 (M+H); LC retention time: 2.21 min.

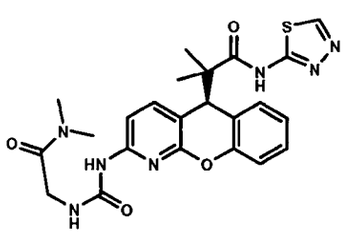
Step 3

[00438] The above product of Step 2 was mixed with pyridine (0.08 mL, 1 mmol) and anhydrous dichlormethane (0.5 mL). Phenyl chloroformate (0.03 mL, 0.24 mmol) was added at 0°C under nitrogen. The mixture was stirred at 0°C for 40 min before 1-(2-aminoethyl)pyrrolidine (0.15 mL, 1.2 mmol) was added. The reaction mixture was heated to 100°C (dichloromethane was distilled off during the heating), stirred at 100°C for 40 min, and then concentrated *in vacuo*. Purification using reverse phase HPLC (YMC S5 20 x 100 mm, 10 min. run, solvent A: 10% MeOH: 90% H_2O: 0.1% TFA, solvent B: 90% MeOH, 10% H_2O, 0.1% TFA) gave a solid (2TFA salt, 17 mg, Y = 59% for step 2 + 3). MS (E+) m/z: 425 (M+H); LC retention time: 2.29 min.

Step 4

[00439] A mixture of the product of Step 3 (16 mg, 0.025 mmol), 2-amino-1,3,4-thiadiazole (15 mg, 0.15 mmol), HOBT hydrate (13 mg, 0.086 mmol), pyridine (0.12 mL, 1.5 mmol), and EDC (24 mg, 0.12 mmol) in acetonitrile (1.0 mL) was heated for 6 h at 80 °C. Concentration *in vacuo* and purification using reverse phase HPLC (YMC S5 20 x 100 mm, 10 min. run, solvent A: 10% MeOH: 90% H_2O: 0.1% TFA, solvent B: 90% MeOH, 10% H_2O, 0.1% TFA) gave the title product, which was lyophilized to give a white solid (7 mg, Y = 37%) as a 2 TFA salt. MS (E+) m/z: 508 (M+H); LC retention time: 2.30 min. ^{1}H NMR (400 MHz, MeOD) δ ppm 9.09 (s, 1 H) 7.54 (d, *J*=8.31 Hz, 1 H) 7.32 - 7.37 (m, 1 H) 7.17 - 7.24 (m, 2 H) 7.11 (td, *J*=7.40, 1.40 Hz, 1 H) 6.83 (d, *J*=8.31 Hz, 1 H) 4.51 (s, 1 H) 3.77 - 3.86 (m, 2 H) 3.74 (t, *J*=5.54 Hz, 2 H) 3.44 (t, *J*=5.79 Hz, 2 H) 3.12 - 3.21 (m, 2 H) 2.18 (br. s., 2 H) 1.99 - 2.09 (m, 2 H) 1.15 (s, 3 H) 1.07 - 1.12 (m, 3 H).

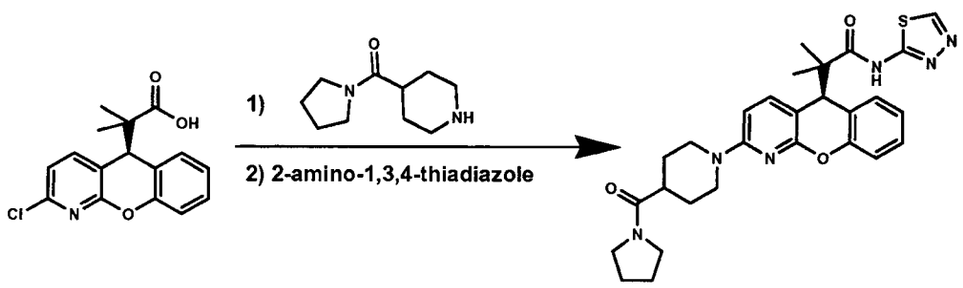
EXAMPLE 402



[00440] The title compound was prepared in the same manner as described for the preparation of the title compound of Example 401. MS (E+) m/z: 496 (M+H); LC

retention time: 2.76 min. ^{1}H NMR (400 MHz, MeOD) δ ppm 9.09 (s, 1 H) 7.49 (d, *J*=8.31 Hz, 1 H) 7.30 - 7.36 (m, 1 H) 7.17 - 7.26 (m, 2 H) 7.05 - 7.10 (m, 1 H) 6.88 (d, *J*=8.06 Hz, 1 H) 4.48 (s, 1 H) 4.24 (s, 2 H) 3.10 (s, 3 H) 3.01 (s, 3 H) 1.15 (s, 3 H) 1.12 (s, 3 H).

EXAMPLE 403



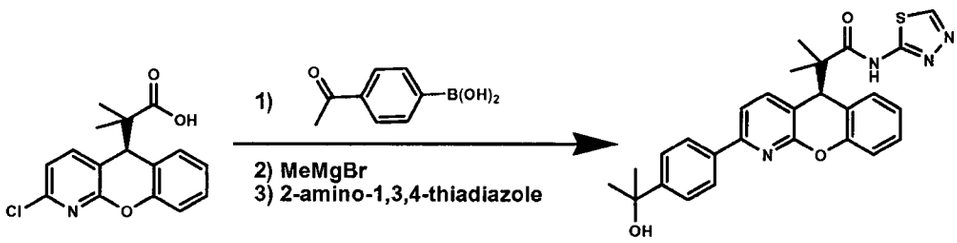
Step 1

[00441] A mixture of the product of Preparation 30b (14 mg, 0.046 mmol), piperidin-4-yl(pyrrolidin-1-yl)methanone (95 mg, 0.521 mmol), and anhydrous DMA (0.1 mL) was stirred at 150°C under nitrogen for 3 hr. Purification using reverse phase HPLC (YMC S5 20 x 100 mm, 10 min. run, solvent A: 10% MeOH: 90% H_2O: 0.1% TFA, solvent B: 90% MeOH, 10% H_2O, 0.1% TFA) gave the product (TFA salt, 22 mg, Y = 85%) as a solid. MS (E+) m/z: 450 (M+H); LC retention time: 3.16 min.

Step 2

[00442] The step was completed in the same manner as described in Example 400, Step 2 to obtain the title compound as a white solid, a TFA salt. MS (ES+) m/z: 533 (M+H); LC retention time: 3.15 min. ^{1}H NMR (400 MHz, MeOD) δ ppm 9.09 (s, 1 H) 7.37 (d, *J*=8.31 Hz, 1 H) 7.27 - 7.32 (m, 1 H) 7.13 - 7.19 (m, 2 H) 7.03 (td, *J*=7.40, 1.20 Hz, 1 H) 6.53 (d, *J*=8.56 Hz, 1 H) 4.42 (s, 1 H) 4.35 (d, *J*=13.35 Hz, 2 H) 3.62 (t, *J*=6.80 Hz, 2 H) 3.41 (t, *J*=6.92 Hz, 2 H) 2.93 (t, *J*=12.72 Hz, 2 H) 2.75 - 2.84 (m, 1 H) 1.96 - 2.04 (m, 2 H) 1.85 - 1.94 (m, 2 H) 1.66 - 1.84 (m, 4 H) 1.12 (br. s., 3 H) 1.11 (br. s., 3 H).

EXAMPLE 404



Step 1

[00443] A mixture of the product of Preparation 30b (45 mg, 0.15 mmol), 4-acetylphenylboronic acid (73 mg, 0.44 mmol), 2 M aqueous solution of potassium phosphate (0.52 mL, 1.0 mmol), and DMF (1 mL) was bubbled with nitrogen for 5 min before tetrakis(triphenylphosphine)palladium(0) (13 mg, 0.011 mmol) was added. The mixture was bubbled with nitrogen for an additional 5 min. After stirred at 90°C under nitrogen for 1.5 h, the mixture was partitioned between saturated aqueous sodium bicarbonate solution (3 mL) and diethyl ether (4 mL). The aqueous was separated, acidified to pH = 6, and extracted with ethyl acetate (3 x 2 mL). The combined ethyl acetate extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the product mixture as a liquid.

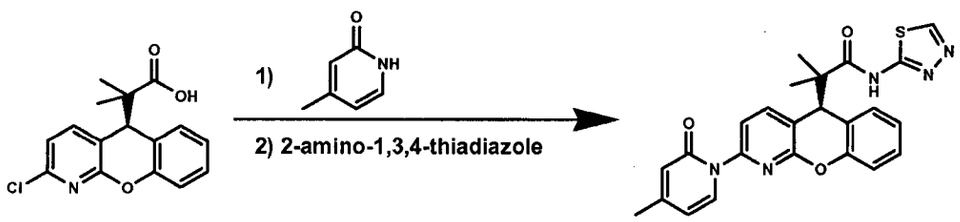
Step 2

[00444] The product mixture of Step 1 was dissolved in anhydrous THF (2 mL) and treated with methyl magnesium bromide solution (3 M in diethyl ether, 0.49 mL, 1.5 mmol) at -78°C under nitrogen. After the mixture was stirred at RT for 30 min, 10% aqueous citric acid solution was added to make the pH = 6. The mixture was extracted with ethyl acetate (3 x 1 mL). The combined ethyl acetate extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification using reverse phase HPLC (YMC S5 20 x 100 mm, 10 min. run, solvent A: 10% MeOH: 90% H_2O: 0.1% TFA, solvent B: 90% MeOH, 10% H_2O, 0.1% TFA) gave the product (TFA salt, 34 mg, Y = 44% for steps 1 + 2) as a white solid. MS (ES+) m/z: 404 (M+H); LC retention time: 3.33 min.

Step 3

[00445] A mixture of the product of Step 2 (18 mg, 0.045 mmol), 2-amino-1,3,4-thiadiazole (23 mg, 0.22 mmol), HOBT hydrate (17 mg, 0.11 mmol), diisopropylethylamine (0.12 mL, 0.67 mmol), and EDC (34 mg, 0.18 mmol) in anhydrous acetonitrile (1.0 mL) was stirred at 80 °C for 1 h and at RT overnight. The mixture was concentrated *in vacuo*. The residue was mixed with ethyl acetate (2 mL), washed with water (1 mL) and saturated aqueous sodium bicarbonate solution (2 x 1 mL), dried over sodium sulfate, and concentrated *in vacuo*. Purification using prep TLC gave the product (12 mg, Y = 47%) as a solid. MS (ES+) m/z: 487 (M+H); LC retention time: 3.34 min. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.91 (s, 1 H) 8.01 (d, *J*=8.31 Hz, 2 H) 7.74 (d, *J*=7.81 Hz, 1 H) 7.58 (d, *J*=8.56 Hz, 2 H) 7.50 (d, *J*=7.81 Hz, 1 H) 7.27 - 7.36 (m, 2 H) 7.24 (d, *J*=7.30 Hz, 1 H) 7.01 - 7.08 (m, 1 H) 4.82 (s, 1 H) 1.62 (s, 6 H) 1.30 (s, 3 H) 1.26 (s, 3 H).

EXAMPLE 405



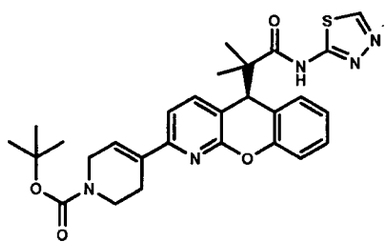
Step 1

[00446] To mixture of the product of Preparation 30b (15 mg, 0.049 mmol), 4-methylpyridin-2(1H)-one (11 mg, 0.099 mmol), copper(I) iodide (4.7 mg, 0.025 mmol), and potassium carbonate (20 mg, 0.15 mmol) was added a solution of N,N'-dimethylcyclohexane-1,2-diamine (11 mg, 0.077 mmol) in anhydrous DMA (0.2 mL) under nitrogen. The mixture was stirred at 120°C for 6 h and at 60°C overnight. Purification using reverse phase HPLC (YMC S5 20 x 100 mm, 10 min. run, solvent A: 10% MeOH: 90% H_2O: 0.1% TFA, solvent B: 90% MeOH, 10% H_2O, 0.1% TFA) and neutralization gave the product (7 mg, Y = 40%) as a solid. MS (ES+) m/z: 377 (M+H); LC retention time: 2.94 min.

Step 2

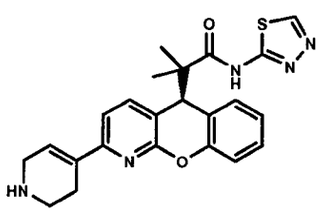
[00447] The step was completed in the same manner as described in Example 400, step 2 to obtain the product as a solid, a TFA salt. MS (ES+) m/z: 460 (M+H); LC retention time: 2.88 min. ^{1}H NMR (400 MHz, MeOD) δ ppm 9.09 (s, 1 H) 7.85 (d, *J*=8.06 Hz, 1 H) 7.80 (d, *J*=7.05 Hz, 1 H) 7.52 (d, *J*=7.81 Hz, 1 H) 7.36 (t, *J*=7.68 Hz, 1 H) 7.24 (br. s., 1 H) 7.22 (br. s., 1 H) 7.11 (t, *J*=7.30 Hz, 1 H) 6.45 (br. s., 1 H) 6.40 (d, *J*=7.05 Hz, 1 H) 4.67 (s, 1 H) 2.30 (s, 3 H) 1.20 (s, 3 H) 1.17 (s, 3 H).

EXAMPLE 406



[00448] The title compound was prepared from the S isomer of Preparation 30 (30b) in the manner described for the preparation of the title compound of Example 162, using commercially available (N-*tert*-butoxycarbonyl)-1,2,3,6-tetrahydropyridine-4-boronic acid pinacol ester. MS (ES+) m/z: 534 (M+H); LC retention time: 3.67 min. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 12.14 (br. s., 1 H) 8.93 (s, 1 H) 7.71 (d, *J*=7.81 Hz, 1 H) 7.24 - 7.30 (m, 3 H) 7.12 (d, *J*=7.81 Hz, 1 H) 6.99 - 7.06 (m, 1 H) 6.72 (br. s., 1 H) 4.89 (s, 1 H) 4.14 (br. s., 2 H) 3.58 - 3.69 (m, 2 H) 2.63 (br. s., 2 H) 1.49 (s, 9 H) 1.28 (s, 3 H) 1.26 (s, 3 H).

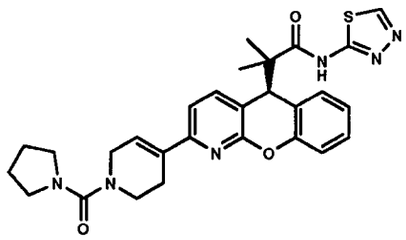
EXAMPLE 407



[00449] The title compound of Example 406 (57 mg, 0.11 mmol) was mixed with dichloromethane (6 mL) and TFA (3 mL). The mixture was stirred at RT for 1 h before concentrated *in vacuo*. Purification using reverse phase HPLC (YMC S5 20 x 100 mm, 10 min. run, solvent A: 10% MeOH: 90% H_2O: 0.1% TFA, solvent B: 90%

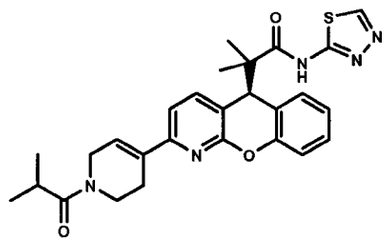
MeOH, 10% H_2O, 0.1% TFA) gave the title compound (2 TFA salt, 47 mg, Y = 67%) as a white solid. MS (ES+) m/z: 434 (M+H); LC retention time: 2.19 min. ^{1}H NMR (400 MHz, MeOD) δ ppm 9.10 (s, 1 H) 7.65 (d, *J*=7.81 Hz, 1 H) 7.35 (d, *J*=7.81 Hz, 2 H) 7.23 (td, *J*=7.93, 1.26 Hz, 2 H) 7.08 - 7.14 (m, 1 H) 6.69 - 6.74 (m, 1 H) 4.60 (s, 1 H) 3.88 - 3.94 (m, 2 H) 3.47 (t, *J*=6.17 Hz, 2 H) 2.84 - 2.94 (m, 2 H) 1.17 (s, 3 H) 1.10 (s, 3 H).

EXAMPLE 408



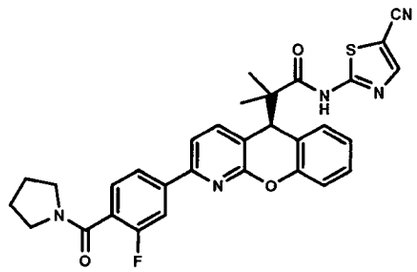
[00450] To a stirred solution of the title compound of Example 407 (14 mg, 0.021 mmol) and N,N-diisopropylethylamine (0.1 mL) in anhydrous THF (1 mL) was added 1-pyrrolidinecarbonyl chloride (0.01 mL, 0.09 mmol) under nitrogen. The mixture was stirred at RT for 45 min before water (0.1 mL) and methanol (1 mL) were added to quench the reaction. The mixture was concentrated *in vacuo*. Purification using reverse phase HPLC (YMC S5 20 x 100 mm, 10 min. run, solvent A: 10% MeOH: 90% H_2O: 0.1% TFA, solvent B: 90% MeOH, 10% H_2O, 0.1% TFA) gave the title compound (TFA salt, 10 mg, Y = 73%) as a solid. MS (ES+) m/z: 531 (M+H); LC retention time: 3.36 min. ^{1}H NMR (400 MHz, MeOD) δ ppm 9.09 (s, 1 H) 7.61 (d, *J*=7.81 Hz, 1 H) 7.31 - 7.37 (m, 1 H) 7.19 - 7.29 (m, 3 H) 7.06 - 7.11 (m, 1 H) 6.69 (br. s., 1 H) 4.57 (s, 1 H) 4.01 - 4.05 (m, 2 H) 3.53 (t, *J*=5.54 Hz, 2 H) 3.39 - 3.45 (m, 4 H) 2.66 (br. s., 2 H) 1.85 - 1.91 (m, 4 H) 1.15 (s, 3 H) 1.12 (s, 3 H).

EXAMPLE 409



[00451] To a stirred solution of HOBT hydrate (20 mg, 0.13 mmol), and N,N-diisopropylethylamine (0.10 mL, 0.57 mmol) in anhydrous acetonitrile (1 mL) was added isobutyryl chloride (0.010 mL, 0.095 mmol) under nitrogen. The mixture was stirred at RT for 10 min before the title compound of Example 10 (11 mg, 0.017 mmol) was added. After the mixture was stirred at RT for 2 h, water (0.1 mL) was added to quench the reaction. The mixture was concentrated *in vacuo*. Purification using reverse phase HPLC (YMC S5 20 x 100 mm, 10 min. run, solvent A: 10% MeOH: 90% H_2O: 0.1% TFA, solvent B: 90% MeOH, 10% H_2O, 0.1% TFA) gave the title compound (TFA salt, 7.6 mg, Y = 74%) as a white solid. MS (ES+) m/z: 504 (M+H); LC retention time: 3.32 min. ^{1}H NMR (400 MHz, MeOD) δ ppm 9.09 (s, 1 H) 7.61 (d, *J*=7.81 Hz, 1 H) 7.26 - 7.37 (m, 2 H) 7.22 (dt, *J*=7.81, 2.27 Hz, 2 H) 7.06 - 7.12 (m, 1 H) 6.69 (br. s., 1 H) 4.57 (s, 1 H) 4.34 (br. s., 1 H) 4.25 (br. s., 1 H) 3.81 (t, *J*=5.67 Hz, 2 H) 2.94 - 3.08 (m, 1 H) 2.72 (br. s., 1 H) 2.61 (br. s., 1 H) 1.11 - 1.16 (m, 12 H).

EXAMPLE 410

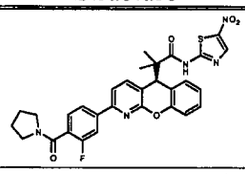
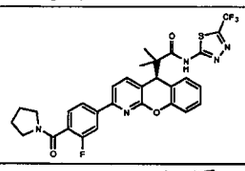
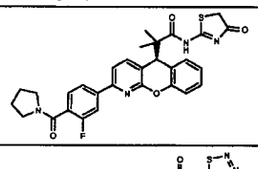
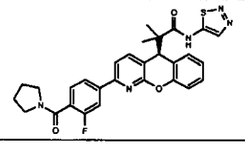


[00452] The product of Step 1 of Example 398 (398a) (12 mg, 0.026 mmol) was mixed with DMF (0.2 mL), N,N-diisopropylethylamine (0.050 mL, 0.29 mmol), HATU (30 mg, 0.078 mmol), and 2-amino-5-cyanothiazole (16 mg, 0.13 mmol). The reaction mixture was stirred at 80°C for 6 hr. Purification using reverse phase HPLC

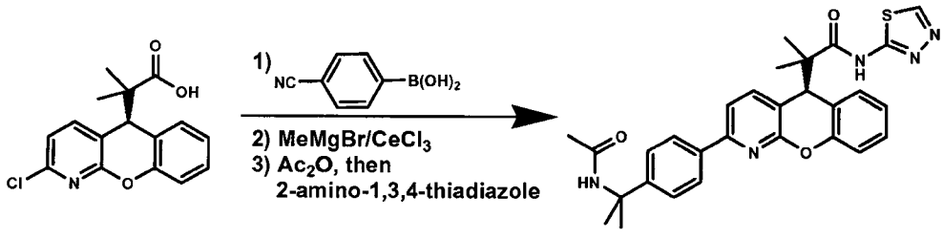
(YMC S5 20 x 100 mm, 10 min. run, solvent A: 10% MeOH: 90% H_2O: 0.1% TFA, solvent B: 90% MeOH, 10% H_2O, 0.1% TFA) gave the title compound (TFA salt, 5.7 mg, Y = 25%) as a yellow solid. MS (ES+) m/z: 568 (M+H); LC retention time: 3.66 min. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.15 (s, 1 H) 7.91 - 7.98 (m, 2 H) 7.73 (d, *J*=2.77 Hz, 2 H) 7.53 (t, *J*=7.43 Hz, 1 H) 7.35 - 7.41 (m, 1 H) 7.21 - 7.30 (m, 2 H) 7.10 - 7.16 (m, 1 H) 4.62 (s, 1 H) 3.63 (t, *J*=6.92 Hz, 2 H) 3.36 - 3.42 (m, 2 H) 1.91 - 2.06 (m, 4 H) 1.18 (s, 3 H) 1.15 (s, 3 H).

EXAMPLES 411 TO 414

[00453] The following Examples 411 to 414 were prepared in the same manner as described for the preparation of the title compound of Example 410.

Example No.	Structure	Rt (min)	M/z $(MH)^+$
411		3.78	588
412		3.88	612
413		3.38	559
414		3.49	544

EXAMPLE 415



Step 1

[00454] A mixture of the product of Preparation 30b (183 mg, 0.60 mmol), 4-cyanophenylboronic acid (240 mg, 1.6 mmol), 2 M aqueous solution of potassium phosphate (2.1 mL, 4.2 mmol), and DMF (6 mL) was bubbled with nitrogen for 5 min before tetrakis(triphenylphosphine)palladium(0) (70 mg, 0.060 mmol) was added. After bubbled with nitrogen for an additional 5 min, the reaction mixture was stirred at 90°C under nitrogen for 4 h. The mixture was concentrated *in vacuo*, mixed with water (5 mL), neutralized with 6N aqueous HCl solution, and extracted with ethyl acetate (3 x 2 mL). The combined ethyl acetate extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification using reverse phase HPLC (YMC S5 20 x 100 mm, 10 min. run, solvent A: 10% MeOH: 90% H_2O: 0.1% TFA, solvent B: 90% MeOH, 10% H_2O, 0.1% TFA) gave the product (195 mg, Y = 87%) as a solid. MS (ES+) m/z: 371 (M+H); LC retention time: 3.41 min.

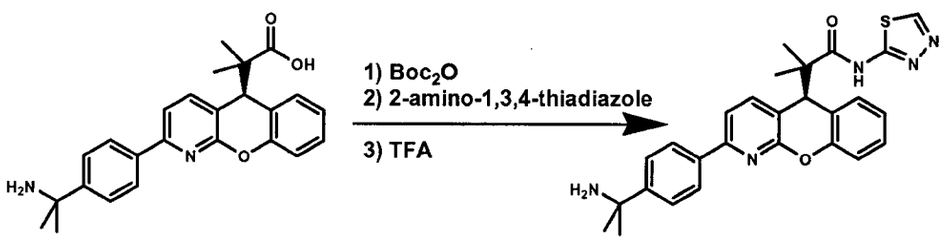
Step 2

[00455] To a stirred cerium(III) chloride (340 mg, 1.4 mmol) in a dry flask was added anhydrous THF (6 mL) under nitrogen. The mixture was stirred at room temperature for 40 min before methyllithium (0.85 mL, 1.4 mmol) was added dropwise at -78°C under nitrogen. After the mixture was stirred at -78°C for 40 min, the product of Step 1 (93 mg, 0.25 mmol) was added. The reaction mixture was stirred at -78°C for 40 min and at RT for 2 hr before water (3 mL) was added. The aqueous layer was neutralized with 10% aqueous citric acid to pH = 8, extracted with ethyl acetate (2 x 2 mL), and then neutralized with 10% aqueous citric acid to pH = 6, extracted with ethyl acetate (2 x 2 mL). The combined organic solutions were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was dissolved in methanol (1.8 mL) and trifluoroacetic acid (0.2 mL). Purification using reverse phase HPLC (YMC S5 20 x 100 mm, 10 min. run, solvent A: 10% MeOH: 90% H_2O: 0.1% TFA, solvent B: 90% MeOH, 10% H_2O, 0.1% TFA) gave the product (TFA salt, 18 mg, Y = 14%) as a yellow solid. (ES+) m/z: 403 (M+H); LC retention time: 2.46 min.

Step 3

[00456] To a clear solution of the product of Step 2 (8.0 mg, 0.015 mmol) and N,N-diisopropylethylamine (0.10 mL, 0.57 mmol) in anhydrous dichloromethane (1 mL) was added acetic anhydride (10 µL, 0.11 mmol) under nitrogen. The reaction mixture was stirred at RT for 1 hr and concentrated *in vacuo*. The residue was mixed with anhydrous MeCN (1 mL), HOBT (40 mg, 0.26 mmol), 2-Amino-1,3,4-thiadiazole (60 mg, 0.59 mmol), EDC (100 mg, 0.52 mmol), and N,N-diisopropylethylamine (0.20 mL, 1.1 mmol). After stirred at 80°C under nitrogen for 2 hr, the mixture was concentrated, mixed with saturated aqueous sodium bicarbonate solution (5 mL), and extracted with dichloromethane (3 x 1 mL). The combined methylene chloride extracts were dried (Na_2SO_4). Flash chromatography purification (0% to 100% ethyl acetate in hexanes then 0=>10% MeOH in ethyl acetate) afforded a crude product, which was purified using reverse phase HPLC (YMC S5 20 x 100 mm, 10 min. run, solvent A: 10% MeOH: 90% H_2O: 0.1% TFA, solvent B: 90% MeOH, 10% H_2O, 0.1% TFA) to give the title compound (TFA salt, 3 mg, Y = 30%).. MS (ES+) m/z: 528 (M+H); LC retention time: 3.24 min. ^{1}H NMR (400 MHz, MeOD) δ ppm 9.10 (s, 1 H) 7.94 (d, *J*=8.31 Hz, 2 H) 7.70 (d, *J*=7.81 Hz, 1 H) 7.59 (d, *J*=7.81 Hz, 1 H) 7.48 (d, *J*=8.31 Hz, 2 H) 7.36 (t, *J*=7.68 Hz, 1 H) 7.20 - 7.29 (m, 2 H) 7.10 (t, *J*=7.43 Hz, 1 H) 4.61 (s, 1 H) 1.96 (s, 3 H) 1.66 (s, 6 H) 1.18 (s, 3 H) 1.16 (s, 3 H)

EXAMPLE 416



Step 1

[00457] To a stirred solution of the product of Step 2 in Example 415 (415b)(12 mg, 0.024 mmol), dioxane (0.5 mL), NaOH (0.097 mL, 0.048 mmol), and acetonitrile (2 mL) was added Boc2O (8.4 µL, 0.036 mmol). The reaction mixture was stirred at

RT for 4 h. After more Boc2O (30 mg) was added, the mixture was stirred at RT for 2 hr and then concentrated *in vacuo*. The residue was mixed with water (0.5 mL), acidified with 10% aqueous citric acid solution to pH = 5, and extracted with ethyl acetate. The combined ethyl acetate extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give a crude product as a yellow liquid.

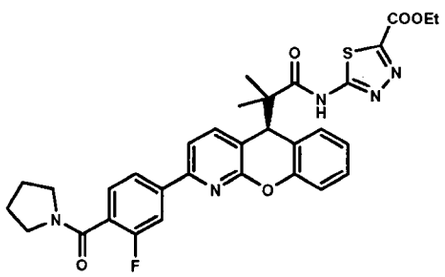
Step 2

[00458] The step was completed in the same manner as described in Example 400, step 2. using the product of Step 1 (416a).

Step 3

[00459] The product of Step 2 was dissolved in methylene chloride (1 mL) and TFA (0.5 mL). The mixture was stirred at RT for 1 hr before concentrated. Purification using reverse phase HPLC (YMC S5 20 x 100 mm, 10 min. run, solvent A: 10% MeOH: 90% H_2O: 0.1% TFA, solvent B: 90% MeOH, 10% H_2O, 0.1% TFA) gave the title compound (2TFA, 7 mg, Y = 40% for steps 1 + 2 + 3) as a white solid. . MS (ES-) m/z: 484 (M-H); LC retention time: 2.66 min. ^{1}H NMR (400 MHz, MeOD) δ ppm 9.11 (s, 1 H) 8.12 (d, *J*=8.56 Hz, 2 H) 7.73 (d, *J*=8.00 Hz, 1 H) 7.61 - 7.68 (m, 3 H) 7.35 - 7.40 (m, 1 H) 7.24 - 7.29 (m, 2 H) 7.13 (td, *J*=7.43, 1.26 Hz, 1 H) 4.64 (s, 1 H) 1.78 (s, 6 H) 1.20 (s, 3 H) 1.15 (s, 3 H).

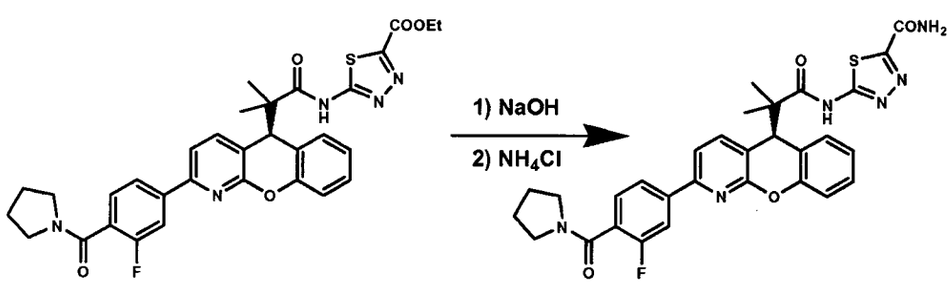
EXAMPLE 417



[00460] To a stirred mixture of the product of Step 1 in Example 398 (400mg, 0.87 mmol), ethyl 5-amino-1,3,4-thiadiazole-2-carboxylate (400mg, 2.3 mmol), HOBT hydrate (140mg, 0.91 mmol), and anhydrous MeCN (10 mL) was added EDC (340mg, 1.8 mmol) at RT under nitrogen, followed by N,N-diisopropylethylamine

(0.2 mL, 1.1 mmol). After stirring at 80°C for 4.5 h, the reaction mixture was concentrated, mixed with water (15 mL) and ethyl acetate (15 mL). The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic solutions were dried (Na_2SO_4), concentrated *in vacuo*, and purified by flash chromatography (20-100% ethyl acetate in hexanes) gave the title product (410 mg, Y = 77%) as a yellow solid. MS (ES+) m/z: 616 (M+H); LC retention time: 3.70 min. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 10.16 (br. s., 1 H) 8.04 (br. s., 1 H) 7.82 - 7.88 (m, 2 H) 7.53 (t, *J*=8.31 Hz, 2 H) 7.31 - 7.34 (m, 2 H) 7.22 (d, *J*=7.55 Hz, 1 H) 7.05 (ddd, *J*=7.87, 5.10, 3.15 Hz, 1 H) 4.86 (s, 1 H) 4.56 (q, *J*=7.13 Hz, 2 H) 3.68 (t, *J*=6.92 Hz, 2 H) 3.36 (t, *J*=6.55 Hz, 2 H) 1.87 - 2.06 (m, 4 H) 1.48 (t, *J*=7.18 Hz, 3 H) 1.35 (s, 3 H) 1.23 (s, 3 H).

EXAMPLE 418



Step 1

[00461] To a stirred solution of the title compound of Example 417 (183 mg, 0.30 mmol) in MeOH (1.5 mL) was added 1M aqueous sodium hydroxide solution (1.0 ml, 1.0 mmol). The reaction mixture was stirred at RT for 1.5 hr before concentrated under reduced pressure to remove methanol and lypholized to remove water to give a yellow solid (207 mg).

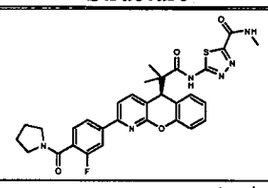
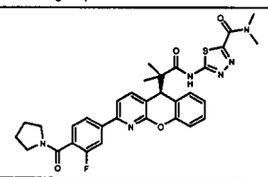
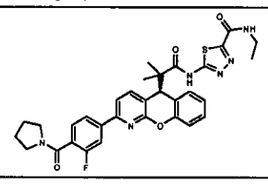
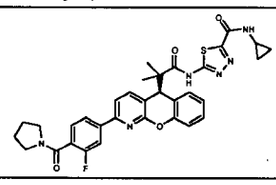
Step 2

[00462] To a dry flask were added the product of Step 1 (21 mg, 0.029 mmol) ammonium chloride (18 mg, 0.34 mmol), N,N-diisopropylethylamine (50 μL, 0.29 mmol), and anhydrous DMF (0.3 mL) at RT under nitrogen. The mixture was stirred at RT for 2 min before PyBOP (20 mg, 0.038 mmol) was added. The mixture was at

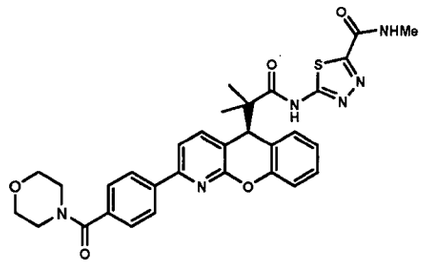
RT for 1 h. Purification using reverse phase HPLC (YMC S5 20 x 100 mm, 10 min. run, solvent A: 10% MeOH: 90% H_2O: 0.1% TFA, solvent B: 90% MeOH, 10% H_2O, 0.1% TFA) gave the title product (TFA salt, 16 mg, Y = 79 %) as a white solid. MS (ES+) m/z: 587 (M+H); LC retention time: 3.34 min. ^{1}H NMR (400 MHz, MeOD) δ ppm 7.90 - 7.97 (m, 2 H) 7.69 - 7.76 (m, 2 H) 7.52 (t, *J*=7.43 Hz, 1 H) 7.35 - 7.40 (m, 1 H) 7.23 - 7.30 (m, 2 H) 7.13 (t, *J*=7.43 Hz, 1 H) 4.63 (s, 1 H) 3.63 (t, *J*=6.92 Hz, 2 H) 3.39 (t, *J*=6.55 Hz, 2 H) 1.91 - 2.06 (m, 4 H) 1.20 (s, 3 H) 1.16 (s, 3 H).

EXAMPLE 419 TO 422

[00463] The following Examples 419 to 422 can be prepared in the same manner as described for the preparation of the title compound of Example 418 from the corresponding amine.

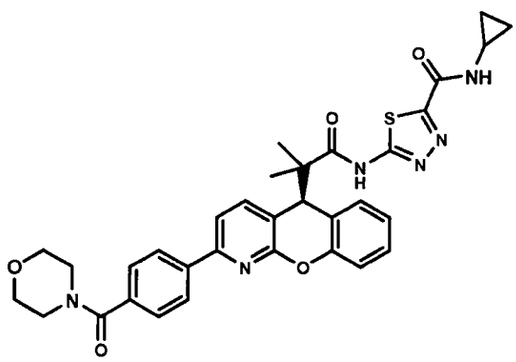
Example No.	Structure	Rt (min)	M/z $(MH)^+$
419		3.41	601
420		3.44	615
421		3.49	615
422		3.52	627

EXAMPLE 422[a]



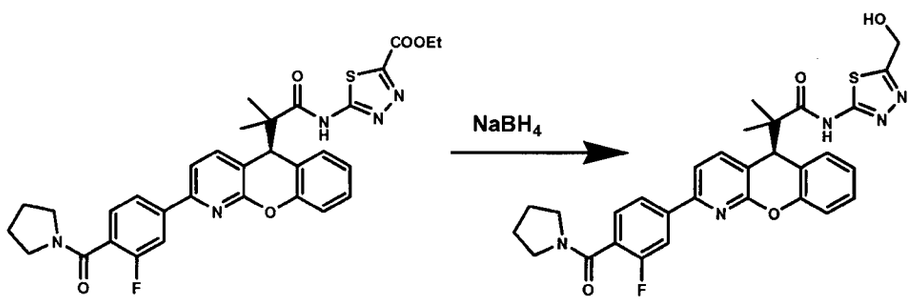
[00464] The title compound was prepared in the same manner described above for the preparation of the title compounds of Examples 419-422, substituting commercially available boronic acid (4-(morpholine-4-carbonyl)phenylboronic acid) in place of 3-fluoro-4-(pyrrolidine-1-carbonyl)phenylboronic acid in the first step of Example 398. MS (ES+) m/z: 599 (M+H); LC retention time: 3.15 min.

EXAMPLE 422[b]



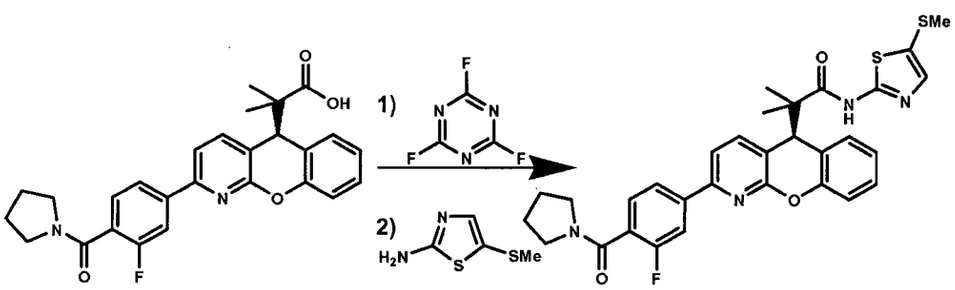
The title compound was prepared in the same manner described above for the preparation of the title compound of Examples 422[a]. MS (ES+) m/z: 625 (M+H); LC retention time: 3.28 min.

EXAMPLE 423



[00465] To a stirred solution of the title compound of Example 417 (17 mg, 0.028 mmol) in THF (0.5 mL) and ethanol (0.5 mL) was added $NaBH_4$ (17mg, 0.45 mmol) portionwise. The mixture was stirred at RT for 1 hr before acetone (1 mL) was added to quench the reaction. The mixture was concentrated *in vacuo*. Purification using reverse phase HPLC (YMC S5 20 x 100 mm, 10 min. run, solvent A: 10% MeOH: 90% H_2O: 0.1% TFA, solvent B: 90% MeOH, 10% H_2O, 0.1% TFA) gave the title compound (TFA salt, 12 mg, Y = 63%) as a white solid. MS (ES+) m/z: 574 (M+H); LC retention time: 3.28 min. ^1H NMR (400 MHz, MeOD) δ ppm 7.90 - 7.98 (m, 2 H) 7.69 - 7.77 (m, 2 H) 7.53 (t, *J*=7.43 Hz, 1 H) 7.35 - 7.40 (m, 1 H) 7.23 - 7.30 (m, 2 H) 7.13 (td, *J*=7.43, 1.26 Hz, 1 H) 4.92 (s, 2 H) 4.63 (s, 1 H) 3.63 (t, *J*=6.92 Hz, 2 H) 3.39 (t, *J*=6.55 Hz, 2 H) 1.91 - 2.06 (m, 4 H) 1.18 (s, 3 H) 1.15 (s, 3 H).

EXAMPLE 424



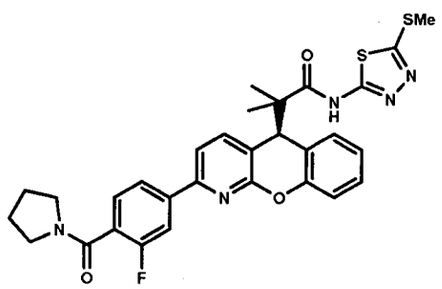
Step 1

[00466] To a solution of the product of Step 1 in Example 398 (170 mg, 0.37 mmol) and pyridine (0.060 mL, 0.74 mmol) in anhydrous dichloromethane (2 mL) was added 2,4,6-trifluoro-1,3,5-triazine (0.062 mL, 0.74 mmol) dropwise at 0°C under nitrogen. After stirred at 0°C for 30 min and at RT for 1.5 hr, the mixture was poured into water (2 mL) at 0°C. The aqueous layer was separated and extracted with methylene chloride (3 x 1 mL). The combined methylene chloride solutions were dried (Na_2SO_4). Flash chromatography purification (20=>100% ethyl acetate in hexanes) afforded the product (153 mg, Y = 90 %) as a white solid. MS (ES+) m/z: 463 (M+H); LC retention time: 3.56 min.

Step 2

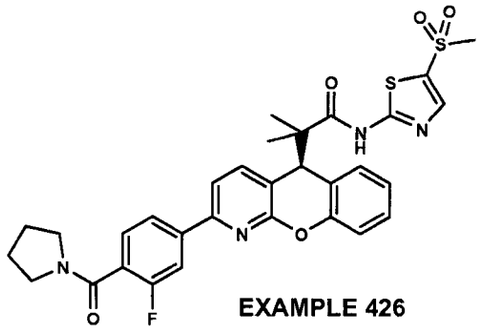
[00467] A mixture of the product of Step 1 (30 mg, 0.065 mmol), 5-(methylthio)thiazol-2-amine (19 mg, 0.13 mmol), pyridine (50 µL, 0.60 mmol), and anhydrous acetonitrile (1 mL) was stirred at RT under nitrogen for 60 h. EDC (15 mg) was added. The mixture was stirred at 80°C 4 h and at 90°C for 2 h. Purification using reverse phase HPLC (YMC S5 20 x 100 mm, 10 min. run, solvent A: 10% MeOH: 90% H_2O: 0.1% TFA, solvent B: 90% MeOH, 10% H_2O, 0.1% TFA) gave the title product (32 mg, Y = 83 % yield) as a yellowish solid. MS (ES+) m/z: 589 (M+H); LC retention time: 3.82 min. ^{1}H NMR (400 MHz, MeOD) δ ppm 7.88 - 7.95 (m, 2 H) 7.73 (d, *J*=8.0 Hz, 1 H) 7.69 (d, *J*=8.0 Hz, 1 H) 7.51 (t, *J*=7.43 Hz, 1 H) 7.43 (s, 1 H) 7.36 (td, *J*=7.8, 1.2 Hz, 1 H) 7.26 (d, *J*=8.56 Hz, 2 H) 7.12 (td, *J*=7.5, 1.0 Hz, 1 H) 4.61 (s, 1 H) 3.62 (t, *J*=6.80 Hz, 2 H) 3.38 (t, *J*=6.67 Hz, 2 H) 2.45 (s, 3 H) 1.91 - 2.06 (m, 4 H) 1.15 (s, 3 H) 1.10 (s, 3 H).

EXAMPLE 425

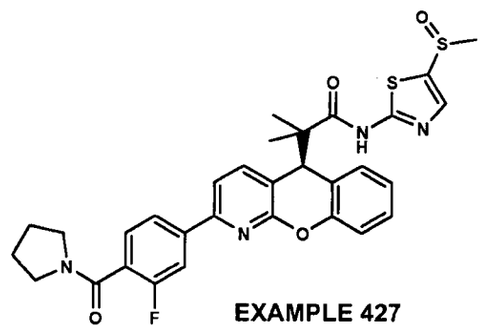


[00468] The title compound was prepared in the same manner as described for the preparation of the title compound of Example 424 from 5-(methylthio)thiadiazol-2-amine. MS (ES+) m/z: 590 (M+H); LC retention time: 3.71 min. ^{1}H NMR (400 MHz, MeOD) δ ppm 7.91 - 7.98 (m, 2 H) 7.75 (d, *J*=8.0 Hz, 1 H) 7.72 (d, *J*=8.0 Hz, 1 H) 7.53 (t, *J*=7.55 Hz, 1 H) 7.35 - 7.41 (m, 1 H) 7.23 - 7.30 (m, 2 H) 7.14 (t, *J*=7.43 Hz, 1 H) 4.61 (s, 1 H) 3.63 (t, *J*=6.92 Hz, 2 H) 3.39 (t, *J*=6.67 Hz, 2 H) 2.76 (s, 3 H) 1.92 - 2.05 (m, 4 H) 1.17 (s, 3 H) 1.13 (s, 3 H).

EXAMPLES 426 AND 427



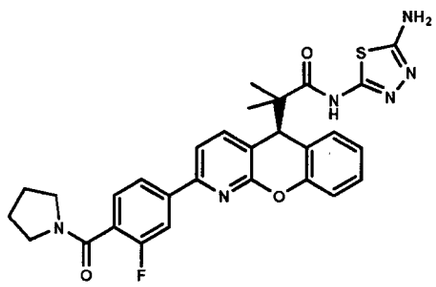
EXAMPLE 426



EXAMPLE 427

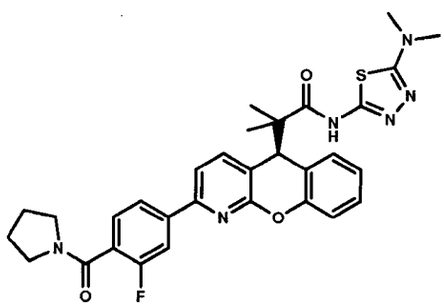
[00469] To a clear solution of the title compound of Example 424 (22 mg, 0.038 mmol) and TFA (15 μL, 0.20 mmol) in dichloromethane (1 mL) was added mCPBA (57-86%, 14 mg) at 0°C. The reaction mixture was stirred at the same temperature for 1.5 h and at RT for 1 h before saturated aqueous sodium bicarbonate solution (1 mL) was added. The aqueous solution was extracted with dichloromethane (2 x 1 mL). The combined dichloromethane solutions were dried (Na_2SO_4). Flash chromatography purification (50=>100% ethyl acetate in heptanes; then 0-20% methanol in ethyl acetate) afforded the sulfoxide (5 mg) and the sulfone (24 mg). Each of them was separately purified using reverse phase HPLC (YMC S5 20 x 100 mm, 10 min. run, solvent A: 10% MeOH: 90% H_2O: 0.1% TFA, solvent B: 90% MeOH, 10% H_2O, 0.1% TFA) to give the title compound of Example 427 (TFA salt, 3 mg, Y = 11%) as a white solid. (MS (ES+) m/z: 605 (M+H); LC retention time: 3.27 min, ^{1}H NMR (400 MHz, MeOD) δ ppm 7.91 - 7.98 (m, 3 H) 7.70 - 7.78 (m, 2 H) 7.53 (t, *J*=7.43 Hz, 1 H) 7.35 - 7.40 (m, 1 H) 7.24 - 7.30 (m, 2 H) 7.13 (td, *J*=7.50, 1.20 Hz, 1 H) 4.64 (s, 1 H) 3.63 (t, *J*=6.92 Hz, 2 H) 3.39 (t, *J*=6.55 Hz, 2 H) 3.09 (s, 3 H) 1.91 - 2.06 (m, 4 H) 1.18 (d, *J*=3.53 Hz, 3 H) 1.14 (d, *J*=3.78 Hz, 3 H)) and the title compound of Example 426 (TFA salt, 19 mg, Y = 69%) as a white solid. (MS (ES+) m/z: 621 (M+H); LC retention time: 3.36 min, ^{1}H NMR (400 MHz, MeOD) δ ppm 8.06 (s, 1 H) 7.89 - 7.96 (m, 2 H) 7.74 (d, *J*=8.0 Hz, 1 H) 7.71 (d, *J*=8.0 Hz, 1 H) 7.52 (t, *J*=7.43 Hz, 1 H) 7.37 (td, *J*=7.7, 1.3 Hz, 1 H) 7.23 - 7.29 (m, 2 H) 7.11 - 7.16 (m, 1 H) 4.62 (s, 1 H) 3.63 (t, *J*=6.92 Hz, 2 H) 3.39 (t, *J*=6.55 Hz, 2 H) 3.30 (s, 3 H) 1.92 - 2.05 (m, 4 H) 1.18 (s, 3 H) 1.14 (s, 3 H)).

EXAMPLE 428



[00470] A mixture of the product of Step 1 of Example 398 (15 mg, 0.032 mmol), 1,3,4-thiadiazole-2,5-diamine (20 mg, 0.17 mmol), and anhydrous DMF (0.2 mL) was sonicated and stirred at RT overnight under nitrogen. Purification using reverse phase HPLC (YMC S5 20 x 100 mm, 10 min. run, solvent A: 10% MeOH: 90% H_2O: 0.1% TFA, solvent B: 90% MeOH, 10% H_2O, 0.1% TFA) gave the title compound (TFA salt, 20 mg, 90 % yield) as a white solid. MS (E+) m/z: 559 (M+H); LC retention time: 3.02 min. ^{1}H NMR (400 MHz, MeOD) δ ppm 7.97 (dd, *J*=8.0, 1.6 Hz, 1 H) 7.94 (dd, *J*=11.21, 1.38 Hz, 1 H) 7.79 (d, *J*=8.0 Hz, 1 H) 7.76 (d, *J*=8.0 Hz, 1 H) 7.54 (t, *J*=7.55 Hz, 1 H) 7.39 (td, *J*=7.8, 1.6 Hz, 1 H) 7.25 - 7.30 (m, 2 H) 7.17 (td, *J*=7.6, 1.2 Hz, 1 H) 4.54 (s, 1 H) 3.63 (t, *J*=6.92 Hz, 2 H) 3.39 (t, *J*=6.55 Hz, 2 H) 1.91 - 2.06 (m, 4 H) 1.15 (s, 3 H) 1.14 (s, 3 H).

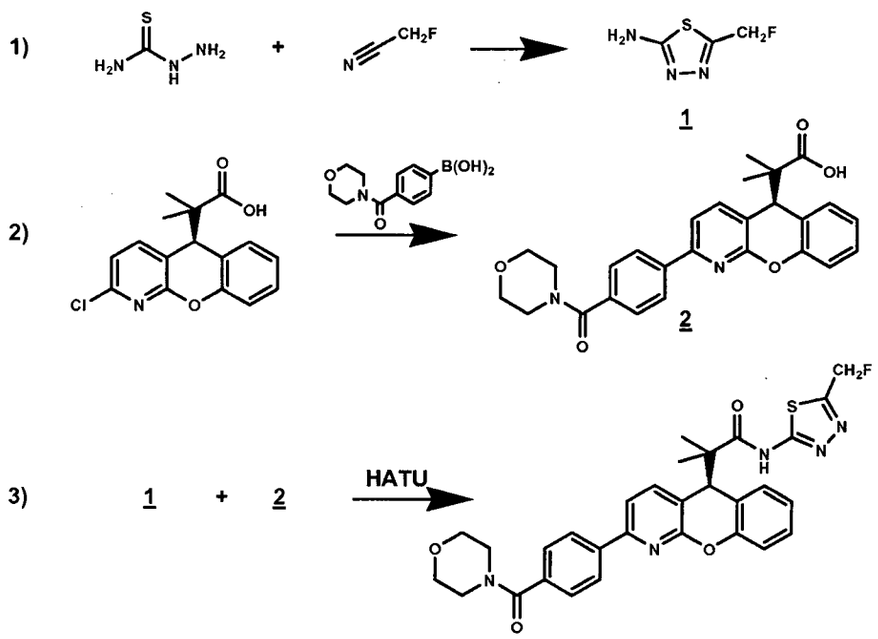
EXAMPLE 429



[00471] A mixture of 5-bromo-1,3,4-thiadiazol-2-amine (90 mg, 0.50 mmol), dimethylamine hydrochloride (410 mg, 5.0 mmol), 2-propanol (0.6 mL), and N,N-diisopropylethylamine (0.90 mL, 5.0 mmol) was stirred at 150°C for 1 h under nitrogen in a CEM microwave reactor. Saturated aqueous sodium bicarbonate solution (6 mL) was added with caution, and the mixture was extracted with ethyl

acetate (4 x 2 mL). The combined ethyl acetate extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give a crude product (16 mg, N2,N2-dimethyl-1,3,4-thiadiazole-2,5-diamine), which was mixed with anhydrous acetonitrile (1 mL), N,N-diisopropylethylamine (0.1 mL, 0.57 mmol), and the product of Step 1 in Example 426 (15 mg, 0.032 mmol). The mixture was stirred at RT under nitrogen overnight. Purification using reverse phase HPLC (YMC S5 20 x 100 mm, 10 min. run, solvent A: 10% MeOH: 90% H_2O: 0.1% TFA, solvent B: 90% MeOH, 10% H_2O, 0.1% TFA) gave the title compound (TFA salt, 4 mg, Y = 18 %) as a white solid. MS (E+) m/z: 587 (M+H); LC retention time: 3.32 min. ^{1}H NMR (400 MHz, MeOD) δ ppm 7.91 - 7.99 (m, 2 H) 7.79 (d, *J*=8.0 Hz, 1 H) 7.75 (d, *J*=8.0 Hz, 1 H) 7.54 (t, *J*=7.55 Hz, 1 H) 7.39 (td, *J*=7.7, 1.2 Hz, 1 H) 7.25 - 7.30 (m, 2 H) 7.16 (td, *J*=7.7, 1.2 Hz, 1 H) 4.56 (s, 1 H) 3.63 (t, *J*=6.92 Hz, 2 H) 3.39 (t, *J*=6.67 Hz, 2 H) 3.26 (s, 6 H) 1.91 - 2.07 (m, 4 H) 1.16 (s, 3 H) 1.14 (s, 3 H).

EXAMPLE 430



Step 1

[00472] A mixture of hydrazinecarbothioamide (550 mg, 6.0 mmol), 2-fluoroacetonitrile (0.34 mL, 6.0 mmol), and TFA (3 mL) was stirred at 60°C for 4 hr.

The mixture was concentrated *in vacuo*. The residue was dissolved in water (15 mL), basified with saturated aqueous sodium bicarbonate solution (20 mL) and saturated aqueous potassium phosphate solution, and mixed with ethyl acetate (10 mL).The solid was filtered, washed with water and ethyl acetate, and dried to give a white solid (100 mg). The filtrate was extracted with ethyl acetate (3 x 10 mL). All organic solutions were combined, dried (Na_2SO_4), and concentrated under reduced pressure. The solid residue obtained was triturated with ethyl acetate to give a white solid (210 mg). Both of the solid were the desired 5-(fluoromethyl)-1,3,4-thiadiazol-2-amine (310 mg, 39% yield). MS (E+) m/z: 134 (M+H); LC retention time: 0.28 min.

Step 2

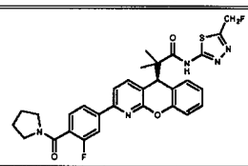
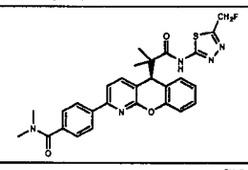
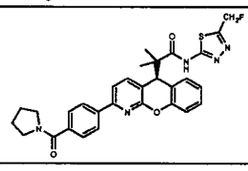
[00473] The step was completed in the same manner as described in Example 398 Step 1 to obtain the product as a white solid. MS (ES+) m/z: 459 (M+H); LC retention time: 3.10 min.

Step 3

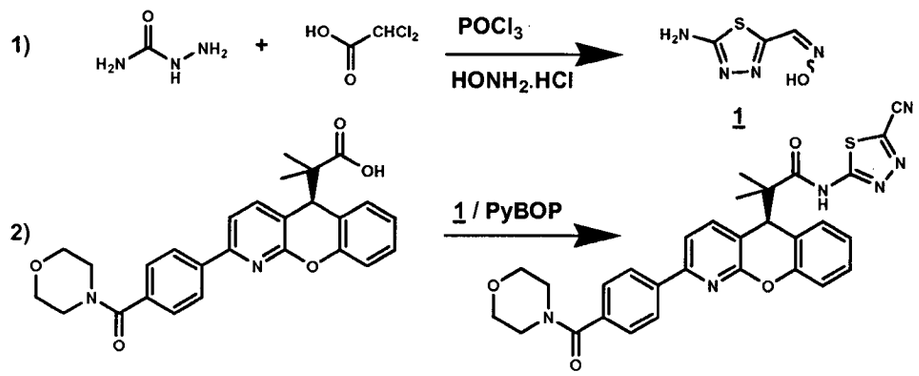
[00474] A mixture of the product of Step 2 (20 mg, 0.044 mmol), the product of Step 1 (17 mg, 0.13 mmol), DMAP (11 mg, 0.087 mmol), HATU (33 mg, 0.087 mmol) and DMF (0.3 mL) was stirred at 80°C under nitrogen for 2 h. After more (10 mg) of the product of Step 1 was added, the mixture was stirred at 80°C for an additional 1 h. Purification using reverse phase HPLC (YMC S5 20 x 100 mm, 10 min. run, solvent A: 10% MeOH: 90% H_2O: 0.1% TFA, solvent B: 90% MeOH, 10% H_2O, 0.1% TFA) gave the title compound (TFA salt, 20 mg, Y = 67%) as a white solid. MS (E+) m/z: 574 (M+H); LC retention time: 3.25 min. ^1H NMR (400 MHz, MeOD) δ ppm 8.13 (d, *J*=8.31 Hz, 2 H) 7.74 (d, *J*=8.0 Hz, 1 H) 7.68 (d, *J*=8.0 Hz, 1 H) 7.55 (d, *J*=8.56 Hz, 2 H) 7.37 (td, *J*=7.7, 1.4 Hz, 1 H) 7.23 - 7.30 (m, 2 H) 7.12 (td, *J*=7.5, 1.0 Hz, 1 H) 5.74 (d, *J*=47.0 Hz, 2 H) 4.63 (s, 1 H) 3.45 - 3.84 (m, 8 H) 1.19 (s, 3 H) 1.16 (s, 3 H).

EXAMPLE 431 TO 433

[00475] The following Examples 431 to 433 were prepared in the same manner as described for the preparation of the title compound of Example 430 from the corresponding commercially available boronic acids.

Example No.	Structure	Rt (min)	M/z $(MH)^+$
431		3.52	576
432		3.32	532
433		3.46	558

EXAMPLE 434



Step 1

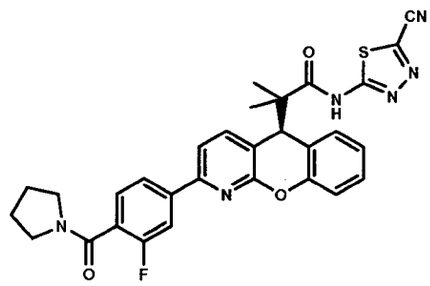
[00476] The step was completed by following a literature procedure (Remers, W.; et al US 3790590). MS (E+) m/z: 145 (M+H); LC retention time: 0.30 min.

Step 2

[00477] To a stirred mixture of the product of Step 2 of Example 430 (20mg, 0.044 mmol), the product of Step 1 (8.80 mg, 0.061 mmol), PyBOP (68 mg, 0.13 mmol),

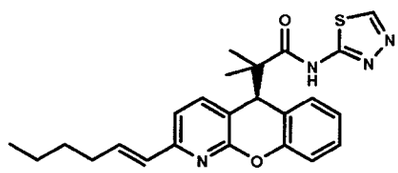
and anhydrous MeCN (0.5 mL) was added diisopropylethylamine (0.053 mL, 0.31 mmol) at RT under nitrogen. The mixture was stirred at RT for 1 h and at 80°C for 2 h. After more (5 mg) of the Step1 product was added, the mixture was stirred at 80°C for an additional 1 h. Purification using reverse phase HPLC (YMC S5 20 x 100 mm, 10 min. run, solvent A: 10% MeOH: 90% H_2O: 0.1% TFA, solvent B: 90% MeOH, 10% H_2O, 0.1% TFA) gave the title product (TFA salt, 15 mg, 0.022 mmol, 51% yield) as a yellow solid. MS (E+) m/z: 567 (M+H); LC retention time: 3.35 min. ^{1}H NMR (400 MHz, MeOD) δ ppm 8.13 (d, *J*=8.56 Hz, 2 H) 7.73 (d, *J*=8.0 Hz, 1 H) 7.69 (d, *J*=8.0 Hz, 1 H) 7.56 (d, *J*=8.31 Hz, 2 H) 7.38 (td, *J*=7.7, 1.4 Hz, 1 H) 7.28 (dd, *J*=8.06, 1.01 Hz, 1 H) 7.23 (dd, *J*=7.68, 1.38 Hz, 1 H) 7.13 (td, *J*=7.5, 1.2 Hz, 1 H) 4.61 (s, 1 H) 3.46 - 3.84 (m, 8 H) 1.20 (s, 3 H) 1.18 (s, 3 H).

EXAMPLE 435



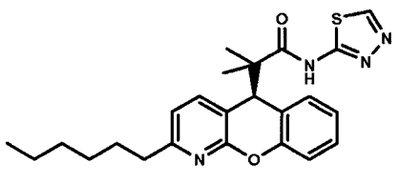
[00478] The title compound was prepared in the same manner as described for the preparation of the title compound of Example 434 from the product of Step 1 in Example 398. MS (ES+) m/z: 569 (M+H); LC retention time: 3.59 min. ^{1}H NMR (400 MHz, MeOD) δ ppm 7.89 - 7.99 (m, 2 H) 7.74 (d, *J*=8.0 Hz, 1 H) 7.72 (d, *J*=8.0 Hz, 1 H) 7.53 (t, *J*=7.43 Hz, 1 H) 7.35 - 7.41 (m, 1 H) 7.28 (d, *J*=8.06 Hz, 1 H) 7.22 (d, *J*=7.55 Hz, 1 H) 7.13 (t, *J*=6.92 Hz, 1 H) 4.62 (s, 1 H) 3.63 (t, *J*=6.80 Hz, 2 H) 3.39 (t, *J*=6.55 Hz, 2 H) 1.89 - 2.08 (m, 4 H) 1.20 (s, 3 H) 1.18 (s, 3 H).

EXAMPLE 436



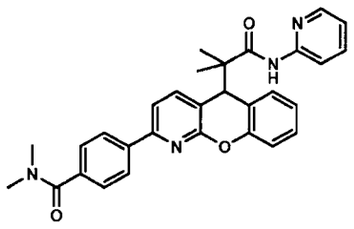
[00479] A stream of nitrogen gas was bubbled through a mixture of the product of the Step 1 of Preparation 53 (53a) (100 mg, 0.26 mmol), *trans*-1-hexen-1-yl boronic acid (66 mg, 0.52 mmol) and (triphenylphosphine)palladium(0) (10 mg, 0.009 mmol) in DMF (1.5 mL) and aqueous potassium phosphate (2.0M, 0.3 mL) for 10 min. The mixture was heated at 100 °C for 2.5 h, then purified by preparative HPLC to give the title compound as a light yellow TFA salt (24 mg, Y = 17%). MS (ES+) m/z: 435 (M+H); LC retention time: 3.95 min.

EXAMPLE 437



[00480] To a solution of the title compound of Example 436 (10 mg, 0.023 mmol) in methanol (2 mL) was added palladium on carbon (10% w/w, 10 mg). The mixture was evacuated, then placed under an atmosphere of hydrogen, and stirred overnight at room temperature. The mixture was then filtered (syringe-tip 0.45 micron PTFE filter), and purified by reverse phase preparative HPLC to afford the title compound (6.1 mg, Y = 48%) as a white powder, TFA salt. MS (ES+) m/z: 437 (M+H); LC retention time: 3.94 min.

EXAMPLE 438



Step 1

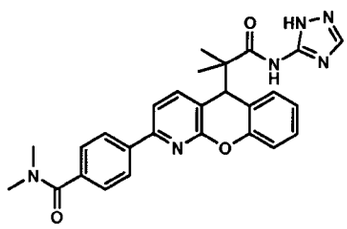
[00481] A 1 M CH_2Cl_2 solution of oxalyl chloride (0.7 mL, 3 eq) was added to a suspension of the acid from Preparation 101 (200 mg, 0.24 mmol) and trace amount

of DMF in CH_2Cl_2 (20 mL) at room temperature. After 20 min, the mixture was concentrated to give the expected acid chloride as an off-white solid.

Step 2

To a CH_2Cl_2 (1.4 mL) solution of the acid chloride from the last step (40 mg, 0.092 mmol) was added 2-aminopyridine (25 mg, 2.9 eq) at room temperature. After 1 h, the mixture was concentrated and purified by preparative reverse-phase HPLC (using Shimadzu 10A liquid chromatographs and Waters Sunfire S10 30 x 250 mm column) to give Example 501 as a white solid (28.8 mg, 43%). 1H NMR (400 MHz, CDCl3) δ ppm 12.14 (s, 1 H), 8.75 (d, *J* = 8.81 Hz, 1 H), 8.18 - 8.37 (m, 2 H), 8.08 (d, *J* = 8.31 Hz, 2 H), 7.83 (d, *J* = 7.81 Hz, 1 H), 7.55 (dd, *J* = 13.22, 8.18 Hz, 3 H), 7.44 (t, *J* = 6.17 Hz, 1 H), 7.28 - 7.38 (m, 2 H), 7.22 (d, *J* = 7.30 Hz, 1 H), 7.03 - 7.14 (m, 1 H), 4.77 (s, 1 H), 3.18 (s, 3 H), 3.04 (s, 3 H), 1.22 (s, 3 H), 1.14 (s, 3 H); MS (ES+) m/z: 493 (M+H); LC retention time: 3.69 min (Analytical HPLC Method D).

EXAMPLE 439



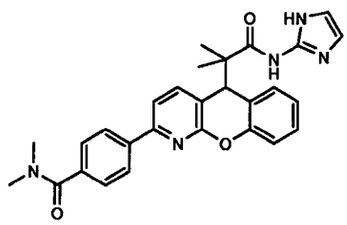
Step 1

[00482] To a CH_2Cl_2 (2 mL) solution of 2-methyl-2-thioisourea sulfate (68.9 mg, 0.366 mmol) and 1 N NaOH (405 μL, 0.405 mmol) at 0 °C was added a solution of the acid chloride from Step 1 of Example 501 (63.7 mg, 0.135 mmol) in CH_2Cl_2 (2 mL). After 1 h at 0 °C, the biphasic mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (2 mL). The combined CH_2Cl_2 phase was concentrated to give the expected product as a light brown solid. MS (ES+) m/z: 489 (M+H); LC retention time: 3.34 min (Analytical HPLC Method D).

Step 2

[00483] A pyridine (1.5 mL) solution of the crude product from the last step, formohydrazide (14 mg, 0.233 mmol) and (*S*)-camphorsulfonic acid (56 mg, 0.241 mmol) was heated at 100 °C in a sealed tube. After 3 h at 100 °C, the mixture was purified by preparative reverse-phase HPLC (using Shimadzu 10A liquid chromatographs and Waters Sunfire S10 30 x 250 mm column) to give the title compound as a white solid (13 mg, 15% yield for 2 steps). 1H NMR (400 MHz, DMSO-d_6) δ ppm 8.16 (d, J = 8.56 Hz, 2 H), 7.87 (d, J = 7.81 Hz, 1 H), 7.74 (d, J = 8.06 Hz, 1 H), 7.52 (d, J = 8.31 Hz, 2 H), 7.33 - 7.42 (m, 2 H), 7.23 - 7.33 (m, 2 H), 7.12 - 7.21 (m, 1 H), 4.82 (s, 1 H), 3.01 (s, 3 H), 2.95 (s, 3 H), 1.02 (s, 3 H), 0.98 (s, 3 H); MS (ES+) m/z: 483 (M+H); LC retention time: 3.55 min (Analytical HPLC Method D).

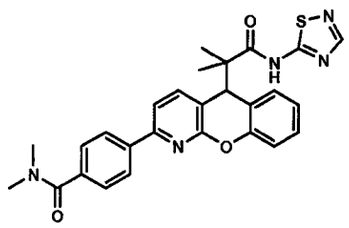
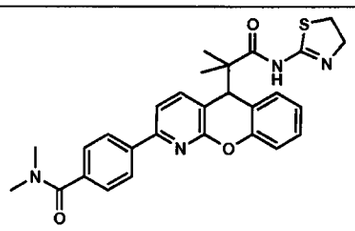
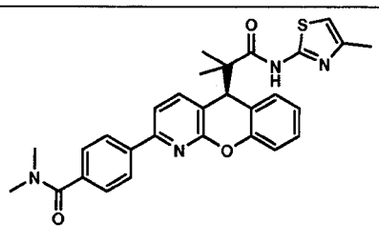
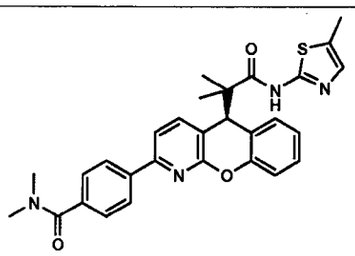
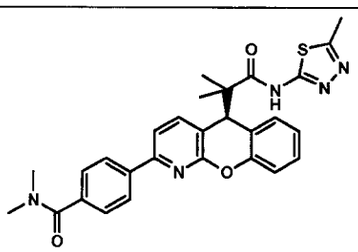
EXAMPLE 440

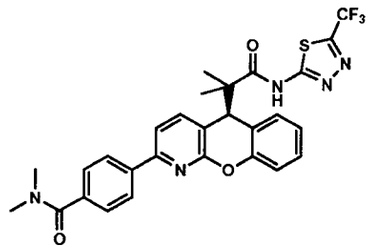
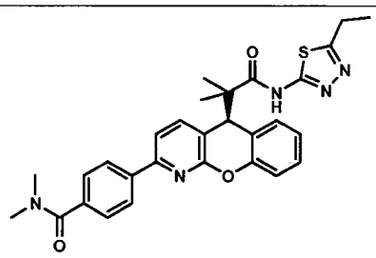
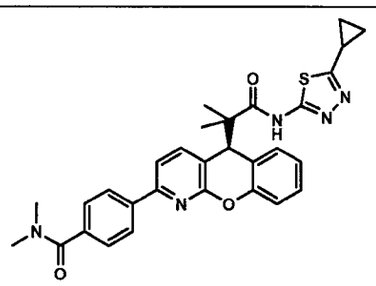
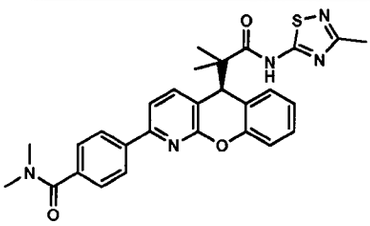


[00484] An acetonitrile (2 mL) solution of the product from Preparation 101 (35.8 mg, 0.086 mmol), 1-trityl-2-aminoimidazole (66.2 mg, 2.4 eq, prepared following a known procedure *J. Med. Chem.* 2000, 43, 27-40), HOBt (30.5 mg, 2.6 eq), EDC (52.5 mg, 3.2 eq) and DIPEA (75 μL, 5 eq) was heated at 60°C for 16 h. The crude mixture was poured into saturated NH_4Cl (20 mL) and extracted with ethyl acetate (10 mL). The ethyl acetate extract was concentrated, dissolved in CH_2Cl_2 (0.5 mL), treated with TFA (0.5 mL) for 20 min and concentrated. Purification by preparative reverse-phase HPLC (using Shimadzu 10A liquid chromatographs and Waters Sunfire S10 30 x 250 mm column) gave Example 503 as a white solid (15.5 mg, 37%). 1H NMR (400 MHz, CDCl3) δ ppm 14.11 (s, 1 H), 8.08 (d, J = 8.56 Hz, 2 H), 7.77 (d, J = 7.81 Hz, 1 H), 7.55 (dd, J = 16.37, 8.06 Hz, 3 H), 7.28 - 7.38 (m, 2 H), 7.15 - 7.22 (m, 1 H), 7.05 - 7.14 (m, 1 H), 6.99 (s, 2 H), 4.66 (s, 1 H), 3.16 (s, 3 H), 3.03 (s, 3 H), 1.21 (s, 3 H), 1.14 (s, 3 H); MS (E+) m/z: 482 (M+H); LC retention time: 3.09 min (Analytical HPLC Method D).

EXAMPLES 441 TO 449

[00485] Following procedure analogous to the preparation of Example 440, the following examples were prepared by couplings between appropriate amines (commercially available) and the acid from Preparation 57 or 65.

Example No.	Structure	Rt (min)*	M/z (M+H)
441		3.97	500
442		3.29	501
443		4.10	513
444		4.12	513
445		3.90	514

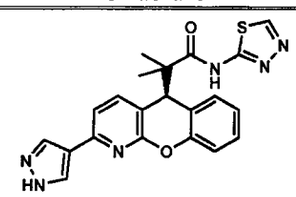
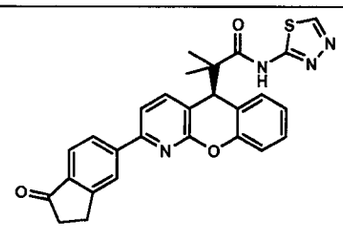
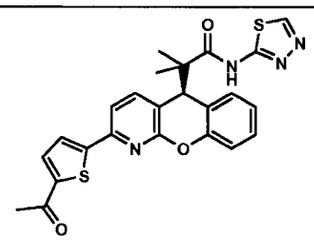
Example No.	Structure	Rt (min)*	M/z (M+H)
446		4.40	568
447		4.06	528
448		4.12	540
449		4.02	514

* Analytical HPLC Method D.

EXAMPLES 450 TO 452

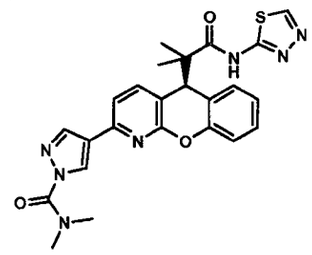
[00486] The following Examples 450 to 452 were prepared in the same manner described for the preparation of the title compounds of Examples 168 to 236, using commercially available boronic acids and the product of Preparation 53a. For Example 451, see *Bioorg. & Med. Chem. Lett.* 2003, 13, 4143-4145.

Example No.	Structure	Rt (min)*	M/z (M+H)

Example No.	Structure	Rt (min)*	M/z (M+H)
450		3.52	419
451		4.01	483
452		3.96	477

* Analytical HPLC Method D.

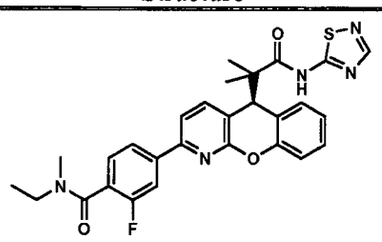
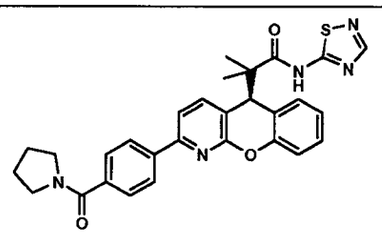
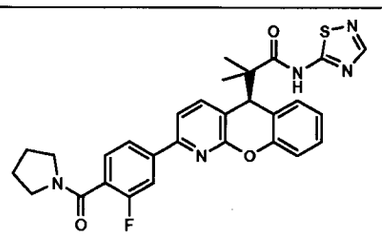
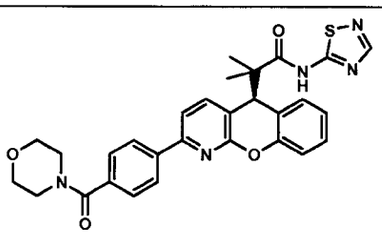
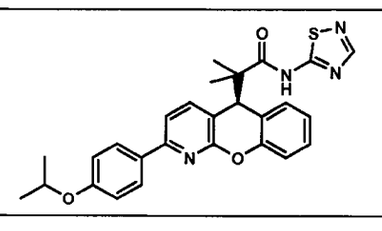
EXAMPLE 453

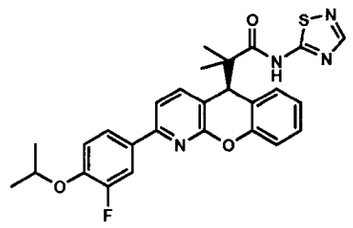
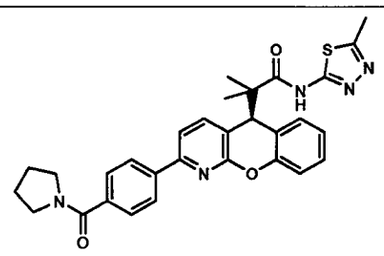
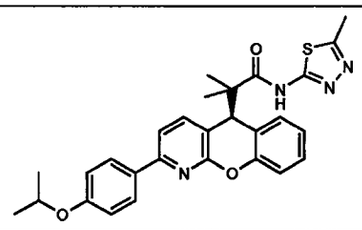


[00487] To a THF (1.5 mL) solution of Example 450 (8.1 mg, 0.019 mmol) and dimethylcarbamyl chloride (14 mg, 6.7 eq) was added DBU (20.2 μL, 7 eq). The resulting mixture was heated at 60°C for 1h, concentrated and purified by flash column chromatography (ISCO, 4 g silica gel cartridge, 20 to 100% ethyl acetate-hexanes) to give the title compound as a white solid (2.5 mg, 26%). 1H NMR (400 MHz, CDCl3) δ ppm 8.89 (s, 1 H), 8.62 (s, 1 H), 8.19 (s, 1 H), 7.61 (d, *J* = 7.81 Hz, 1 H), 7.26 - 7.37 (m, 3 H), 7.15 - 7.21 (m, 1 H), 7.01 - 7.09 (m, 1 H), 4.63 (s, 1 H), 3.26 (s, 6 H), 1.24 (s, 3 H), 1.23 (s, 3 H); MS (E+) m/z: 490 (M+H); LC retention time: 3.74 min (Analytical HPLC Method D).

EXAMPLES 454 TO 461

[00488] Following procedure analogous to preparation of Example 440, the following examples were prepared by couplings between 5-amino-1,2,4-thiadiazole or 2-amino-5-methyl-1,3,4-thiadiazole and the acids from Preparations 67 to 70 and 72 to 73.

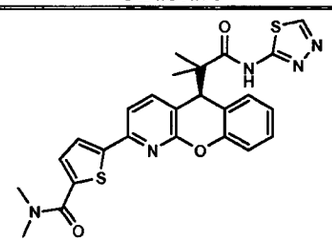
Example No.	Structure	Rt (min)*	M/z (M+H)
454		4.18	532
455		4.12	526
456		4.21	544
457		3.95	542
458		4.60	487

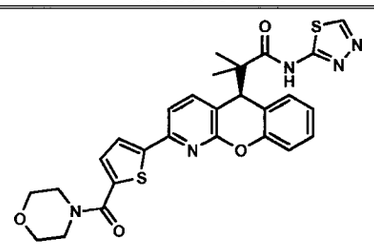
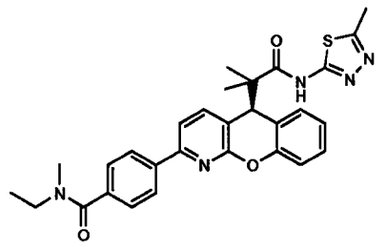
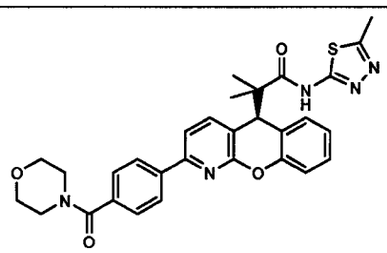
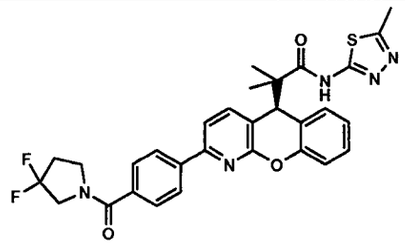
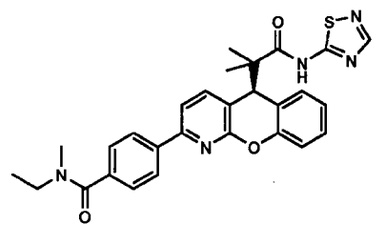
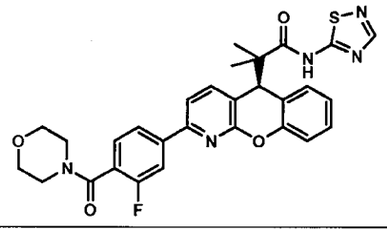
Example No.	Structure	Rt (min)*	M/z (M+H)
459		4.60	505
460		4.07	540
461		4.52	501

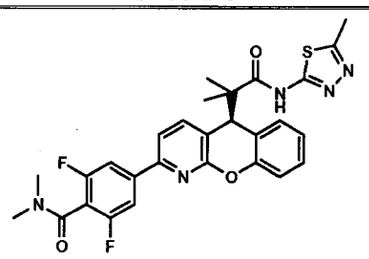
* Analytical HPLC Method D.

EXAMPLES 462 TO 469

[00489] Following procedure analogous to preparation of Example 440, the following examples were prepared by coupling between commercially available amines and the acid from Preparations 78 to 82.

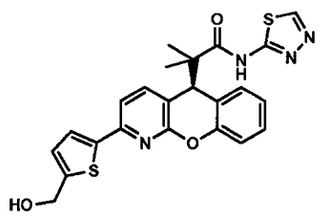
Example No.	Structure	Rt (min)*	M/z (M+H)
462		3.78	506

Example No.	Structure	Rt (min)*	M/z (M+H)
463		3.77	548
464		4.02	528
465		3.89	556
466		4.10	576
467		4.09	514
468		4.07	560

Example No.	Structure	Rt (min)*	M/z (M+H)
469		4.00	550

* Analytical HPLC Method D.

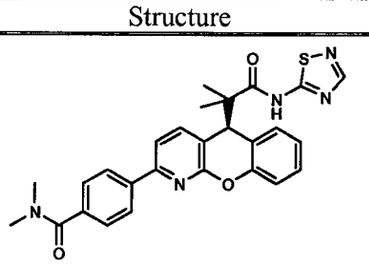
EXAMPLE 470

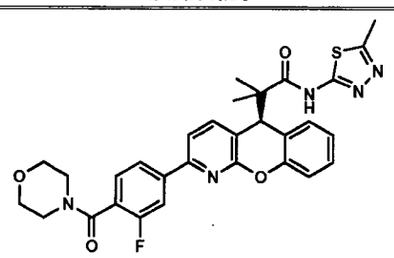
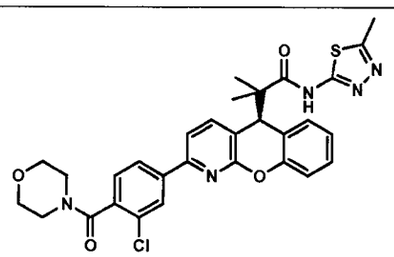
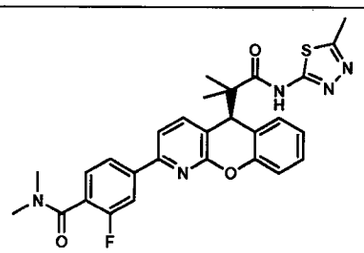
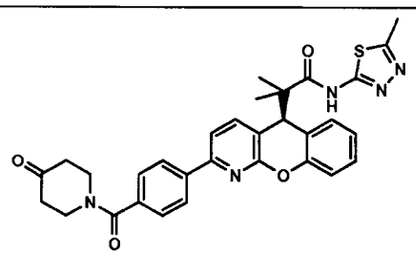
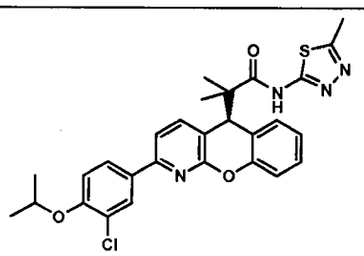
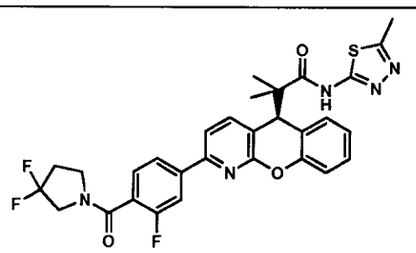


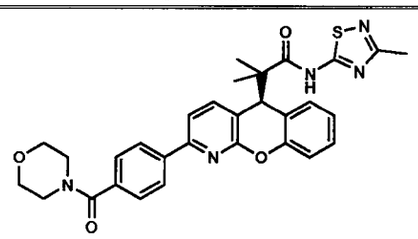
[00490] Using procedure analogous to preparation of Example 440, the title compound was prepared by coupling between 2-amino-1,3,4-thiadiazole and the acid from Preparation 66. 1H NMR (400 MHz, CDCl3) δ ppm 8.87 (s, 1 H), 7.49 - 7.60 (m, 2 H), 7.36 - 7.40 (m, 1 H), 7.28 - 7.33 (m, 2 H), 6.99 - 7.12 (m, 3 H), 4.86 (s, 2 H), 4.48 (s, 1 H), 1.26 (s, 3 H), 1.21 (s, 3 H); MS (E+) m/z: 465 (M+H); LC retention time: 3.73 min (Analytical HPLC Method D).

EXAMPLES 471 TO 478

[00491] Following procedure analogous to Preparation 57, the following examples were prepared by Suzuki coupling between boronic acids (commercially available or prepared in Preparations 58, 61 and 64) and intermediates from Preparations 75 to 77.

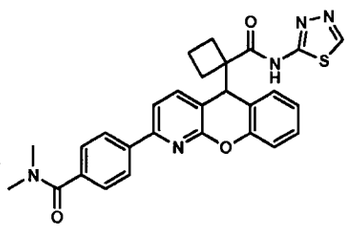
Example No.	Structure	Rt (min)*	M/z (M+H)
471		3.97	500

Example No.	Structure	Rt (min)*	M/z (M+H)
472		4.00	574
473		4.07	590
474		3.98	532
475		3.85	568
476		4.68	535
477		4.16	594

Example No.	Structure	Rt (min)*	M/z (M+H)
478		3.99	556

* Analytical HPLC Method D.

EXAMPLE 479



Step 1

[00492] A 1.6 M hexane solution of n-butyllithium (2.72 mL, 4.34 mmol) was added to a solution of diisopropylamine (440 mg, 4.34 mmol) in THF (6 mL) at -78 °C over 5 minutes. The resultant solution was warmed to 0 °C for 30 min and cooled to -78 °C. A solution of ethyl cyclobutanecarboxylate (464 mg, 3.62 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at -78 °C for 30 min. Chlorotrimethylsilane (0.597 mL, 4.71 mmol) was added. The mixture was warmed to room temperature over 1 h, quenched with saturated $NaHCO_3$ (5 mL), diluted with diethyl ether (200 mL), washed with water (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated to give (cyclobutylidene(ethoxy)methoxy)trimethylsilane, which was taken to next step without further purification.

Step 2

[00493] A 1.0 M dichloromethane solution titanium(IV) chloride (0.254 mL, 0.254 mmol) was added to a solution of the product from Preparation 83 (80 mg, 0.231 mmol) in dichloromethane (10 mL) at 0 °C. After 10 min at 0 °C, the crude (cyclobutylidene(ethoxy)methoxy)trimethylsilane (350 mg, ~1.75 mmol) was added.

After 1 h at 0 °C, the mixture was quenched with saturated $NaHCO_3$ (5 mL), diluted with dichloromethane (80 mL), washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (silica gel, 50-100% ethyl acetate in hexanes) gave ethyl 1-(2-(4-(dimethylcarbamoyl)phenyl)-5H-chromeno[2,3-b]pyridin-5-yl)cyclobutanecarboxylate (80 mg, 76%). MS (ES+) m/z: 457 (M+H).

Step 3

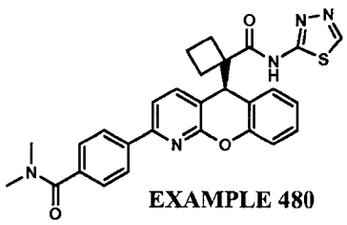
[00494] Sodium propane-2-thiolate (172 mg, 1.75 mmol) was added to a solution of the product from Step 2 (80 mg, 0.175 mmol) in DMF (5 mL) at room temperature. After 15 h at 60 °C, the mixture was cooled to room temperature and adjusted pH2-3 with 1 N aqueous HCl. After addition of ethyl acetate (100 mL), the mixture was washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated. Purification by preparative HPLC gave the desired 1-(2-(4-(dimethylcarbamoyl)phenyl)-5H-chromeno[2,3-b]pyridin-5-yl)cyclobutanecarboxylic acid (45 mg, 60%). MS (ES+) m/z: 429 (M+H).

Step 4

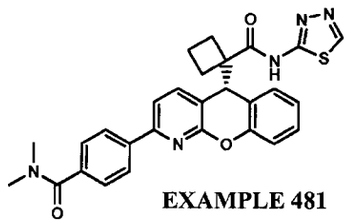
[00495] The mixture of the product from Step 3 (22 mg, 0.051 mmol), 1,3,4-thiadiazol-2-amine (10.4 mg, 0.103 mmol), EDC (19.7 mg, 0.103 mmol), HOBT (15.7 mg, 0.103 mmol) and DIEA (0.036 mL, 0.205 mmol) in acetonitrile (2 mL) was heated to 70 °C for 15 h. Then the mixture was cooled to room temperature, quenched with saturated $NaHCO_3$ (2 mL), diluted with ethyl acetate (60 mL), washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated. The residue was purified by preparative HPLC to give the title compound (12 mg, 46%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.93 (s, 1H), 8.93 (s, 1H), 8.06 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 7.6 Hz, 1H), 7.53 (m, 2H), 7.37 (d, J = 7.6 Hz, 1H), 7.28 (m, 3H), 7.07 (m, 1H), 4.69 (s, 1H), 3.14 (s, 3H), 3.01 (s, 3H), 2.45 (m, 4H), 1.67 (m, 1H), 1.31 (m, 1H); MS (ES+) m/z: 512 (M+H); HPLC retention time: 1.65 min (Analytical HPLC Method F).

CC0291

EXAMPLES 480 AND 481



EXAMPLE 480



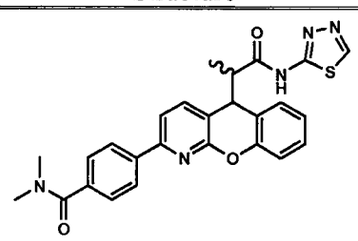
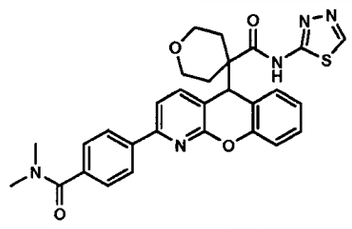
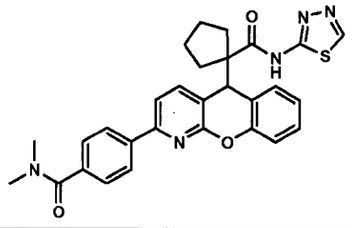
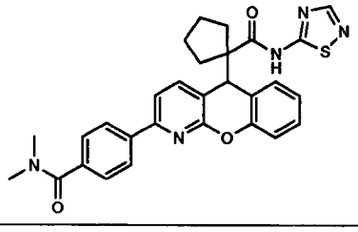
EXAMPLE 481

[00496] The title compound of Example 480 (400 mg, 0.783 mmol) was purified by chiral SFC (AD-H column, CO_2/MeOH = 65/35) to provide Example 480 (fast eluting enantiomer, 113 mg, 28%) and Example 481 (slow eluting enantiomer, 120 mg, 30%). Data for Example 480: ^{1}H-NMR (400 MHz, MeOH-d_4) δ 9.10 (s, 1H), 8.12 (d, J = 8.4 Hz, 2H), 7.75 (m, 2H), 7.56 (d, J = 8.4 Hz, 2H), 7.39 (m, 2H), 7.25 (m, 2H), 4.58 (s, 1H), 3.15 (s, 3H), 3.07 (s, 3H), 2.37 (m, 3H), 2.29 (m, 1H), 1.56 (m, 1H), 1.20 (m, 1H); MS (ES+) m/z: 512 (M+H); HPLC retention time: 1.65 min (Analytical HPLC Method F). Data for Example 481: MS (ES+) m/z: 512 (M+H); HPLC retention time 1.65 min (Analytical HPLC Method F). Both enantiomers were analyzed using chiral HPLC (Chiralpak AD-H column: 0.46x25 cm, 5 μm; temperature: 40 °C; flow rate: 2.0 mL/min; mobile phase: CO_2/MeOH(65/35); detector wavelength: 252 nm). Retention times for Examples 480 and 481 are 13.0 and 18.0 min, respectively.

EXAMPLES 482 TO 485

[00497] Examples 482 to 485 were prepared in a sequence similar to Example 479, substituting methyl propionate and ethyl cyclobutanecarboxylate for ethyl cyclobutanecarboxylate. Example 484 and 485 were prepared following a sequence similar to Preparation 17, substituting (cyclopentylidene(methoxy)methoxy)trimethylsilane for methyl trimethylsilyl dimethylketene acetal, Preparation 57 and coupling with 2-amino-1,3,4-thiadiazole or 5-amino-1,2,4-thiadiazole.

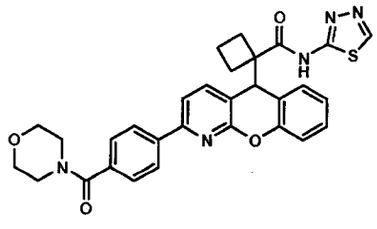
Example No.	Structure	Rt (min)*	M/z (M+H)

Example No.	Structure	Rt (min)*	M/z (M+H)
482		3.65*	486
483		1.89**	542
484		3.86*	526
485		4.04*	526

* Analytical HPLC Method D.

** Analytical HPLC Method F.

EXAMPLES 486 AND 487



Step 1

[00498] Following procedure similar to Step 2 of Example 479, the alcohol from Preparation 84 (700 mg, 2.10 mmol) was reacted with (cyclobutylidene(ethoxy)methoxy)trimethylsilane to give methyl 4-(5-(1-(ethoxycarbonyl)cyclobutyl)-5H-chromeno[2,3-b]pyridin-2-yl)benzoate (250 mg, 27%). MS (ES+) m/z: 444 (M+H).

Step 2

[00499] A 1 N aqueous solution of NaOH (5 mL, 5.00 mmol) was added to a solution of the product from Step 1 (250 mg, 0.564 mmol) in MeOH (10 mL) at room temperature. After 24 h at 80 °C, the mixture was cooled to room temperature and adjusted pH2-3 with 1 N aqueous HCl. MeOH was evaporated *in vacuo*. The brown precipitate in the aqueous residue was collected by filtration and dried under vacuum to give 4-(5-(1-carboxycyclobutyl)-5H-chromeno[2,3-b]pyridin-2-yl)benzoic acid (210 mg, 93%). MS (ES+) m/z: 402 (M+H).

Step 3

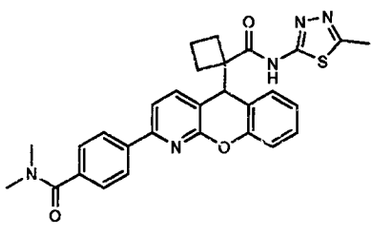
[00500] A mixture of the product from Step 2 (50 mg, 0.125 mmol), EDC (71.6 mg, 0.374 mmol), HOBT (57.2 mg, 0.374 mmol) and DIEA (0.131 mL, 0.747 mmol) in acetonitrile (2 mL) was stirred at room temperature for 10 min and cooled to 0 °C. A solution of morpholine (13.1 mg, 0.149 mmol) in acetonitrile (1 mL) was added dropwise. The resultant mixture was stirred at 0 °C for 1 h, quenched with saturated NH_4Cl (2 mL). After addition of ethyl acetate (60 mL), the mixture was washed with water (5 mL), brine (5 mL), dried ($MgSO_4$) and concentrated to provide 1H-benzo[d][1,2,3]triazol-1-yl 1-(2-(4-(morpholine-4-carbonyl)phenyl)-5H-chromeno[2,3-b]pyridin-5-yl)cyclobutanecarboxylate (75 mg), which was taken to next step without further purification. MS (ES+) m/z: 588 (M+H).

Step 4

[00501] Following similar procedure as Step 4 of Example 479, the product from Step 3 (73.5 mg, 0.125 mmol) was converted to the desired product (32 mg, 46%). The racemic mixture was separated by chiral SFC (AD-H column, CO_2/MeOH = 65/35) to provide Example 486 (fast eluting enantiomer, 10 mg) and Example 487

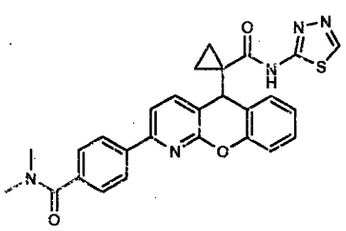
(slow eluting enantiomer, 10 mg). Data for Example 486: ^{1}H-NMR (400 MHz, MeOH-d_4) δ 8.99 (s, 1H), 8.02 (d, J = 8.4 Hz, 2H), 7.63 (m, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.27 (m, 2H), 7.13 (m, 2H), 4.45 (s, 1H), 3.40-3.80 (m, 8H), 2.25 (m, 3H), 2.15 (m, 1H), 1.40 (m, 1H), 1.15 (m, 1H); MS (ES+) m/z: 554 (M+H); HPLC retention time: 2.01 min (Analytical HPLC Method E). Data for Example 487: MS (ES+) m/z: 554 (M+H); HPLC retention time: 2.02 min (Analytical HPLC Method E). Both enantiomers were analyzed using chiral HPLC (Chiralpak AD-H column: 0.46x25 cm, 5 μm; temperature: 40 °C; flow rate: 3.0 mL/min; mobile phase: CO_2/MeOH(65/35); detector wavelength: 270 nm). Retention times for Examples 486 and 487 are 9.2 and 13.4 min, respectively.

EXAMPLE 488



[00502] Following similar procedure to Steps 3 and 4 of Examples 486 and 487, the product from Step 2 of Examples 486 and 487 (50 mg, 0.125 mmol) was converted to the title compound (5.8 mg, 7%). MS (ES+) m/z: 526 (M+H); HPLC retention time: 2.03 min (Analytical HPLC Method E).

EXAMPLE 489



Step 1

[00503] Following similar procedure to Step 2 of Example 479, alcohol from Preparation 83 (160 mg, 0.462 mmol) was converted to methyl 2-(2-(4-

(dimethylcarbamoyl)phenyl)-5H-chromeno[2,3-b]pyridin-5-yl)acetic acid (170 mg, 92%). MS (ES+) m/z: 403 (M+H); HPLC retention time: 1.65 min (Analytical HPLC Method F).

Step 2

[00504] A 1.6 M hexane solution of n-butyllithium (0.38 mL, 0.62 mmol) was added to a solution of diisopropylamine (0.089 mL, 0.62 mmol) in THF (5 mL) at -78 °C over 5 min. The resultant solution was warmed to 0 °C for 30 min and cooled to -78 °C. A solution of the product from Step 1 (100 mg, 0.248 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at -78 °C for 30 min and at -30 °C for 30 min. Formaldehyde (60 mg) was bubbled into the mixture by a stream of N2 at -30 °C. The resultant mixture was stirred at -30 °C for 30 min, quenched with MeOH (1 mL) and warmed to room temperature. After addition of ethyl acetate (80 mL), the mixture was washed with saturated $NaHCO_3$ (10 mL), water (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (silica, 50-100% ethyl acetate in hexanes) to provide methyl 2-(2-(4-(dimethylcarbamoyl)phenyl)-5H-chromeno[2,3-b]pyridin-5-yl)-3-hydroxypropanoate (80 mg, 74%). MS (ES+) m/z: 433 (M+H).

Step 3

[00505] Methanesulfonyl chloride (0.072 mL, 0.925 mmol) was added to a mixture of the product from Step 2 (80 mg, 0.185 mmol), TEA (0.258 mL, 1.85 mmol) and DMAP (24.9 mg, 0.203 mmol) in DCM (2 mL) at 0 °C. After 1 h at this temperature, the mixture was concentrated *in vacuo*. The residue was suspended in benzene (4 mL), treated with DBU (0.139 mL, 0.925 mmol) and stirred at room temperature for 1 h. Saturated $NaHCO_3$ (5 mL) and ethyl acetate (100 mL) were added. The mixture was washed with water (2x10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (silica, 50-100% ethyl acetate in hexanes) to provide methyl 2-(2-(4-(dimethylcarbamoyl)phenyl)-5H-chromeno[2,3-b]pyridin-5-yl)acrylate (45 mg, 59%). MS (ES+) m/z: 415 (M+H); HPLC retention time: 1.73 min (Analytical HPLC Method F).

Step 4

[00506] Sodium hydride (5.2 mg, 0.13 mmol, 60% in mineral oil) was added to a solution of trimethyl sulfoxonium iodide (28.7 mg, 0.13 mmol) in DMSO (1 mL) at room temperature. After 30 min at room temperature, the mixture was added to a solution of the product from Step 3 (45 mg, 0.109 mmol) in DMSO (1 mL). The resultant mixture was stirred at room temperature for 10 min and quenched with saturated $NaHCO_3$ (1 mL). After addition of ethyl acetate (80 mL), the mixture was washed with water (2x10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (silica, 50-100% ethyl acetate in hexanes) to provide methyl 1-(2-(4-(dimethylcarbamoyl)phenyl)-5H-chromeno[2,3-b]pyridin-5-yl)cyclopropanecarboxylate (12 mg, 26%). MS (ES+) m/z: 429 (M+H).

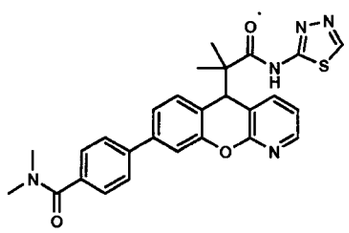
Step 5

[00507] A 1 N aqueous solution of NaOH (0.5 mL, 0.500 mmol) was added to a solution of the product from Step 4 (11 mg, 0.026 mmol) in MeOH (1 mL) at room temperature. The mixture was heated to 60 °C for 3 h, cooled to room temperature and adjusted pH2-3 with 1 N aqueous HCl. Following addition of ethyl acetate (60 mL), the mixture was washed with brine (10 mL), dried ($MgSO_4$) and concentrated to give 1-(2-(4-(dimethylcarbamoyl)phenyl)-5H-chromeno[2,3-b]pyridin-5-yl)cyclopropanecarboxylic acid as crude material (11 mg), which was taken to the next step directly. MS (ES+) m/z: 415 (M+H).

Step 6

[00508] Following similar procedure to Step 4 of Example 479, the product from Step 5 (11 mg, 0.027 mmol) was converted to the title compound (5.0 mg, 40%). ^{1}H-NMR (400 MHz, MeOH-d_4) δ 8.90 (s, 1H), 8.42 (s, 1H), 8.00 (d, J = 8.4 Hz, 2H), 7.85 (m, 1H), 7.58 (m, 1H), 7.43 (d, J = 8.4 Hz, 2H), 7.24 (m, 2H), 7.10 (m, 2H), 4.65 (s, 1H), 3.02 (s, 3H), 2.94 (s, 3H), 1.13 (m, 4H); MS (ES+) m/z: 498 (M+H); HPLC retention time: 2.04 min (Analytical HPLC Method E).

EXAMPLE 490



Step 1

[00509] A 1.6 M hexane solution of n-butyllithium (39.8 mL, 63.6 mmol) was added to a solution of diisopropylamine (9.45 mL, 66.3 mmol) in THF (100 mL) at -78 °C over 10 min. The resultant solution was stirred at 0 °C for 30 min and cooled to -78 °C. Acetonitrile (3.32 mL, 63.6 mmol) dropwise. The mixture was stirred at -78 °C for 30 min and then added a solution of 4-chloro-2-fluorobenzoate (5.00 g, 26.5 mmol) in THF (5 mL) at -78 °C dropwise. After stirring for 1 h at -78 °C, the reaction mixture was quenched with brine (20 mL), warmed to room temperature and adjusted to pH1-2 with 1N aqueous HCl. Following addition of ethyl acetate (400 mL), the mixture was washed with water (40 mL), brine (40 mL), dried ($MgSO_4$) and concentrated to provide 3-(4-chloro-2-fluorophenyl)-3-oxopropanenitrile as tan solid (5.10 g, 97%). MS (ES+) m/z: 198 (M+H).

Step 2

[00510] A mixture of (E)-3-(dimethylamino)acrylaldehyde (3.26 g, 32.9 mmol), the product from Step 1 (5. 00 g, 25.3 mmol) and acetic acid (7.24 mL, 127 mmol) in DMF (40 mL) was heated to 120 °C for 48 h and cooled to room temperature. Ethyl acetate (400 mL) was added and the mixture washed with saturated $NaHCO_3$ (40 mL), water (40 mL), brine (40 mL), dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (silica, 10-40% ethyl acetate in hexanes) to provide 8-chloro-5H-chromeno[2,3-b]pyridin-5-one (600 mg, 10%). MS (ES+) m/z: 232 (M+H).

Step 3

[00511] Sodium borohydride (490 mg, 13.0 mmol) was added to a solution of the product from Step 2 (600 mg, 2.59 mmol) in MeOH (16 mL) and dichloromethane (4 mL) at 0 °C. After 2 h at this temperature, the mixture was quenched with saturated $NaHCO_3$ (5 mL). The organic solvents were evaporated *in vacuo*. The residue was dissolved in dichloromethane (100 mL), washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated to crude 8-chloro-5H-chromeno[2,3-b]pyridin-5-ol (600 mg), which was taken directly to the next step. MS (ES+) m/z: 234 (M+H).

Step 4

[00512] Following similar procedure as Step 2 of Example 479, the product from step 3 (600 mg, 2.59 mmol) was converted to methyl 2-(8-chloro-5H-chromeno[2,3-b]pyridin-5-yl)-2-methylpropanoate (450 mg, 55%). MS (ES+) m/z: 318 (M+H).

Step 5

[00513] A 25 mL flask containing $Pd(dba)_2$ (25.3 mg, 0.044 mmol) was flushed with N_2. Dioxane (2 mL) and a 1.0 M THF solution of tricyclohexylphosphine (0.106 mL, 0.106 mmol) were added. The resultant black mixture was stirred at room temperature for 30 min. Bis(pinacolato)diboron (123 mg, 0.485 mmol), potassium phosphate (64.9 mg, 0.661 mmol) and the product from Step 4 (140 mg, 0.441 mmol) were added successively. The mixture was heated to 80 °C for 15 h and cooled to room temperature. Following addition of water (5 mL) and dichloromethane (80mL), the mixture was washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (silica, 0-40% ethyl acetate in hexanes) to provide methyl 2-methyl-2-(8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5H-chromeno[2,3-b]pyridin-5-yl)propanoate (65 mg, 36%). MS (ES+) m/z: 410 (M+H).

Step 6

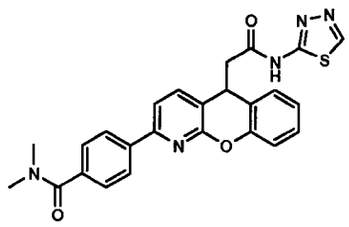
[00514] A mixture of the product from Step 5 (65 mg, 0.159 mmol), 4-bromo-N,N-dimethylbenzamide (72.4 mg, 0.318 mmol), 2.0 M aqueous potassium phosphate (0.397 mL, 0.794 mmol) and $Pd(Ph_3P)_4$ (27.5 mg, 0.024 mmol) in DMF (3 mL) was purged with N_2, heated to 100 °C for 15 h, and cooled to room temperature. After

addition of ethyl acetate (80 mL), the mixture was washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (silica, 30-100% ethyl acetate in hexanes) to provide methyl 2-(8-(4-(dimethylcarbamoyl)phenyl)-5H-chromeno[2,3-b]pyridin-5-yl)-2-methylpropanoate (50 mg, 73%). MS (ES+) m/z: 431 (M+H).

Step 7

[00515] Following similar procedures to Step 4 to 5 of Example 479, the product from Step 6 (50 mg, 0.116 mmol) was converted to the title compound (3.0 mg, 5%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.38 (s, 1H), 7.75 (m, 1H), 7.63 (m, 2H), 7.52 (m, 3H), 7.35 (m, 2H), 7.20 (m, 2H), 4.62 (s, 1H), 3.20 (s, 3H), 3.09 (s, 3H), 1.27 (s, 3H), 1.26 (s, 3H); MS (ES+) m/z: 500 (M+H); HPLC retention time: 2.01 min (Analytical HPLC Method E).

EXAMPLE 491



Step 1

[00516] Allylchlorodimethylsilane (0.124 mL, 0.85 mmol) and indium chloride (18.8 mg, 0.085 mmol) were added to a yellow solution of the alcohol from Preparation 83 (147 mg, 0.425 mmol) in dichloromethane (25 mL). After 15 h at room temperature, another portion of allylchlorodimethylsilane (0.124 mL, 0.85 mmol) was added. After additional 6 h at rt, the mixture was concentrated and purified by silica gel chromatography (50% to 100% ethyl acetate in hexane) to give 4-(5-allyl-5H-chromeno[2,3-b]pyridin-2-yl)-N,N-dimethylbenzamide as a yellow liquid (160 mg, ~90% pure). MS (ES+) m/z: 371 (M+H); HPLC retention time: 4.05 min (Analytical HPLC Method D).

Step 2

[00517] Ozone was bubbled through a solution of the product from Step 1 (40 mg, 0.108mmol) in dichloromethane (3 mL) and methanol (3 mL) at -78 °C until the solution turned blue. The solution was purged with nitrogen until the blue color disappeared. Polystyrene-supported triphenylphosphine (432 mg, 1 mmol/g) was added. After 6 h of stirring at ambient temperature, the mixture was filtered through a celite plug and the plug rinsed with ethyl acetate. The filtrate was concentrated to crude N,N-dimethyl-4-(5-(2-oxoethyl)-5H-chromeno[2,3-b]pyridin-2-yl)benzamide, which was used without purification. MS (ES+) m/z: 405 (M+MeOH+H).

Step 3

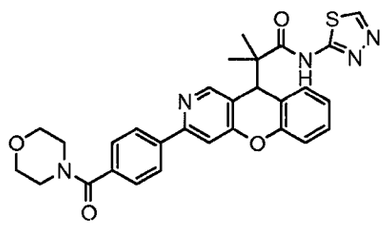
[00518] To a mixture of the aldehyde from Step 2, potassium dihydrogenphosphaste (0.047 ml, 0.810 mmol), and sodium chlorite (0.098 g, 1.080 mmol) were added t-butanol (4 ml), a 2 M THF solution of 2-methyl-2-butene (2 ml, 4.00 mmol) and water (2 ml). After stirring at rt for 2 h, the organic solvent was evaporated *in vacuo*. The residue was taken up in ethyl acetate (50 mL), washed with brine (2x10 mL), dried ($MgSO_4$) and concentrated. Silica gel chromatography, using 0 to 20% of methano in dichloromethane gave impure 2-(2-(4-(dimethylcarbamoyl)phenyl)-5H-chromeno[2,3-b]pyridin-5-yl)acetic acid, which was taken to next step without further purification.

Step 4

[00519] To a solution of the impure acid from Step 3 in acetonitrile (5 mL) was added HOBT (24.81 mg, 0.162 mmol), EDC (31.1 mg, 0.162 mmol), 1,3,4-thiadiazol-2-amine (21.84 mg, 0.216 mmol) and Hunig's Base (0.094 ml, 0.540 mmol). The mixture was stirred at room temperature for 3 h and at 60 °C for 1 h. The organic solvents were evaporated *in vacuo*. The residue was diluted with saturated NH_4Cl (10 mL) and extracted with dichloromethane (3x10 mL). The combined extracts were concentrated and purified by reverse-phase HPLC (YMC ODS S5 30x100 mm column) to give the title compound as a TFA salt (11.6 mg, 18% yield over three steps). ^{1}H-NMR (400 MHz, MeOH-d_4) δ 8.93 (s, 1H), 7.98 -7.96 (m, 2H), 7.77 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.45 – 7.41 (m, 2H), 7.26 – 7.18 (m, 2H),

7.12 – 7.10 (m, 1H), 7.04 – 7.00 (m, 1H), 4.66 (t, J = 6.9 Hz, 1H), 3.02 (s, 3H), 2.93 (s, 3H), 2.88-2.85 (m, 2H); MS (ES+) m/z: 472 (M+H); HPLC retention time: 3.58 min (Analytical HPLC Method D).

EXAMPLE 492



Step 1

[00520] A 2.5 M hexane solution of BuLi (16.46 mL, 41.1 mmol) was added dropwise to a solution of diisopropylamine (6.11 mL, 42.9 mmol) in THF (150 mL) at -78 °C. The mixture was stirred at 0 °C for 15 min and cooled to -78 °C. Acetone (3.02 mL, 41.1 mmol) was added dropwise. After 2 h at -78 °C, 2-chlorobenzoyl chloride (3.00 g, 17.14 mmol) in THF (10 mL) was added dropwise. The flask was rinsed with THF (2 mL) and added. After 1 h at -78 °C, the mixture was quenched with brine (200 mL) and acidified to pH ~1 with 1 N HCl. The organic solvents were evaporated *in vacuo*. The aqueous residue was extracted with EtOAc (3x100 mL). The combined extracts were dried ($MgSO_4$) and concentrated to give crude 1-(2-chlorophenyl)butane-1,3-dione as a yellow liquid. The crude material was taken to next step without purification. MS (ES+) m/z: 197 (M+H).

Step 2

[00521] A mixture of crude 1-(2-chlorophenyl)butane-1,3-dione from the previous step and 1,1-dimethoxy-N,N-dimethylmethanamine (2.042 g, 17.14 mmol) in toluene (20 mL) was heated to reflux for 2 h and concentrated. Silica gel chromatography, using 70 to 100% ethyl acetate in hexanes gradient, gave 1-(2-chlorophenyl)-2-((dimethylamino)methylene)butane-1,3-dione as a red, viscous oil (2.20 g, 51% yield for 2 steps). MS (ES+) m/z: 252 (M+H); HPLC retention time: 2.51 min (Analytical HPLC Method D).

Step 3

[00522] A 1.0 M hexane solution of LiHMDS (19.86 mL, 19.86 mmol) was added dropwise to a solution of 1-(2-chlorophenyl)-2-((dimethylamino)methylene)butane-1,3-dione (2.00 g, 7.95 mmol) and methyl 4-(chlorocarbonyl)benzoate (1.894 g, 9.53 mmol) in THF (100 mL) at -78 °C. After 1 h at -78 °C, the cold bath was removed and acetic acid (5 mL) and ammonium acetate (1.225 g, 15.89 mmol) were added. The mixture was heated to 70 °C for 1 h, at reflux for 1.5 h, concentrated to dryness *in vacuo* and taken up in N,N-dimethlyacetamide (50 mL). After addition of acetic acid (5 mL), the mixture was heated to 140 °C for 24 h, cooled to room temperature, diluted with MeOH (100 mL) and water (10 mL), cooled to 0 °C for 30 min and filtered. The solid was washed with MeOH three times to give a 7:3 mixture of methyl 4-(10-oxo-10H-chromeno[3,2-c]pyridin-3-yl)benzoate and 4-(10-oxo-10H-chromeno[3,2-c]pyridin-3-yl)benzoic acid.

Step 4

[00523] A mixture of the products from Step 3, 1 N solution of NaOH (50 mL, 50.0 mmol), MeOH (50 mL) and THF (50 mL) was heated to reflux. After 1 h, additional MeOH (50 mL) and DMF (10 mL) were added to help dissolving the starting material. After a total of 6 h at reflux, the mixture was cooled to room temperature and acidified to pH~3 with 1 N HCl. The precipitate was collected by filtration and washed with water three times to give 4-(10-oxo-10H-chromeno[3,2-c]pyridin-3-yl)benzoic acid as a tan solid (906 mg, 36% for 2 steps). MS (ES+) m/z: 318 (M+H).

Step 5

[00524] HOBt (145 mg, 0.945 mmol), EDC (181 mg, 0.945 mmol) and Hunig's base (0.550 mL, 3.15 mmol) were added to a suspension of 4-(10-oxo-10H-chromeno[3,2-c]pyridin-3-yl)benzoic acid (200 mg, 0.630 mmol) in DMF (15 mL) and CH_2Cl_2 (10 mL) at room temperature. After 5 min, morpholine (0.110 mL, 1.261 mmol) was added. After 13 h at rt, the mixture was quenched with saturated NH_4Cl (50 mL) and extracted with CH_2Cl_2 (3x50 mL). The combined extracts were dried

($MgSO_4$) and concentrated to give crude 3-(4-(morpholine-4-carbonyl)phenyl)-10H-chromeno[3,2-c]pyridin-10-one, which was taken to next reaction without purification. MS (ES+) m/z: 387 (M+H).

Step 6

[00525] $NaBH_4$ (0.238 g, 6.30 mmol) was added to a suspension of the crude 3-(4-(morpholine-4-carbonyl)phenyl)-10H-chromeno[3,2-c]pyridin-10-one from Step 5 in MeOH (50 mL) and CH_2Cl_2 (20 mL) at 0 °C. After 1 h at 0 °C, the mixture remained a suspension, and HPLC and LCMS indicated no product was formed. The cold bath was removed. Additional MeOH (50 mL), CH_2Cl_2 (30 mL) and $NaBH_4$ (0.5 g) were added. After 2.5 h, another batch of $NaBH_4$ (0.5 g) was added. After 30 min, the mixture was quenched with saturated NH_4Cl (100 mL). The organic solvent was evaporated *in vacuo*. The aqueous residue was extracted with CH_2Cl_2 (3x100 mL). The combined extracts were dried ($MgSO_4$) and concentrated to give crude (4-(10-hydroxy-10H-chromeno[3,2-c]pyridin-3-yl)phenyl)(morpholino)methanone, which was taken to the next reaction without purification.

Step 7

[00526] To a solution of the crude (4-(10-hydroxy-10H-chromeno[3,2-c]pyridin-3-yl)phenyl)(morpholino)methanone from Step 6 in CH_2Cl_2 (50 mL) at 0 °C was added a 1 M CH_2Cl_2 solution of titanium(IV) chloride (1.890 mL, 1.89 mmol). The resultant tan suspension was stirred at 0 °C for 5 min. Methyl trimethylsilyl dimethylketene acetal (0.512 mL, 2.52 mmol) was added. The mixture was stirred at 0 °C for 1 h, quenched with saturated $NaHCO_3$ (50 mL) and filtered through a celite pad to remove the insoluble titanium salt. The filter pad was rinsed with CH_2Cl_2. The two phases of the filtrate were separated. The aqueous phase was extracted with CH_2Cl_2 (2x50 mL). The combined CH_2Cl_2 phase (72170-085-01) was dried ($MgSO_4$) and concentrated. Silica gel chromatography, using 60-100% ethyl acetate in hexane gradient, gave methyl 2-methyl-2-(3-(4-(morpholine-4-carbonyl)phenyl)-10H-chromeno[3,2-c]pyridin-10-yl)propanoate as a white solid (179.2 mg, 60% yield over 3 steps).

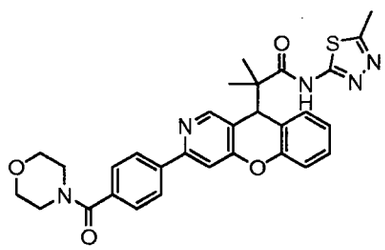
Step 8

[00527] Sodium 2-propanethiolate (58.5 mg, 0.596 mmol) was added to a solution of methyl 2-methyl-2-(3-(4-(morpholine-4-carbonyl)phenyl)-10H-chromeno[3,2-c]pyridin-10-yl)propanoate (140.9 mg, 0.298 mmol) in DMF (5 mL) and the mixture was heated to 50 °C. After 1 h at 50 °C, additional sodium 2-propanethiolate (58.5 mg) was added. The mixture was stirred at 50 °C overnight. Another portion of sodium 2-propanethiolate (200 mg) was added. After another hour at 50 °C, the mixture was quenched with saturated NH_4Cl (20 mL) and extracted with EtOAc (4x20 mL). The combined extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated to give 2-methyl-2-(3-(4-(morpholine-4-carbonyl)phenyl)-10H-chromeno[3,2-c]pyridin-10-yl)propanoic acid as a solid (145.5 mg). MS (ES+) m/z: 459 (M+H); HPLC retention time: 3.51 min (Analytical HPLC Method D).

Step 9

[00528] Hunig's base (0.072 mL, 0.410 mmol) was added to a mixture of 2-methyl-2-(3-(4-(morpholine-4-carbonyl)phenyl)-10H-chromeno[3,2-c]pyridin-10-yl)propanoic acid (31.3 mg, 0.068 mmol), HOBT (20.91 mg, 0.137 mmol), EDC (26.2 mg, 0.137 mmol) and 1,3,4-thiadiazol-2-amine (20.71 mg, 0.205 mmol) in DMF (2 mL). The mixture was stirred at room temperature for 5 min, at 60 °C for 1 h, at 80 °C for 4 h and concentrated. Purification by preparative reverse-phase HPLC (using Shimadzu 10A liquid chromatographs and Waters Sunfire S10 30 x 250 mm column) gave Example XX as a white solid (25.5 mg, 57% yield), assumed as TFA salt. 1H NMR (400 MHz, CD3OD) δ ppm 9.13 (s, 1 H), 8.63 (s, 1 H), 8.07 (s, 1 H), 8.05 (d, J = 8.26 Hz, 2 H), 7.70 (d, J = 8.22 Hz, 2 H), 7.45-7.49 (m, 1 H), 7.36-7.38 (m, 2 H), 7.28-7.30 (m, 1 H), 4.83 (s, 1 H), 3.81 (br s, 4 H), 3.68 (br s, 2 H), 3.50 (br s, 2 H), 1.27 (s, 3 H), 1.25 (s, 3H); MS (E+) m/z: 542 (M+H); LC retention time: 3.52 min (Analytical HPLC Method D).

EXAMPLE 493



[00529] Following procedure analogous to Step 9 of Example 492, the title compound was prepared from 2-methyl-2-(3-(4-(morpholine-4-carbonyl)phenyl)-10H-chromeno[3,2-c]pyridin-10-yl)propanoic acid and 5-methyl 1,3,4-thiadiazol-2-amine. MS (E+) m/z: 556 (M+H); LC retention time: 3.68 min (Analytical HPLC Method D).

BIOLOGICAL ACTIVITY DATA

[00530] The AP-1 activity of Examples 1 to 491 is given where the AP-1 EC_{50} is less than 1 uM. Accompanying AP-1 maximum inhibition values are also given. Where the AP-1 EC50 is greater than 1 uM and/or the maximal inhibition is less than 20 %, the glucocorticoid receptor (GR) binding affinity (Ki) is given.

[00531] The data presented below were obtained using the assays referred to in the able and described herein in the ASSAY section *supra*.

Example No.	GR (Ki, nM) (GR Binding Assay (I)[a])	GR (Ki, nM) (GR Binding Assay (II)[b])	AP-1 EC_{50}, nM (Cellular Trans-repression Assay)	AP-1 Max%inh (Cellular Trans-repression Assay)
1			156.90	69.29
2				42.73
3				47.84
4				56.46
5			58.20	65.97
6			460.60	67.91
7			302.70	64.91
8			546.20	69.02
9		154.20		
10			16.80	86.50
11			881.90	68.50
12			460.60	67.91
13			566.50	60.26

Example No.	GR (Ki, nM) (GR Binding Assay (I)[a])	GR (Ki, nM) (GR Binding Assay (II)[b])	AP-1 EC_{50}, nM (Cellular Trans-repression Assay)	AP-1 Max%inh (Cellular Trans-repression Assay)
14		5455.00		
15			501.30	65.89
16			303.40	59.92
17			334.90	67.95
18			541.90	37.62
19				52.68
20			473.30	46.87
21				60.79
22		1637.00		
23		445.20		
24			15.72	78.77
25		41.10		
26				26.90
27				14.96
28				43.67
29			139.00	66.36
30			337.80	67.25
31			178.70	69.38
32			301.50	67.61
33			31.76	55.20
34			3.52	71.85
35			80.64	72.28
36		1040.00		
37		1.40		
38				70.38
39		39.70		
40			461.00	47.76
41			5.82	73.76
42			3.70	73.41
43			13.41	71.92
44				69.30
45			102.40	71.48
46			90.23	67.62
47			534.10	66.66
48		60.90		
49			40.29	68.76
50			165.20	74.75
51			6.87	77.91
52			212.90	70.81
53			78.51	72.00
54			13.11	71.39

Example No.	GR (Ki, nM) (GR Binding Assay (I)[a])	GR (Ki, nM) (GR Binding Assay (II)[b])	AP-1 EC_{50}, nM (Cellular Trans-repression Assay)	AP-1 Max%inh (Cellular Trans-repression Assay)
55			21.47	75.53
56		233.30		
57			11.54	74.78
58			3.71	70.02
59			11.76	58.39
60		35.70		
61		909.00		
62		58.00		
63				75.82
64			19.86	79.28
65			345.40	32.22
66		665.20		
67		107.00		
68		820.20		
69		515.40		
70		761.70		
71		517.20		
72	>1154			
73			735.40	60.62
74			318.60	71.16
75		29.00		
76		76.40		
77			91.63	73.89
78			163.80	65.08
79			9.42	62.34
80	56.09			
81		242.90		
82			125.80	72.61
83			15.03	69.64
84		103.70		
85				88.40
86		32.90		
87			91.11	45.95
88			127.70	49.23
89			18.08	68.32
90			6.43	59.47
91		2554.00		
92		1200.00		
93		1266.00		
94		403.50		
95			574.10	52.19

Example No.	GR (Ki, nM) (GR Binding Assay (I)[a])	GR (Ki, nM) (GR Binding Assay (II)[b])	AP-1 EC_{50}, nM (Cellular Trans-repression Assay)	AP-1 Max%inh (Cellular Trans-repression Assay)
96		22.10		
97		296.00		
98		88.70		
99		18.30		
100			256.10	71.73
101	19.76			
102			57.97	45.01
103	6.06			
104	4.50			
105			12.19	30.54
106			24.12	48.41
107			833.30	22.82
108	13.60			
109			182.50	60.22
110			183.40	35.68
111			14.60	40.67
112		9.30		
113	62.63			
114	49.90			
115			3.90	31.34
116	346.10			
117	123.10			
118	76.60			
119			83.02	45.30
120			29.63	40.32
121			59.45	44.82
122	79.97			
123	17.82			
124	65.14			
125			94.33	33.24
126			49.73	30.84
127		29.70		
128			92.02	66.34
129			307.30	39.52
130			111.00	31.48
131			970.00	45.65
132			95.98	50.08
133			584.90	61.32
134		444.10		
135		537.30		
136		141.40		

Example No.	GR (Ki, nM) (GR Binding Assay (I)[a])	GR (Ki, nM) (GR Binding Assay (II)[b])	AP-1 EC_{50}, nM (Cellular Trans-repression Assay)	AP-1 Max%inh (Cellular Trans-repression Assay)
137		221.50		
138		11.40		
139			95.54	26.80
140			93.65	64.12
141			92.10	44.23
142		156.20		
143		744.40		
144		5455.00		
145		1162.00		
146		37.00		
147		4026.00		
148		11.10		
149		11.00		
150		26.90		
151	7.58			
152		10.90		
153			982.50	73.55
154			236.10	46.25
155		31.80		
156		80.90		
157		186.40		
158			200.00	62.52
159			478.80	30.33
160		5455.00		
161		36.60		
162		255.50		
163			16.78	49.60
163[a]			4.9	64.40
164[a]			8.5	57.97
165[a]			9.8	53.39
166[a]			14.5	56.11
164			5.58	57.26
165			25.63	56.92
166			43.40	54.18
167			36.57	57.94
168	485.60			
169			92.74	48.82
170			182.30	44.12
171	7.15	10.20		
172			13.21	59.04

Example No.	GR (Ki, nM) (GR Binding Assay (I)[a])	GR (Ki, nM) (GR Binding Assay (II)[b])	AP-1 EC_{50}, nM (Cellular Trans-repression Assay)	AP-1 Max%inh (Cellular Trans-repression Assay)
173			82.49	44.82
174	10.16			
175	51.98	49.40		
176			118.50	43.54
177	>1154	459.70		
178	10.58	4.70		
179	64.62	37.90		
180	22.82	14.60		
181	>1154	182.70		
182			108.60	33.12
183	44.43	20.40		
184	6606.00	263.10		
185	>1154	697.40		
186	386.10	84.60		
187	33.10	34.40		
188	28.88	8.10		
189	19.63	11.70		
190	11.53	5.70		
191			22.64	37.51
192	12.33	13.10		
193	11.14	8.50		
194	4.63	7.10		
195	735.70	505.30		
196	6.26	15.90		
197	9.27	23.30		
198			22.17	34.38
199			27.60	48.94
200			133.80	53.76
201			36.34	65.46
202			218.60	38.37
203	4.61	13.10		
204			42.75	44.75
205			8.50	57.72
206			21.31	54.73
207			32.61	37.96
208			12.25	54.08
209			14.30	50.21
210			77.73	39.38
211			41.28	49.63
212			19.59	63.05
213	7.95			

Example No.	GR (Ki, nM) (GR Binding Assay (I)[a])	GR (Ki, nM) (GR Binding Assay (II)[b])	AP-1 EC_{50}, nM (Cellular Trans-repression Assay)	AP-1 Max%inh (Cellular Trans-repression Assay)
214	1.37			
215	2.50			
216	4.14			
217			41.03	45.81
218	1.24			
219			180.30	35.87
220			105.20	52.23
221			28.92	62.97
222			100.20	61.88
223			838.90	27.87
224	8.06			
225			919.70	45.65
226			18.14	49.05
227			37.94	42.50
228			51.53	28.32
229			42.01	39.34
230			550.10	52.33
231			733.40	38.36
232	4.57			
233	11.29			
234			405.40	27.08
235	4.85			
236	9.44			
237	6.04			
238			601.00	62.32
239			12.43	44.85
240			51.87	61.72
241			25.28	46.83
242	412.30			
243	>1154			
244	>1154			
245	1.01			
246			325.40	81.76
247			4.74	52.38
248			21.45	55.87
249			11.20	42.38
250			17.84	48.42
251			17.45	54.92
252			34.61	60.94
253	6.28			

Example No.	GR (Ki, nM) (GR Binding Assay (I)[a])	GR (Ki, nM) (GR Binding Assay (II)[b])	AP-1 EC_{50}, nM (Cellular Trans-repression Assay)	AP-1 Max%inh (Cellular Trans-repression Assay)
254			23.62	41.80
255	16.11			
256	180.30			
257			12.44	63.96
258			533.50	40.99
259			72.21	23.33
260			23.14	67.28
261			4.74	52.38
262	18.19			
263			15.42	58.05
264			115.20	33.74
265	126.20			
266			11.20	42.38
267			568.70	40.78
268	9.45			
269	14.75			
270	20.94			27.98
271	218.00			
272	12.58			
273	19.91			20.96
274			234.10	62.19
275	2.60			26.02
276	4.05			27.21
277	81.32			24.52
278	30.53			
279	20.84			
280	10.75			33.52
281	33.50			
282	13.41			
283	9.21			24.64
284	17.37			
285	5.84			45.31
286	12.15			49.83
287	16.82			
288	13.80			35.54
289	19.98			24.29
290	20.36			28.80
291	43.96			26.99
292	10.84			
293	10.43			25.39
294	29.30			59.35

Example No.	GR (Ki, nM) (GR Binding Assay (I)[a])	GR (Ki, nM) (GR Binding Assay (II)[b])	AP-1 EC_{50}, nM (Cellular Trans-repression Assay)	AP-1 Max%inh (Cellular Trans-repression Assay)
295	38.73			24.36
296	19.13			
297	>1154			
298	241.90			25.36
299	13.28			
300			14.83	61.77
301	20.25			28.57
302	126.30			
303	278.00			28.59
304	149.00			
305	24.71			38.32
306	9.85			43.48
307	67.51			37.14
308	313.00			
309			41.50	34.95
310			785.90	52.93
311	25.77			
312			266.70	73.06
313	4.65			
314			18.01	69.78
315			749.90	40.86
316			60.90	35.90
317	23.69			
318			63.08	27.55
319	110.30			
320	13.11			
321	30.56			
322	18.89			
323	3.69			
324			431.10	54.88
325			90.21	56.09
326	10.49			
327			8.93	59.45
328			18.63	66.06
329			582.70	40.81
330			21.94	60.62
331			33.71	36.28
332	9.56			
333			24.69	52.71
334			3.36	36.22
335			37.94	55.97

Example No.	GR (Ki, nM) (GR Binding Assay (I)[a])	GR (Ki, nM) (GR Binding Assay (II)[b])	AP-1 EC_{50}, nM (Cellular Trans-repression Assay)	AP-1 Max%inh (Cellular Trans-repression Assay)
336			20.40	55.80
337			102.80	51.49
338	311.80			
339			184.70	38.40
340			54.77	67.61
341			14.82	50.27
342			51.68	41.54
343			18.44	29.68
344			39.64	44.55
345			124.30	54.25
346	3.04			
347	5.63			
348			300.30	34.37
349	5.88			31.72
350			519.90	45.06
351	146.70			
352	42.06			
353	13.03			
354	20.10			28.93
355	19.56			
356	581.90			
357	31.36			29.62
358	40.50			
359	30.08			
360	154.10			
361	14.62			
362	804.70			
363			247.10	47.74
364			244.20	58.90
365	18.25			
366	200.00			
367	692.30			
368			38.59	46.80
369			33.04	55.45
370			34.22	57.60
371			22.27	48.73
372			28.28	52.42
373			32.80	45.61
374			30.91	50.87
375			82.80	51.24
376			34.42	45.09

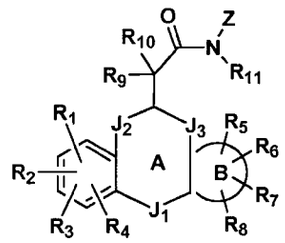
Example No.	GR (Ki, nM) (GR Binding Assay (I)[a])	GR (Ki, nM) (GR Binding Assay (II)[b])	AP-1 EC_{50}, nM (Cellular Trans-repression Assay)	AP-1 Max%inh (Cellular Trans-repression Assay)
377			32.72	49.10
378			72.62	48.18
379			73.97	51.21
380			100.60	53.58
381			45.25	52.00
382			205.80	47.22
383			46.32	41.78
384			61.85	42.30
385			96.47	28.99
386			89.04	34.32
387			82.02	52.49
388			34.22	57.60
389			50.54	55.20
390			42.77	56.63
391			52.02	44.08
392			49.73	44.82
393			53.37	43.80
394	4.00			
395	1.19			
396	10.62			
397	40.89			
398			479.60	50.00
399			332.90	69.30
400	37.32			
401			778.30	35.10
402	698.60			
403	61.21			
404			22.49	70.62
405	423.70			
406	176.30			
407	958.20			
408			363.90	24.10
409	78.16			
410			53.32	48.15
411			161.10	58.47
412	22.27			
413	37.74			
414	589.00			
415	64.10			
416	94.46			
417			67.32	54.11

Example No.	GR (Ki, nM) (GR Binding Assay (I)[a])	GR (Ki, nM) (GR Binding Assay (II)[b])	AP-1 EC_{50}, nM (Cellular Trans-repression Assay)	AP-1 Max%inh (Cellular Trans-repression Assay)
418			82.09	29.07
419			71.86	46.63
420			41.94	42.14
421			49.78	42.56
422			84.14	41.58
422[a]			51.50	50.45
422[b]			46.72	63.52
423			81.98	30.36
424			150.30	59.58
425			84.43	49.89
426			117.10	31.80
427			187.80	25.13
428			30.29	26.89
429			67.27	41.78
430			34.69	47.22
431			69.04	41.78
432			52.66	40.25
433			40.97	46.21
434			197.10	38.45
435			291.80	27.88
436			95.67	44.01
437	11.06			
438	53.10			
439	65.80			
440	20.97			
441			63.91	52.35
442			126.60	50.14
443			134.40	51.70
444			44.20	57.54
445			38.48	45.74
446			412.60	27.69
447			95.37	53.02
448			178.40	56.59
449			126.40	48.87
450			59.16	26.30
451	5.57			
452			11.11	53.38
453	17.60			
454			25.34	49.46
455			24.61	58.63
456			41.48	45.84

Example No.	GR (Ki, nM) (GR Binding Assay (I)[a])	GR (Ki, nM) (GR Binding Assay (II)[b])	AP-1 EC_{50}, nM (Cellular Trans-repression Assay)	AP-1 Max%inh (Cellular Trans-repression Assay)
457			16.56	51.89
458			53.25	35.19
459			101.70	35.43
460			30.33	56.91
461			53.38	50.80
462	3.78			
463			45.30	26.23
464			18.20	54.01
465			16.55	61.53
466			28.25	56.07
467			14.97	57.51
468			35.39	53.30
469	49.82			
470			24.60	43.03
471			63.91	52.35
472			26.92	47.04
473			40.19	52.52
474			85.40	37.88
475	18.31			
476	16.37			
477			39.75	44.78
478			16.02	41.78
479			47.00	44.36
480			27.01	43.97
481			579.30	33.76
482	44.97			
483	426.20			
484			19.32	29.79
485			42.36	38.86
486			15.78	50.34
487	>1154			
488			42.92	34.48
489	143.80			
490	14.82			
491	>1154			
492			182.00	28.40
493	108.90			

WHAT IS CLAIMED IS:

1. A compound according to formula (I),



I ,

an enantiomer, diastereomer, tautomer, or a pharmaceutically-acceptable salt thereof, wherein:

Z is selected from heterocyclo, heteroaryl and cyano;

A is selected from a 5- to 8- membered carbocyclic ring and a 5- to 8-membered heterocyclic ring;

the B ring is selected from a cycloalkyl, cycloalkenyl, aryl, heterocyclo ring, and heteroaryl ring, wherein the B ring is fused to the A ring, and the B ring is optionally substituted by one to four groups which are the same or different and are independently selected from R_5, R_6, R_7, and R_8;

J_1, J_2, and J_3 are the same or different and at each occurrence are independently $-A_1QA_2-$;

Q is independently at each occurrence selected from a bond, O, S, S(O), and $S(O)_2$;

A_1 and A_2 are the same or different and at each occurrence are independently selected from a bond, C_{1-3}alkylene, substituted C_{1-3}alkylene, C_{2-4}alkenylene, and substituted C_{2-4}alkenylene, provided that A_1 and A_2 are chosen so that ring A is a 5- to 8-membered carbocyclic ring or a 5- to 8-membered heterocyclic ring;

R_1, R_2, R_3, R_4, R_5, R_6, R_7, and R_8 are the same or different and at each occurrence are independently selected from (i) hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, nitro, cyano, OR_{12}, $-NR_{12}R_{13}$, $-C(=O)R_{12}$, $-CO_2R_{12}$, $-C(=O)NR_{12}R_{13}$, $-OC(=O)NR_{12},R_{13}$, $-\underset{R_d}{N}C(=O)NR_{12}R_{13}$, $-OC(=O)R_{12}$,

-$NR_{12}C(=O)R_{13}$, -$NR_{12}C(O)OR_{13}$, -$NR_{12}C(S)OR_{13}$, $S(O)_pR_{16}$, $NR_{12}SO_2R_{16}$, dialkylaminoalkoxy, alkoxyalkyloxyalkyloxy, $SO_2NR_{12}R_{13}$, cycloalkyl, cycloalkenyl, cycloalkynyl, heterocyclo, aryl, and heteroaryl; and/or (ii) where possible, each one of R_1-R_8 is taken together with any one of R_1-R_8 located on an adjacent atom to form a fused ring; and/or (iii) where possible any one of R_1-R_8 is taken together with any one of R_1-R_8 located on the same atom to form an oxo, alkenyl, substituted alkenyl, cycloalkyl, cycloalkenyl, or heterocyclo group;

R_9 and R_{10} are the same or different and at each occurrence are independently selected from (i) hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, nitro, cyano, OR_{14}, $NR_{14}R_{15}$, $C(=O)R_{14}$, CO_2R_{14}, $C(=O)NR_{14}R_{15}$, -O-$C(=O)R_{14}$, $NR_{14}C(=O)R_{15}$, $NR_{14}C(=O)OR_{15}$, $NR_{14}C(=S)OR_{15}$, $S(O)_pR_{17}$, $NR_{14}SO_2R_{17}$, $SO_2NR_{14}R_{15}$, cycloalkyl, cycloalkenyl, heterocyclo, aryl, and heteroaryl; or (ii) together with the atom to which the are attached, R_9 and R_{10} are taken together to form a carbonyl, alkenyl, substituted alkenyl, cycloalkyl, cycloalkenyl, or heterocyclo group;

R_{11} is selected from hydrogen, alkyl, substituted alkyl, C(=O)alkyl, CO_2(alkyl), SO_2alkyl, alkoxy, amino, substituted amino, aryl, heteroaryl, heterocyclo, and cycloalkyl;

R_{12}, R_{13}, R_{14}, and R_{15}, are the same or different and at each occurrence are independently selected from (i) hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclo; or (ii) where possible R_{12} is taken together with R_{13}, and/or where possible R_{14} is taken together with R_{15} to form a heteroaryl or heterocyclo ring;

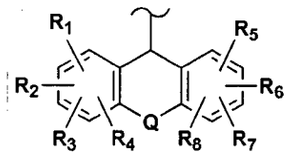
R_{16} and R_{17}, are the same or different and at each occurrence are independently selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclo;

R_d is H, alkyl or aryl; and

p is 0, 1 or 2,

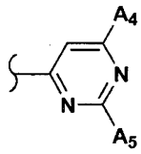
provided that

(1) where the tricyclic moiety in the formula I compound is



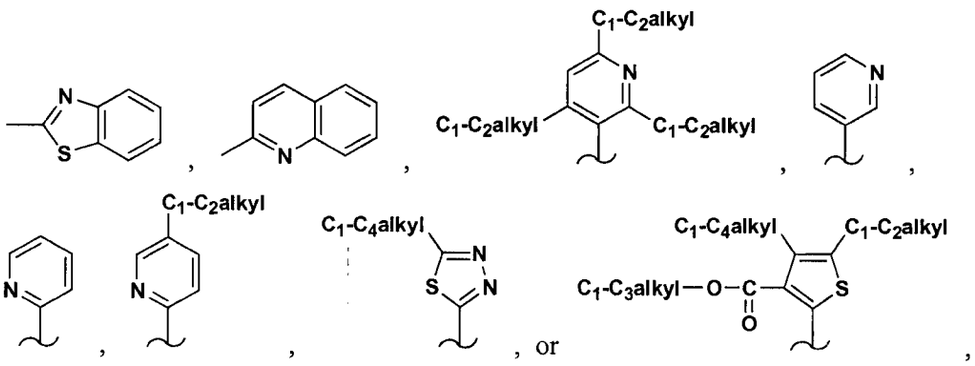
where Q is O and R_1 to R_8 are each H, then

(a) Z is other than

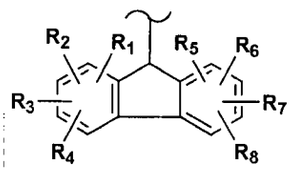


where A_4 and A_5 are the same or different and are independently H or C_1-C_2alkyl-; or

(b) Z is other than



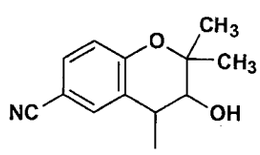
(2) where the tricyclic moiety is



where R_1 to R_8 are each H,

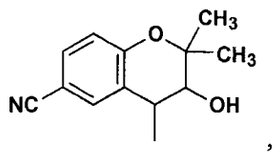
then

(a) Z is other than



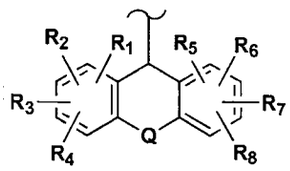
, or

(b) where Z is



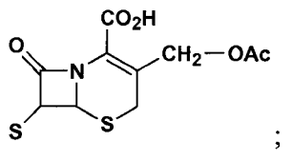
then R_{11} is other than a substituted C_1-C_2-alkylene;

(3) where the tricyclic moiety is



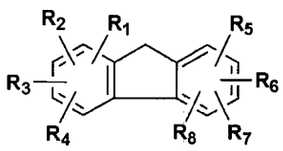
where Q is S or SO_2, and R_1 to R_8 are each H,

then Z is other than

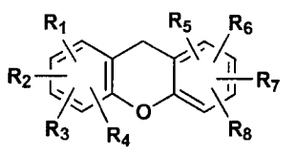


;

(4) where the tricyclic moiety is

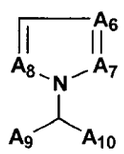


or



where R_1 to R_8 are each H,

then Z is other than



where A_6, A_7 and A_8 are independently N or CH,

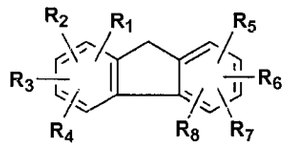
A_9 is $-(CH_2)_d-A_{11}$ where d is 0 to 4;

A_{11} is OH, CO_2H, 5-tetrazolyl, $-COO(C_1-C_4alkyl)_{n_a}$ or CN-;

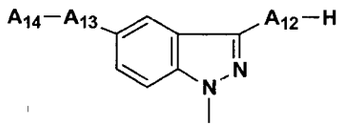
n_a is 0 to 4; and

A_{10} is C_4-C_7 straight chain alkyl;

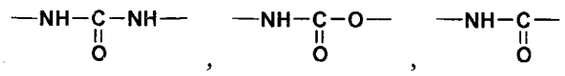
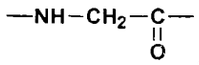
(5) where the tricyclic moiety is



then Z is other than



where A_{12} is O or S; and

A_{13} is O or an NH,  , or  ,

wherein the last 3 groups are joined to the aromatic ring through the N-atom;

A_{14} is H,

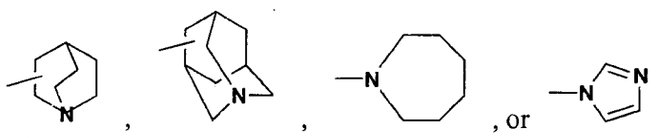
alkyl,

C_3-C_7 cycloalkyl,

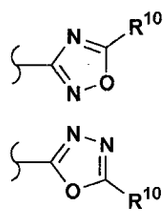
phenyl, naphthyl, anthranyl or fluorenyl optionally substituted, or

a quinolin-2-ylmethoxy or pyridin-ylmethoxy; or

Z is other than

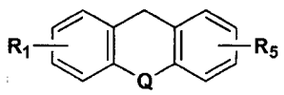
 , or ; or

Z is other than



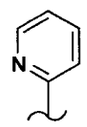
where R^{10} is a non-aromatic azacyclic or non-aromatic azabicyclic ring system;

(6) where the tricyclic moiety is



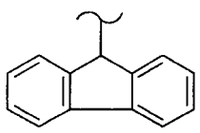
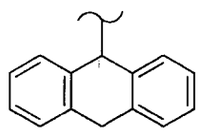
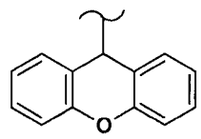
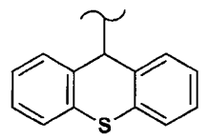
Q is -O-, -S-, -C(R^3R^4)-, -CH_2CH_2-, -CH=CH-CH_2-, -CH_2-CH=CH-, -CH_2-(C=O)-, -(C=O)-CH_2-, $CH_2CH_2CH_2$-, -CH=CH-, -O-CH_2-, -CH_2-O-, -O-CH_2-O-, -CH_2-O-CH_2-, -S-CH_2-, -CH_2-S-, -CH(R^5)CH_2-, -CH_2CH(R^5)-, -(C=O)-, or -(S=O)- wherein R^3 and R^4 independently are hydrogen or C_{1-7}-alkyl; and wherein R^5 is C_{1-7}-alkyl or phenyl;

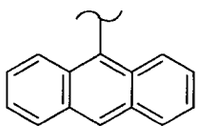
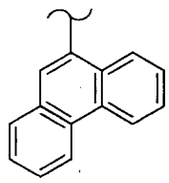
then Z is other than



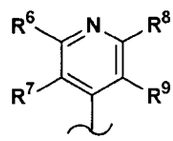
;

(7) where the tricyclic moiety is


,

,

,

,


or

,

then Z is other than



wherein:

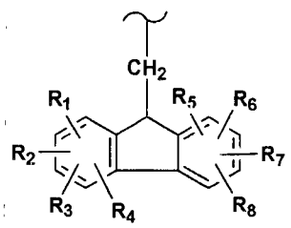
R^6 and R^7 are each independently selected from C_1-C_6alkyl, halo-C_1-C_6alkyl containing 1 to 5 halogen atoms, C_1-C_2alkoxy-C_1-C_6alkyl, nitro-C_1-C_6alkyl, cyano-C_1-C_6alkyl, C_1-C_2alkanoyl-C_1-C_6alkyl, C_1-C_2alkoxycarbonyl-C_1-C_6alkyl, C_1-C_2alkylthio-C_1-C_6alkyl, C_1-C_2alkanesulfinyl-C_1-C_6alkyl, C_1-C_2alkanesulfonyl-C_1-C_6alkyl, C_2-C_6alkenyl, halo-C_2-C_6alkenyl containing 1-5 halogen atoms,

C_2-C_6alkynyl, halo-C_2-C_6alkynyl containing 1-5 halogen atoms, C_3-C_7cycloalkyl and halogen; or

R^6 and R^7, taken together, form a saturated or unsaturated 5- to 7-membered carbocyclic or heterocyclic ring which may contain one or two hetero atoms selected from O and S; and

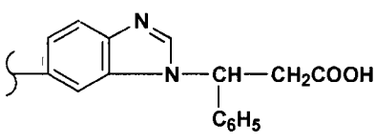
R^8 and R^9 are each independently selected from hydrogen, C_1-C_6alkyl and halogen;

(8) where the tricyclic moiety is



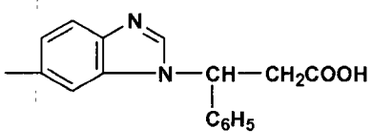
then

a) Z is other than



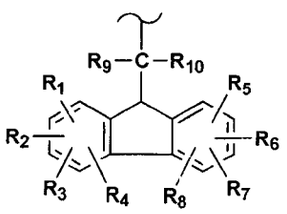
or a homolog thereof,

b) if Z is

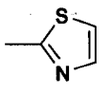


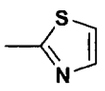
or a homolog thereof, then R_{11} is other than H; or

(9) where the tricyclic moiety is

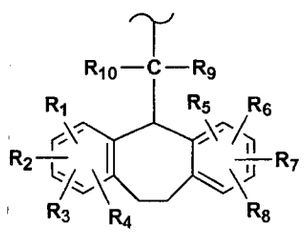


then

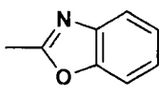
a) Z is other than substituted or unsubstituted  , or

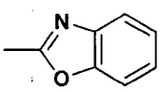
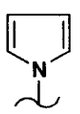
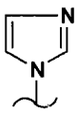
b) where Z is substituted or unsubstituted  , then at least one or R_9 and R_{10} is other than H and/or R_{11} is other than H;

(10) where the tricyclic moiety is

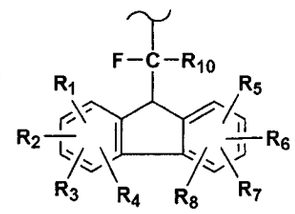


then

a) Z is other than  ,

b) where Z is  ,  ,  ,  , or  , then R_{11} is other than H and/or at least one of R_9 and R_{10} is other than H;

(11) where the tricyclic moiety is

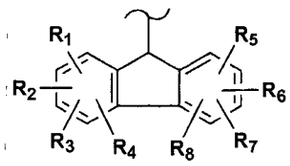


then

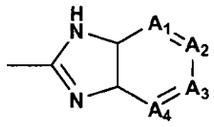
a) Z is other than heteroaryl, or

b) where Z is heteroaryl, then R_{11} is other than H and/or R_{10} is other than H; or

(12) where the tricyclic moiety is

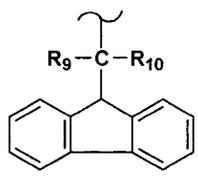


then R_1, R_2, R_3, R_4, R_5, R_6, R_7 and R_8 is other than

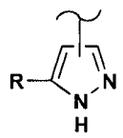


wherein A_1, A_2, A_3 and A_4 are selected from CR_a or N, where R_a is H or a substituent; or

(13) where the tricyclic moiety is

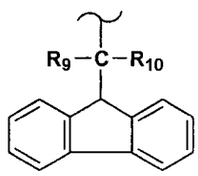


then Z is other than



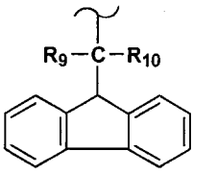
where R is C_3-C_6cycloalkyl optionally substituted by C_1-C_6alkyl or arylalkyl or a homolog thereof;

(14) where the tricyclic moiety is



and Z is heteroaryl containing or heterocyclyl containing an N atom in the ring, then the Z heteroaryl or heterocyclyl cannot be substituted with an R′A group where R′ is optionally substituted heterocyclic or phenyl and A is $(CH_2)_{0\text{-}2}(O)_{0 \text{ or } 1}$ or $(CR^3R^4)_{0 \text{ or } 1}NR^5(CO)_{0 \text{ or } 1}$ where R^3, R^4 = H or R^3 + R^4-imino and R^5 = H or alkyl;

(15) where the tricyclic moiety is

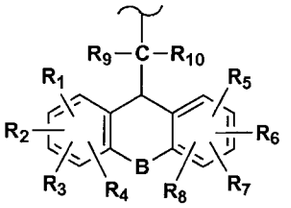


and Z is other than a 5-7 membered heterocyclic ring containing an N, O and/or S which heterocyclic ring is substituted by $-D-A-\overset{O}{\overset{\|}{C}}-R^1$ where D is $^{1-4}$Calkylene, O or S,

A is a 3 to 7 carbocyclic ring or a 5- to 7-membered heterocyclic ring containing N, O and/or S, and

R^1 is OH, alkoxy, or $NR^{10}R^{11}$ where R^{10} and R^{11} can be H or alkyl which Z and/or also may be optionally substituted by 1-3 group which can be C_{1-4}alkyl, C_{1-4}alkoxy, halo, trihalomethyl, CN, or NO_2; or

(16) where the tricyclic moiety is



where B is O or S, then

a) Z is other than optionally substituted dihydrofuryl or optionally substituted dihydrothienyl,

b) or if Z is optionally substituted dihydrofuryl or optionally substituted dihydrothienyl, then

1) at least one of R_9 and/or R_{10} is other than H, or

2) R_{11} is other than H or lower alkyl.

2. A compound as defined in Claim 1, or an enantiomer, diastereomer, tautomer, or a pharmaceutically-acceptable salt thereof, wherein:

B is a phenyl, pyridinyl or pyrazinyl ring;

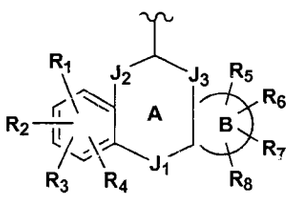
J_1 is O, S, SO, SO_2, a bond, CH_2, or CH_2CH_2; and

J_2 and J_3 are each a bond.

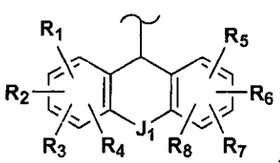
3. A compound as defined in Claims 1-2, or an enantiomer, diastereomer, tautomer, or a pharmaceutically-acceptable salt thereof, wherein J_1 is O, S, SO, SO_2, or a bond.

4. A compound as defined in Claims 1-3, or an enantiomer, diastereomer, tautomer, or a pharmaceutically-acceptable salt thereof, wherein B is a pyridinyl ring substituted with aryl or substituted aryl.

5. A compound as defined in Claims 1-3, or an enantiomer, diastereomer, tautomer, or a pharmaceutically-acceptable salt thereof, wherein the tricyclic moiety:



is



.

6. A compound as defined in Claims 1-5, or an enantiomer, diastereomer, tautomer, or a pharmaceutically-acceptable salt thereof,

R_2, R_3, and R_4 are each hydrogen;

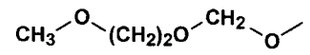
R_6, R_7, and R_8 are each hydrogen;

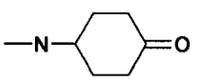
R_1 is selected from hydrogen, CF_3, alkoxy, halogen, hydroxyl, and dialkylaminoalkoxy; and

R_5 is selected from hydrogen, CF_3, alkoxy, halogen, amino, dialkylamino, heterocyclo, aryl, carboxyaryl, alkoxyaryl, alkylaryl, heterocyclocarbonylaryl, alkoxy(halo)aryl, carboxy(halo)aryl, dialkylaminocarbonylaryl, alkylamino, hydroxyl, dialkylaminoalkoxy, arylalkylamino, alkoxyarylalkylamino,

alkylheterocyclo, arylalkyl, heterocycloalkoxy, arylheterocyclo, arylalkyl(alkyl)amino, haloaryl, dialkylaminoaryl, haloaryl, alkoxyalkoxyalkoxyl, alkylcarbonylamino, heteroaryl, dialkylaryl, hydroxyaryl, alkoxycarbonylaryl, alkylcarbonylaminoaryl, alkylsulfonylaminoaryl, aryloxyaryl, alkylthioaryl, aminoaryl, alkylcarbonylaryl, arylalkoxyaryl, and cyanoaryl.

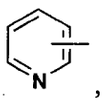
7. A compound as defined in Claims 1-5, or an enantiomer, diastereomer, tautomer, or a pharmaceutically-acceptable salt thereof, wherein R_1, R_2 and R_3 are each hydrogen; and R_4 is selected from hydrogen, CF_3, alkoxy, dialkylaminoalkoxy, hydroxyl and alkoxyalkyoxyalkoxy, an enantiomer, diastereomer, or tautomer thereof, or a prodrug ester thereof, or a pharmaceutically-acceptable salt thereof.

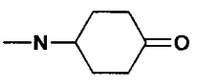
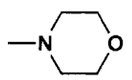
8. A compound as defined in Claims 1-5, and 7, or an enantiomer, diastereomer, tautomer, or a pharmaceutically-acceptable salt thereof, wherein R_1, R_2, and R_3 are each hydrogen, and R_4 is selected from hydrogen, CF_3, CH_3O, $N(CH_3)_2CH_2CH_2O$-, OH, and  .

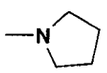
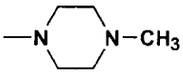
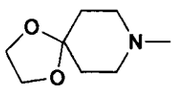
9. A compound as defined in Claim 1-8, or an enantiomer, diastereomer, tautomer, or a pharmaceutically-acceptable salt thereof, wherein R_5, R_6, and R_7 are each hydrogen and R_8 is selected from hydrogen, hydroxyl, CF_3, alkoxy, halogen, dialkylaminoalkoxy, alkoxyalkyloxyalkyloxy, alkylamino, heterocyclo, arylalkylamino, alkoxyarylalkylamino, dialkylamino,  , alkoxyaryl, aryl, trifluoromethoxylaryl, carboxyaryl, haloalkyl, dialkylaminoaryl, naphthyl, alkylphenyl, CF_3aryl, alkylcarbonylaminoaryl, dialkylaryl, hydroxyaryl, alkoxycarbonylaryl, alkylcarbonylaminoaryl, alkylsulfonylaminoaryl, arylaryl, alkylsulfonylaryl, aminoaryl, arylalkyloxyarylcyanoaryl, and alkylaryl.

10. A compound as defined in Claims 1-9, or an enantiomer, diastereomer, tautomer, or a pharmaceutically-acceptable salt thereof, wherein R_5, R_6, and R_7 are each hydrogen and R_8 is selected from hydrogen, Cl, $(CH_3)_2N(CH_2)_2O$-, $CH_3OCH_2CH_2OCH_2O$-, benzylamino, methoxybenzylamino, $N(CH_3)_2CH_2CH_2O$-,

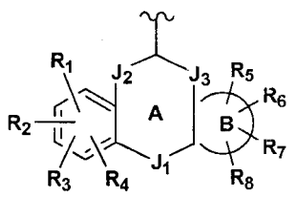
OH, CF_3, CH_3O-, dimethylamino, methoxyphenyl, phenyl, $CF_3OC_6H_4$-, CO_2H-C_6H_4, CN-C_6H_4, s-C_4H_9-C_6H_4-C_2H_5O-C_6H_4, s-C_4H_9-C_6H_4, -C_3H_7-C_6H_4-, n-C_4H_9-O-C_6H_4-, C_2H_5-C_6H_4-, t-C_4H_9-C_6H_4-, $CH_3COC_6H_4$-, $C_6H_5CH_2OC_6H_4$-, C_6H_5-C_6H_4-, C_6H_5-O-C_6H_4-, $CH_3SC_6H_4$-, $NH_2C_6H_4$-, CH_3-SO_2-NHC_6H_4-, F-C_6H_4, C_6H_5-, ClC_6H_4,

-diCH_3amino, naphthyl, $CH_3C_6H_4$, $CF_3C_6H_4$-, $CH_3CONHC_6H_4$-, $CH_3OC_6H_4$,  ,

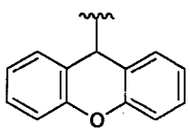
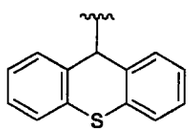
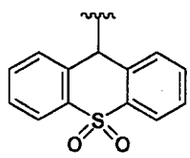
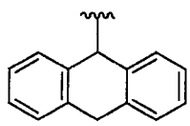
di-$CH_3C_6H_3$-, HOC_6H_4-, $CH_3OCOC_6H_4$-,  ,  ,

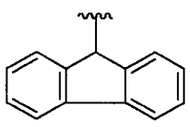
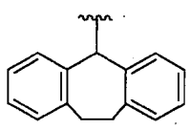
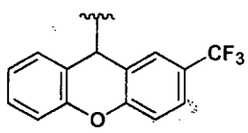
 ,  and  .

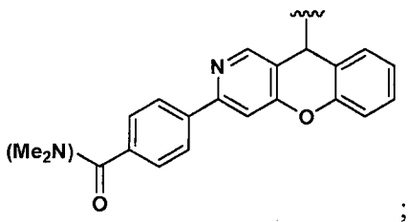
11. A compound as defined in Claims 1-2, or an enantiomer, diastereomer, tautomer, or a pharmaceutically-acceptable salt thereof, wherein



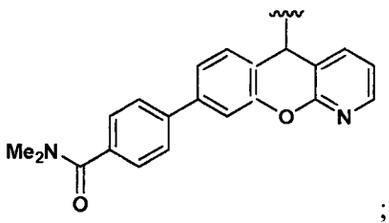
is

 ;  ;  ;  ;

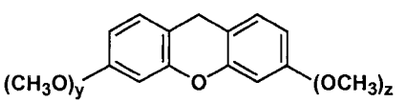
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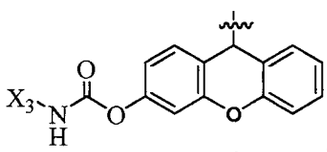
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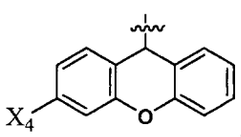
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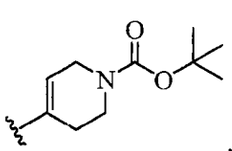
, where z is 0 or 1 and y is 0 or 1;



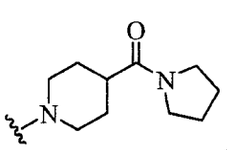
, where X_3 is benzyl, $(CH_2)_3CH_3$, Ethyl, CH_2(2-furyl), cyclohexyl, $(CH_2)_7CH_3$, $(CH_2)_2$(phenyl), CH_2(2-thienyl), CH_2(4-fluorophenyl), tert-butyl, $CH(CH_3)$ethyl, $(CH_2)_2$(4-methoxyphenyl), 4-methoxyphenyl, or CH_2(cyclohexyl);



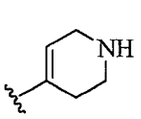
, where X_4 is NHC(O)O(cyclohexyl), NHC(O)O(methyl), -C≡C-$(CH_2)_2CH_3$, C(O)NHCH$_2$(phenyl), C(O)CH_3, -NHC(O)NH(CH_2)(O)N$(Me)_2$, -NHC(O)NH(CH_2)(N-pyrollidinyl),



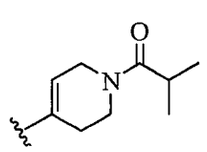
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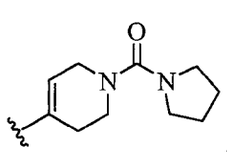
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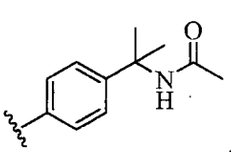
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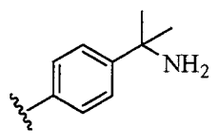
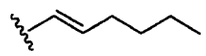
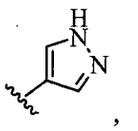
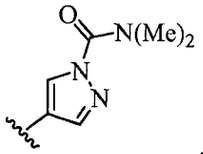
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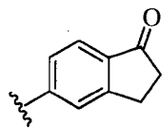
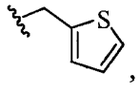
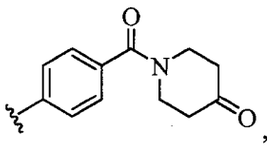
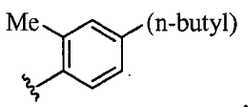


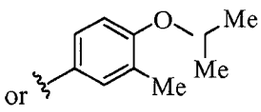
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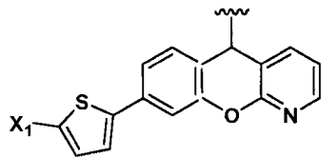
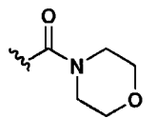
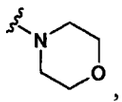


,

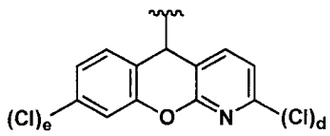


, -(CH2)$_5$CH$_3$,


,

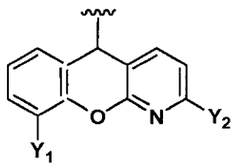




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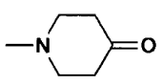
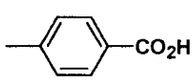
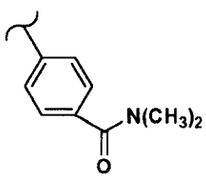
or 
;

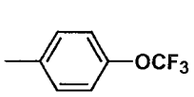
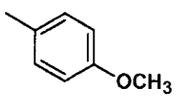
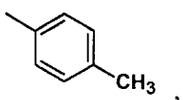

, where X_1 is CO_2H, 
, N(Me)$_2$, 
, or

C(O)CH$_3$;

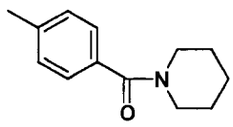
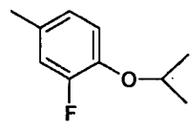
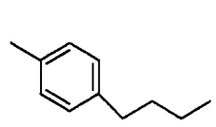
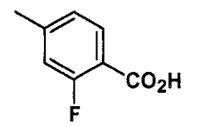
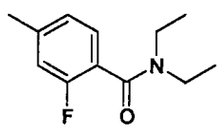
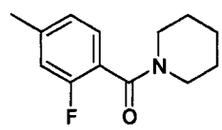
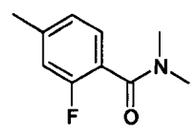
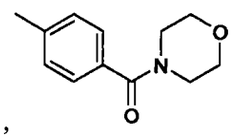
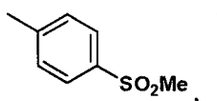
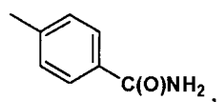
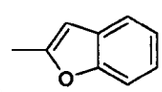
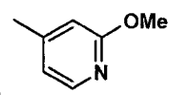
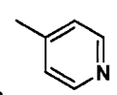

, where d is 0 or 1 and e is 0 or 1;

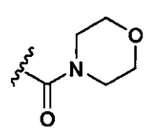
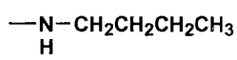
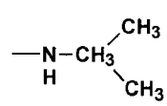

, where Y_1 is hydrogen or halogen; and Y_2 is

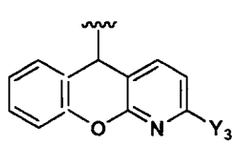
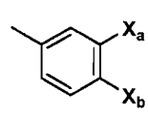
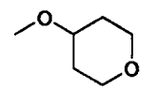
–OCH$_3$, -N(CH$_3$)$_2$, 


,

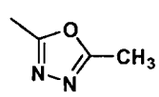




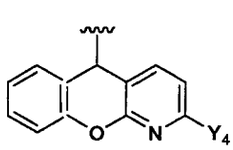
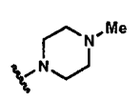
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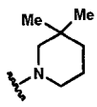
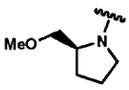
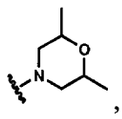














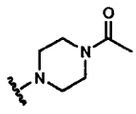
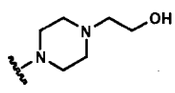
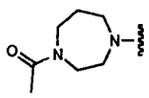
C(O)NMe$_2$,  Cl,  , or  ;

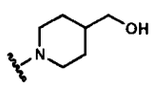
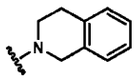
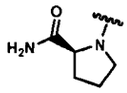
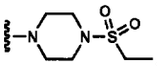
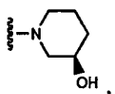
5  , where Y_3 is  , X_a is hydrogen or fluoro, and X_b is selected from cyclohexyl, -O(isopropyl), hydroxyl, hydrogen, -S(ethyl), SO_2(ethyl), SO_2(isopropyl), $C(O)CH_3$, -O(n-propyl), CH_2CO_2H, $SO_2N(CH_3)_2$, SO_2(N-morpholinyl), $C(OH)Me_2$, $SO_2NHCH_2CH_3$, SO_2NH(cyclopropyl), SO_2NH(isopropyl), CH2CO_2CH_3, $CH(OH)CH_3$, CH(OH)(Isopropyl), $S(O)CH_3$,  ,

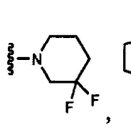
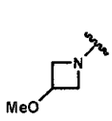
10 O(cyclohexyl), O(cyclopentyl), and  ;

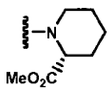
 , where Y_4 is NR_aR_b, NEt_2, piperidine, NMe_2, NMeEt, pyrrolidine, NHMe, NMe(*n*-Pr), NMe(Bn),  , morpholine, NMe(*i*-Pr), NEt_2, NMe_2, piperidine, NEt_2, NEt_2, piperidine, piperidine, piperidine, $NMe(CH_2)_2CN$, 4-Me-,

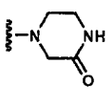
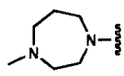
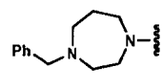
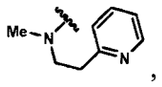
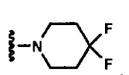
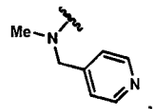
piperidine, 4-OH-piperidine, $NMe(CH_2)_2CH(CH_3)_2$,  ,  ,  ,

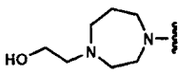
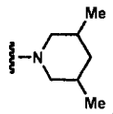
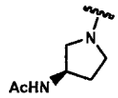
 ,  , $N(Me)(CH_2)_2Ph$,  , 4-Bn-piperidine,

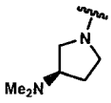
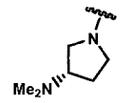
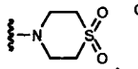
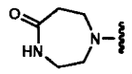
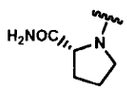
 ,  , 4-Ph-piperidine,  ,  ,  ,

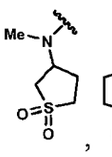
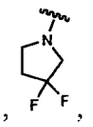
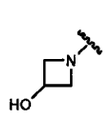
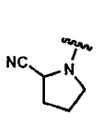
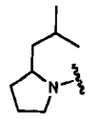
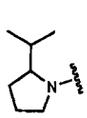
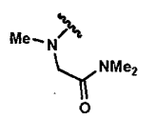
 , $NMe(CH_2)_2SO_2Me$,  ,  , 4-(CF_3)-piperidine,

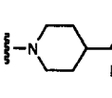
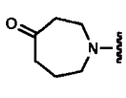
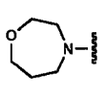
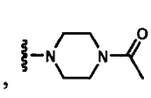
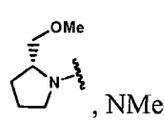
 , $NMe(n\text{-}Bu)$, $NMeCH_2CO_2Me$, $NMe(CH_2)_2OH$, $NMe(CH_2)_2OMe$,

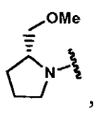
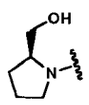
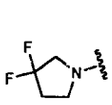
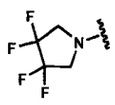
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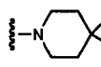
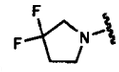
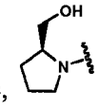
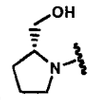
$NMe(CH_2)_2O(t\text{-}Bu)$,  , $N((CH_2)_2OH)_2$,  ,  ,

 ,  , 4-OMe-piperidine,  ,  ,  ,

 ,  ,  ,  ,  ,  ,  , $NEt(CH_2)_2OH$,

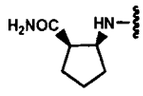
 ,  ,  ,  ,  , $NMe(CH_2)_2CN$,

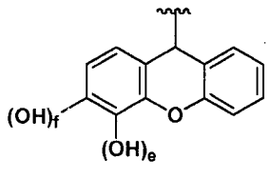
morpholinyl, $NMe(i\text{-}Pr)$,  ,  , ,  , $NEtMe$,  ,

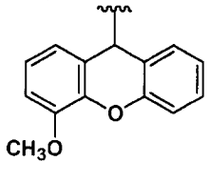
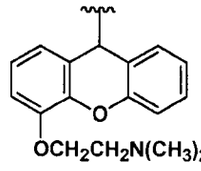
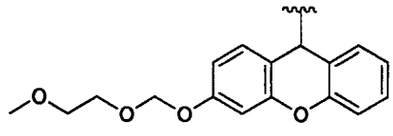
NMe(CH_2)CO_2H,  ,  , pyrrolidine,  , NMe(*n*-Pr),  ,

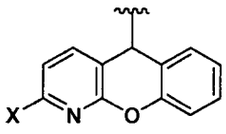
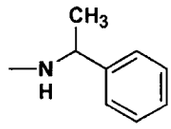
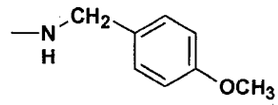
NMeEt, NMe(*n*-Pr), NMe_2, NHMe, NHBn,  ,  ,  , NH*i*Pr,

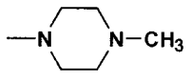
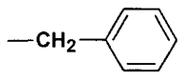
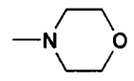
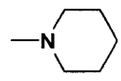
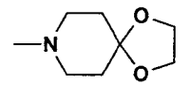
$NH(CH_2)_2Ph$, $NH(CH_2)_2Ome$, $NH(CH_2)_2C(CH_3)_3$, $NH(CH_2)_2OH$, NH(*n*-Pr),

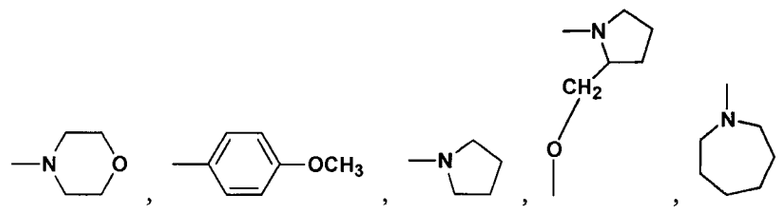
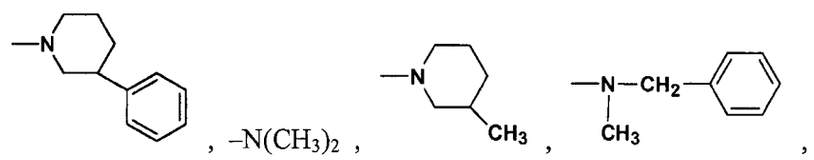
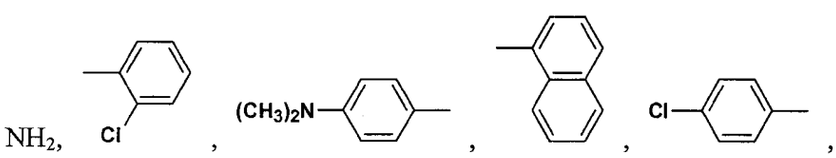
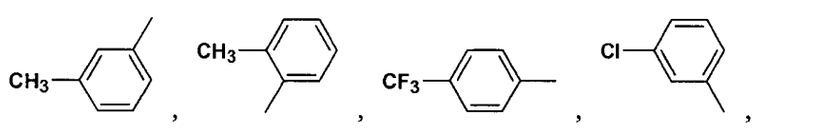
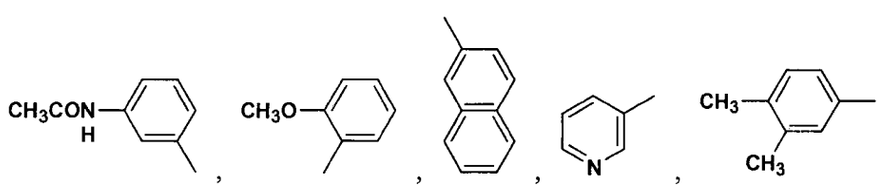
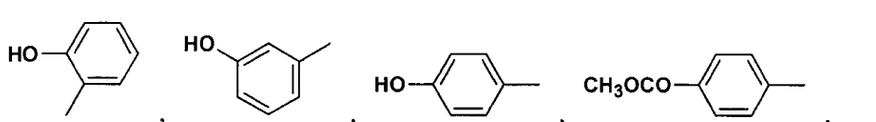
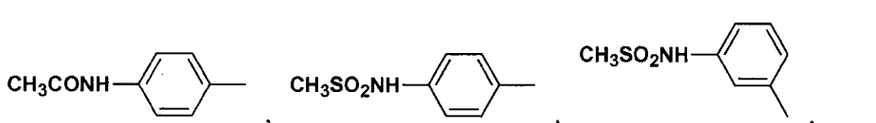
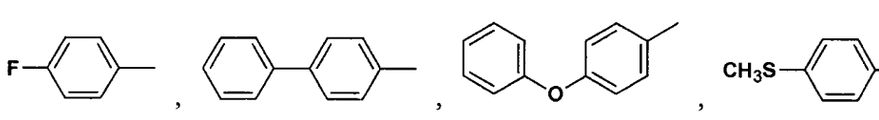
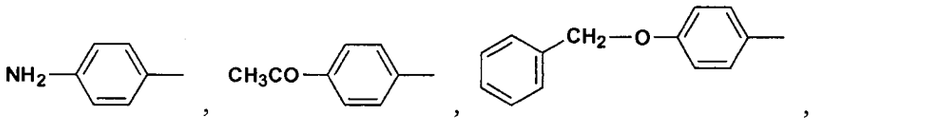
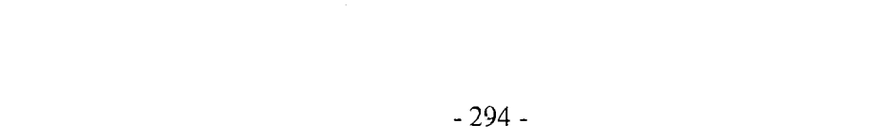
$NH(CH_2)_3OH$,  , or NHMe;

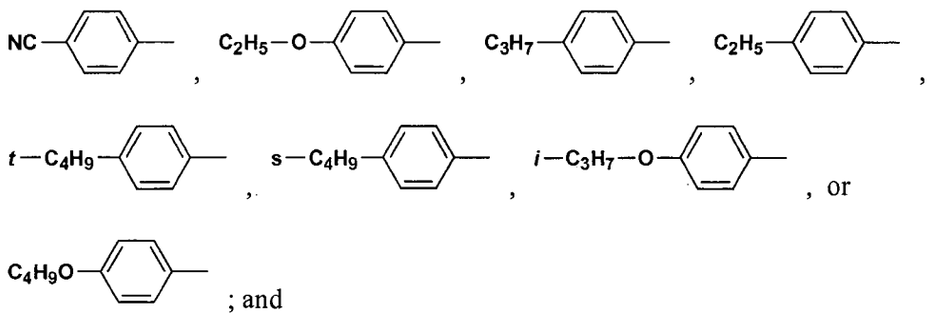
 , where e is 0 or 1 and f is 0 or 1, provided that only one of e and f can be 1;

 ;  ;  ;

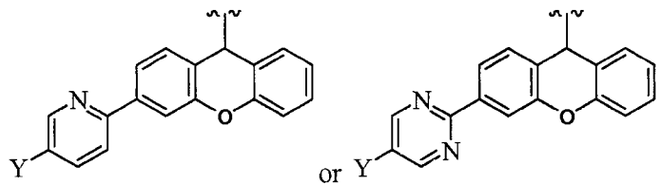
 , where X is  ,  ,

 ,  ,  ,  ,  ,



; and



, where Y is C_{1-6}alkyl, C(O)N(C_{1-6}alkyl)$_2$, COOH, and OC_{1-6}alkyl.

12. A compound as defined in Claims 1-11, or an enantiomer, diastereomer, tautomer, or a pharmaceutically-acceptable salt thereof, wherein:

R_9 and R_{10} are each independently selected from hydrogen, alkyl, and substituted alkyl;

or together with the atom to which they are attached, R_9 taken together with R_{10} forms a C_{3-6}cycloalkyl; and

R_{11} is hydrogen.

13. A compound as defined in Claims 1-12, or an enantiomer, diastereomer, tautomer, or a pharmaceutically-acceptable salt thereof, wherein R_9 and R_{10} are each independently selected from hydrogen, methyl, cyclopropyl, cyclobutyl, and cyclopentyl.

14. A compound as defined in Claims 1-13, or an enantiomer, diastereomer, tautomer, or a pharmaceutically-acceptable salt thereof, wherein:

Z is a 5- to 6-membered heteroaryl or heterocyclo group, each group substituted with one, two or three groups which are the same or different and are independently selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl,

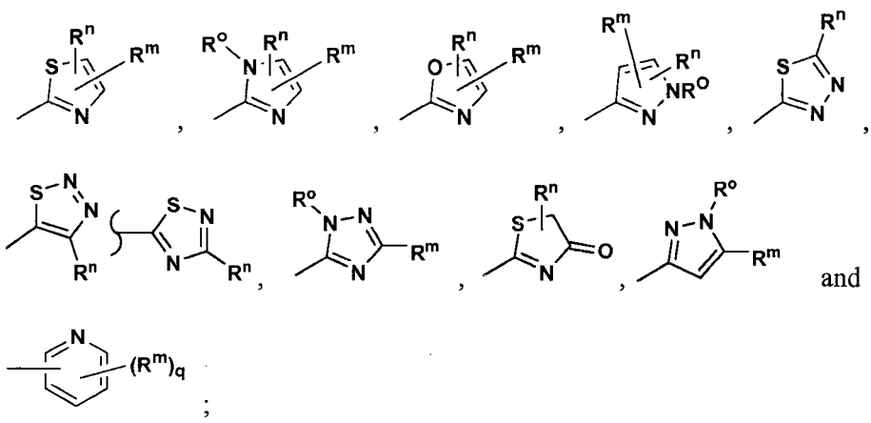
substituted alkenyl, alkynyl, substituted alkynyl, nitro, cyano, OR^c, NR^aR^b, $C(=O)R^a$, CO_2R^a, $C(=O)NR^aR^b$, $-O-C(=O)R^a$, $NR^aC(=O)R^b$, $NR^aC(=O)OR^b$, $NR^aC(=S)OR^b$, $S(O)_pR^c$, $NR^aSO_2R^c$, $SO_2NR^aR^b$, cycloalkyl, cycloalkenyl, heterocyclo, aryl, and heteroaryl;

R^a and R^b are the same or different and at each occurrence are independently selected from (i) hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclo; or (ii) where possible together with the atoms to which they are attached R^a is taken together with R^b to form a heteroaryl or heterocyclo ring; and

R^c at each occurrence is independently selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclo.

15. A compound as defined in Claims 1-14, or an enantiomer, diastereomer, tautomer, or a pharmaceutically-acceptable salt thereof, wherein:

Z is selected from:



;

R^m and R^n are the same or different and at each occurrence are independently selected from hydrogen, halogen, alkoxy, $-COR_1^a$, $-CO_2R_1^a$, $-C(O)N(R_1^a)(R_1^b)$, C_{1-6}alkyl, CF_3, substituted alkyl, aryl-NHC(O)-aryl, aryl, arylalkyl, CH_2OH, $-SR_1^a$, $S(O)_{1-2}R_1^c$, $N(R_1^a)(R_1^b)$, CH_2F, cyano, C_{3-6}cycloalkyl, and a 5 to-7-membered heteroaryl with a heteroatom selected from N, O or S;

R^o is hydrogen or C_{1-6}alkyl;

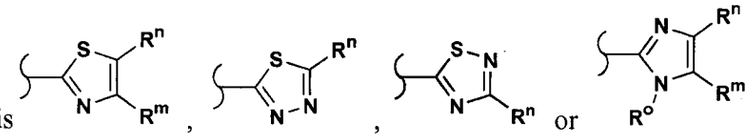
R_1^a and R_1^b are the same or different and at each occurrence are independently selected from hydrogen, alkyl, substituted alkyl, C(=O)alkyl, CO_2(alkyl), SO_2alkyl, alkenyl, substituted alkenyl, alkoxy, amino, substituted amino, aryl, heteroaryl, heterocyclo, and cycloalkyl, provided R_1^a and R_1^b are not both alkoxy, amino, or substituted amino;

or R_1^a and R_1^b, where possible can be taken together with the nitrogen to which they are attached to form a 5-, 6- or 7-membered heteroaryl or cycloheteroalkyl ring which contains 1, 2 or 3 hetero atoms which can be N, O, or S;

R_1^c is selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, amino, substituted amino, heteroaryl, heterocyclo, cycloalkyl, and aryl; and

q is 1 or 2.

16. A compound as defined in Claims 1-15, or an enantiomer, diastereomer, tautomer, or a pharmaceutically-acceptable salt thereof, wherein

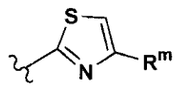
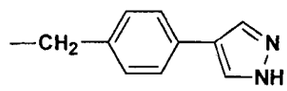
Z is  ;

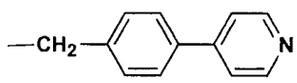
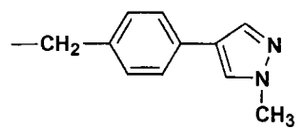
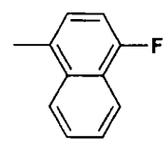
R^m and R^n are the same or different and at each occurrence are independently selected from hydrogen, -C(O)N(R_1^a)(R_1^b), C_{1-6}alkyl, CF_3, CH_2OH, -SR_1^a, N(R_1^a)(R_1^b), CH_2F, cyano, and C_{3-6}cycloalkyl;

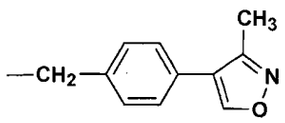
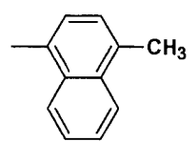
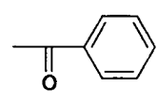
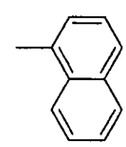
R^o is hydrogen or C_{1-6}alkyl; and

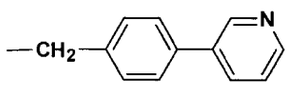
R_1^a and R_1^b are the same or different and at each occurrence are independently selected from hydrogen, C_{1-6}alkyl, and C_{3-6}cycloalkyl.

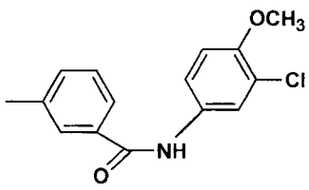
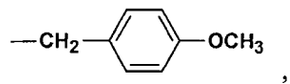
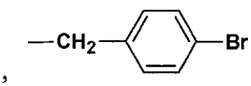
17. A compound as defined in Claims 1-15, or an enantiomer, diastereomer, tautomer, or a pharmaceutically-acceptable salt thereof, wherein:

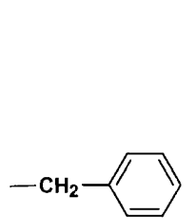
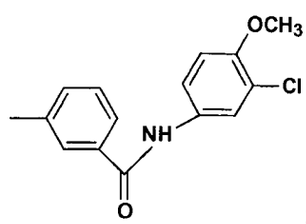
Z is  , where R^m is  ,

 ,  ,  ,

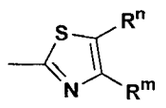
 ,  ,  ,  ,

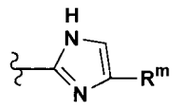
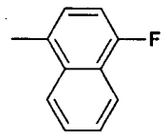
 , H, CH_3, $-CO_2C_2H_5$, $-CO_2CH_3$,

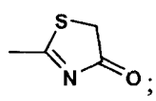
 ,  ,  ,

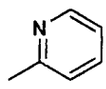
 ,  ;

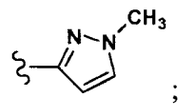
, where R^n is $S(CH_3)$, $S(O)(CH_3)$, $S(O)_2CH_3$, and CH_3;

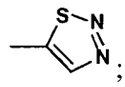
Z is  , where R^n is CH_3, R^m is CH_3;

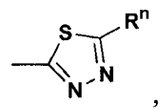
Z is  , where R^m is  or H;

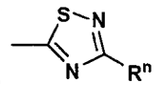
Z is  ;

Z is  ;

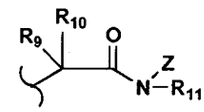
Z is  ;

Z is  ;

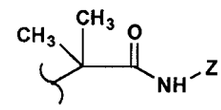
Z is  , where R^n is CH_3, H, CF_3, C(O)OEt, $C(O)NH_2$, C(O)NH(cyclopropyl), $C(O)NHCH_3$, C(O)NHEt, CH_2OH, S(methyl), $N(methyl)_2$, CH_2F, cyano, ethyl, or cyclopropyl; or

Z is  , where R^n is CH_3 or H.

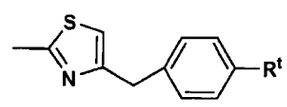
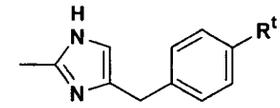
18. A compound as defined in Claims 1-15, or an enantiomer, diastereomer, tautomer, or a pharmaceutically-acceptable salt thereof, wherein



is



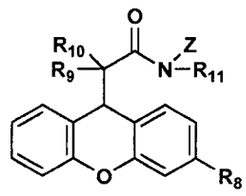
where Z is

 or 

where R^t is H or alkyl,

an enantiomer, diastereomer, or tautomer thereof, or a pharmaceutically-acceptable salt thereof.

19. A compound as defined in Claims 1-3, 5-10, and 14-18 having the structure



or an enantiomer, diastereomer, tautomer or a pharmaceutically acceptable salt thereof, wherein:

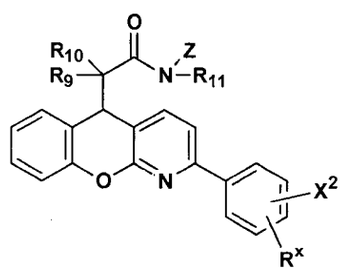
R_8 is hydroxy, cyano, $-C(=O)NR_{14}R_{15}$, $-CO_2R_{14}$, $-C(NH_2)=NOH$, $-NR_{14}C(=O)OR_{15}$, $-OC(O)NR_{14}R_{15}$, $-NHC(O)NR_{14}R_{15}$, or $-NHC(O)R_{15}$;

R_9 and R_{10} are the same or different and at each occurrence are independently selected from (i) hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, nitro, cyano, $-OR_{14}$, $-NR_{14}R_{15}$, $-C(=O)R_{14}$, $-CO_2R_{14}$, $-C(=O)NR_{14}R_{15}$, $-O-C(=O)R_{14}$, $-NR_{14}C(=O)R_{15}$, $-NR_{14}C(=O)OR_{15}$, $-NR_{14}C(=S)OR_{15}$, $-S(O)_pR_{17}$, $-NR_{14}SO_2R_{17}$, $-SO_2NR_{14}R_{15}$, cycloalkyl, cycloalkenyl, heterocyclo, aryl, and heteroaryl; or (ii) together with the atom to which the are attached, R_9 and R_{10} are taken together to form a carbonyl, alkenyl, substituted alkenyl, cycloalkyl, cycloalkenyl, or heterocyclo group;

R_{11} is selected from hydrogen, alkyl, substituted alkyl, C(=O)alkyl, CO_2(alkyl), SO_2alkyl, alkoxy, amino, substituted amino, aryl, heteroaryl, heterocyclo, and cycloalkyl; and

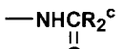
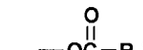
Z is a heteroaryl ring which is linked via a carbon atom to the N atom.

20. A compound as defined in Claims 1-4, 6-10, and 14-19, having the structure



an enantiomer, diastereomer, tautomer, or a pharmaceutically-acceptable salt thereof, wherein:

X^2 is halogen, alkoxy, H, or alkyl;

R^x is H, $C(O)NR_2^aR_2^b$, OR_2^c, R_2^a, COOH, CF_3,  ,  , $-NHSO_2R_2^c$, aryl, aryloxy, alkylthio, amino, acyl or cyano;

R_2^a and R_2^b are the same or different and at each occurrence are independently selected from hydrogen, alkyl, substituted alkyl, C(=O)alkyl, CO_2(alkyl), SO_2alkyl, hydrogen, alkenyl, substituted alkenyl, alkoxy, amino, substituted amino, aryl, heteroaryl, heterocyclo, and cycloalkyl;

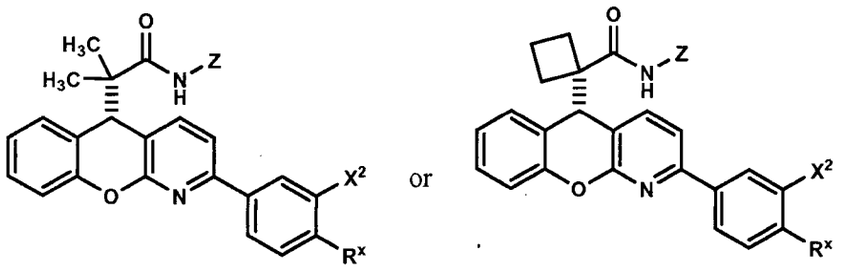
or R_2^a and R_2^b, where possible can be taken together with the nitrogen to which they are attached to form a 5-, 6- or 7-membered heteroaryl or cycloheteroalkyl ring which contains 1, 2 or 3 hetero atoms which can be N, O, or S;

R_2^c is selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, amino, substituted amino, heteroaryl, heterocyclo, cycloalkyl, and aryl;

R_9 and R_{10} are the same or different and at each occurrence are independently selected from (i) hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, nitro, cyano, OR_{14}, $NR_{14}R_{15}$, $C(=O)R_{14}$, CO_2R_{14}, $C(=O)NR_{14}R_{15}$, $-O-C(=O)R_{14}$, $NR_{14}C(=O)R_{15}$, $NR_{14}C(=O)OR_{15}$, $NR_{14}C(=S)OR_{15}$, $S(O)_pR_{17}$, $NR_{14}SO_2R_{17}$, $SO_2NR_{14}R_{15}$, cycloalkyl, cycloalkenyl, heterocyclo, aryl, and heteroaryl; or (ii) together with the atom to which they are attached, R_9 and R_{10} are taken together to form a carbonyl, alkenyl, substituted alkenyl, cycloalkyl, cycloalkenyl, or heterocyclo group; and

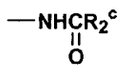
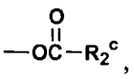
R_{11} is selected from hydrogen, alkyl, substituted alkyl, C(=O)alkyl, CO_2(alkyl), SO_2alkyl, alkoxy, amino, substituted amino, aryl, heteroaryl, heterocyclo, and cycloalkyl.

21. A compound as defined in Claims 1-4, 6-10 and 14-20, or an enantiomer, diastereomer, tautomer, or a pharmaceutically-acceptable salt thereof, having the structure:



wherein:

X^2 is H, halogen, or alkyl;

R^x is H, $C(O)NR_2^aR_2^b$, OR_2^a, R_2^a, COOH, CF_3,  ,  , $-NHSO_2R_2^c$, aryl, aryloxy, alkylthio, amino, acyl or cyano;

R_2^a is selected from hydrogen, alkyl, substituted alkyl, C(=O)alkyl, CO_2(alkyl), SO_2alkyl, hydrogen, alkenyl, substituted alkenyl, alkoxy, amino, substituted amino, aryl, heteroaryl, heterocyclo, and cycloalkyl;

R_2^b is selected from alkyl, substituted alkyl, C(=O)alkyl, CO_2(alkyl), SO_2alkyl, hydrogen, alkenyl, substituted alkenyl, alkoxy, amino, substituted amino, aryl, heteroaryl, heterocyclo, and cycloalkyl;

or R_2^a and R_2^b are taken together with the nitrogen to which they are attached to form a 5-, 6- or 7-membered heteroaryl or cycloheteroalkyl ring which contains 1, 2 or 3 hetero atoms which can be N, O, or S; and

R_2^c is selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, amino, substituted amino, heteroaryl, heterocyclo, cycloalkyl, and aryl.

22. A compound selected from:

N-{4-[4-(4-pyridinyl)benzyl]-1,3-thiazol-2-yl}-2-(9H-xanthen-9-yl)acetamide,

N-[4-(4-fluoro-1-naphthyl)-1,3-thiazol-2-yl]-2-(9H-xanthen-9-yl)acetamide,

N-[4-(4-methyl-1-naphthyl)-1,3-thiazol-2-yl]-2-(9H-xanthen-9-yl)acetamide,

N-[4-(1-naphthyl)-1,3-thiazol-2-yl]-2-(9H-xanthen-9-yl)acetamide,

2-methyl-N-{4-[4-(4-pyridinyl)benzyl]-1,3-thiazol-2-yl}-2-(9H-thioxanthen-9-yl)propanamide,

2-methyl-N-[4-(1-naphthyl)-1,3-thiazol-2-yl]-2-(9H-thioxanthen-9-yl)propanamide,

2-methyl-N-[4-(4-methyl-1-naphthyl)-1,3-thiazol-2-yl]-2-(9H-thioxanthen-9-yl)propanamide,

N-[4-(4-fluoro-1-naphthyl)-1,3-thiazol-2-yl]-2-methyl-2-(9H-thioxanthen-9-yl)propanamide,

2-methyl-N-1,3-thiazol-2-yl-2-(9H-thioxanthen-9-yl)propanamide,

2-(10,10-dioxido-9H-thioxanthen-9-yl)-N-[4-(4-fluoro-1-naphthyl)-1,3-thiazol-2-yl]-2-methylpropanamide,

2-(10,10-dioxido-9H-thioxanthen-9-yl)-2-methyl-N-[4-(1-naphthyl)-1,3-thiazol-2-yl]propanamide,

2-(10,10-dioxido-9H-thioxanthen-9-yl)-2-methyl-N-[4-(4-methyl-1-naphthyl)-1,3-thiazol-2-yl]propanamide,

2-(10,10-dioxido-9H-thioxanthen-9-yl)-2-methyl-N-1,3-thiazol-2-ylpropanamide,

2-(9,10-dihydro-9-anthracenyl)-2-methyl-N-[4-(1-naphthyl)-1,3-thiazol-2-yl]propanamide,

2-(9,10-dihydro-9-anthracenyl)-2-methyl-N-[4-(4-methyl-1-naphthyl)-1,3-thiazol-2-yl]propanamide,

2-(9,10-dihydro-9-anthracenyl)-N-[4-(4-fluoro-1-naphthyl)-1,3-thiazol-2-yl]-2-methylpropanamide,

2-(9H-fluoren-9-yl)-2-methyl-N-1,3-thiazol-2-ylpropanamide,

2-(9H-fluoren-9-yl)-2-methyl-N-[4-(1-naphthyl)-1,3-thiazol-2-yl]propanamide,

2-(9H-fluoren-9-yl)-2-methyl-N-[4-(4-methyl-1-naphthyl)-1,3-thiazol-2-yl]propanamide,

2-(9H-fluoren-9-yl)-N-[4-(4-fluoro-1-naphthyl)-1,3-thiazol-2-yl]-2-methylpropanamide,

2-(2-hydroxy-9H-fluoren-9-yl)-2-methyl-N-1,3-thiazol-2-ylpropanamide,

ethyl 2-{[2-(10,11-dihydro-5H-dibenzo[a,d][7]annulen-5-yl)-2-methylpropanoyl]amino}-1,3-thiazole-4-carboxylate,

2-(10,11-dihydro-5H-dibenzo[a,d][7]annulen-5-yl)-2-methyl-N-{4-[4-(4-pyridinyl)benzyl]-1,3-thiazol-2-yl}propanamide,

2-(10,11-dihydro-5H-dibenzo[a,d][7]annulen-5-yl)-2-methyl-N-[4-(4-methyl-1-naphthyl)-1,3-thiazol-2-yl]propanamide,

2-(10,11-dihydro-5H-dibenzo[a,d][7]annulen-5-yl)-2-methyl-N-1,3-thiazol-2-ylpropanamide,

N-[4-(4-fluoro-1-naphthyl)-1,3-thiazol-2-yl]-2-(9H-thioxanthen-9-yl)acetamide,

N-[4-(4-methyl-1-naphthyl)-1,3-thiazol-2-yl]-2-(9H-thioxanthen-9-yl)acetamide,

N-[4-(1-naphthyl)-1,3-thiazol-2-yl]-2-(9H-thioxanthen-9-yl)acetamide,

N-(3-chloro-4-methoxyphenyl)-3-(2-{[2-methyl-2-(9H-xanthen-9yl)propanoyl]amino}-1,3-thiazol-4-yl)benzamide,

2-methyl-N-[4-(1-naphthyl)-1,3-thiazol-2-yl]-2-(9H-xanthen-9-yl)propanamide,

2-methyl-N-[4-(4-methyl-1-naphthyl)-1,3-thiazol-2-yl]-2-(9H-xanthen-9-yl)propanamide,

N-[4-(4-fluoro-1-naphthyl)-1,3-thiazol-2-yl]-2-methyl-2-(9H-xanthen-9-yl)propanamide,

N-[4-(4-methoxybenzyl)-1,3-thiazol-2-yl]-2-methyl-2-(9H-xanthen-9-yl)propanamide,

2-methyl-N-{4-[4-(4-pyridinyl)benzyl]-1,3-thiazol-2-yl}-2-(9H-xanthen-9-yl)propanamide,

N-[4-(4-bromobenzyl)-1,3-thiazol-2-yl]-2-methyl-2-(9H-xanthen-9-yl)propanamide,

N-(4-benzyl-1,3-thiazol-2-yl)-2-methyl-2-(9H-xanthen-9-yl)propanamide,

N-(3-chloro-4-methoxyphenyl)-3-(2-{[2-methyl-2-(9H-xanthen-9-yl)propanoyl]amino}-1,3-thiazol-4-yl)benzamide,

2-methyl-N-1,3-thiazol-2-yl-2-(9H-xanthen-9-yl)propanamide,

N-[4-(4-fluoro-1-naphthyl)-1H-imidazol-2-yl]-2-methyl-2-(9H-xanthen-9-yl)propanamide,

2-methyl-N-1,3,4-thiadiazol-2-yl-2-(9H-xanthen-9-yl)propanamide,

N-[4-(4-fluoro-1-naphthyl)-1,3-thiazol-2-yl]-2-methyl-2-[2-(trifluoromethyl)-9H-xanthen-9-yl]propanamide,

2-methyl-N-{4-[4-(1H-pyrazol-4-yl)benzyl]-1,3-thiazol-2-yl}-2-(9H-xanthen-9-yl)propanamide,

2-methyl-N-{4-[4-(1-methyl-1H-pyrazol-4-yl)benzyl]-1,3-thiazol-2-yl}-2-(9H-xanthen-9-yl)propanamide,

N-{4-[4-(3,5-dimethyl-4-isoxazolyl)benzyl]-1,3-thiazol-2-yl}-2-methyl-2-(9H-xanthen-9-yl)propanamide,

N-(4-benzoyl-1,3-thiazol-2-yl)-2-methyl-2-(9H-xanthen-9-yl)propanamide,

N-[4-(4-fluoro-1-naphthyl)-1,3-thiazol-2-yl]-2-(3-methoxy-9H-xanthen-9-yl)-2-methylpropanamide,

2-(3-methoxy-9H-xanthen-9-yl)-2-methyl-N-[4-(4-methyl-1-naphthyl)-1,3-thiazol-2-yl]propanamide,

N-(4-benzyl-1,3-thiazol-2-yl)-2-(3-methoxy-9H-xanthen-9-yl)-2-methylpropanamide,

ethyl 2-{[2-(3-methoxy-9H-xanthen-9-yl)-2-methylpropanoyl]amino}-1,3-thiazole-4-carboxylate,

N-[4-(4-methoxybenzyl)-1,3-thiazol-2-yl]-2-(3-methoxy-9H-xanthen-9-yl)-2-methylpropanamide,

N-[4-(4-bromobenzyl)-1,3-thiazol-2-yl]-2-(3-methoxy-9H-xanthen-9-yl)-2-methylpropanamide,

2-(3-methoxy-9H-xanthen-9-yl)-2-methyl-N-{4-[4-(4-pyridinyl)benzyl]-1,3-thiazol-2-yl}propanamide,

2-(3-methoxy-9H-xanthen-9-yl)-2-methyl-N-[4-(1-naphthyl)-1,3-thiazol-2-yl]propanamide,

2-(3-methoxy-9H-xanthen-9-yl)-2-methyl-N-{4-[4-(3-pyridinyl)benzyl]-1,3-thiazol-2-yl}propanamide,

2-[(9R)-3-methoxy-9H-xanthen-9-yl]-2-methyl-N-1,3-thiazol-2-ylpropanamide,

2-[(9S)-3-methoxy-9H-xanthen-9-yl]-2-methyl-N-1,3-thiazol-2-ylpropanamide,

N-1H-imidazol-2-yl-2-[(9S)-3-methoxy-9H-xanthen-9-yl]-2-methylpropanamide,

2-[(9S)-3-methoxy-9H-xanthen-9-yl]-2-methyl-N-1,3,4-thiadiazol-2-ylpropanamide,

2-(5H-chromeno[2,3-b]pyridin-5-yl)-N-[4-(4-fluoro-1-naphthyl)-1,3-thiazol-2-yl]-2-methylpropanamide,

2-(5H-chromeno[2,3-b]pyridin-5-yl)-2-methyl-N-{4-[4-(4-pyridinyl)benzyl]-1,3-thiazol-2-yl}propanamide,

2-(5H-chromeno[2,3-b]pyridin-5-yl)-2-methyl-N-1,3,4-thiadiazol-2-ylpropanamide,

2-(5H-chromeno[2,3-b]pyridin-5-yl)-2-methyl-N-1,2,4-thiadiazol-5-ylpropanamide,

2-(5H-chromeno[2,3-b]pyridin-5-yl)-2-methyl-N-1,3-thiazol-2-ylpropanamide,

ethyl 2-{[2-(5H-chromeno[2,3-b]pyridin-5-yl)-2-methylpropanoyl]amino}-1,3-thiazole-4-carboxylate,

2-(5H-chromeno[2,3-b]pyridin-5-yl)-2-methyl-N-(5-methyl-1,3-thiazol-2-yl)propanamide,

2-(5H-chromeno[2,3-b]pyridin-5-yl)-2-methyl-N-(4-methyl-1,3-thiazol-2-yl)propanamide,

2-(5H-chromeno[2,3-b]pyridin-5-yl)-2-methyl-N-(5-methyl-1,3,4-thiadiazol-2-yl)propanamide,

2-(2-chloro-5H-chromeno[2,3-b]pyridin-5-yl)-N-[4-(4-fluoro-1-naphthyl)-1,3-thiazol-2-yl]-2-methylpropanamide,

2-(2-chloro-5H-chromeno[2,3-b]pyridin-5-yl)-2-methyl-N-[4-(1-naphthyl)-1,3-thiazol-2-yl]propanamide,

2-(2-chloro-5H-chromeno[2,3-b]pyridin-5-yl)-2-methyl-N-1,3-thiazol-2-ylpropanamide,

2-(2-chloro-5H-chromeno[2,3-b]pyridin-5-yl)-2-methyl-N-1,3,4-thiadiazol-2-ylpropanamide,

N-[4-(4-methoxybenzyl)-1,3-thiazol-2-yl]-2-(2-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)-2-methylpropanamide,

N-[4-(4-fluoro-1-naphthyl)-1,3-thiazol-2-yl]-2-(2-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)-2-methylpropanamide,

2-(2-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)-2-methyl-N-{4-[4-(4-pyridinyl)benzyl]-1,3-thiazol-2-yl}propanamide,

2-(4-hydroxy-9H-xanthen-9-yl)-2-methyl-N-1,3-thiazol-2-ylpropanamide,

N-[4-(4-fluoro-1-naphthyl)-1,3-thiazol-2-yl]-2-(4-methoxy-9H-xanthen-9-yl)-2-methylpropanamide,

2-(4-methoxy-9H-xanthen-9-yl)-2-methyl-N-{4-[4-(4-pyridinyl)benzyl]-1,3-thiazol-2-yl}propanamide,

2-(4-methoxy-9H-xanthen-9-yl)-2-methyl-N-1,3-thiazol-2-ylpropanamide,

2-{4-[2-(dimethylamino)ethoxy]-9H-xanthen-9-yl}-N-[4-(4-methoxybenzyl)-1,3-thiazol-2-yl]-2-methylpropanamide,

N-(4,5-dimethyl-1,3-thiazol-2-yl)-2-[(9S)-3-hydroxy-9H-xanthen-9-yl]-2-methylpropanamide,

2-[(9S)-3-hydroxy-9H-xanthen-9-yl]-2-methyl-N-(5-methyl-1,3-thiazol-2-yl)propanamide,

2-[(9S)-3-hydroxy-9H-xanthen-9-yl]-2-methyl-N-(4-methyl-1,3-thiazol-2-yl)propanamide,

2-[(9S)-3-hydroxy-9H-xanthen-9-yl]-2-methyl-N-1,3-thiazol-2-ylpropanamide,

2-[(9S)-3-hydroxy-9H-xanthen-9-yl]-2-methyl-N-1,3,4-thiadiazol-2-ylpropanamide,

N-(4,5-dimethyl-1,3-thiazol-2-yl)-2-[(9R)-3-hydroxy-9H-xanthen-9-yl]-2-methylpropanamide,

2-[(9R)-3-hydroxy-9H-xanthen-9-yl]-2-methyl-N-(5-methyl-1,3-thiazol-2-yl)propanamide,

9H-xanthene-9-acetamide, 3-hydroxy-alpha,alpha-dimethyl-N-(4-methyl-2-thiazolyl)-, (9R)-,

9H-xanthene-9-acetamide, 3-hydroxy-alpha,alpha-dimethyl-N-2-thiazolyl-, (9R)-,

9H-xanthene-9-acetamide, 3-hydroxy-alpha,alpha-dimethyl-N-1,3,4-thiadiazol-2-yl-, (9R)-,

4-thiazolecarboxylic acid, 2-[[2-(3-hydroxy-9H-xanthen-9-yl)-2-methyl-1-oxopropyl]amino]-, ethyl ester,

4-thiazolecarboxylic acid, 2-[[2-[3-[(2-methoxyethoxy)methoxy]-9H-xanthen-9-yl]-2-methyl-1-oxopropyl]amino]-, ethyl ester,

9H-xanthene-9-acetamide, 3-[(2-methoxyethoxy)methoxy]-alpha,alpha-dimethyl-N-2-thiazolyl-,

4-thiazolecarboxylic acid, 2-[[2-(3-hydroxy-9H-xanthen-9-yl)-2-methyl-1-oxopropyl]amino]-, methyl ester,

2-(3-hydroxy-9H-xanthen-9-yl)-2-methyl-N-(5-methyl-1,3,4-thiadiazol-2-yl)propanamide,

2-methyl-2-[2-(methylamino)-5H-chromeno[2,3-b]pyridin-5-yl]-N-1,3-thiazol-2-ylpropanamide,

2-{2-[(4-methoxybenzyl)amino]-5H-chromeno[2,3-b]pyridin-5-yl}-2-methyl-N-1,3,4-thiadiazol-2-ylpropanamide,

2-methyl-2-[2-(4-morpholinyl)-5H-chromeno[2,3-b]pyridin-5-yl]-N-1,3,4-thiadiazol-2-ylpropanamide,

2-methyl-2-[2-(1-pyrrolidinyl)-5H-chromeno[2,3-b]pyridin-5-yl]-N-1,3,4-thiadiazol-2-ylpropanamide,

2-methyl-2-[2-(4-methyl-1-piperazinyl)-5H-chromeno[2,3-b]pyridin-5-yl]-N-1,3,4-thiadiazol-2-ylpropanamide,

2-methyl-2-[2-(1-piperidinyl)-5H-chromeno[2,3-b]pyridin-5-yl]-N-1,3,4-thiadiazol-2-ylpropanamide,

2-[2-(benzylamino)-5H-chromeno[2,3-b]pyridin-5-yl]-2-methyl-N-1,3,4-thiadiazol-2-ylpropanamide,

2-methyl-2-[(5R)-2-(1-piperidinyl)-5H-chromeno[2,3-b]pyridin-5-yl]-N-1,3,4-thiadiazol-2-ylpropanamide,

2-[(5R)-2-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-5H-chromeno[2,3-b]pyridin-5-yl]-2-methyl-N-1,3,4-thiadiazol-2-ylpropanamide,

2-{(5R)-2-[(4-methoxybenzyl)amino]-5H-chromeno[2,3-b]pyridin-5-yl}-2-methyl-N-1,3,4-thiadiazol-2-ylpropanamide,

2-methyl-2-[(5R)-2-(1-pyrrolidinyl)-5H-chromeno[2,3-b]pyridin-5-yl]-N-1,3,4-thiadiazol-2-ylpropanamide,

2-methyl-2-[(5S)-2-(1-piperidinyl)-5H-chromeno[2,3-b]pyridin-5-yl]-N-1,3,4-thiadiazol-2-ylpropanamide,

2-[(5S)-2-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)-5H-chromeno[2,3-b]pyridin-5-yl]-2-methyl-N-1,3,4-thiadiazol-2-ylpropanamide,

2-{(5S)-2-[(4-methoxybenzyl)amino]-5H-chromeno[2,3-b]pyridin-5-yl}-2-methyl-N-1,3,4-thiadiazol-2-ylpropanamide,

2-methyl-2-[(5S)-2-(1-pyrrolidinyl)-5H-chromeno[2,3-b]pyridin-5-yl]-N-1,3,4-thiadiazol-2-ylpropanamide,

2-methyl-2-[(5S)-2-{[(1S)-1-phenylethyl]amino}-5H-chromeno[2,3-b]pyridin-5-yl]-N-1,3,4-thiadiazol-2-ylpropanamide,

2-methyl-2-[(5S)-2-{[(1R)-1-phenylethyl]amino}-5H-chromeno[2,3-b]pyridin-5-yl]-N-1,3,4-thiadiazol-2-ylpropanamide,

2-{(5S)-2-[(2S)-2-(methoxymethyl)-1-pyrrolidinyl]-5H-chromeno[2,3-b]pyridin-5-yl}-2-methyl-N-1,3,4-thiadiazol-2-ylpropanamide,

2-{(5S)-2-[(2R)-2-(methoxymethyl)-1-pyrrolidinyl]-5H-chromeno[2,3-b]pyridin-5-yl}-2-methyl-N-1,3,4-thiadiazol-2-ylpropanamide,

2-[(5S)-2-(1-azepanyl)-5H-chromeno[2,3-b]pyridin-5-yl]-2-methyl-N-1,3,4-thiadiazol-2-ylpropanamide,

2-methyl-2-[(5S)-2-(3-phenyl-1-piperidinyl)-5H-chromeno[2,3-b]pyridin-5-yl]-N-1,3,4-thiadiazol-2-ylpropanamide,

2-methyl-2-[(5S)-2-(1-piperidinyl)-5H-chromeno[2,3-b]pyridin-5-yl]-N-1,3-thiazol-2-ylpropanamide,

2-[(5S)-2-(dimethylamino)-5H-chromeno[2,3-b]pyridin-5-yl]-2-methyl-N-1,3,4-thiadiazol-2-ylpropanamide,

2-methyl-2-[(5S)-2-(3-methyl-1-piperidinyl)-5H-chromeno[2,3-b]pyridin-5-yl]-N-1,3,4-thiadiazol-2-ylpropanamide,

2-{2-[(4-methoxybenzyl)amino]-5H-chromeno[2,3-b]pyridin-5-yl}-2-methyl-N-1,3-thiazol-2-ylpropanamide,

2-methyl-2-[2-(4-morpholinyl)-5H-chromeno[2,3-b]pyridin-5-yl]-N-1,3-thiazol-2-ylpropanamide,

2-[2-(butylamino)-5H-chromeno[2,3-b]pyridin-5-yl]-2-methyl-N-1,3-thiazol-2-ylpropanamide,

2-{2-[benzyl(methyl)amino]-5H-chromeno[2,3-b]pyridin-5-yl}-2-methyl-N-1,3-thiazol-2-ylpropanamide,

2-[2-(isopropylamino)-5H-chromeno[2,3-b]pyridin-5-yl]-2-methyl-N-1,3-thiazol-2-ylpropanamide,

2-(2-amino-5H-chromeno[2,3-b]pyridin-5-yl)-2-methyl-N-1,3-thiazol-2-ylpropanamide,

2-(2-amino-5H-chromeno[2,3-b]pyridin-5-yl)-2-methyl-N-1,3,4-thiadiazol-2-ylpropanamide,

2-[2-(dimethylamino)-5H-chromeno[2,3-b]pyridin-5-yl]-2-methyl-N-1,3-thiazol-2-ylpropanamide,

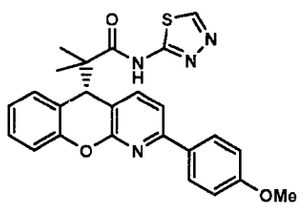
2-methyl-2-[(5R)-2-(4-oxo-1-piperidinyl)-5H-chromeno[2,3-b]pyridin-5-yl]-N-1,3-thiazol-2-ylpropanamide,

2-methyl-2-[(5S)-2-(4-oxo-1-piperidinyl)-5H-chromeno[2,3-b]pyridin-5-yl]-N-1,3-thiazol-2-ylpropanamide,

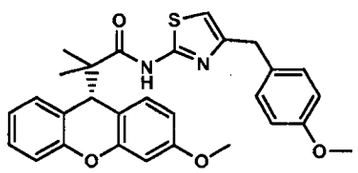
2-[(5R)-2-(4-methoxyphenyl)-5H-chromeno[2,3-b]pyridin-5-yl]-2-methyl-N-1,3,4-thiadiazol-2-ylpropanamide,

2-methyl-2-[(5S)-2-(4-methylphenyl)-5H-chromeno[2,3-b]pyridin-5-yl]-N-1,3,4-thiadiazol-2-ylpropanamide,

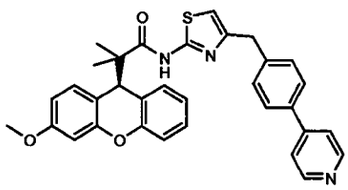
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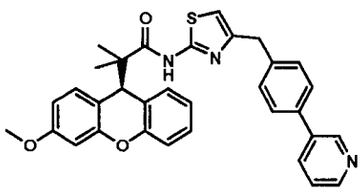


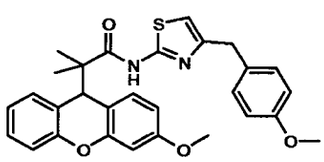
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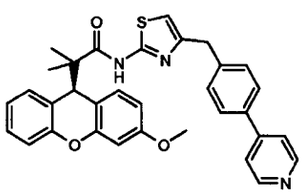


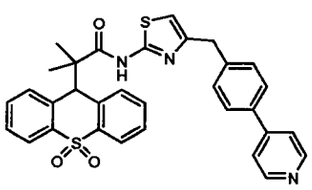
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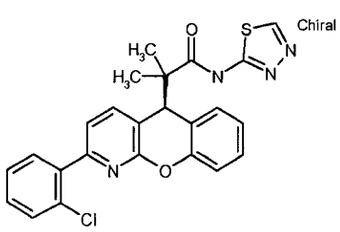

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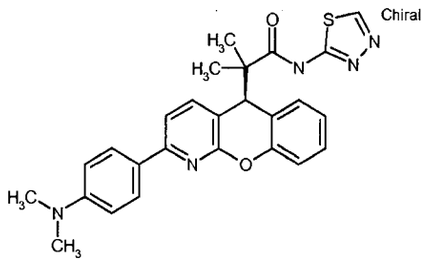

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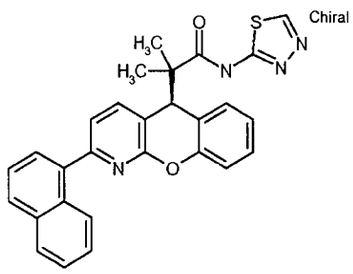

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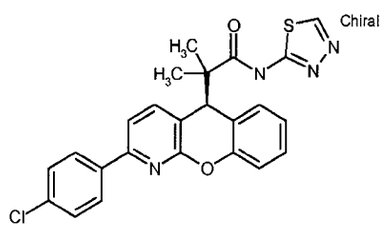

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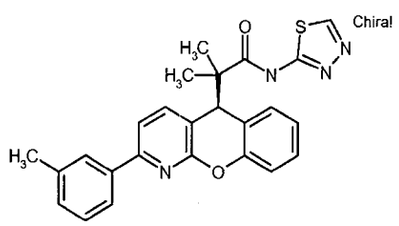
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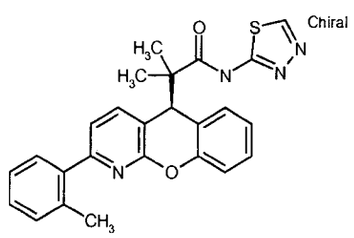
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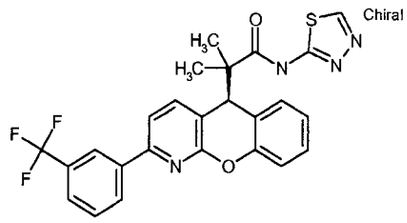
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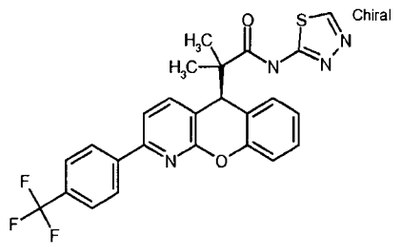
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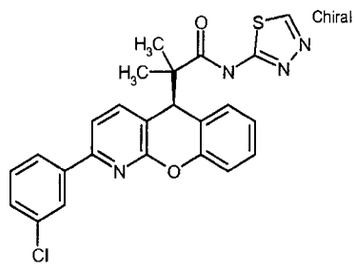
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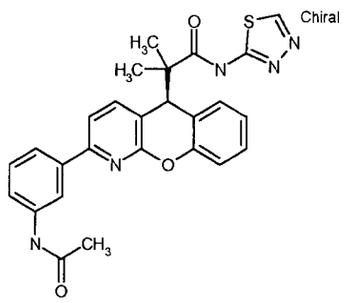
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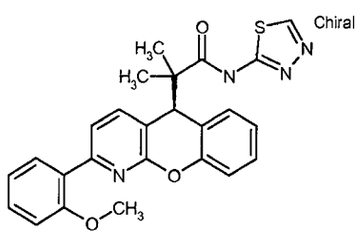
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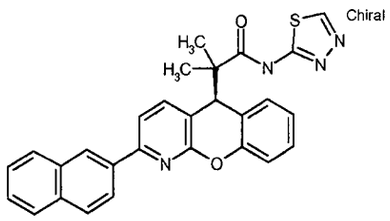
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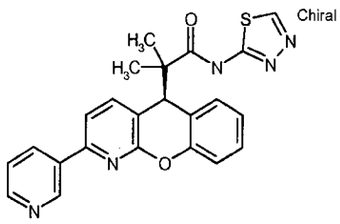
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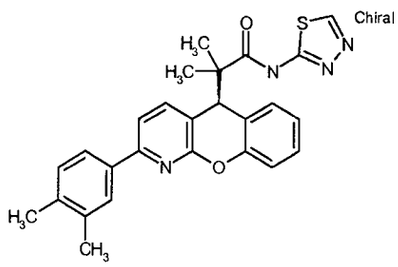
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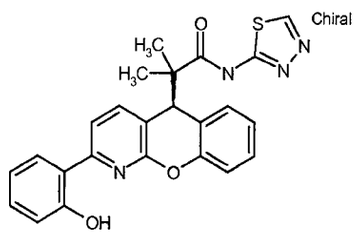
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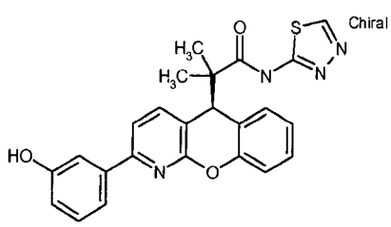
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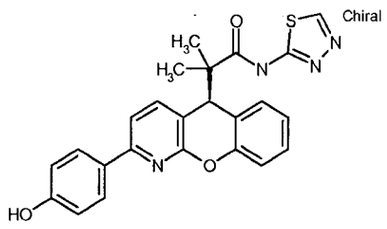
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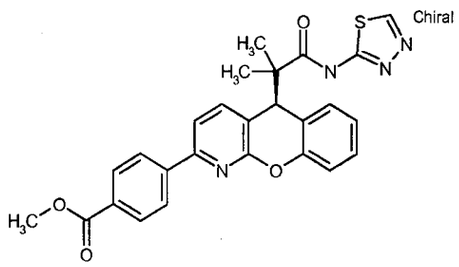
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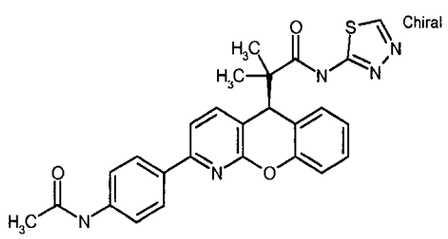
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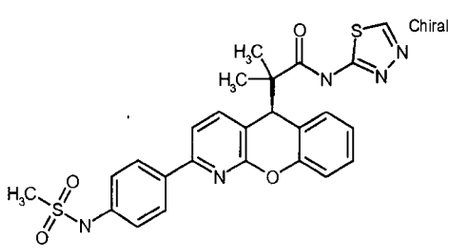
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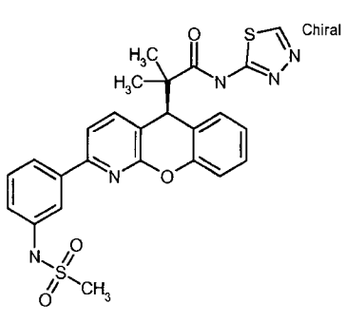
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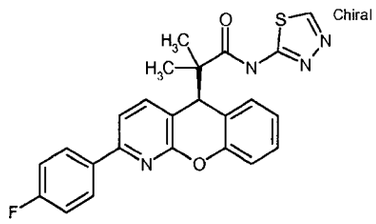
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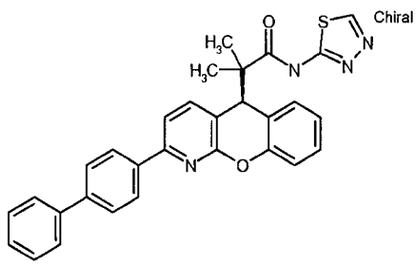
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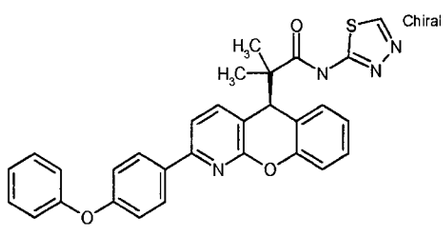
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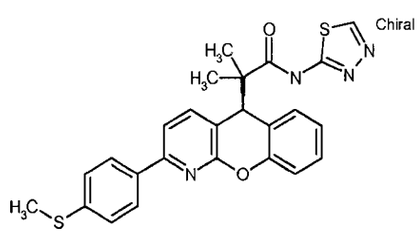
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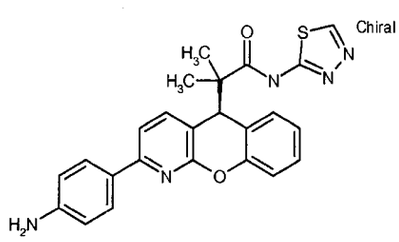
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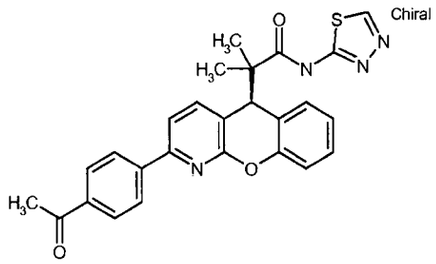
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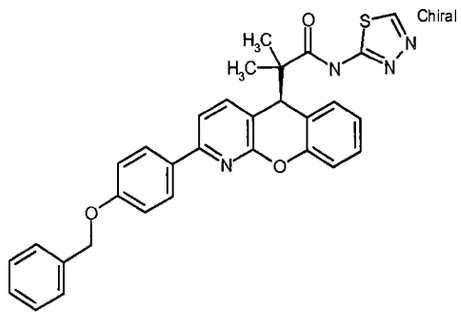
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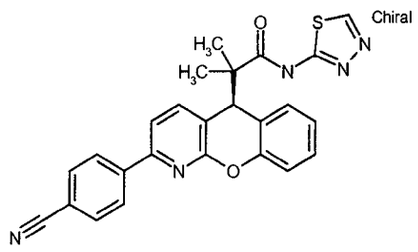
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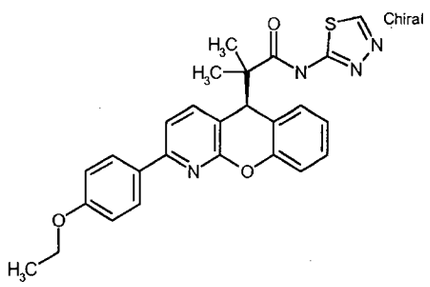
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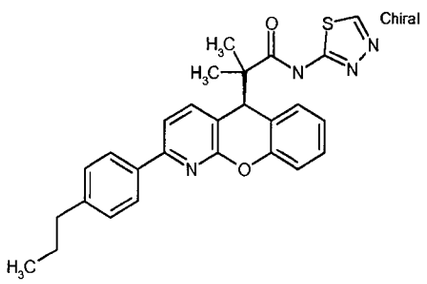
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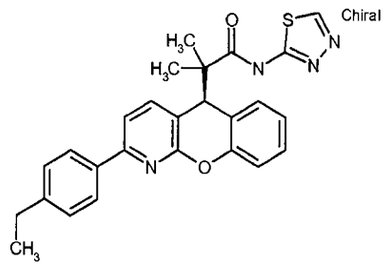
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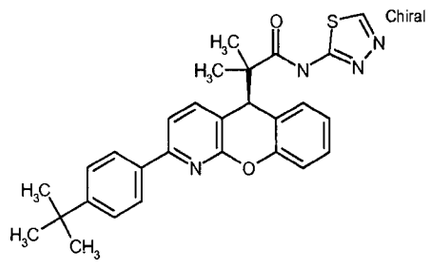
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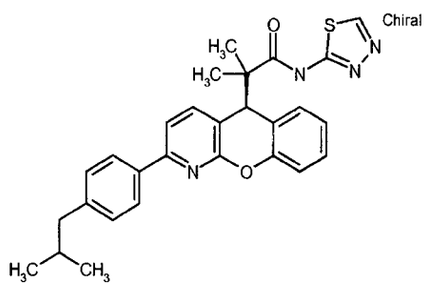
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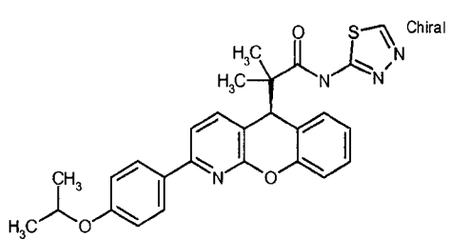
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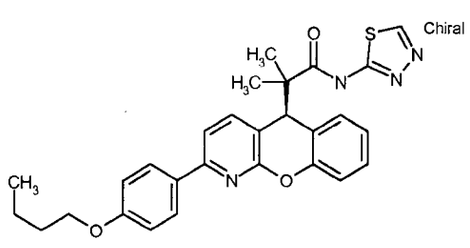
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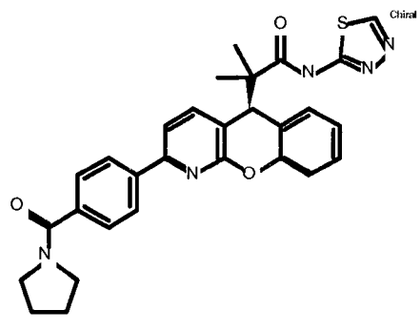
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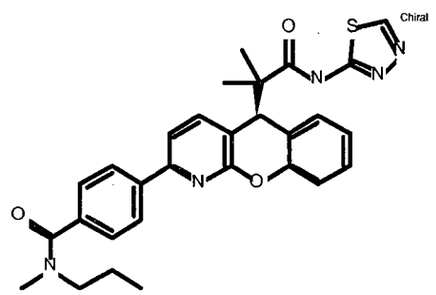
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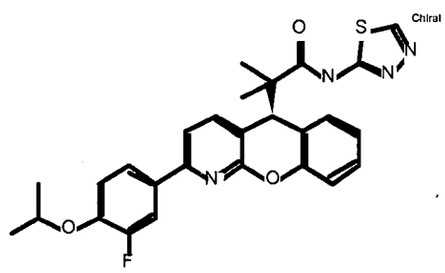
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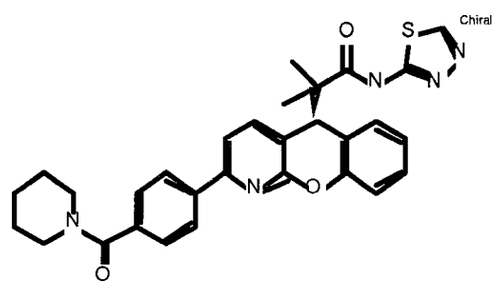
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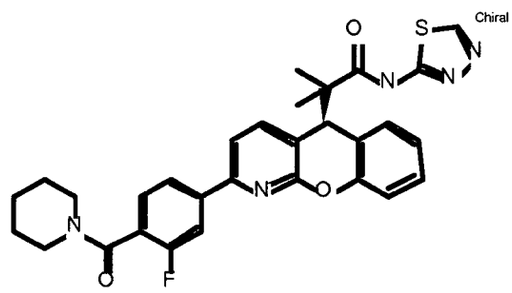
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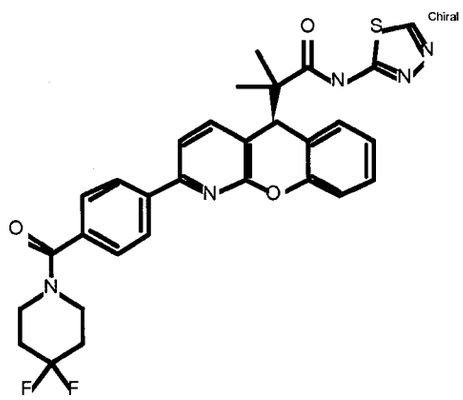
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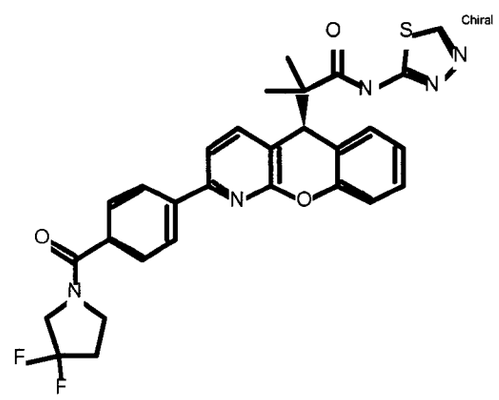
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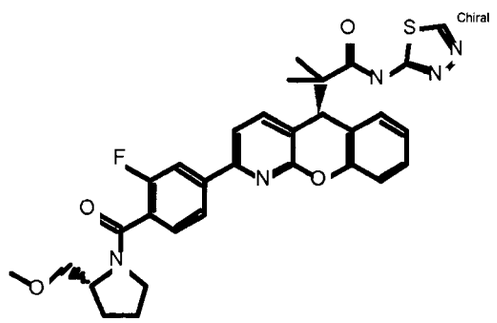
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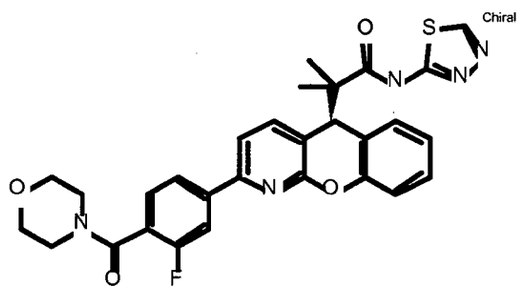
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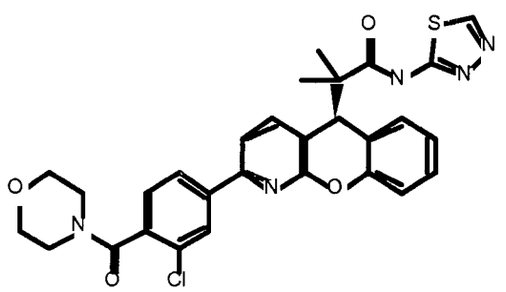
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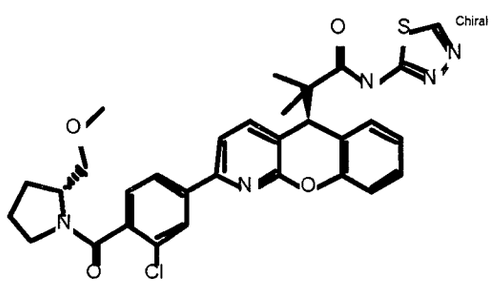
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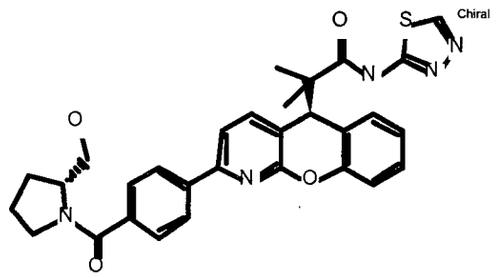
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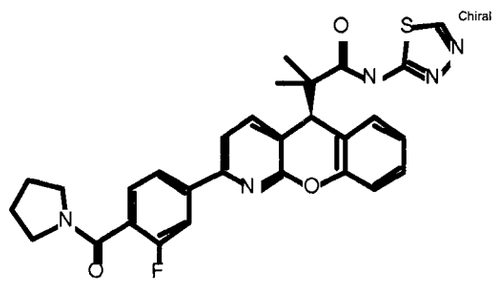
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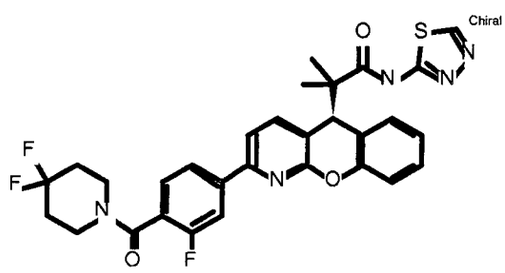
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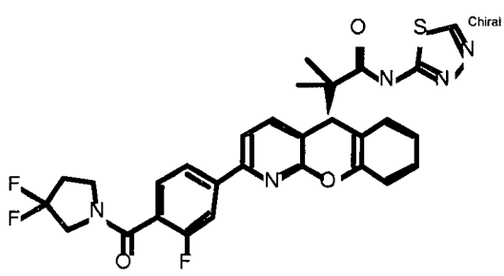
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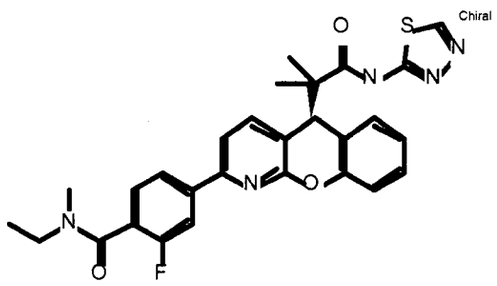
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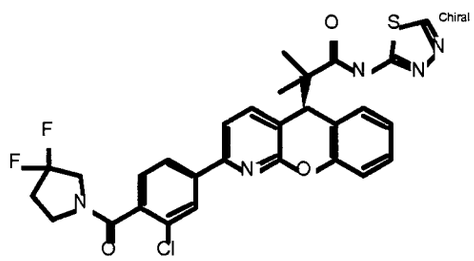
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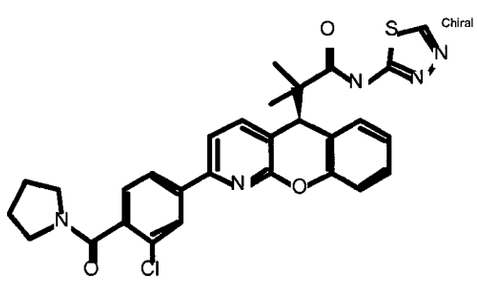
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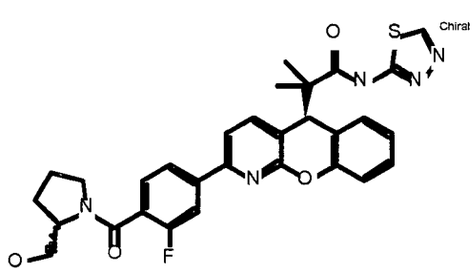
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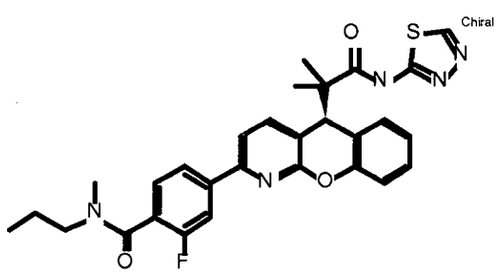
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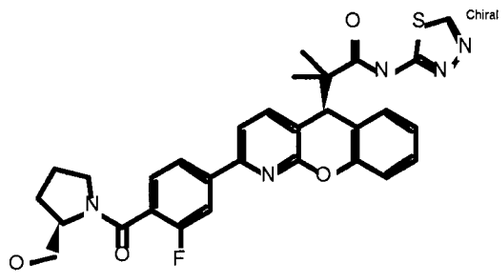
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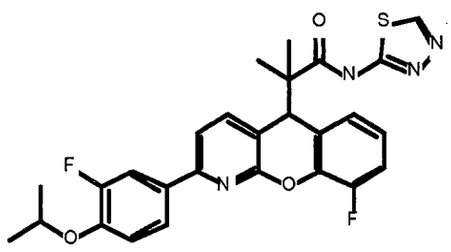
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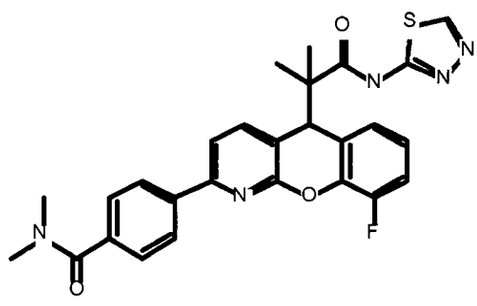
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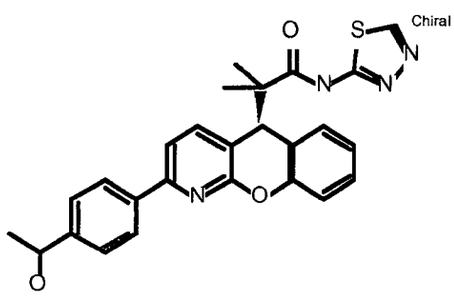
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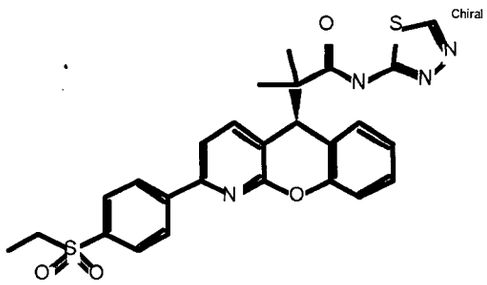
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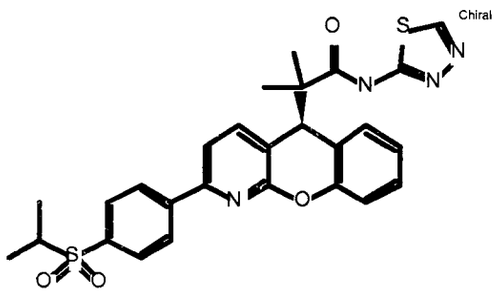

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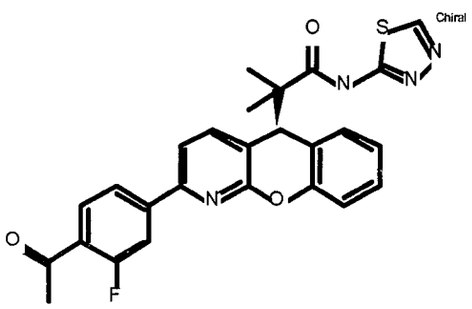
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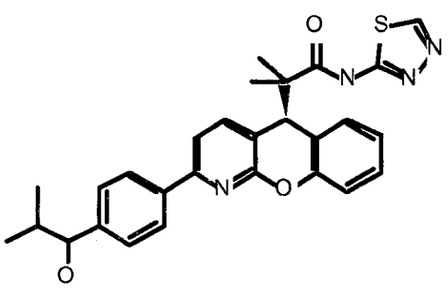

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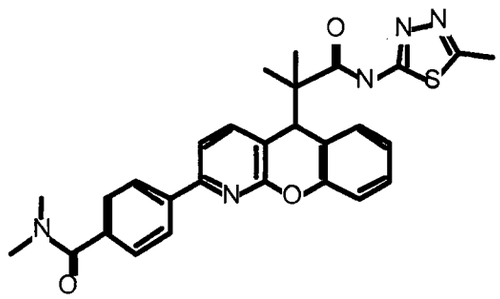
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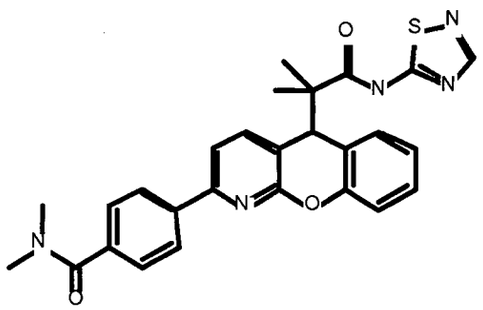

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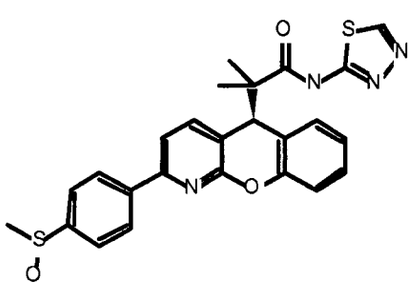




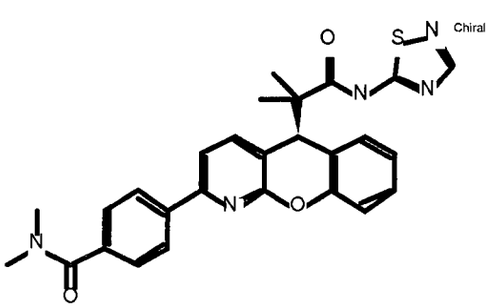
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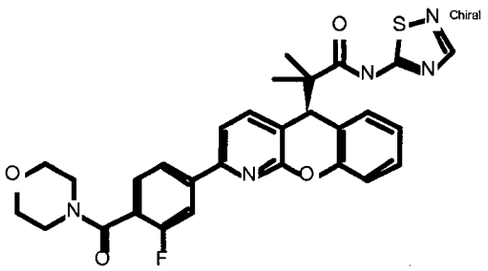
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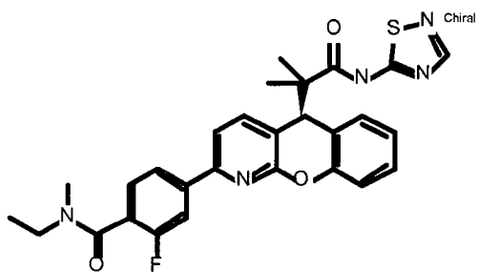
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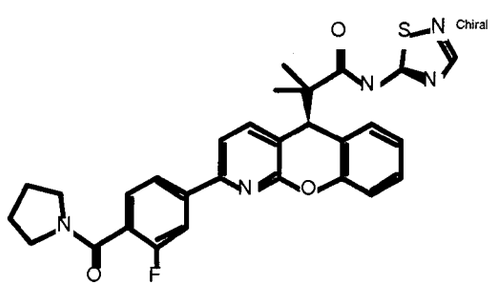
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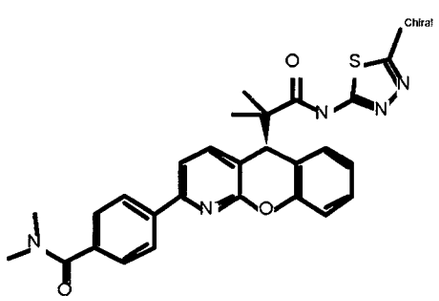
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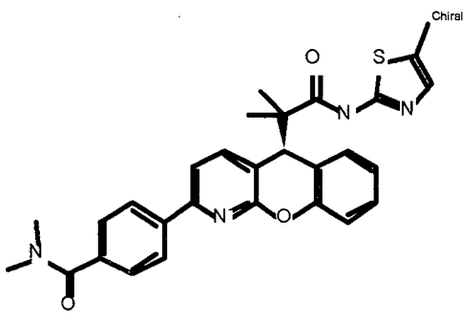
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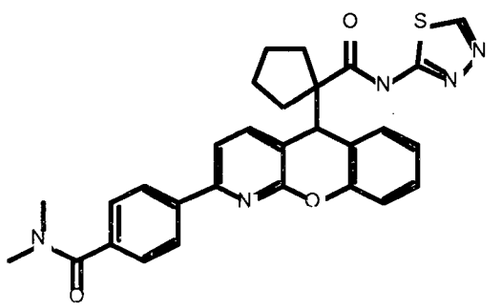
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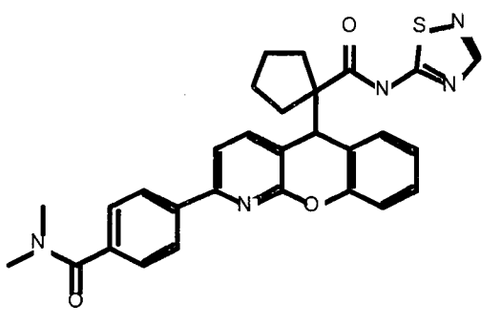
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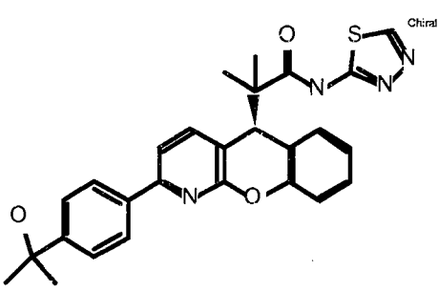
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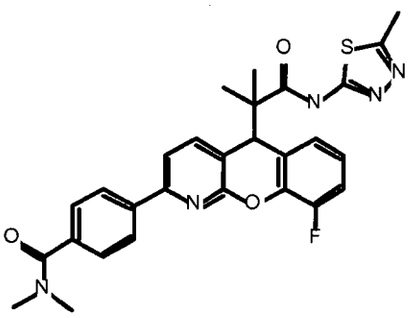
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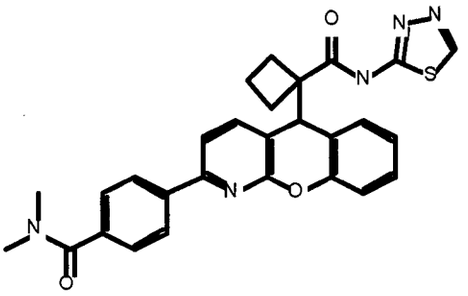
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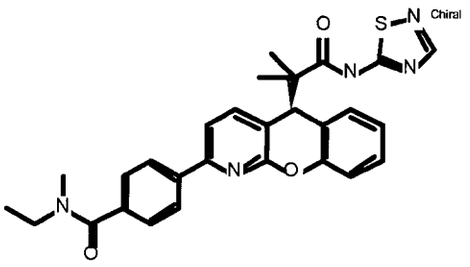
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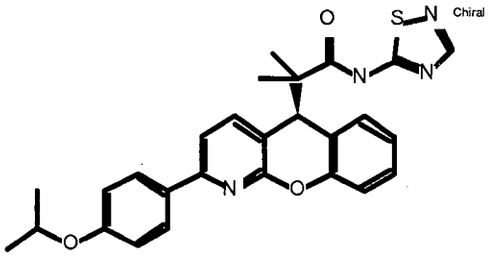
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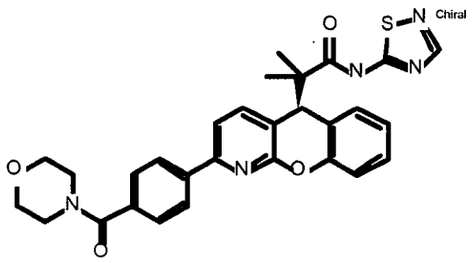
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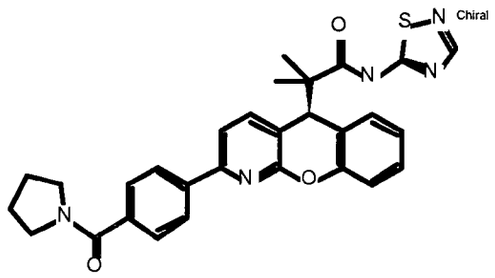
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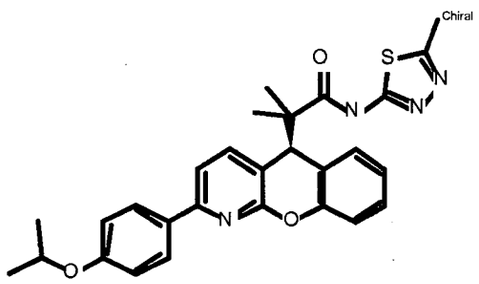
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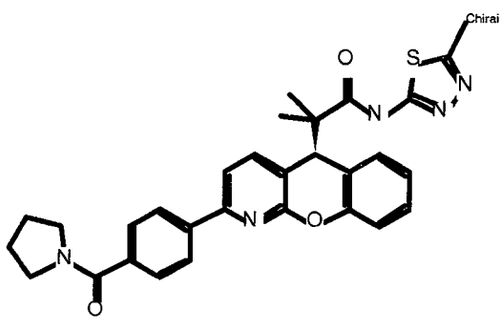
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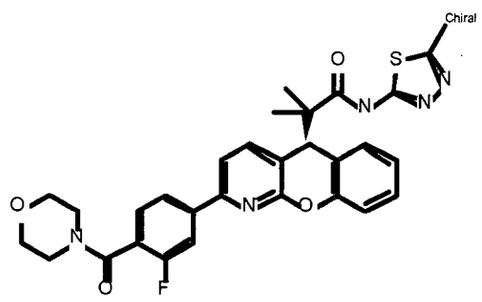
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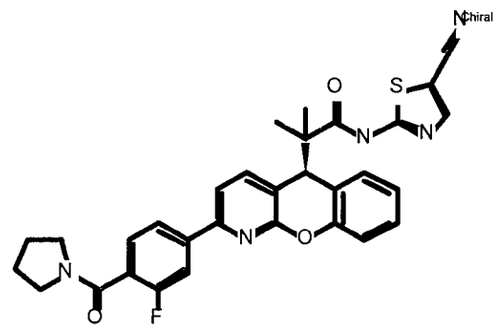
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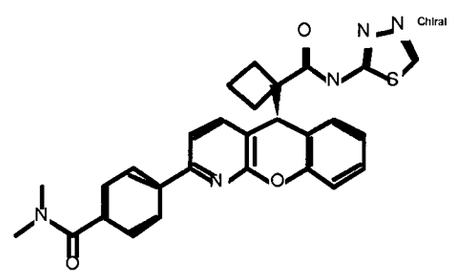
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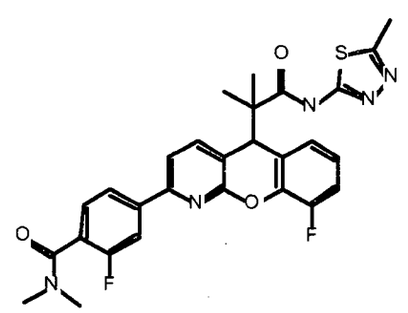
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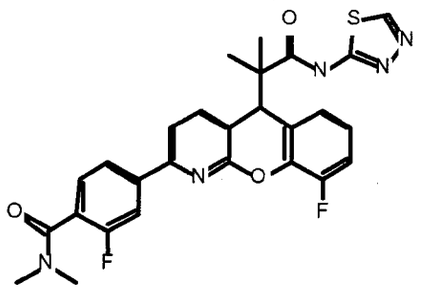
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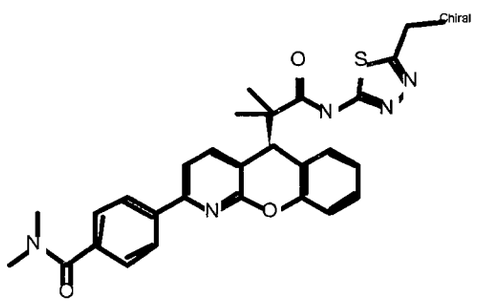

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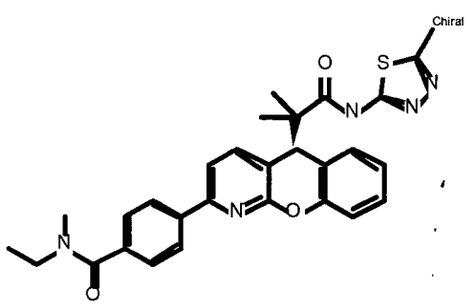
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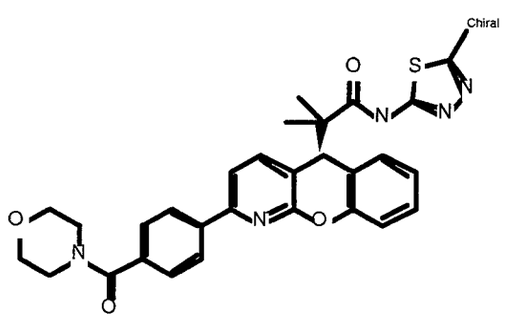

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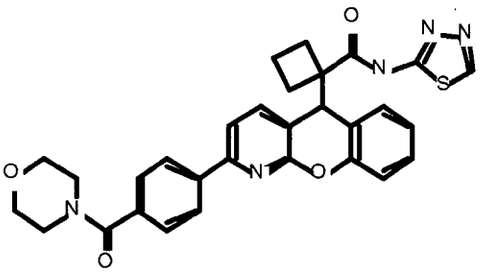
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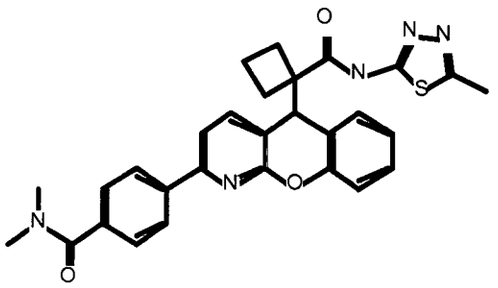

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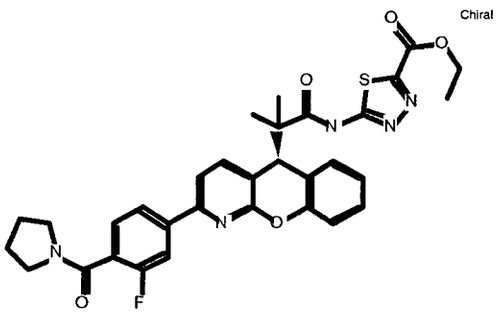

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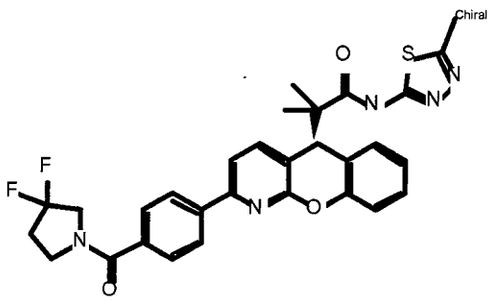
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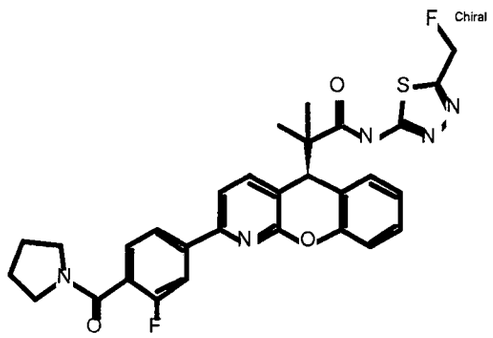
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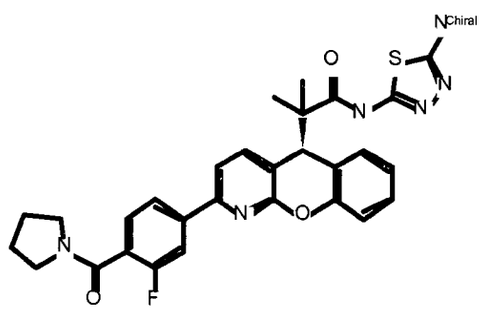
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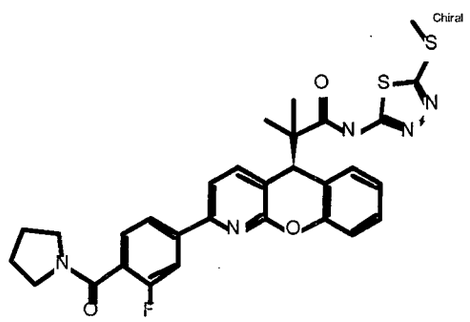
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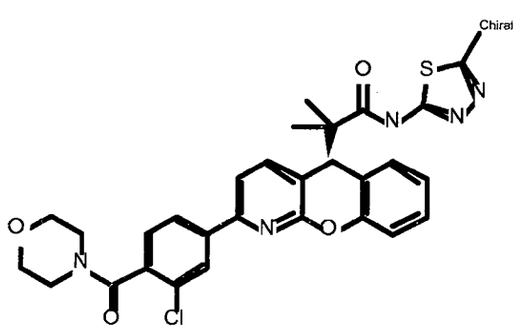
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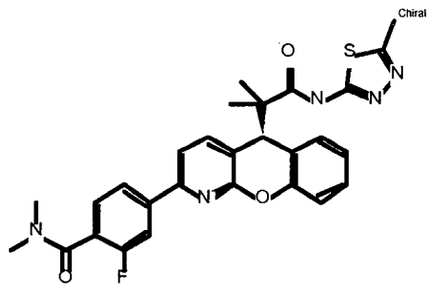
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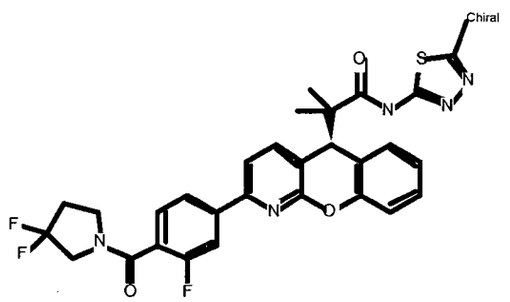
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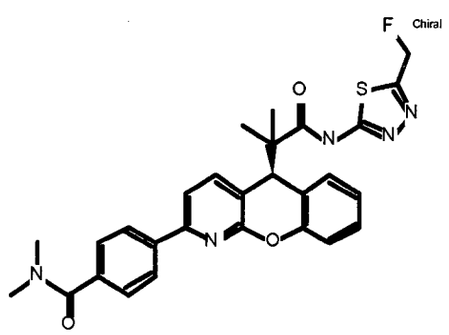
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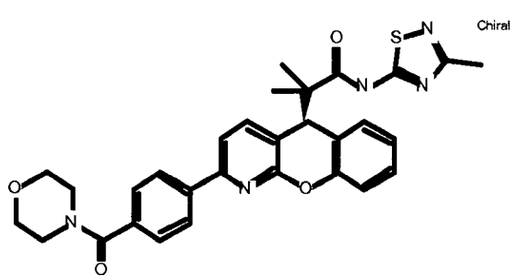
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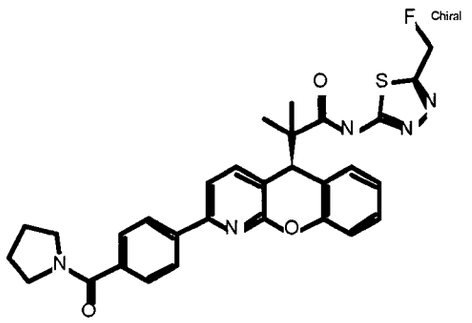
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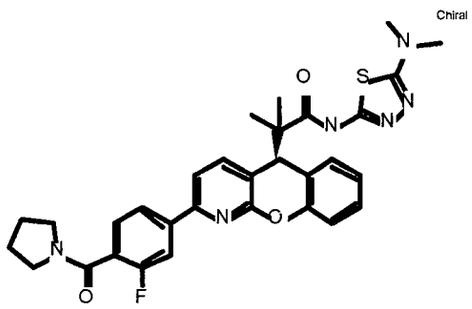
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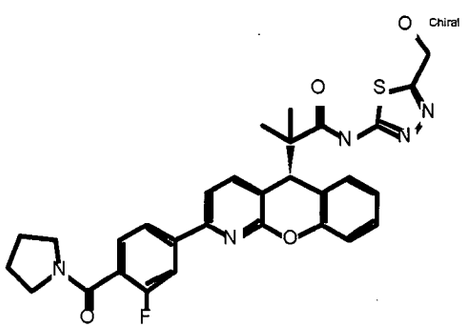
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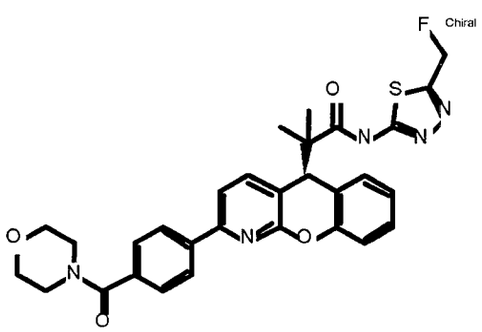
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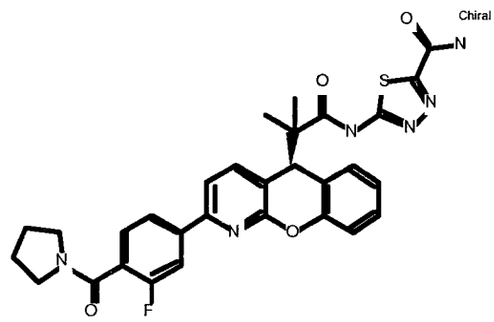
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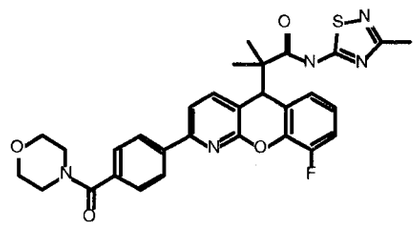

O
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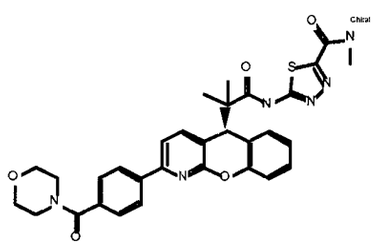
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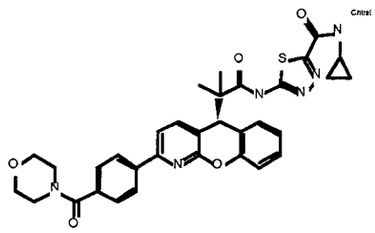

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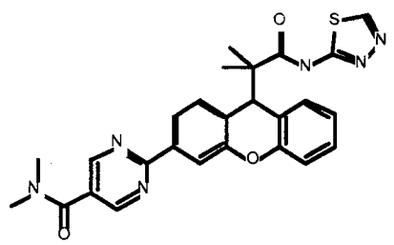

Chiral



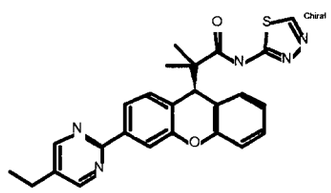

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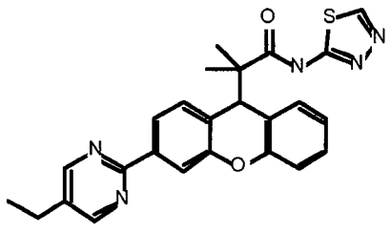
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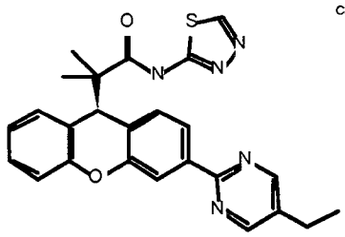


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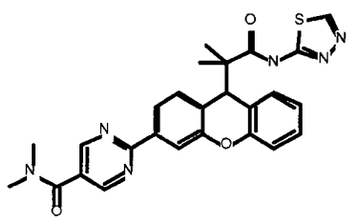


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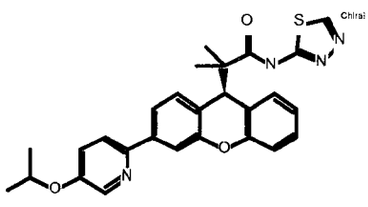
Chiral



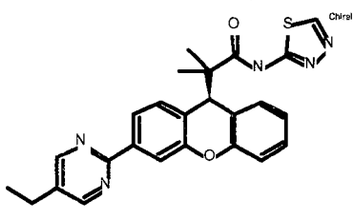
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,



, and



23. Use of a compound as defined in Claims 1-22 for the manufacture of a medicament for treating a disease or disorder selected from an endocrine disorder, rheumatic disorder, collagen disease, dermatologic disease, allergic disease, ophthalmic disease, respiratory disease, hematologic disease, gastrointestinal disease, inflammatory disease, immune disease, neoplastic disease and metabolic disease.

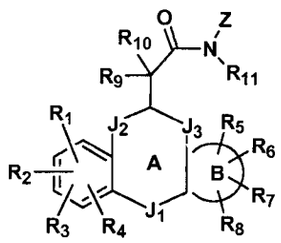
24. Use, as defined in Claim 23, wherein the disease or disorder is an inflammatory or autoimmune disease selected from transplant rejection of kidney, liver, heart, lung, pancreas, bone marrow, cornea, small bowel, skin allografts, skin homografts, heart valve xenograft, serum sickness, and graft vs. host disease, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, asthma, inflammatory bowel disease, Crohn's disease, ulcerative colitis, pyoderma gangrenum, systemic lupus erythematosis, myasthenia gravis, psoriasis, dermatitis, dermatomyositis; eczema, seborrhoea, pulmonary inflammation, eye uveitis, hepatitis, Graves' disease, Hashimoto's thyroiditis, autoimmune thyroiditis, Behcet's or Sjorgen's syndrome,

pernicious or immunohaemolytic anaemia, atherosclerosis, Addison's disease, idiopathic adrenal insufficiency, autoimmune polyglandular disease, glomerulonephritis, scleroderma, morphea, lichen planus, viteligo, alopecia areata, autoimmune alopecia, autoimmune hypopituatarism, Guillain-Barre syndrome, and alveolitis; contact hypersensitivity, delayed-type hypersensitivity, contact dermatitis, uticaria,skin allergies, respiratory allergies, hayfever, allergic rhinitis and gluten-sensitive enteropathy, osteoarthritis, acute pancreatis, chronic pancreatitis, acute respiratory distress syndrome, Sezary's syndrome, restenosis, stenosis and artherosclerosis, congenital adrenal hyperplasia, nonsuppurative thyroiditis, hypercalcemia associated with cancer, juvenile rheumatoid arthritis, Ankylosing spondylitis, acute and subacute bursitis, acute nonspecific tenosynovitis, acute gouty arthritis, post-traumatic osteroarthritis, synovitis of osteoarthritis, epicondylitis, acute rheumatic carditis, pemphigus, bullous dermatitis herpetitformis, severe erythema multiforme, exfoliative dermatitis, psoriasis, seborrheic dermatitis, seasonal or perennial allergic rhinitis, bronchial asthma, contact dermatitis, atopic dermatitis, drug hypersensitivity reactions, allergic conjuncivitis, keratitis, herpes zoster ophthalmicus, iritis and iridocyclitis, chorioretinitis, optic neuritis, symptomatic sarcoidosis, fulminating or disseminated pulmonary tuberculosis chemotherapy, idiopathic thrombocytopenic purpura in adults, secondary thrombocytopenia in adults, acquired (autoimmune) hemolytic anemia, leukemias and lymphomas in adults, acute leukemia of childhood, ulcerative colitis, regional enteritis, Crohn's disease, Sjogren's syndrome, autoimmune vasculitis, multiple sclerosis, myasthenia gravis, sepsis, and chronic obstructive pulmonary disease.

25. Use, as defined in Claims 23-24, wherein the disease or disorder is selected from transplant rejection, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, asthma, inflammatory bowel disease, systemic lupus, erythematosis, and psoriasis.

26. A pharmaceutical composition comprising a compound as defined in Claims 1-22 and a pharmaceutically acceptable carrier therefor.

27. A compound according to formula (I),



I ,

an enantiomer, diastereomer, or tautomer thereof, or a prodrug ester thereof, or a pharmaceutically-acceptable salt thereof, in which:

Z is selected from heterocyclo and heteroaryl;

A is selected from a 5- to 8- membered carbocyclic ring and a 5- to 8-membered heterocyclic ring;

B is selected from a cycloalkyl, cycloalkenyl, aryl, heterocyclo ring, and heteroaryl ring, wherein the B ring is fused to the A ring, and the B ring is optionally substituted by one to four groups which are the same or different and are independently selected from R_5, R_6, R_7, and R_8;

J_1, J_2, and J_3 are the same or different and at each occurrence are independently $-A_1QA_2-$;

Q is independently at each occurrence selected from a bond, O, S, S(O), and $S(O)_2$;

A_1 and A_2 are the same or different and at each occurrence are independently selected from a bond, C_{1-3}alkylene, substituted C_{1-3}alkylene, C_{2-4}alkenylene, and substituted C_{2-4}alkenylene, provided that A_1 and A_2 are chosen so that ring A is a 5- to 8-membered carbocyclic ring or a 5- to 8-membered heterocyclic ring;

R_1, R_2, R_3, R_4, R_5, R_6, R_7, and R_8 are the same or different and at each occurrence are independently selected from (i) hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, nitro, cyano, OR_{12}, $NR_{12}R_{13}$, $C(=O)R_{12}$, CO_2R_{12}, $C(=O)NR_{12}R_{13}$, $-O-C(=O)R_{12}$, $NR_{12}C(=O)R_{13}$, $NR_{12}C(O)OR_{13}$, $NR_{12}C(S)OR_{13}$, $S(O)_pR_{16}$, $NR_{12}SO_2R_{16}$, dialkylaminoalkoxy, alkoxyalkyloxyalkyloxy, $SO_2NR_{12}R_{13}$, cycloalkyl, cycloalkenyl, cycloalkynyl, heterocyclo, aryl, and heteroaryl; and/or (ii) where possible each one of R_1-R_8 is taken together with any one of R_1-R_8 located on an adjacent atom to form a

fused ring; and/or (iii) where possible any one of R_1-R_8 is taken together with any one of R_1-R_8 located on the same atom to form an oxo, alkenyl, substituted alkenyl, cycloalkyl, cycloalkenyl, or heterocyclo group;

R_9 and R_{10} are the same or different and at each occurrence are independently selected from (i) hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, nitro, cyano, OR_{14}, $NR_{14}R_{15}$, $C(=O)R_{14}$, CO_2R_{14}, $C(=O)NR_{14}R_{15}$, $-O-C(=O)R_{14}$, $NR_{14}C(=O)R_{15}$, $NR_{14}C(=O)OR_{15}$, $NR_{14}C(=S)OR_{15}$, $S(O)_pR_{17}$, $NR_{14}SO_2R_{17}$, $SO_2NR_{14}R_{15}$, cycloalkyl, cycloalkenyl, heterocyclo, aryl, and heteroaryl; or (ii) where possible R_9 and R_{10} are taken together to form an oxo, alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, cycloalkenyl, or heterocyclo group;

R_{11} is selected from hydrogen, alkyl, substituted alkyl, C(=O)alkyl, CO_2(alkyl), SO_2alkyl, alkoxy, amino, substituted amino, aryl, heteroaryl, heterocyclo, and cycloalkyl;

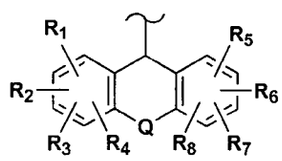
R_{12}, R_{13}, R_{14}, and R_{15}, are the same or different and at each occurrence are independently selected from (i) hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclo; or (ii) where possible R_{12} is taken together with R_{13}, and/or where possible R_{14} is taken together with R_{15} to form a heteroaryl or heterocyclo ring;

R_{16} and R_{17}, are the same or different and at each occurrence are independently selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclo; and

p is 0, 1 or 2,

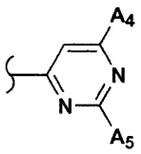
provided that

(1) where the tricyclic moiety in the formula I compound is



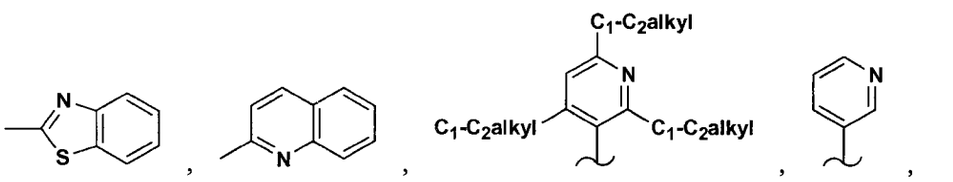
where Q is O and R_1 to R_8 are each H, then

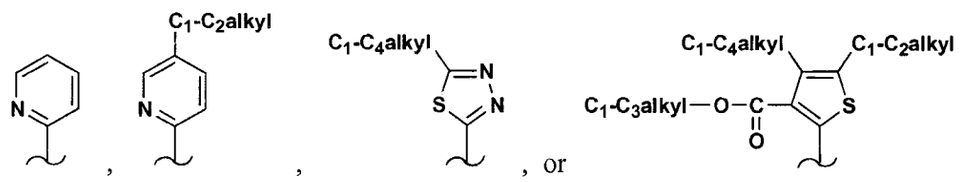
(a) Z is other than



where A_4 and A_5 are the same or different and are independently H or C_1-C_2alkyl-; or

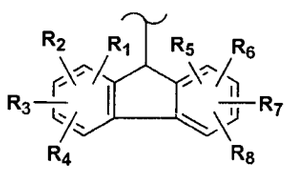
(b) Z is other than





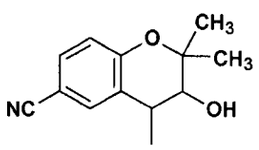
or

(2) where the tricyclic moiety is

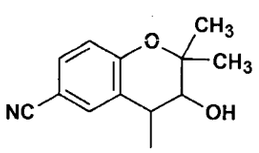


where R_1 to R_8 are each H,

then Z is other than

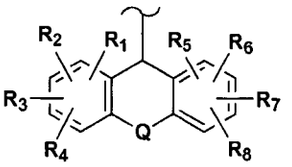


or where Z is



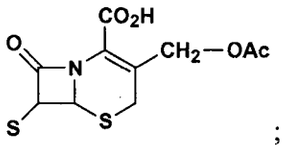
R_{11} is other than a substituted C_1-C_2-alkylene;

(3) where the tricyclic moiety is



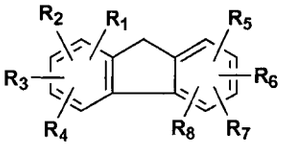
where Q is S or SO_2, and R_1 to R_8 are each H,

then Z is other than

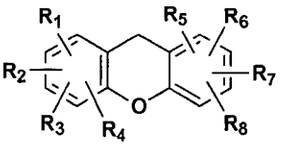


;

(4) where the tricyclic moiety is

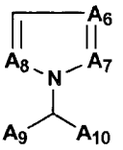


or



where R_1 to R_8 are each H,

then Z is other than



where A_6, A_7 and A_8 are independently N or CH,

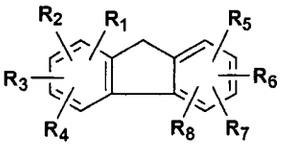
A_9 is $-(CH_2)_d-A_{11}$ where d is 0 to 4;

A_{11} is OH, CO_2H, 5-tetrazolyl, $-COO(C_1-C_4alkyl)_{n_a}$ or CN-;

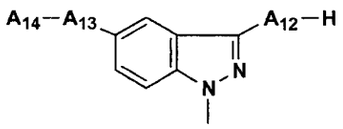
n_a is 0 to 4; and

A_{10} is C_4-C_7 straight chain alkyl;

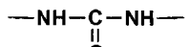
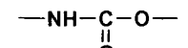
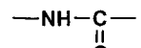
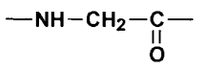
(5) where the tricyclic moiety is



then Z is other than



where A_{12} is O or S; and

A_{13} is O or an NH,  ,  ,  , or  ,

wherein the last 3 groups are joined to the aromatic ring through the N-atom;

A_{14} is H,

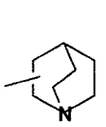
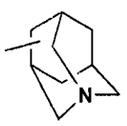
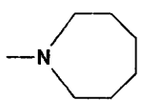
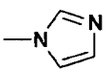
alkyl,

C_3-C_7 cycloalkyl,

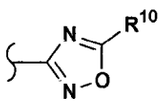
phenyl, naphthyl, anthranyl or fluorenyl optionally substituted, or

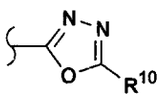
a quinolin-2-ylmethoxy or pyridin-ylmethoxy; or

Z is other than

 ,  ,  , or  ; or

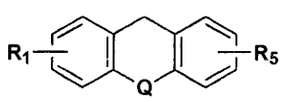
Z is other than





where R^{10} is a non-aromatic azacyclic or non-aromatic azabicyclic ring system;

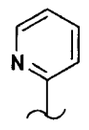
(6) where the tricyclic moiety is



Q is -O-, -S-, -C(R^3R^4)-, -CH_2CH_2-, -CH=CH-CH_2-, -CH_2-CH=CH-, -CH_2-(C=O)-, -(C=O)-CH_2-, $CH_2CH_2CH_2$-, -CH=CH-, -O-CH_2-, -CH_2-O-, -O-CH_2-O-, -CH_2-O-CH_2-, -S-CH_2-, -CH_2-S-, -CH(R^5)CH_2-, -CH_2CH(R^5)-, -(C=O)-, or -(S=O)-

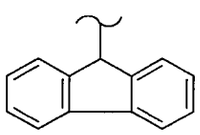
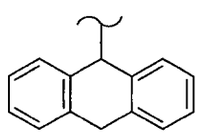
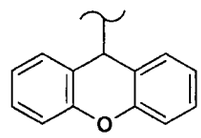
wherein R^3 and R^4 independently are hydrogen or C_{1-7}-alkyl; and wherein R^5 is C_{1-7}-alkyl or phenyl;

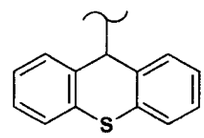
then Z is other than



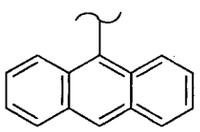
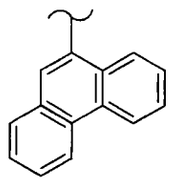
; or

(7) where the tricyclic moiety is

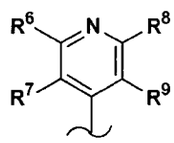

,

,


,


,


or

,

then Z is other than



wherein:

R^6 and R^7 are each independently selected from C_1-C_6alkyl, halo-C_1-C_6alkyl containing 1 to 5 halogen atoms, C_1-C_2alkoxy-C_1-C_6alkyl, nitro-C_1-C_6alkyl, cyano-C_1-C_6alkyl, C_1-C_2alkanoyl-C_1-C_6alkyl, C_1-C_2alkoxycarbonyl-C_1-C_6alkyl, C_1-C_2alkylthio-C_1-C_6alkyl, C_1-C_2alkanesulfinyl-C_1-C_6alkyl, C_1-C_2alkanesulfonyl-C_1-C_6alkyl, C_2-C_6alkenyl, halo-C_2-C_6alkenyl containing 1-5 halogen atoms, C_2-C_6alkynyl, halo-C_2-C_6alkynyl containing 1-5 halogen atoms, C_3-C_7cycloalkyl and halogen; or

R^6 and R^7, taken together, form a saturated or unsaturated 5- to 7-membered carbocyclic or heterocyclic ring which may contain one or two hetero atoms selected from O and S; and

000397

R^8 and R^9 are each independently selected from hydrogen, C_1-C_6alkyl and halogen.

MODULADORES DEL RECEPTOR GLUCOCORTICOIDE, Y/O DE AP-1, Y/O DE LA ACTIVIDAD DE NF-κB Y SU USO

Descripción de la invención

La presente invención se refiere a nuevos compuestos no esteroidales que son moduladores efectivos del receptor glucocorticoide, y/o de AP-1, y/o de la actividad de NF-κB y de esta manera son útiles para el tratamiento de enfermedades tales como enfermedades inflamatorias o inmunitarias asociadas, y a un método para usar tales compuestos para tratar estas y otras enfermedades relacionadas.

Los factores de transcripción NF-kB y AP-1 están involucrados en la regulación de la expresión de un número de genes involucrados en mediar la respuesta inflamatoria e inmunitaria. NF-kB regula la transcripción de genes que incluyen TNF-α, IL-1, IL-2, IL-6, moléculas de adhesión (tales como E-selectina) y quimiocinas (tales como Rantes), entre otros. AP-1 regula la producción de las citocinas TNF-α, IL-1, IL-2, así como, metaloproteasas de matriz. Las terapias de fármacos que direccionan TNF-α, un gen cuya expresión se regula tanto por NF-κB como AP-1, han mostrado que son altamente eficaces en varias enfermedades inflamatorias humanas que incluyen artritis reumatoide y enfermedad de Crohn. En consecuencia, NF-κB y AP-1 juegan papeles clave en el incio y perpetuación de trastornos inflamatorios e inmunitarios. Véase Baldwin, A.S., Journal of Clin. Investigation, 107, 3 (2001);

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Firestein, G.S., y Manning, A.M., Arthritis and Rheumatism, 42, 609 (1999); y Peltz, G., Curr. Opin. in Biotech., 8, 467 (1997).

Hay muchas moléculas de señalización (cinasas y fosfatasas) en dirección ascendente de AP-1 y NF-κB que son objetivos de fármacos terapéuticos potenciales. La cinasa JNK juega un papel esencial para regular la fosforilación y activación posterior de c-jun, una de las subunidades que contituyen el complejo AP-1 (fos/c-jun). Los compuestos que inhiben JNK han mostrado que son eficaces en modelos animales de enfermedad inflamatoria. Véase Manning, A.M. y Davis, R.J., Nature Rev. Drug Disc., V. 2, 554 (2003). Una cinasa crítica para la activación de NF-κB es la cinasa IκB (IKK). Esta cinasa juega un papel en la forforilación de IκB. Una vez que IκB se fosforila, experimenta la degradación que lleva a la liberación de NF-κB que puede transubicarse en los núcleos y activar la transcripción de los genes descritos anteriormente. Un inhibidor de IKK se ha mostrado que es eficaz en modelos animales de enfermedad inflamatoria. Véase Burke, J.R., Curr. Opin. Drug Discov. Devel., Sep;6(5), 720-8, (2003).

Además de inhibir las cascadas de la señalización involucrada en la activación de NF-κB y AP-1, el receptor glucocorticoide se ha mostrado que inhibe la actividad de NF-κB y AP-1 por medio de interacciones físicas. El receptor glucocorticoide (GR) es un miembro de la familia del

receptor de hormona nuclear de factores de transcripción, y un miembro de la familia de hormona esteroide de los factores de transcripción. La afinidad de etiquetado de la proteína del receptor glucocorticoide permite la producción de anticuerpos contra el receptor que facilita la clonación del receptor glucocorticoide. Para resultados en humanos véase Weinberger et al., Science, 228, 740-742 (1985); Weinberger et al., Nature, 318, 670-672 (1986) y para resultados en ratas véase Miesfeld, R., Nature, 312, 779-781 (1985).

Los glucocorticoides que interactúan con GR se han usado durante 50 años para tratar enfermedades inflamatorias. Se ha mostrado claramente que los glucocorticoides ejercen su actividad antiinflamatoria por medio de la inhibición por GR de los factores de transcripción NF-κB y AP-1. Esta inhibición se llama trans-represión. Se ha mostrado que el mecanismo primario para la inhibición de estos factores de transcripción por GR es por medio de una interacción física directa. Esta interacción altera el complejo del factor de transcripción e inhibe la capacidad de NF-κB y AP-1 para estimular la transcripción. Véase Jonat, C. et al., Cell, 62, 1189 (1990); Yang-Yen, H.F. et al, Cell, 62, 1205 (1990); Diamond, M.I. et al., Science 249, 1266 (1990); y Caldenhoven, E. et al., Mol. Endocrinol., 9, 401 (1995). Otros mecanismos tales como la captura de co-activadores por GR también se han propuesto.

Véase Kamei, Y. et al., Cell, 85, 403 (1996); y Chakravarti, D. et al., Nature, 383, 99 (1996).

Además de causar la trans-represión, la interacción de un glucorticoide con GR puede causar que GR induzca la transcripción de ciertos genes. Esta inducción de transcripción se llama transactivación. La transactivación requiere dimerización de GR y enlace a un elemento de respuesta glucocorticoide (GRE).

Los recientes estudios que usan ratones defectuosos en dimerización GR transgénicos que no enlazan el ADN muestran que las actividades de transactivación (enlace de ADN) de GR podrían separarse del efecto trans-represor (no enlace de ADN) de GR. Estos estudios también indican que muchos de los efectos secundarios de la terapia de glucocorticoides se deben a la capacidad de GR para inducir la transcripción de varios genes involucrados en el metabolismo, mientras que, la trans-represión, que no requiere enlace de ADN, lleva a la supresión de la inflamación. Véase Reichardt, H.M. et al., Cell, 93, 531 (1998) y Reichardt, H.M., EMBO J., 20, 7168 (2001).

Los compuestos que modulan la actividad de AP-1 y NF-κB serían útiles en el tratamiento de enfermedades inflamatorias e inmunitarias y trastornos tales como osteoartritis, artritis reumatoide, esclerosis múltiple, asma, enfermedad inflamatoria del intestino, rechazo de trasplante y enfermedad de injerto contra hospedero.

También, con respecto a la trayectoria del receptor glucocorticoide, se conoce que los glucocorticoides son agentes antiinflamatorios potentes. Sin embargo, su uso sistémico se limita por los efectos secundarios. Los compuestos que mantienen la eficacia antiinflamatoria de los glucocorticoides mientras minimizan los efectos secundarios tales como diabetes, osteoporosis y glaucoma serían de mayor beneficio para un número muy grande de pacientes con enfermedades inflamatorias.

Adicionalmente con relación a GR, la técnica está en necesidad de compuestos que sean antagonistas de la transactivación. Tales compuestos pueden ser útiles en el tratamiento de enfermedades metabólicas asociadas con niveles incrementados de glucocorticoides, tales como diabetes, osteoporosis y glaucoma.

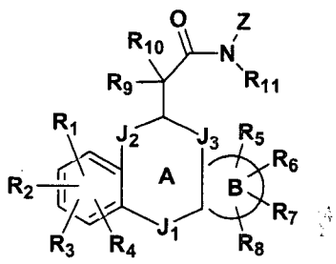
Adicionalmente con relación a GR, la técnica está en necesidad de compuestos que causen la transactivación. Tales compuestos pueden ser útiles en el tratamiento de enfermedades metabólicas asociadas con deficiencia en glucocorticoides. Tales enfermedades incluyen enfermedad de Addison.

La presente invención se refiere a nuevos compuestos no esteroidales que son moduladores efectivos del receptor glucocorticoide, y/o de AP-1, y/o de la actividad de NF-κB ypor consiguiente son útiles en tratamientos de enfermedades tales como enfermedades inflamatorias o enfermedades

GT396

inmunitarias asociadas, y/u obesidad y diabetes, y a un método para usar tales compuestos para tratar estas y otras enfermedades relacionadas.

De acuerdo con un aspecto de la invención, los compuestos proporcionados tienen la estructura de la fórmula I



I

un enantiómero, diastereómero, tautómero, o una sal farmacéuticamente aceptable del mismo, en donde:

Z se selecciona del heterociclo, heteroarilo y ciano;

A se selecciona de un anillo carbocíclico de 5 hasta 8 elementos y un anillo heterocíclico de de 5 hasta 8 elementos;

el anillo B se selecciona de un cicloalquilo, cicloalquenilo, arilo, anillo heterociclo, y anillo heteroarilo, en donde el anillo B se fusiona al Anillo A, y el anillo B es opcionalmente substituido por uno hasta cuatro grupos que son los mismos o diferentes y son independientemente seleccionados de R_5, R_6, R_7, y R_8;

J_1, J_2, y J_3 son los mismos o diferentes y cada que se presentan son independientemente $-A_1QA_2-$;

Q es independientemente cada que se presenta seleccionado

de un enlace, O, S, S(O), y $S(O)_2$;

A_1 y A_2 son los mismos o diferentes y cada que se presentan son independientemente seleccionados de un enlace, alquileno C_{1-3}, alquileno C_{1-3} substituido, alquenileno C_{2-4}, y alquenileno C_{2-4} substituido, con la condición de que A_1 y A_2 se eligen para que el anillo A es un anillo carbocíclico de 5 hasta 8 elementos o un anillo heterocíclico de 5 hasta 8 elementos;

R_1, R_2, R_3, R_4, R_5, R_6, R_7, y R_8 son los mismos o diferentes y cada que se presentan son independientemente seleccionados de (i) hidrógeno, halógeno, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, alcoxi, alcoxi substituido, nitro, ciano, OR_{12}, $-NR_{12}R_{13}$, $-C(=O)R_{12}$, $-CO_2R_{12}$, $-C(=O)NR_{12}R_{13}$, $-OC(=O)NR_{12},R_{13}$, $-NC(=O)NR_{12}R_{13}$ (con R_d), $-OC(=O)R_{12}$, $-NR_{12}C(=O)R_{13}$, $-NR_{12}C(O)OR_{13}$, $-NR_{12}C(S)OR_{13}$, $S(O)_pR_{16}$, $NR_{12}SO_2R_{16}$, dialquiloaminoalcoxi, alcoxialquilooxialquilooxi, $SO_2NR_{12}R_{13}$, cicloalquilo, cicloalquenilo, cicloalquinilo, heterociclo, arilo, y heteroarilo; y/o (ii) en donde sea posible, cada uno de R_1-R_8 se toma junto con cualquiera de R_1-R_8 localizado en un átomo adyacente para formar un anillo fusionado; y/o (iii) en donde sea posible cualquiera de R_1-R_8 se toma junto con cualquiera de R_1-R_8 localizados en el mismo átomo para formar un oxo, alquenilo, alquenilo substituido, cicloalquilo, cicloalquenilo,

CCC398

o grupo heterociclo;

R_9 y R_{10} son los mismos o diferentes y cada que se presentan son independientemente seleccionados de (i) hidrógeno, halógeno, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, nitro, ciano, OR_{14}, $NR_{14}R_{15}$, $C(=O)R_{14}$, CO_2R_{14}, $C(=O)NR_{14}R_{15}$, $-O-C(=O)R_{14}$, $NR_{14}C(=O)R_{15}$, $NR_{14}C(=O)OR_{15}$, $NR_{14}C(=S)OR_{15}$, $S(O)_pR_{17}$, $NR_{14}SO_2R_{17}$, $SO_2NR_{14}R_{15}$, cicloalquilo, cicloalquenilo, heterociclo, arilo, y heteroarilo; o (ii) junto con el átomo al cual se enlazan, R_9 y R_{10} se toman juntos para formar un carbonilo, alquenilo, alquenilo substituido, cicloalquilo, cicloalquenilo, o un grupo heterociclo;

R_{11} se selecciona de hidrógeno, alquilo, alquilo substituido, C alquilo(=O), CO_2(alquilo), SO_2alquilo, alcoxi, amino, amino substituido, arilo, heteroarilo, heterociclo, y cicloalquilo;

R_{12}, R_{13}, R_{14}, y R_{15}, son los mismos o diferentes y cada que se presentan son independientemente seleccionados de (i) hidrógeno, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, cicloalquilo, cicloalquenilo, arilo, heteroarilo, y heterociclo; o (ii) en donde sea posible R_{12} se toma junto con R_{13}, y/o en donde sea posible R_{14} se toma junto con R_{15} para formar un heteroarilo o anillo heterociclo;

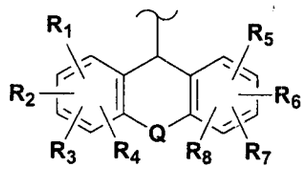
R_{16} y R_{17}, son los mismos o diferentes y cada que se presentan son independientemente seleccionados de alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, cicloalquilo, cicloalquenilo, arilo, heteroarilo, y heterociclo;

R_d es H, alquilo o arilo; y

p es 0, 1 ó 2,

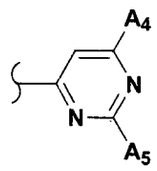
con la condición de que

(1) donde la porción tricíclica en el compuesto de la fórmula I es



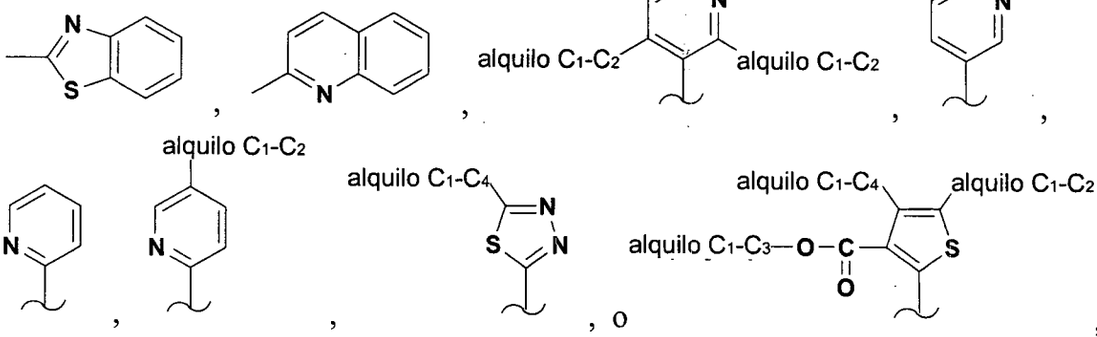
donde Q es O y R_1 hasta R_8 son cada uno H, entonces

(a) Z es diferente a

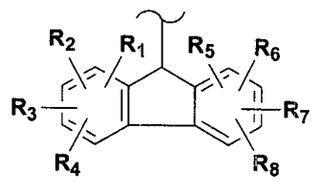


donde A_4 y A_5 son los mismos o diferentes y son independientemente H o alquilo C_1-C_2; o

(b) Z es diferente a



(2) donde la porción tricíclica es

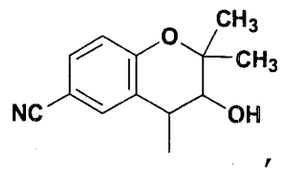


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donde R_1 hasta R_8 son cada uno H,

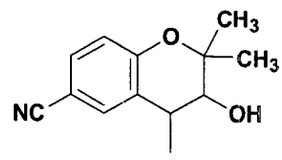
entonces

(a) Z es diferente a



, o

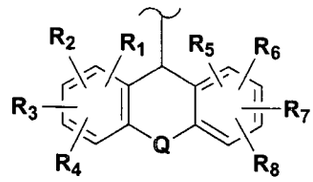
(b) donde Z es



,

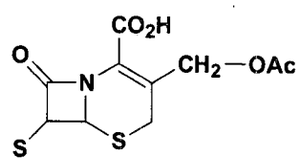
entonces R_{11} es diferente a un alquileno C_1-C_2 substituido;

(3) donde la porción tricíclica es



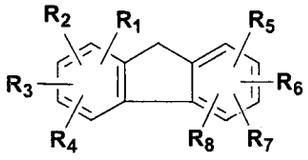
donde Q es S o SO_2, y R_1 hasta R_8 son cada uno H,

entonces Z es diferente a

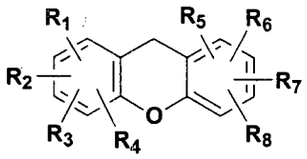


;

(4) donde la porción tricíclica es

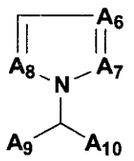


o



donde R_1 hasta R_8 son cada una H,

entonces Z es diferente a



donde A_6, A_7 y A_8 son independientemente N o CH,

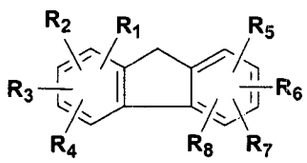
A_9 es $-(CH_2)_d-A_{11}$ donde d es 0 hasta 4;

A_{11} es OH, CO_2H, 5-tetrazolilo, $-COO(\text{alquilo } C_1\text{-}C_4)_{n_a}$ o CN-;

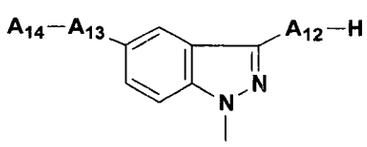
n_a es 0 hasta 4; y

A_{10} es alquilo C_4-C_7 de cadena recta;

(5) donde la porción tricíclica es

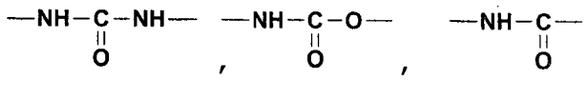
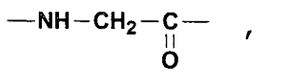


entonces Z es diferente a



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donde A_{12} es O o S; y

A_{13} es O o un NH,  , o  ,

en donde los últimos 3 grupos se enlazan al anillo aromático a través del átomo N;

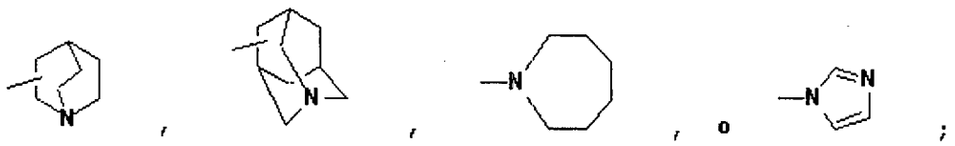
A_{14} es H,

alquilo,

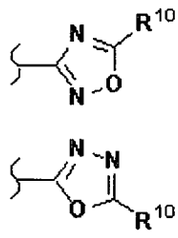
cicloalquilo C_3-C_7,

fenilo, naftilo, antranilo o fluorenilo opcionalmente substituido, o un quinolin-2-ilmetoxi o piridin-ilmetoxi; o

Z es diferente a

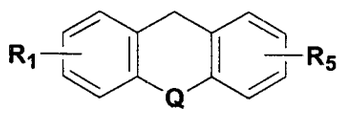
 ;

Z es diferente a



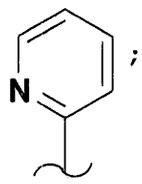
donde R^{10} es un sistema de anillo azaciclíco no aromático o azabiciclíco no aromático;

(6) donde la porción tricíclica es



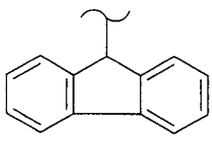
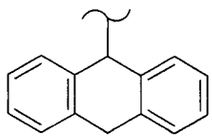
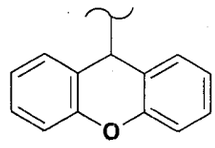
Q es -O-, -S-, $-C(R^3R^4)-$, $-CH_2CH_2-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-$, $-CH_2-(C=O)-$, $-(C=O)-CH_2-$, $CH_2CH_2CH_2-$, $-CH=CH-$, $-O-CH_2-$, $-CH_2-O-$, $-O-CH_2-O-$, $-CH_2-O-CH_2-$, $-S-CH_2-$, $-CH_2-S-$, $-CH(R^5)CH_2-$, $-CH_2CH(R^5)-$, $-(C=O)-$, o $-(S=O)-$ en donde R^3 y R^4 independientemente son hidrógeno o alquilo C_{1-7}; y en donde R^5 es alquilo C_{1-7} o fenilo;

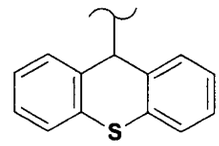
entonces Z es diferente a



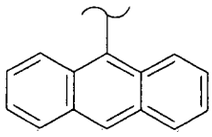
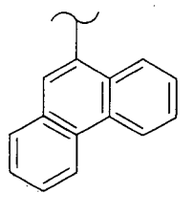
;

(7) donde la porción tricíclica es

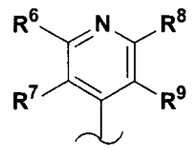

,

,


,


,


o

,

entonces Z es diferente a



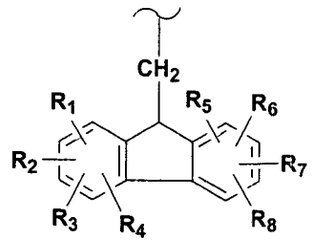
en donde:

R^6 y R^7 son cada uno independientemente seleccionados de alquilo C_1-C_6, halo-alquilo C_1-C_6 que contienen 1 hasta 5 átomos de halógeno, alcoxi C_1-C_2-alquilo C_1-C_6, nitro- alquilo C_1-C_6, ciano-alquilo C_1-C_6, alcanoil C_1-C_2-alquilo C_1-C_6, alcoxicarbonilo C_1-C_2-alquilo C_1-C_6, alquiltio C_1-C_2-alquilo C_1-C_6, alcanosulfonilo C_1-C_2-alquilo C_1-C_6, alcanosulfonilo C_1-C_2-alquilo C_1-C_6, alquenilo C_2-C_6, halo- alquenilo C_2-C_6 que contiene 1-5 átomos de halógeno, alquinilo C_2-C_6, halo- alquinilo C_2-C_6 que contiene 1-5 átomos de halógeno, cicloalquilo C_3-C_7 y halógeno; o

R^6 y R^7, tomados juntos, forman un anillo heterocíclico o carbocíclico de 5 hasta 7 elementos saturados o no saturados el cual puede contener uno o dos hetero átomos seleccionados de O y S; y

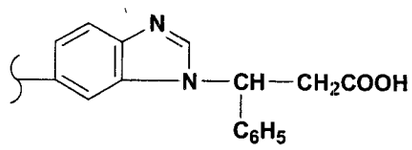
R^8 y R^9 son cada uno independientemente seleccionados de hidrógeno, alquilo C_1-C_6 y halógeno;

(8) donde la porción tricíclica es



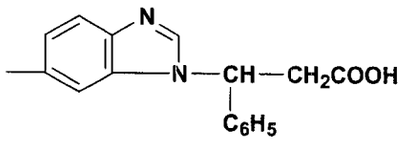
entonces

a) Z es diferente a



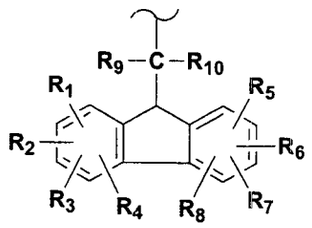
o un homólogo del mismo,

b) si Z s

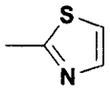


o un homólogo del mismo, entonces R_{11} es diferente a H; o

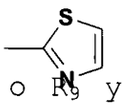
(9) donde la porción tricíclica es



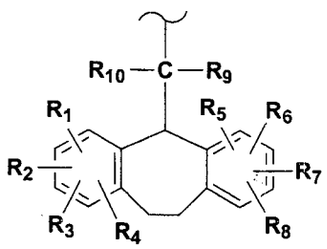
entonces

a) Z es diferente a  substituido o no substituido,

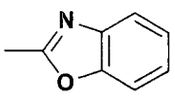
o

b) donde Z es  substituido o no substituido, entonces al menos uno o R_9 y R_{10} es diferente a H y/o R_{11} es diferente a H;

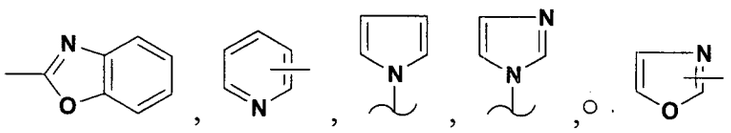
(10) donde la porción tricíclica es



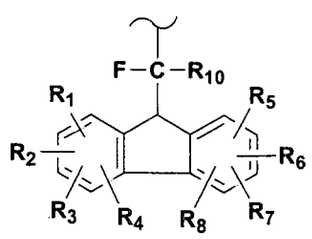
entonces

a) Z es diferente a  ,

b) donde Z es

 , entonces R_{11} es diferente a H y/o al menos uno de R_9 y R_{10} es diferente a H;

(11) donde la porción tricíclica es

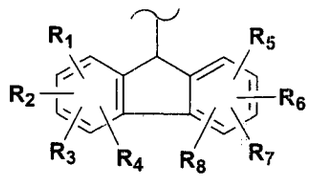


entonces

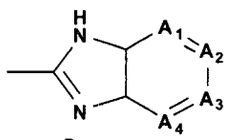
a) Z es diferente a heteroarilo, o

b) donde Z es heteroarilo, entonces R_{11} es diferente a H y/o R_{10} es diferente a H; o

(12) donde la porción tricíclica es

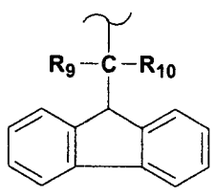


entonces R_1, R_2, R_3, R_4, R_5, R_6, R_7 y R_8 es diferente a

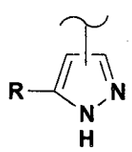


en donde A_1, A_2, A_3 y A_4 son seleccionados de CR_a o N, donde R_a es H o un substituyente; o

(13) donde la porción tricíclica es

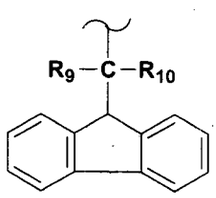


entonces Z es diferente a



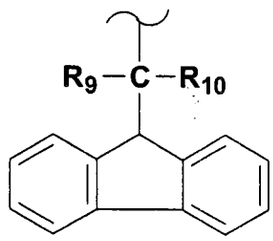
donde R es cicloalquilo C_3-C_6 opcionalmente substituido por alquilo C_1-C_6 o ariloalquilo o un homólogo del mismo;

(14) donde la porción tricíclica es

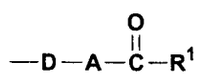


y Z es heteroarilo o heterociclilo que contienen un átomo N en el anillo, entonces el Z heteroarilo o heterociclilo no puede ser substituido con un grupo R'A donde R' es heterocíclico opcionalmente substituido o fenilo y A es $(CH_2)_{0-2}(O)_{0\ o\ 1}$ o $(CR^3R^4)_{0\ o\ 1}NR^5(CO)_{0\ o\ 1}$ donde R^3, R^4 = H o R^3 + R^4-imino y R^5 = H o alquilo;

(15) donde la porción tricíclica es



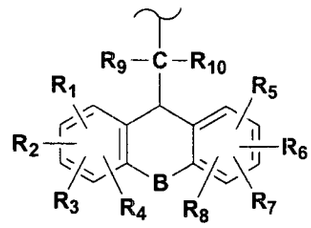
y Z es diferente a un anillo heterocíclico de 5-7 elementos que contienen un N, O y/o S, tal anillo

heterocíclico está substituido por  donde D es alquilenoC $^{1-4}$, O o S,

A es un anillo carbocíclico de 3 hasta 7 elementos o un anillo heterocíclico de 5 hasta 7 elementos que contienen N, O y/o S, y

R^1 es OH, alcoxi, o $NR^{10}R^{11}$ donde R^{10} y R^{11} pueden ser H o alquilo que Z y/o también puede ser opcionalmente substituido por el grupo 1-3 en cual puede ser alquilo C_{1-4}, alcoxi C_{1-4}, halo, trihalometilo, CN, o NO_2; o

(16) donde la porción tricíclica es



donde B es O u S, entonces

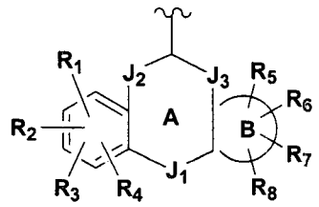
a) Z es diferente a dihidrofurilo opcionalmente substituido o dihidrotienilo opcionalmente substituido,

b) o si Z es dihidrofurilo opcionalmente substituido o dihidrotienilo opcionalmente substituido, entonces

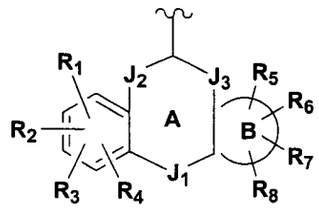
1) al menos uno de R_9 y/o R_{10} es diferente a H, o

2) R_{11} es diferente a H o alquilo inferior.

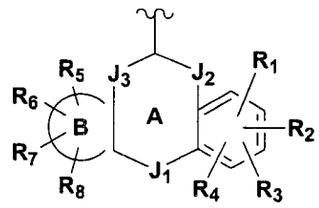
La porción tricíclica



como se usa en la presente incluyen las porciones



y



Las porciones B preferidas son arilo y heteroarilo e incluyen fenilo, piridinilo y pirazinilo.

En las porciones anteriores, se prefiere que

B es un anillo de fenilo, piridinilo o pirazinilo;

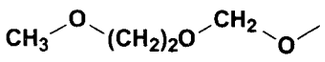
J_1 es O, S, SO, SO_2, un enlace, CH_2, o CH_2CH_2; y

J_2 y J_3 son cada uno un enlace.

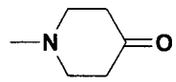
Más preferentemente J_1 es O, S, SO, SO_2, o un enlace, especialmente O, S, SO, o SO_2.

Más preferentemente B es piridinilo substituido con arilo o arilo substituido.

Más preferentemente R_1, R_2, R_3 son cada uno hidrógeno, y R_4 es hidrógeno, CF_3, CH_3O, $N(CH_3)_2CH_2CH_2O$-, OH,



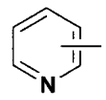
,

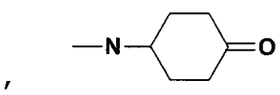
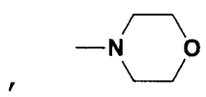
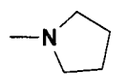
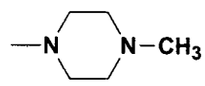
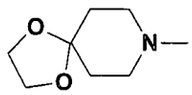
R_5, R_6, y R_7 son cada uno hidrógeno y R_8 es hidrógeno, hidróxilo, CF_3, alcoxi, halógeno, dialquiloaminoalcoxi, alquilooxialquilooxialquilooxi, alquiloamino, heterociclo, piridilo, ariloalquiloamino, alcoxiariloalquiloamino, dialquiloamino,  , alcoxiarilo, arilo, trifluorometoxilarilo, carboxiarilo, haloalquilo, dialquiloaminoarilo, naftilo, alquilofenilo, CF_3arilo, alquilocarboniloaminoarilo, dialquiloarilo, hidroxiarilo, alcoxicarboniloarilo, alquilocarboniloaminoarilo, alquilosulfoniloaminoarilo, ariloarilo, alquilosulfoniloarilo, aminoarilo, ariloalquilooxiarilocianoarilo, o alquiloarilo.

Más preferentemente R_5, R_6, y R_7 son cada uno hidrógeno; y

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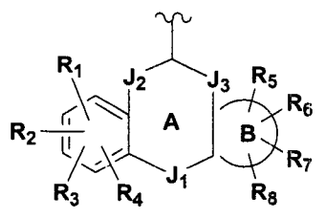
R_8 se selecciona de hidrógeno, Cl, $(CH_3)_2N(CH_2)_2O-$, $CH_3OCH_2CH_2OCH_2O-$, bencilamino, metoxibencilamino, $N(CH_3)_2CH_2CH_2O-$, OH, CF_3, CH_3O-, dimetilamino, metoxifenilo, fenilo, $CF_3OC_6H_4-$, $CO_2H-C_6H_4$, $CN-C_6H_4$, $s-C_4H_9-C_6H_4-C_2H_5O-C_6H_4$, $s-C_4H_9-C_6H_4$, $-C_3H_7-C_6H_4-$, $n-C_4H_9-O-C_6H_4-$, $C_2H_5-C_6H_4-$, $t-C_4H_9-C_6H_4-$, $CH_3COC_6H_4-$, $C_6H_5CH_2OC_6H_4-$, $C_6H_5-C_6H_4-$, $C_6H_5-O-C_6H_4-$, $CH_3SC_6H_4-$, $NH_2C_6H_4-$, $CH_3-SO_2-NHC_6H_4-$, $F-C_6H_4$, C_6H_5-, ClC_6H_4, -diCH3amino, naftilo, $CH_3C_6H_4$, $CF_3C_6H_4-$,

$CH_3CONHC_6H_4-$, $CH_3OC_6H_4$,  , di-$CH_3C_6H_3-$, HOC_6H_4-, $CH_3OCOC_6H_4-$

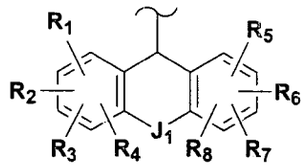
 ,  ,  ,  y  .

Se prefiere que en los compuestos de la fórmula I de la invención donde Z es heteroarilo o heterociclo y el heteroarilo y/o heterociclo está fusionado al grupo arilo, el punto de enlace del grupo fusionado al átomo N del  estará con la porción heteroarilo o heterociclo y no con la porción arilo.

En las modalidades preferidas, la porción



(también referida como la porción tricíclica) es



Las modalidades más preferidas son aquellas donde J_1 es O, S, SO, SO_2, un enlace, CH_2, o CH_2CH_2;

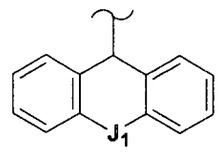
R_1 se selecciona de hidrógeno, CF_3, alcoxi, halógeno, hidróxilo y dialquiloaminoalcoxi; y

R_5 se selecciona de hidrógeno, CF_3, alcoxi, halógeno, amino, dialquiloamino, heterociclo, arilo, carboxiarilo, alcoxiarilo, alquiloarilo, heterociclocarboniloarilo, alcoxi(halo)arilo, carboxi(halo)arilo, dialquiloaminocarboniloarilo, alquiloamino, hidróxilo, dialquiloaminoalcoxi, ariloalquiloamino, alcoxiariloalquiloamino, alquiloheterociclo, ariloalquilo, heterocicloalcoxi, ariloheterociclo, ariloalquilo(alquilo)amino, haloarilo, dialquiloaminoarilo, haloarilo, alcoxialcoxialcoxil, alquilocarboniloamino, heteroarilo, dialquiloarilo, hidroxiarilo, alcoxicarbonilarilo, alquilocarboniloaminoarilo, alquilosulfoniloaminoarilo, arilooxiarilo, alquiltioarilo, aminoarilo, alquilocarboniloarilo, ariloalcoxiarilo, y cianoarilo.

También preferidos son los compuestos de la fórmula I

(1) donde la porción tricíclica es exclusiva de

413



donde J_1 es diferente a un enlace, $-CH_2CH_2-$, o $-CH=CH-$; y

(2) donde la porción tricíclica del anillo B incluye uno, dos o tres hetero átomos seleccionados de N, O, y S, preferiblemente N.

Los compuestos preferidos de la invención dentro del alcance de la fórmula I son aquellos, incluyendo todos los enantiómeros y diastereómeros, o ésteres de profármacos o sales o hidratos farmacéuticamente aceptables del mismo, en cual

Z es un grupo heteroarilo o heterociclo de 5 hasta 6 elementos, cada grupo substituido con uno, dos o tres grupos que son los mismos o diferentes y son independientemente seleccionados de hidrógeno, halógeno, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, nitro, ciano, OR^c, NR^aR^b, $C(=O)R^a$, CO_2R^a, $C(=O)NR^aR^b$, $-O-C(=O)R^a$, $NR^aC(=O)R^b$, $NR^aC(=O)OR^b$, $NR^aC(=S)OR^b$, $S(O)_pR^c$, $NR^aSO_2R^c$, $SO_2NR^aR^b$, cicloalquilo, cicloalquenilo, heterociclo, arilo, y heteroarilo;

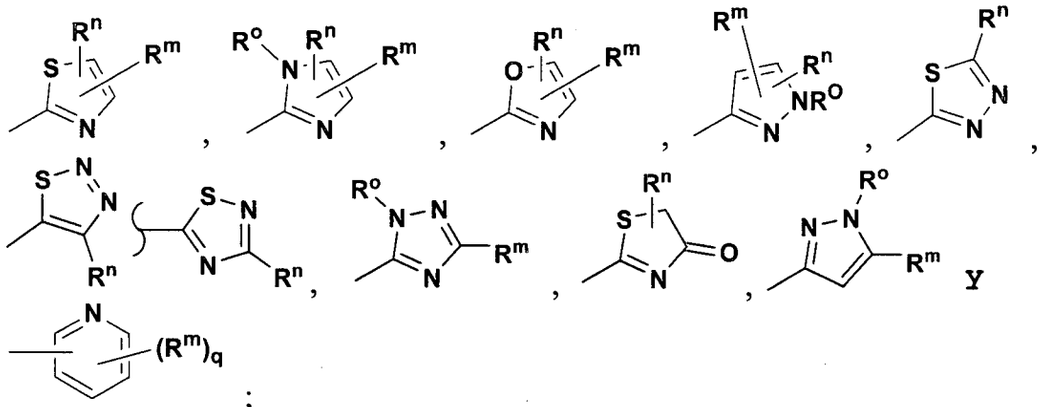
R^a y R^b son los mismos o diferentes y cada que se presentan son independientemente seleccionados de (i) hidrógeno, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, cicloalquilo,

cicloalquenilo, arilo, heteroarilo, y heterociclo; o (ii) en donde sea posible junto con los átomos a los cuales van a ser enlazados, R^a se toma junto con R^b para formar un anillo heteroarilo o anillo heterociclo; y

R^c cada que se presenta es independientemente seleccionado de alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, cicloalquilo, cicloalquenilo, arilo, heteroarilo, y heterociclo.

Más preferentemente, Z se selecciona de

Z se selecciona de:



;

R^m y R^n son los mismos o diferentes y cada que se presentan son independientemente seleccionados de cualesquiera de los substituyentes de heteroarilo para Z precisado anteriormente y son preferiblemente seleccionados de hidrógeno, halógeno, alcoxi, $-COR_1^a$, $-CO_2R_1^a$, $-C(O)N(R_1^a)(R_1^b)$, C_{1-6}alquilo, CF_3, alquilo substituido, arilo-NHC(O)-arilo, arilo, ariloalquilo, CH_2OH, $-SR_1^a$, $S(O)_{1-2}R_1^c$, $N(R_1^a)(R_1^b)$, CH_2F,

ciano, cicloalquilo C_{3-6}, y un heteroarilo de 5 hasta 7 elementos con un heteroátomo seleccionado de N, O o S;

R^o es hidrógeno o alquilo C_{1-6};

R_1^a y R_1^b son los mismos o diferentes y cada que se presentan son independientemente seleccionados de hidrógeno, alquilo, alquilo substituido, C(=O)alquilo, CO_2(alquilo), SO_2alquilo, alquenilo, alquenilo substituido, alcoxi, amino, amino substituido, arilo, heteroarilo, heterociclo, y cicloalquilo, siempre que R_1^a y R_1^b ambos no sean alcoxi, amino, o amino substituido;

o R_1^a y R_1^b, en donde sea posible pueden ser tomados junto con el nitrógeno al cual se enlazan para formar un anillo heteroarilo o cicloheteroalquilo de 5-, 6- o 7-elementos el cual contiene 1, 2 o 3 hetero átomos que pueden ser N, O, o S;

R_1^c se selecciona de alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, alcoxi, amino, amino substituido, heteroarilo, heterociclo, cicloalquilo, y arilo; y

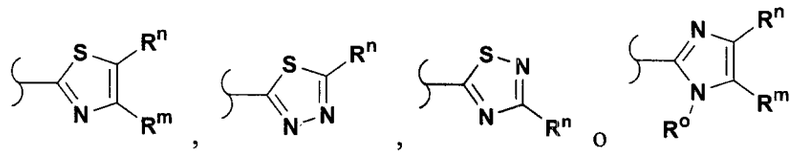
q es 1 ó 2.

R_1^c se selecciona de hidrógeno, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, alcoxi, amino, amino substituido, heteroarilo, heterociclo, cicloalquilo, y arilo;

R^o es hidrógeno o alquilo; y

q es 1 ó 2.

Aún, más preferentemente, Z se selecciona de



R^m y R^n son los mismos o diferentes y cada que se presentan son independientemente seleccionados de hidrógeno, $-C(O)N(R_1^a)(R_1^b)$, alquilo C_{1-6}, CF_3, CH_2OH, $-SR_1^a$, $N(R_1^a)(R_1^b)$, CH_2F, ciano, y cicloalquilo C_{3-6};

R^o es hidrógeno o alquilo C_{1-6}; y

R_1^a y R_1^b son los mismos o diferentes y cada que se presentan son independientemente seleccionados de hidrógeno, alquilo C_{1-6}, y cicloalquilo C_{3-6}.

En otras modalidades preferidas R^m se selecciona de hidrógeno, alquilo C_1-C_4, fenilo, CO_2alquilo, naftilo, quinolinil, y $-C(R^{18})(R^{19})$-T en donde el naftilo o grupo quinolinil es substituido por uno o más substituyentes seleccionados del grupo que consiste de hidrógeno, amino, hidroxi, alquilo C_{1-4}, alcoxi C_{1-4}, perfluoro substituido, alquilo C_{1-4} (por ejemplo CF_3), ciano, nitro, $-C(O)NHR^{22}$ (donde R^{22} es fenilo el cual puede opcionalmente ser substituido), y halógeno;

R^n se selecciona de hidrógeno, bromo, cloro, y CH_3;

T se selecciona de un anillo de cicloalquilo,

cicloalquenilo, heterociclo, arilo, y heteroarilo donde cada anillo está substituido por 0-4 R^{20} y 0-1 R^{21};

R^{18} y R^{19} son los mismos o diferentes y son independientemente cada que se presenta seleccionados de hidrógeno, halógeno, hidroxi, alquilo, alquenilo, alquinilo, alcoxi, ciano, nitro, NR^aR^b, and CHO; o

R^{18} y R^{19} son combinados para formar =O o un doble enlace, en donde un carbono ligado al doble enlace está substituido por hidrógeno, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, alcoxi, amino, amino substituido, heteroarilo, heterociclo, cicloalquilo, o arilo; y

R^{20} y R^{21} son los mismos o diferentes y cada que se presentan son independientemente seleccionados de hidrógeno, halógeno, hidroxi, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, alcoxi, arilooxi, arilo, cicloalquilo, heteroarilo, heterociclo, ciano, heteroariloaminocarbonil, heterociclocarbonil, cianoalquilo, alquiloaminoalquilo, hidroxialquilo, hidroxiarilo, ariloxialquilo, alcoxialquilo, nitro, oxo, $NR_1{}^aR_1{}^b$, CHO, CO_2alquilo, $CONR_1{}^aR_1{}^b$, $CH_2NR_1{}^aR_1{}^b$, CO_2H, CH_2OH, $CH_2NHC(O)R_1{}^c$, $NHCOR_1{}^c$, $NHCONR_1{}^aR_1{}^b$, $NHSO_pR_1{}^c$,

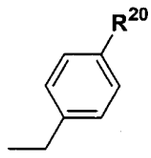
418

$-SO_2NR_1{}^aR_1{}^b$, $NR^aSO_2NR_1{}^aR_1{}^b$, y $NR^aSO_pR_1{}^c$; o

R^7 y R^8 localizados en átomos adyacentes pueden ser tomados juntos para formar un anillo heterociclo, heteroarilo, arilo o cicloalquilo opcionalmente substituido.

En una modalidad más preferida,

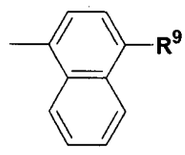
R^n es H;

R^m es 

;

R^{18} y R^{19} son los mismos o diferentes y cada que se presentan son independientemente seleccionados de hidrógeno, halógeno, y hidroxi; o R^{18} y R^{19} son combinados para formar =O; y

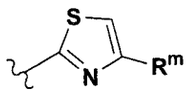
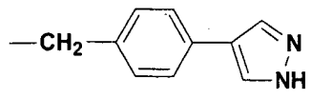
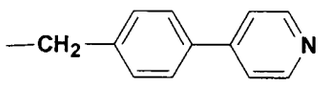
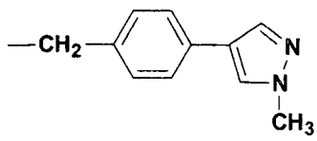
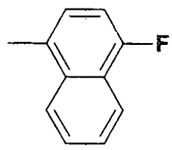
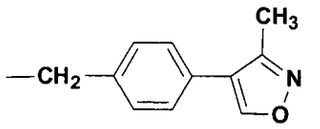
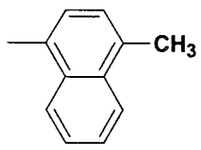
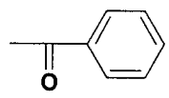
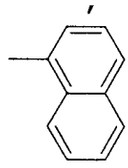
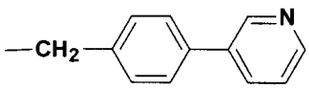
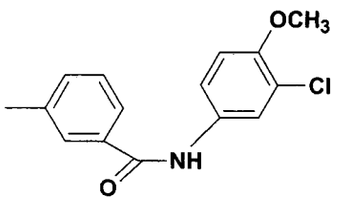
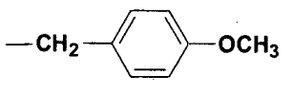
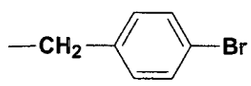
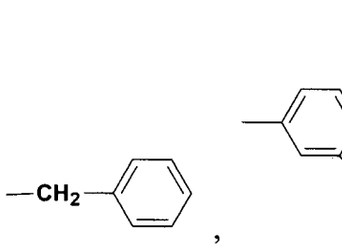
R^{20} se selecciona de alcoxi C_{1-4}, halógeno, pirimidina, isoxazol, pirazol, y piridina, donde los grupos de alcoxi C_{1-4}, pirimidina, isoxazol, pirazol o piridina están substituidos por hidrógeno, morfolinilo, alcoxi C_{1-4}, y alquilo C_{1-4};

o R^m se selecciona de 

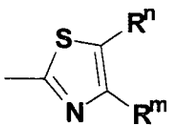
, y CO_2alquilo C_{1-4}; y

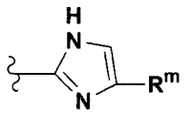
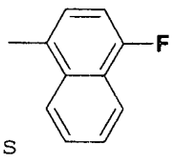
R^9 se selecciona de metilo, CF_3, fluoro, cloro, y bromo.

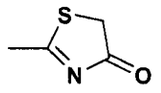
En modalidades aún más preferidas,

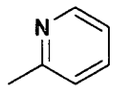
Z es  , donde R^m es  ,  ,  ,  ,  ,  ,  ,  , ,  , H, CH_3, $-CO_2C_2H_5$, $-CO_2CH_3$,  ,  ,  ,  ;

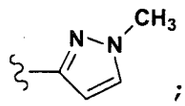
donde R^n es $S(CH_3)$, $S(O)(CH_3)$, $S(O)_2CH_3$, y CH_3;

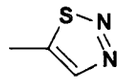
Z es  , donde R^n es CH_3, R^m es CH_3;

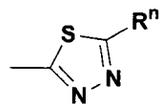
Z es  , donde R^m es  o H;

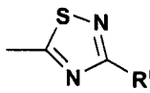
Z es  ;

Z es  ;

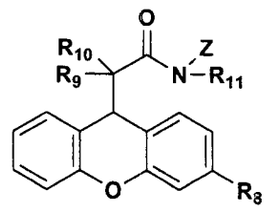
Z es  ;

Z es  ;

Z es  donde R^n es CH_3, H, CF_3, C(O)OEt, $C(O)NH_2$, C(O)NH(ciclopropilo), $C(O)NHCH_3$, C(O)NHEt, CH_2OH, S(metilo), $N(metilo)_2$, CH_2F, ciano, etilo, o ciclopropilo; o

Z es  , donde R^n es CH_3 o H.

También son preferidos los compuestos que tienen la estructura



o un enantiómero, diastereómero, tautómero o una sal farmacéuticamente aceptable del mismo, en donde:

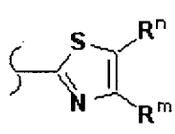
R_8 es hidroxi, ciano, $-C(=O)NR_{14}R_{15}$, $-CO_2R_{14}$, $-C(NH_2)=NOH$, $-NR_{14}C(=O)OR_{15}$, $-OC(O)NR_{14}R_{15}$, $-NHC(O)NR_{14}R_{15}$, o $-NHC(O)R_{15}$;

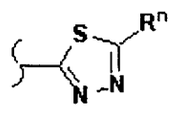
R_9 y R_{10} son los mismos o diferentes y cada que se presentan

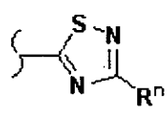
son independientemente seleccionados de (i) hidrógeno, halógeno, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, nitro, ciano, $-OR_{14}$, $-NR_{14}R_{15}$, $-C(=O)R_{14}$, $-CO_2R_{14}$, $-C(=O)NR_{14}R_{15}$, $-O-C(=O)R_{14}$, $-NR_{14}C(=O)R_{15}$, $-NR_{14}C(=O)OR_{15}$, $-NR_{14}C(=S)OR_{15}$, $-S(O)_pR_{17}$, $-NR_{14}SO_2R_{17}$, $-SO_2NR_{14}R_{15}$, cicloalquilo, cicloalquenilo, heterociclo, arilo, y heteroarilo; o (ii) junto con el átomo al cual se enlaza, R_9 y R_{10} se toman juntos para formar un grupo carbonilo, alquenilo, alquenilo substituido, cicloalquilo, cicloalquenilo, o heterociclo;

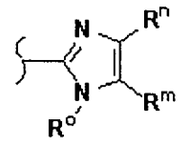
R_{11} se selecciona de hidrógeno, alquilo, alquilo substituido, C(=O)alquilo, CO_2(alquilo), SO_2alquilo, alcoxi, amino, amino substituido, arilo, heteroarilo, heterociclo, y cicloalquilo; y

Z es un anillo heteroarilo el cual es ligado por medio de un átomo de carbono al átomo N donde Z es preferiblemente



,


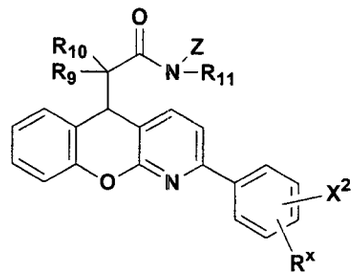
,


o


y

R^n, R^m, y R^o son como se define arriba.

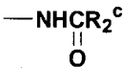
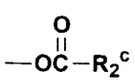
Además, son preferidos los compuestos de la estructura



o un enantiómero, diastereómero, o tautómero del mismo, o

un éster de profármaco del mismo, o una sal farmacéuticamente aceptable del mismo, en donde:

X^2 es halógeno, alcoxi, H, o alquilo;

R^x es H, $C(O)NR_2{}^aR_2{}^b$, $OR_2{}^c$, $R_2{}^a$, COOH, CF_3,  ,  , $-NHSO_2R_2{}^c$, arilo, ariloxi, alquiltio, amino, acilo o ciano;

$R_2{}^a$ y $R_2{}^b$ son los mismos o diferentes y cada que se presentan son independientemente seleccionados de hidrógeno, alquilo, alquilo substituido, C(=O)alquilo, CO_2(alquilo), SO_2alquilo, hidrógeno, alquenilo, alquenilo substituido, alcoxi, amino, amino substituido, arilo, heteroarilo, heterociclo, y cicloalquilo;

o $R_2{}^a$ y $R_2{}^b$, en donde sea posible pueden ser tomados junto con el nitrógeno al cual se enlazan para formar un anillo cicloheteroalquilo o heteroarilo de 5-, 6- o 7 elementos el cual contiene 1, 2 ó 3 hetero átomos los cuales pueden ser N, O, o S;

$R_2{}^c$ se selecciona de hidrógeno, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, alcoxi, amino, amino substituido, heteroarilo, heterociclo, cicloalquilo, y arilo;

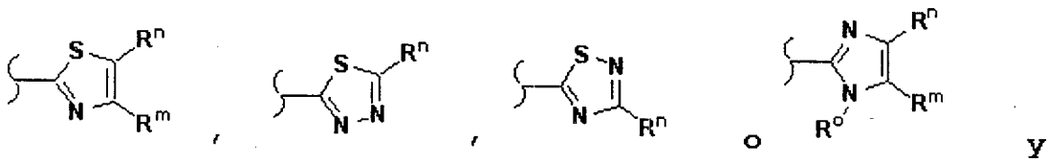
R_9 y R_{10} son los mismos o diferentes y cada que se

423

presentan son independientemente seleccionados de (i) hidrógeno, halógeno, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, nitro, ciano, OR_{14}, $NR_{14}R_{15}$, $C(=O)R_{14}$, CO_2R_{14}, $C(=O)NR_{14}R_{15}$, $-O-C(=O)R_{14}$, $NR_{14}C(=O)R_{15}$, $NR_{14}C(=O)OR_{15}$, $NR_{14}C(=S)OR_{15}$, $S(O)_pR_{17}$, $NR_{14}SO_2R_{17}$, $SO_2NR_{14}R_{15}$, cicloalquilo, cicloalquenilo, heterociclo, arilo, y heteroarilo; o (ii) junto con el átomo al cual se enlazan, R_9 y R_{10} se toman juntos para formar un grupo carbonilo, alquenilo, alquenilo substituido, cicloalquilo, cicloalquenilo, o heterociclo; y

R_{11} se selecciona de hidrógeno, alquilo, alquilo substituido, C(=O)alquilo, CO_2(alquilo), SO_2alquilo, alcoxi, amino, amino substituido, arilo, heteroarilo, heterociclo, y cicloalquilo.

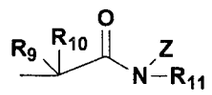
En una modalidad más preferida, Z es un anillo heteroarilo el cual es ligado por medio de un átomo de carbono al átomo de N, donde Z es preferiblemente

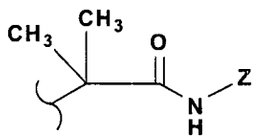


R^n, R^m, y R^o son como se definieron anteriormente.

También son preferidos

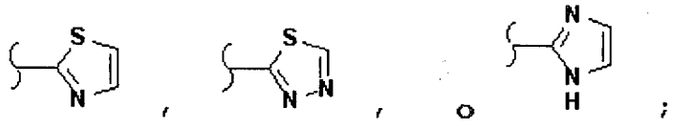
(1) compuestos de la fórmula I donde

es 

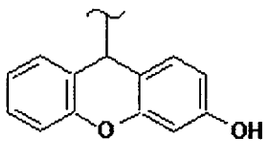


donde

Z es

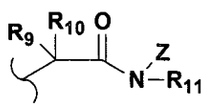


y la porción tricíclica es

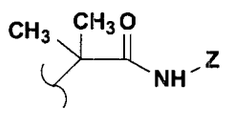


; y

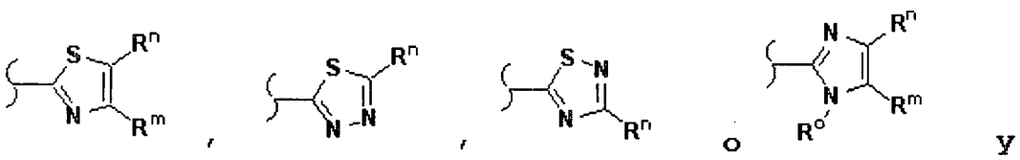
(2) compuestos de la fórmula I en donde



es

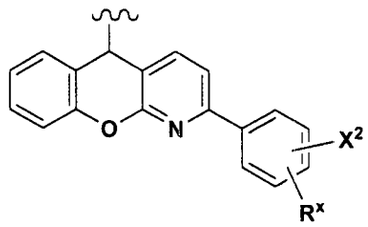


Z es

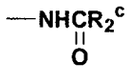


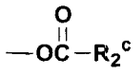
R^n, R^m, y R^o son como se definen arriba;

la porción tricíclica es



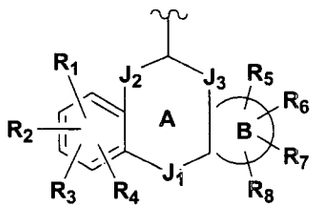
X^2 es halógeno, alcoxi, H, o alquilo; y

R^x es H, $C(O)NR_2{}^aR_2{}^b$, $OR_2{}^c$, $R_2{}^a$, COOH, CF_3,  ,

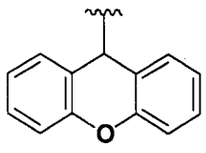
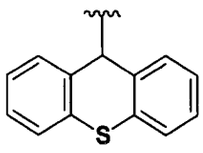
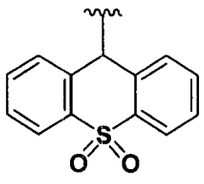
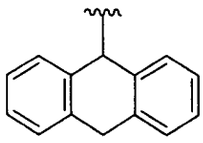
 , $-NHSO_2R_2{}^c$, arilo, ariloxi, alquiltio, amino, acilo o ciano;

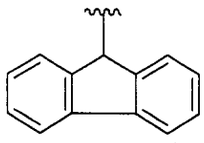
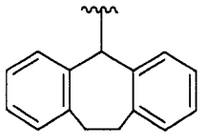
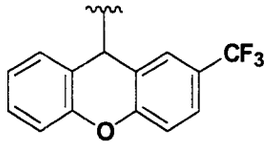
(donde $R_2{}^a$, $R_2{}^b$ y $R_2{}^c$ son como se definen posteriormente en la presente).

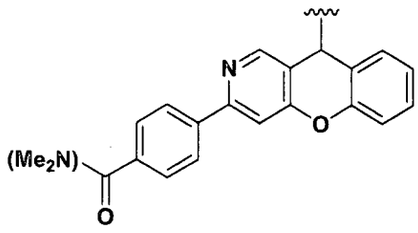
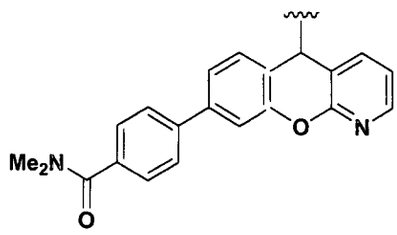
En otras modalidades preferidas,

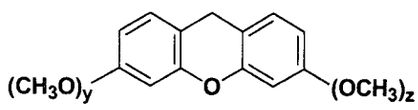


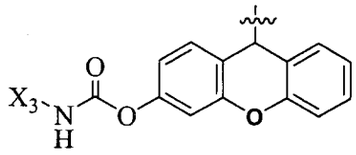
es

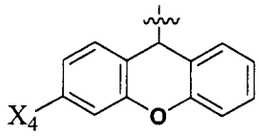
 ;  ;  ;  ;

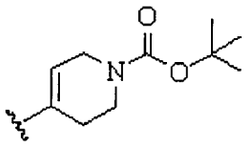
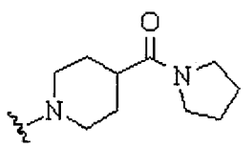
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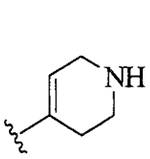
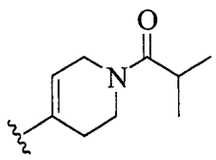
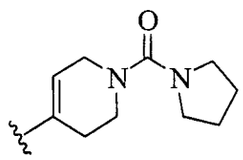
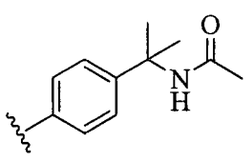


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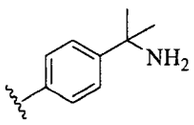
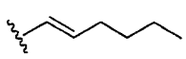
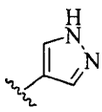
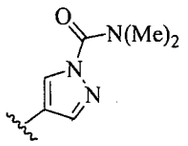

, donde Z es 0 ó 1 e y es 0 ó 1;

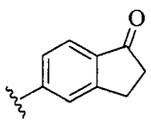
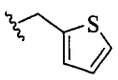
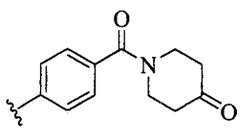

, donde X_3 es bencilo, $(CH_2)_3CH_3$, etilo, CH_2(2-furilo), ciclohexilo, $(CH_2)_7CH_3$, $(CH_2)_2$(fenilo), CH_2(2-tienilo), CH_2(4-fluorofenilo), terc-butilo, $CH(CH_3)$etilo, $(CH_2)_2$(4-metoxifenilo), 4-metoxifenilo, o CH_2(ciclohexilo);

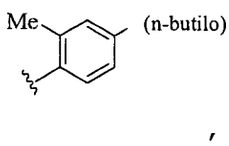

, donde X_4 es NHC(O)O(ciclohexilo), NHC(O)O(metilo), -C≡C-$(CH_2)_2CH_3$, C(O)NHCH$_2$(fenilo), C(O)CH_3, -NHC(O)NH(CH_2)(O)N$(Me)_2$, -NHC(O)NH(CH_2)(N-pirrolidinilo),

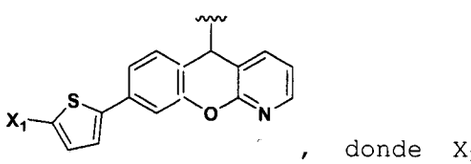

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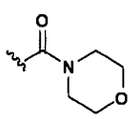





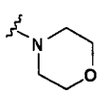





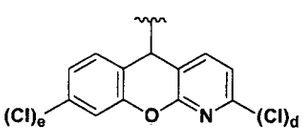




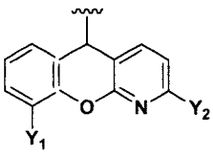


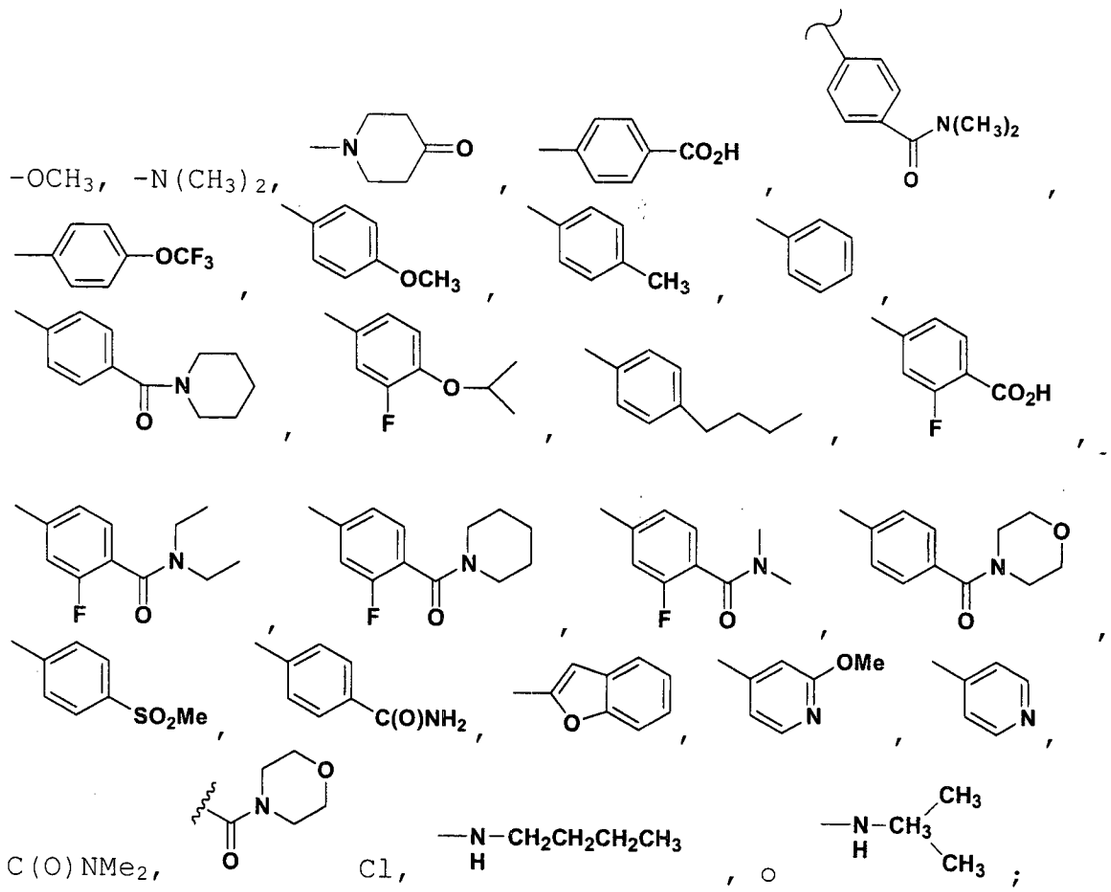


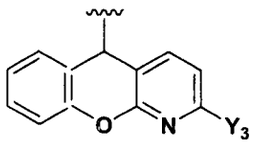


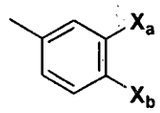




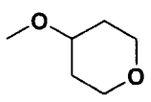


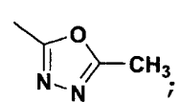




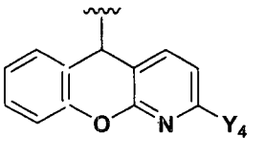
, donde Y_3 es 

, X_a es hidrógeno o fluoro, y X_b se selecciona de ciclohexilo, -O(isopropilo), hidróxilo, hidrógeno, -S(etilo), SO_2(etilo), SO_2(isopropilo), $C(O)CH_3$, -O(n-propilo), CH_2CO_2H, $SO_2N(CH_3)_2$, SO_2(N-morfolinilo), $C(OH)Me_2$, $SO_2NHCH_2CH_3$, SO_2NH(ciclopropilo), SO_2NH(isopropilo), $CH2CO_2CH_3$, $CH(OH)CH_3$, CH(OH)(Isopropilo), $S(O)CH_3$,

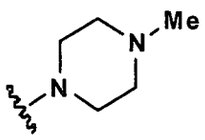


, O(ciclohexilo), O(ciclopentilo), y 

;

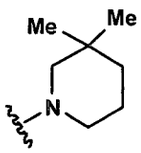


, donde Y_4 es NR_aR_b, NEt_2, piperidina, NMe_2,

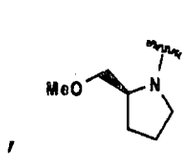
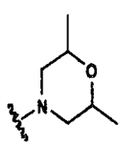
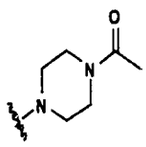
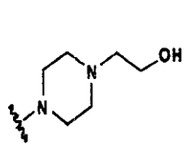
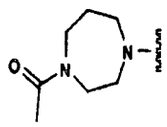
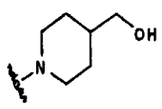
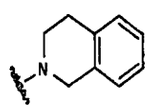
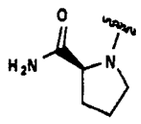
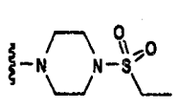
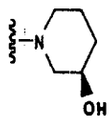
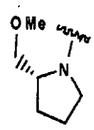
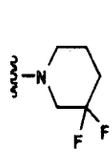
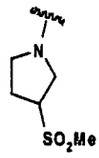
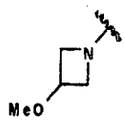
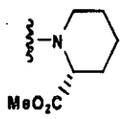
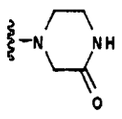
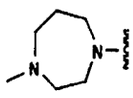
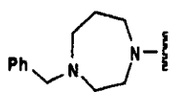
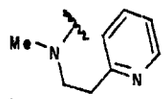
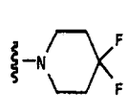
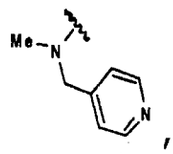
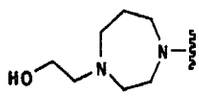
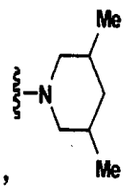
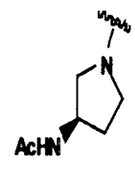
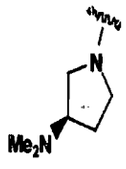
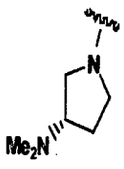


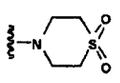
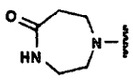
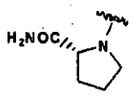
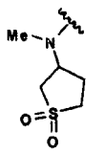
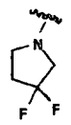
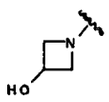
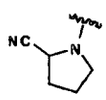
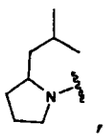
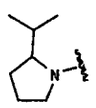
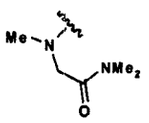
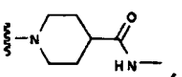
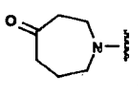
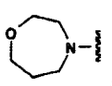
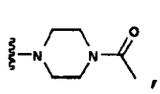
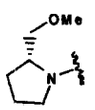
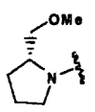
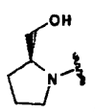
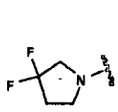
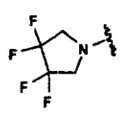
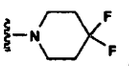
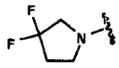
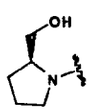
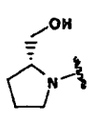
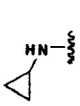
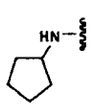
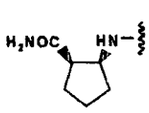
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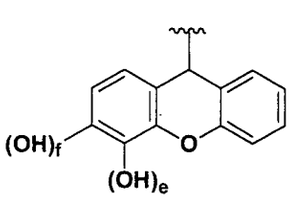
NMeEt, pirrolidina, NHMe, NMe(n-Pr), NMe(Bn), morfolina, NMe(i-Pr), NEt_2, NMe_2, piperidina, NEt_2, NEt_2, piperidina, piperidina, piperidina, $NMe(CH_2)_2CN$, 4-Me-,

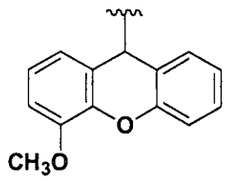
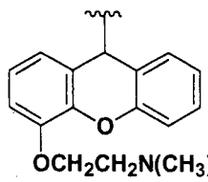
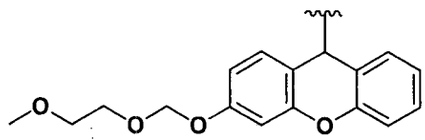


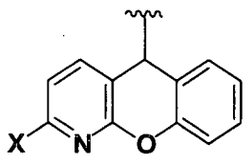
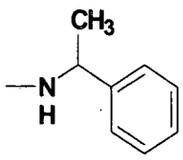
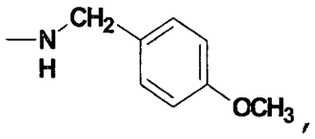
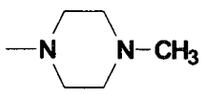
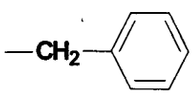
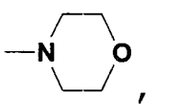
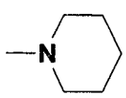
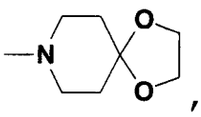
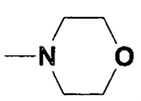
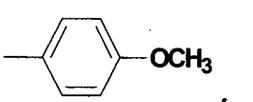
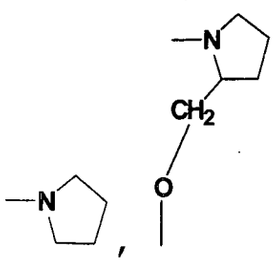
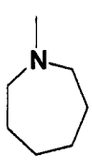
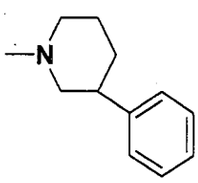
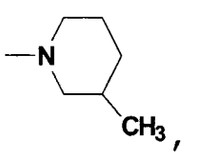
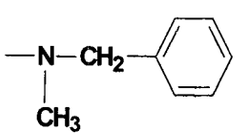
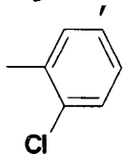
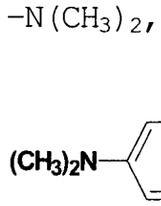
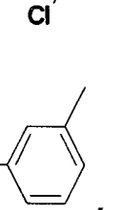
piperidina, 4-OH-piperidina, $NMe(CH_2)_2CH(CH_3)_2$,

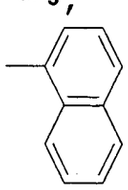
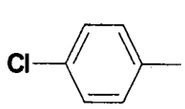




, N(Me)$(CH_2)_2$Ph,

,4-Bn-piperidina,


, 4-Ph-piperidina,




NMe$(CH_2)_2SO_2Me$,



, 4-(CF_3)-piperidina,

, NMe(*n*-Bu), $NMeCH_2CO_2Me$, NMe$(CH_2)_2$OH, NMe$(CH_2)_2$OMe,






,
NMe$(CH_2)_2$O(*t*-Bu),

,




$N((CH_2)_2OH)_2$,
, 4-OMe,

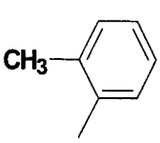
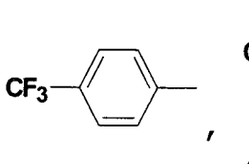
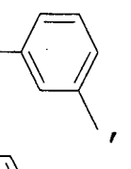
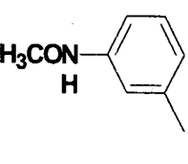
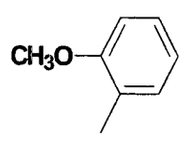
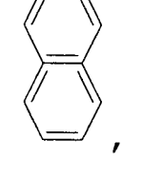
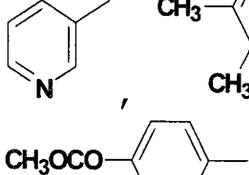
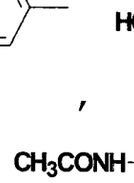
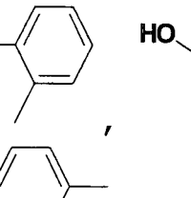
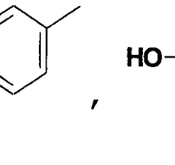
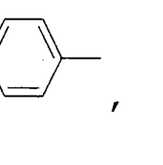
piperidina,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , NEt(CH$_2$)$_2$OH,  ,  ,  ,  ,  , NMe(CH$_2$)$_2$CN,  , NMe(*i*-Pr),  ,  , NEtMe,  , NMe(CH$_2$)CO$_2$H,  ,  , pirrolidina,  , NMe(*n*-Pr),  , NMeEt, NMe(*n*-Pr), NMe$_2$, NHMe, NHBn,  ,  ,  , NHiPr, NH(CH$_2$)$_2$Ph, NH(CH$_2$)$_2$Ome, NH(CH$_2$)$_2$C(CH$_3$)$_3$, NH(CH$_2$)$_2$OH, NH(*n*-Pr), NH(CH$_2$)$_3$OH,  , o NHMe;

 , donde e es 0 ó 1 y f es 0 ó 1, con la condición de que solo uno de e y f pueda ser 1;

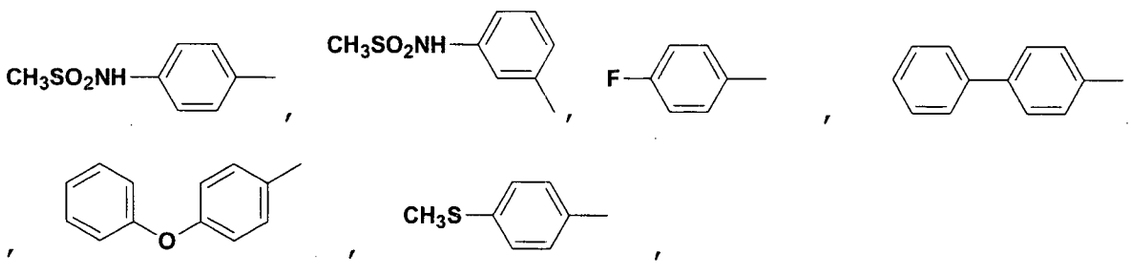

donde X es
















, NH_2,


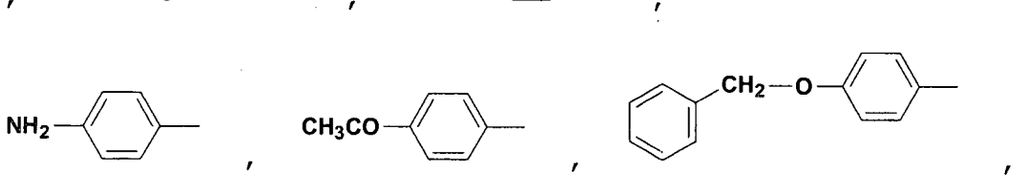



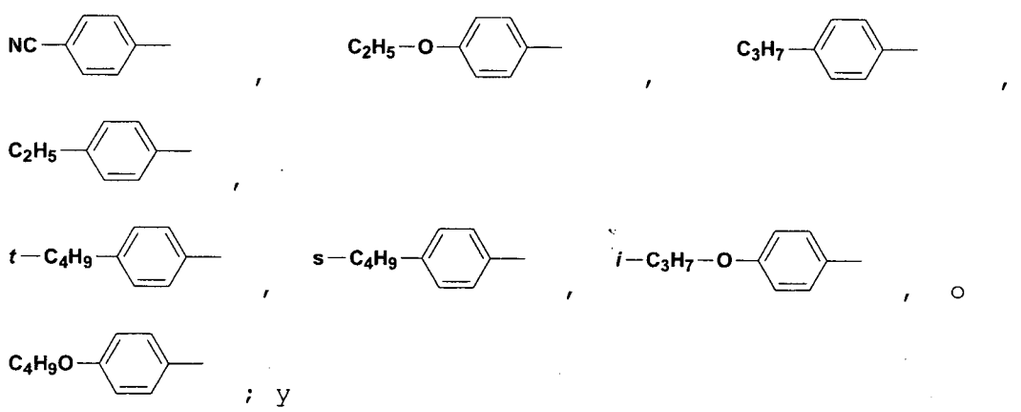














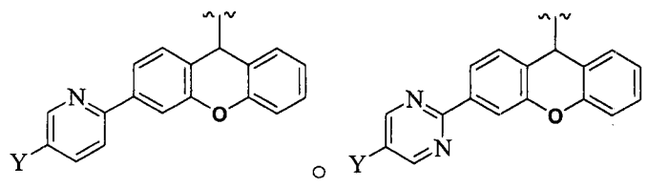






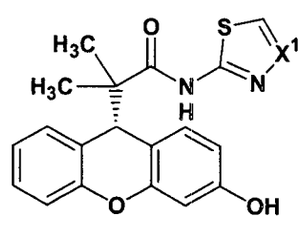


; y



, donde Y es alquilo C_{1-6}, $C(O)N(C_{1-6}alquilo)_2$, COOH, y O alquilo C_{1-6}.

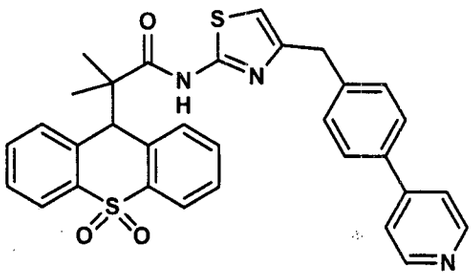
Son más preferidos compuestos de la estructura



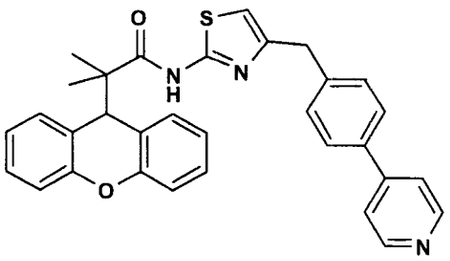
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X^1 = CH, o

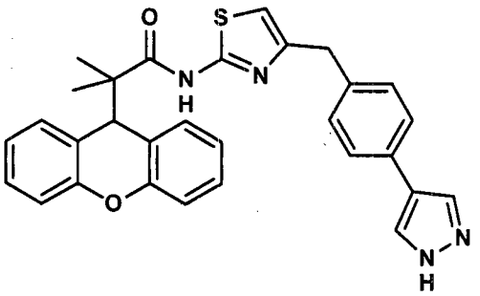
X^1 = N,



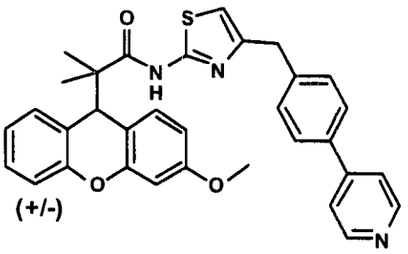
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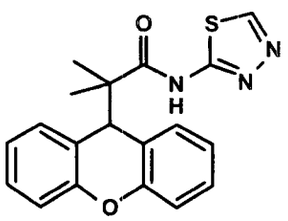
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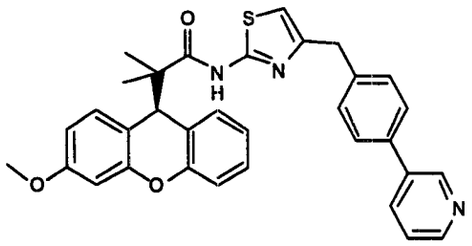
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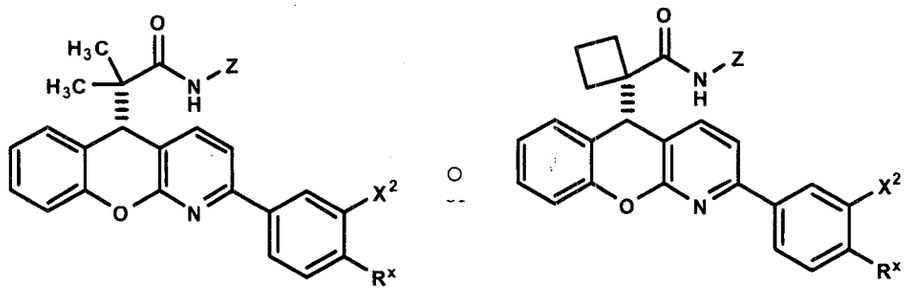
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y compuestos de la estructura



en donde:

X^2 es H, halógeno, o alquilo;

R^x es H, $C(O)NR_2^aR_2^b$, OR_2^a, R_2^a, COOH, CF_3, $-NHCR_2^c$ (=O), $-OC(=O)-R_2^c$, $-NHSO_2R_2^c$, arilo, ariloxi, alquiltio, amino, acilo o ciano;

R_2^a se selecciona de hidrógeno, alquilo, alquilo substituido, C alquilo(=O), CO_2(alquilo), SO_2alquilo, hidrógeno, alquenilo, alquenilo substituido, alcoxi, amino, amino substituido, arilo, heteroarilo, heterociclo, y cicloalquilo;

R_2^b se selecciona de alquilo, alquilo substituido, C alquilo(=O), CO_2(alquilo), SO_2alquilo, hidrógeno, alquenilo, alquenilo substituido, alcoxi, amino, amino substituido,

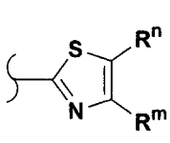
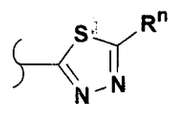
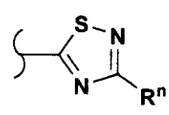
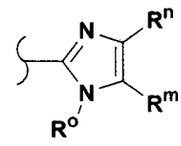
arilo, heteroarilo, heterociclo, y cicloalquilo;

o R_2^a y R_2^b son tomados juntos con el nitrógeno al cual se enlazan para formar un anillo cicloheteroalquilo o heteroarilo de 5-, 6- o 7 elementos el cual contiene 1, 2 ó 3 hetero átomos que pueden ser N, O, o S; y

R_2^c se selecciona de alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, alcoxi, amino, amino substituido, heteroarilo, heterociclo, cicloalquilo, y arilo.

En donde R^a, R^b y R^c son como se definen anteriormente en la presente, preferiblemente $C(O)NR^aR^b$, alcoxi o alquilo.

Todavía más preferentemente, Z se selecciona de




y

;

R^m y R^n son los mismos o diferentes y cada que se presentan son independientemente seleccionados de hidrógeno, $-C(O)N(R_1^a)(R_1^b)$, alquilo C_{1-6}, CF_3, CH_2OH, $-SR_1^a$, $N(R_1^a)(R_1^b)$, CH_2F, ciano, y cicloalquilo C_{3-6};

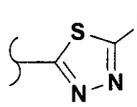
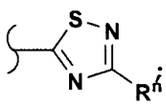
R^o es hidrógeno o alquilo C_{1-6}; y

R_1^a y R_1^b son los mismos o diferentes y cada que se presentan son independientemente seleccionados de hidrógeno, C_{1-6}alquilo, y cicloalquilo C_{3-6}.

Aún más preferido es el S-enantiómero sobre el R-enantiómero.

Aún más preferentemente R^x está en la posición 4 y R^x es amida terciaria (esto es, $R^x = C(O)NR^aR^b$), alcoxi, o alquilo.

Más preferentemente es $X^2 = F$.

Se prefiere más es donde Z es  o  y R^n es CH_3, H, CF_3, C(O)OEt, $C(O)NH_2$, C(O)NH(ciclopropilo), $C(O)NHCH_3$, C(O)NHEt, CH_2OH, S(metilo), $N(metilo)_2$, CH_2F, ciano, etilo, o ciclopropilo.

En otra modalidad de la presente invención, se proporcionan composiciones farmacéuticas para tratar trastornos endocrinos, trastornos reumáticos, enfermedades de colágeno, enfermedad dermatológica, enfermedad alérgica, enfermedad oftálmica, enfermedad respiratoria, enfermedad hematológica, enfermedad gastrointestinal, enfermedad inflamatoria, enfermedad autoinmunitaria, diabetes, obesidad, y enfermedad neoplásica, así como otros usos como se describe en la presente, que incluyen una cantidad terapéuticamente efectiva (dependiendo del uso) de un compuesto de la fórmula (I) de la invención y un portador farmacéuticamente aceptable.

Todavía en otra modalidad, la presente invención proporciona un método para tratar trastornos endocrinos, trastornos reumáticos, enfermedades de colágeno, enfermedad dermatológica, enfermedad alérgica, enfermedad oftálmica, enfermedad respiratoria, enfermedad hematológica, enfermedad gastrointestinal, enfermedad inflamatoria, enfermedad

inmunitaria, enfermedad metabólica (diabetes y/u obesidad), y enfermedad neoplásica. Una enfermedad asociada con el producto de expresión de un gen cuya transcripción se estimula o reprime por receptores glucocorticoides, o una enfermedad asociada con AP-1- y/o transcripción inducida por NF-κB, o una enfermedad asociada con AP-1 y/o expresión de gen dependiente de NF-κB, en donde la enfermedad está asociada con la expresión de un gen bajo el control regulador de AP-1 y/o NF-κB (particularmente AP-1), incluyendo enfermedades y trastornos inmunitarios e inflamatorios como se describe de aquí en adelante, que incluye la etapa de administrar una cantidad terapéuticamente efectiva de un compuesto de la fórmula (I) de la invención a un paciente.

Otra modalidad de la presente invención involucra un método para tratar una enfermedad o trastorno asociado con el producto de expresión de un gen cuya transcripción se estimula o reprime por receptores glucocorticoides, o un método para tratar una enfermedad o trastorno asociado con AP-1- y/o transcripción inducida por NF-κB- (particularmente AP-1-), o un método para tratar una enfermedad o trastorno asociado con expresión del gen dependiente de AP-1 y/o NF-κB (particularmente AP-1), en donde la enfermedad está asociada con la expresión de un gen bajo el control regulador de AP-1 y/o NF-κB (particularmente AP-1), tales como trastornos inflamatorios e inmunitarios, cáncer y trastornos de tumor,

tales como tumores sólidos, linfomas y leucemia, e infecciones por hongos tales como micosis fungoides.

El término "enfermedad asociada con la transactivación de GR", como se usa en la presente, se refiere a una enfermedad asociada con el producto de transcripción de un gen cuya transcripción se transactiva por una GR. Tales enfermedades incluyen, pero no se limitan a: osteoporosis, diabetes, glaucoma, pérdida muscular, inflamación facial, cambios de personalidad, hipertensión, obesidad, depresión, y SIDA, la condición de una cicatrización de heridas, insuficiencia adrenocortical primaria o secundaria, y enfermedad de Addison.

El término "tratar", "tratado", o "tratamiento," en todas las formas gramaticales, como se usan en la presente se refieren a la prevención, reducción, o alivio, alivio parcial o completo, o cura de una enfermedad, trastorno, o condición, en donde la prevención indica el tratamiento de una persona en riesgo desarrollar tal enfermedad, trastorno o condición.

Los términos "receptor glucocorticoide" y "GR", como se usa en la presente, se refiere a ya sea un miembro de la familia del receptor de la hormona nuclear ("NHR") de factores de transcripción que se enlazan a glucocorticoides y ya sea estimulan o reprimen la transcripción, o a GR-beta.

Estos términos, como se usan en la presente, se refieren al receptor glucocorticoide de cualquier fuente, incluyendo pero sin estar limitado a: receptor glucocorticoide humano

como se describe en Weinberger, et al., Science, 228:740-742 (1985), y en Weinberger, et al., Nature, 318:670-672 (1986); receptor glucocorticoide de la rata como se describe en Miesfeld, R., Nature, 312:779-781 (1985); receptor glucocorticoide del ratón como se describe en Danielson, M. et al., EMBO J., 5:2513; receptor glucocorticoide de la oveja como se describe en Yang, K. et al., J. Mol. Endocrinol., 8:173-180 (1992); receptor glucocorticoide de tamarino como se describe en Brandon, D.D. et al., J. Mol. Endocrinol. 7:89-96 (1991); y GR-beta humano como se describe en Hollenberg, S.M. et al., Nature, 318:635 (1985); Bamberger, C.M. et al., J. Clin Invest., 95:2435 (1995).

El término, "enfermedad o trastorno asociado con AP-1 y/o NF-κB" como se usa en la presente, se refiere a una enfermedad asociada con el producto de expresión de un gen bajo el control regulador de AP-1 y/o NF-κB. Tales enfermedades incluyen, pero no se limitan a: enfermedades y trastornos inmunitarios e inflamatorios; cáncer y trastornos de tumor, tales como tumores sólidos, linfomas y leucemia; e infecciones por hongos tales como micosis fungoides.

El término "enfermedades o trastornos inflamatorios o asociados con lo inmunitario" se usa en la presente para abarcar cualquier condición, enfermedad, o trastorno que tiene un componente inflamatorio o inmunitario, incluyendo, pero no limitado a, cada una de las siguientes condiciones: rechazo de

trasplante (por ejemplo, de riñón, hígado, corazón, pulmón, páncreas (por ejemplo, células de los islotes), médula ósea, córnea, intestino delgado, aloinjertos de piel, homoinjertos de piel (tales como los empleados en tratamiento de quemaduras), xenoinjertos de válvula cardiaca, enfermedad del suero, y enfermedad de injerto contra hospedero, enfermedades autoinmunitarias, tales como artritis reumatoide, artritis psoriática, esclerosis múltiple, diabetes de Tipo I y Tipo II, diabetes juvenil, obesidad, asma, enfermedad inflamatoria del intestino (tales como enfermedad de Crohn y colitis ulcerativa), gangrena de pioderma, lupus (lupus eritematoso sistémico), miastenia grave, psoriasis, dermatitis, dermatomitosis; eccema, seborrea, inflamación pulmonar, uveítis ocular, hepatitis, enfermedad de Grave, tiroiditis de Hashimoto, tiroditis autoinmunitaria, síndrome de Behcet o Sjorgen (ojos/boca secos), anemia perniciosa o inmunohemolítica, aterosclerosis, enfermedad de Addison (enfermedad autoinmunitaria de las glándulas adrenales), insuficiencia adrenal idiopática, enfermedad poliglandular autoinmunitaria (también conocida como síndrome poliglandular autoinmunitario), glomerulonefritis, escleroderma, morfea, lichen planus, vitiligo (despigmentación de la piel), alopecia areata, alopecia autoinmunitaria, hipopituitarismo autoinmunitario, síndrome de Guillain-Barre, y alveolitis; enfermedades hipersensibles mediadas por células T, incluyendo

hipersensibilidad por contacto, hipersensibilidad de tipo retardado, dermatitis de contacto (incluyendo la que se debe contacto con plantas venenosas), urticaria, alergias de la piel, alergias respiratorias (rinitis polínica, rinitis alérgica) y enteropatía sensible al gluten (enfermedad celiaca); enfermedades inflamatorias tales como osteoartritis, pancreatitis aguda, pancreatitis crónica, síndrome de tensión respiratoria aguda, síndrome de Sezary y enfermedades vasculares que tiene un componente inflamatorio y o proliferador tal como restenosis, estenosis y aterosclerosis. Las enfermedades o trastornos inflamatorios o asociados con lo inmunitario también incluyen, pero no se limitan a: trastornos endocrinos, trastornos reumáticos, enfermedades del colágeno, enfermedad dermatológica, enfermedad alérgica, enfermedad oftálmica, enfermedad respiratoria, enfermedad hematológica, enfermedad gastrointestinal, enfermedad inflamatoria, enfermedad autoinmunitaria, hiperplasia congénita adrenal, tiroiditis no supurante, hipercalcemia asociada con cáncer, artritis reumatoide juvenil, espondilitis anquilosante, bursitis aguda y subaguda, tenosinovitis no específica aguda, artritis por gota aguda, osteoartritis pos-traumática, sinovitis de osteoartritis, epicondilitis, carditis reumática aguda, pénfigo, dermatitis bulosa herpetiforme, eritema severo multiforme, dermatitis exfoliante, dermatitis seborreica, rinitis alérgica estacional o perene, asma bronquial,

dermatitis por contacto, dermatitis atópica, reacciones de hipersensibilidad a fármacos, conjuntivitis alérgica, queratitis, herpes zoster oftálmica, iritis e iridociclitis, corioretinitis, neuritis óptica, sarcoidosis sintomática, quimioterapia de tuberculosis pulmonar fulminante o diseminada, púrpura trombocitopénica idiopática en adultos, trombocitopenia secundaria en adultos, anemia hemolítica adquirida (autoinmunitaria), leucemias y linfomas en adultos, leucemia aguda de inicio en la infancia, enteritis regional, vasculitis autoinmunitaria, esclerosis múltiple, enfermedad pulmonar obstructiva crónica, rechazo al trasplante de órganos sólidos, sepsis. Los tratamientos preferidos incluyen tratamiento de rechazo al trasplante, artritis reumatoide, artritis psoriática, esclerosis múltiple, asma, enfermedad inflamatoria del intestino, lupus eritematoso sistémico, psoriasis y enfermedad pulmonar crónica.

En consecuencia, una modalidad de la presente invención es un método para tratar una enfermedad o trastorno seleccionado de un trastorno endocrino, trastorno reumático, enfermedad de colágeno, enfermedad dermatológica, enfermedad alérgica, enfermedad oftálmica, enfermedad respiratoria, enfermedad hematológica, enfermedad gastrointestinal, enfermedad inflamatoria, enfermedad inmunitaria, enfermedad neoplásica y enfermedad metabólica, que comprende administrar al paciente que necesita el tratamiento, una cantidad

terapéuticamente efectiva de un compuesto como se define en la reivindicación 1.

En una modalidad preferida, la enfermedad o trastorno es una enfermedad inflamatoria o autoinmunitaria seleccionada de rechazo al trasplante de riñón, hígado, corazón, pulmón, páncreas, médula ósea, córnea, intestino delgado, aloinjertos de piel, homoinjertos de piel, xenoinjeto de válvula cardiaca, enfermedad del suero, y enfermedad de injerto contra hospedero, artritis reumatoide, artritis psoriática, esclerosis múltiple, asma, enfermedad inflamatoria del intestino, enfermedad de Crohn, colitis ulcerativa, gangrena de pioderma, lupus eritematoso sistémico, miastenia grave, psoriasis, dermatitis, dermatomitosis; eccema, seborrea, inflamación pulmonar, uveítis ocular, hepatitis, enfermedad de Grave, tiroiditis de Hashimoto, tiroditis autoinmunitaria, síndrome de Behcet o Sjorgen, anemia perniciosa o inmunohemolítica, aterosclerosis, enfermedad de Addison, insuficiencia adrenal idiopática, enfermedad poliglandular autoinmunitaria, glomerulonefritis, escleroderma, morfea, líquen plano, vitíligo, alopecia areata, alopecia autoinmunitaria, hipopituitarismo autoinmunitario, síndrome de Guillain-Barre, y alveolitis; hipersensibilidad por contacto, hipersensibilidad de tipo retardado, dermatitis por contacto, urticaria, alergias de la piel, alergias respiratorias, rinitis polínica, rinitis alérgica y enteropatía sensible al

gluten, osteoartritis, pancreatitis aguda, pancreatitis crónica, síndrome de tensión respiratoria aguda, síndrome de Sezary, restenosis, estenosis y arterioesclerosis, hiperplasia congénita adrenal, tiroiditis no supurante, hipercalcemia asociada con cáncer, artritis reumatoide juvenil, espondilitis anquilosante, bursitis aguda y subaguda, tenosinovitis no específica aguda, artritis por gota aguda, osteroartritis post-traumática, sinovitis de osteoartritis, epicondilitis, carditis reumática aguda, pénfigo, dermatitis herpetiforme bulosa, eritema severo multiforme, dermatitis exfoliante, psoriasis, dermatitis seborreica, rinitis alérgica estacional o perene, asma bronquial, dermatitis por contacto, dermatitis atópica, reacciones de hipersensibilidad a fármacos, conjuntivitis alérgica, queratitis, herpes zoster oftálmica, iritis e iridociclitis, corioretinitis, neuritis óptica, sarcoidosis sintomática, quimioterapia de tuberculosis pulmonar fulminante o diseminada, púrpura trombocitopénica idiopática en adultos, trombocitopenia secundaria en adultos, anemia hemolítica adquirida (autoinmunitaria), leucemias y linfomas en adultos, leucemia aguda de inicio en la infancia, colitis ulcerativa, enteritis regional, enfermedad de Crohn, síndrome de Sjogren, vasculitis autoinmunitaria, esclerosis múltiple, miastenia grave, sepsis, y enfermedad pulmonar obstructiva crónica.

Aún en una modalidad más preferible, la enfermedad o

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trastorno es seleccionado de rechazo al trasplante, artritis reumatoide, artritis psoriática, esclerosis múltiple, asma, enfermedad inflamatoria del intestino, lupus sistémico, eritematosis, y psoriasis.

Además, de conformidad con la presente invención se proporciona un método para tratar una enfermedad asociada con la transcripción inducida por AP-1 e/o inducida por NF-κB (particularmente transcripción inducida por AP-1), en donde un compuesto de la fórmula (I) de la invención se administra a un paciente en riesgo desarrollar la enfermedad en una cantidad terapéuticamente efectiva para inducir la trans-represión NHR de la transcripción inducida por AP-1 e/o inducida por NF-κB (particularmente transcripción inducida por AP-1), por lo cual se trata la enfermedad.

Otros agentes terapéuticos, tales como aquellos descritos posteriormente, puede emplearse con los compuestos de la invención en los métodos actuales. En los métodos de la presente invención, tales otros agentes terapéuticos pueden administrarse antes de, simultáneamente con o después de la administración de los compuestos de la presente invención.

En una modalidad particular, los compuestos de la presente invención son útiles para el tratamiento de los trastornos ejemplares anteriormente mencionados sin tener en cuenta su etiología, por ejemplo, para el tratamiento de rechazo al trasplante, artritis reumatoide, enfermedad

inflamatoria del intestino, e infecciones virales.

Todavía en otra modalidad, se contemplan combinaciones farmacéuticas que comprende un compuesto como se define en la reivindicación 1, un enantiómero, diaestereómero, un tautómero de los mismos, o un éster de profármaco de los mismos, o una sal farmacéuticamente aceptable de los mismos, y un inmunodepresor, un agente anticancerígeno, un agente anti-viral, un agente antiinflamatorio, un agente antifúngico, un antibiótico, un agente de hiperproliferación anti-vascular, un agente antidepresivo, un agente reductor de lípidos, un agente modulador de lípidos, un agente antibiabético, un agente anti-obesidad, un agente anti-hipertensor, un inhibidor de agregación de plaquetas, y/o un agente antiosteoporosis, en donde el agente antidiabético es 1, 2, 3 o más de una biguanida, una sulfonil urea, un inhibidor de glucosidasa, un agonista PPAR γ, un agonista doble de PPAR α/γ, un inhibidor SLGT2, un inhibidor DPP4, un inhibidor aP2, un sintetizador de insulina, un péptido-1 de tipo glucagón (GLP-1), insulina y meglitinida, en donde el agente anti-obesidad es un agonista adrenérgico beta 3, un inhibidor de lipasa, un inhibidor de la reabsorción de serotonina (y dopamina), un agonista del receptor de tiroides, un inhibidor aP2 y/o un agente anorectivo, en donde el agente que reduce los lípidos es un inhibidor MTP, un inhibidor de HMG CoA reductasa, un inhibidor de la escualeno sintetasa, un derivado de ácido fíbrico, un

sobreregulador de la actividad del receptor de LDL, un inhibidor de lipoxigenasa, o un inhibidor ACAT, en donde el agente antihipertensor es un inhibidor de ACE, antagonista del receptor de angiotensina II, inhibidor NEP/ACE, bloqueador del canal de calcio y/o bloqueador β-adrenérgico.

Las combinaciones más preferidas son aquellas en donde el agente antidiabético es 1, 2, 3 ó más de metformina, gliburida, glimepirida, glipirida, glipizida, clorpropamida, gliclazida, acarbosa, miglitol, pioglitazona, troglitazona, rosiglitazona, insulina, Gl-262570, isaglitazona, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinida, nateglinida, KAD1129, AR-HO39242, GW-409544, KRP297, AC2993, LY315902, P32/98 y/o NVP-DPP-728A, en donde el agente anti-obesidad es orlistat, ATL-962, AJ9677, L750355, CP331648, sibutramina, topiramato, axocina, dexanfetamina, fentermina, fenilpropanolamina, y/o mazindol, en donde el agente reductor de lípidos es pravastatina, lovastatina, simvastatina, atorvastatina, cerivastatina, fluvastatina, itavastatina, visastatina, fenofibrato, gemfibrozil, clofibrato, avasimiba, TS-962, MD-700, colestagel, niacina y/o LY295427, en donde el agente antihipertensor es un inhibidor ACE que es captoprilo, fosinoprilo, enalaprilo, lisinoprilo, quinaprilo, benazeprilo, fentiaprilo, ramiprilo o moexiprilo; un inhibidor de NEP/ACE que es omapatrilat, ácido [S[(R*,R*)]-hexahidro-6-[(2-mercapto-1-oxo-3-fenilpropil)amino]-2,2-dimetil-7-oxo-1H-

azepin-1-acético (gemopatrilat) o CGS 30440;

un antagonista del receptor de angiotensina II que es irbesartan, losartan o valsartan;

besilato de amlodipina, prazosina HCl, verapamilo, nifedipina, nadolol, propranolol, carvedilol, o clonidina HCl, en donde el inhibidor de la agregación de plaquetas es aspirina, clopidogrel, ticlopidina, dipiridamol o ifetroban;

el inmunodepresor es una ciclosporina, micofenolato, interferon-beta, desoxispergolina, FK-506 o Ant.-IL-2;

el agente anti-cáncer es azatiprina, 5-fluorouracilo, ciclofosfamida, cisplatina, metotrexato, tiotepa, o carboplatina;

el agente anti-viral es abacavir, aciclovir, ganciclovir, zidanocin, o vidarabina; y

el fármaco antiinflamatorio es ibuprofeno, celecoxib, rofecoxib, aspirina, naproxeno, cetoprofeno, diclofenaco sodio, indometacina, piroxicam, prednisona, dexametasona, hidrocortisona, o diacetato de triamcinolona.

La invención puede abarcarse en otras formas específicas sin salirse del espíritu o atributos esenciales de los mismos. Esta invención también abarca todas las combinaciones de aspectos y modalidades alternativas de la invención notados en la presente. Se entenderá que cualesquiera y todas las modalidades pueden tomarse en conjunto con cualesquiera de otras modalidades para describir modalidades adicionales de la

presente invención. Adicionalmente, cualesquiera de los elementos de una modalidad son un medio para combinarse con cualesquiera y todas los otros elementos de cualesquiera de las modalidades para describir modalidades adicionales.

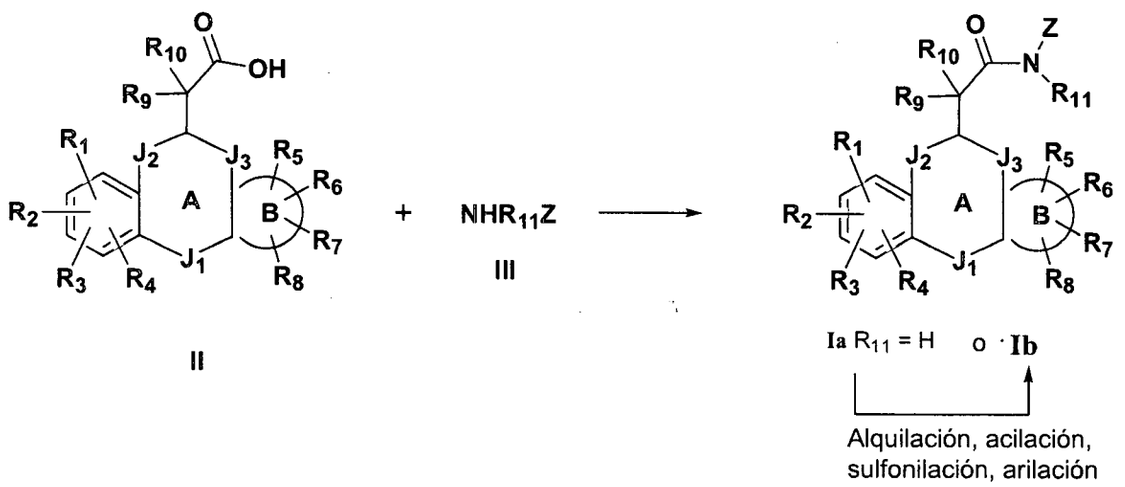
Métodos de preparación

Los compuestos de la presente invención pueden sintetizarse por muchos métodos disponibles para aquellos expertos en la técnica de la química orgánica. Los esquemas sintéticos generales para preparar compuestos de la presente invención se describen abajo. Estos esquemas son ilustrativos y no significan limitar las técnicas posibles que alguien experto en la técnica pueden usar para preparar los compuestos descritos en la presente. Los diferentes métodos para preparar los compuestos de la presente invención serán evidentes para aquellos expertos en la técnica. Adicionalmente, las diversas etapas en la síntesis pueden realizarse en una secuencia alterna con objeto de proporcionar el compuesto o compuestos deseados. Los ejemplos de compuestos de la presente invención preparados por métodos descritos en los esquemas generales se dan en las secciones de preparaciones y ejemplos establecidos de aquí en adelante. Los compuestos de los ejemplos se preparan típicamente como mezclas racémicas. La preparación de ejemplos homoquirales puede llevarse a cabo por técnicas conocidas por alguien experto en la técnica. Por ejemplo, los compuestos homoquirales pueden prepararse por separación de productos racémicos por HPLC preparativa de fase quiral. Alternativamente, los compuestos de los ejemplos pueden prepararse por métodos conocidos para dar productos

enantioméricamente enriquecidos. Estos incluyen, pero no se limitan a, la incorporación de funcionalidades auxiliares quirales en intermediarios racémicos que sirven para controlar la diaestereoselectividad de transformaciones, proporcionando productos enantio-enriquecidos durante el desdoblamiento del auxiliar quiral.

Esquema de reacción 1

Condensación del ácido carboxílico II con amina III para formar el producto I



El Esquema de reacción 1 ilustra la preparación de compuestos del título de la invención (I) a partir de los ácidos carboxílicos intermediarios II. Las amidas I pueden prepararse a partir de II por muchas de las trayectorias conocidas para preparar carboxamidas por la condensación deshidratada de ácidos carboxílicos y aminas. Por ejemplo, la condensación del ácido II con amina ($NR_{11}Z$, III, donde R_{11} = H, alquilo, cicloalquilo, alcoxi, dialquilamino, arilo o heteroarilo) puede efectuarse por el tratamiento de II con un reactivo activante, tal como una carbodiimida soluble en agua (EDC), en presencia de un N-hidroxi

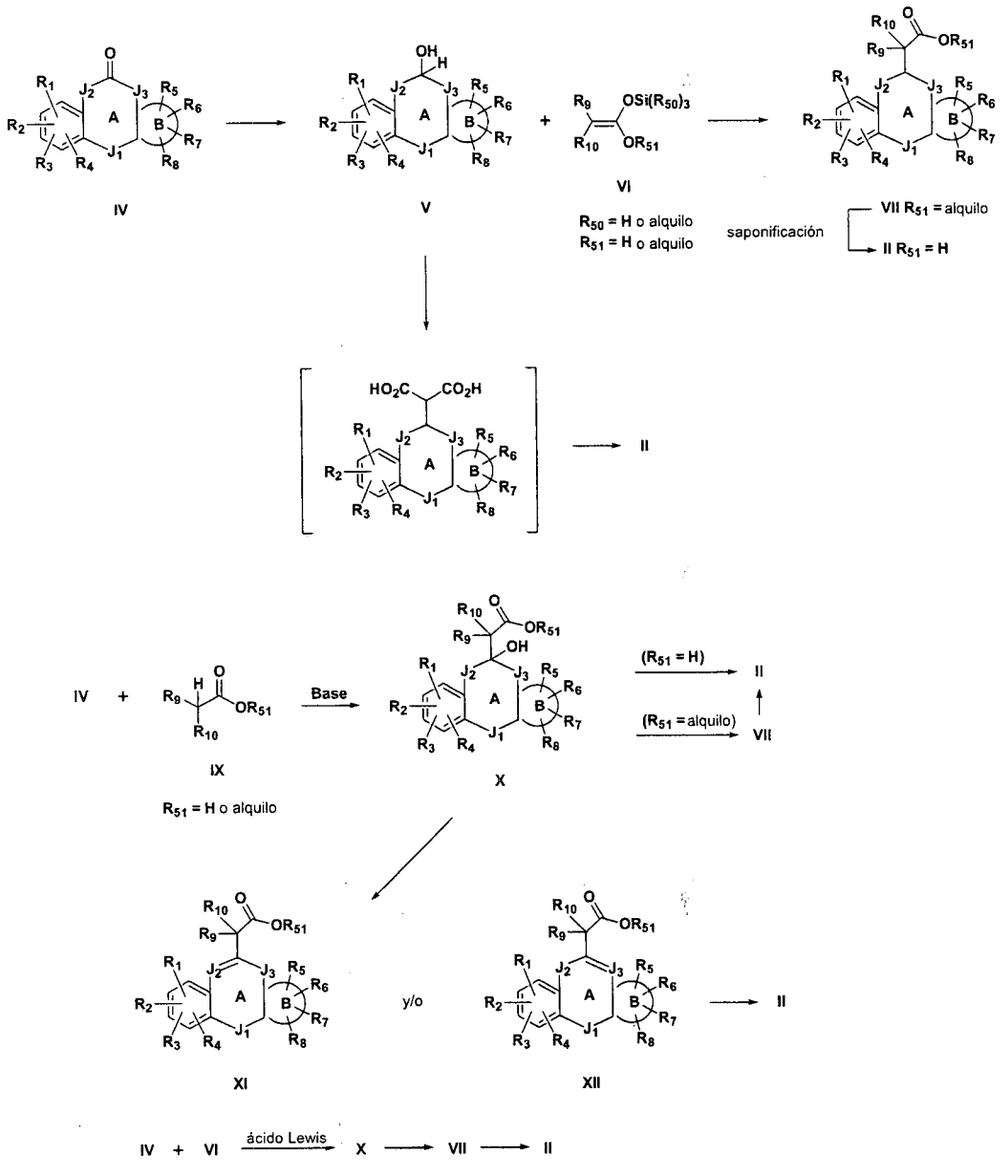
triazol (HOAt o HOBt, o similares) y amina en presencia de base (preferiblemente trietilamina, diisopropiletilamina, o similares) en un solvente aprótico polar apropiado (N,N-dimetilformamida, acetonitrilo, diclorometano, o similares). El ácido carboxílico II también puede convertirse a un cloruro ácido por tratamiento con un agente de cloración apropiado (cloruro de tionilo, cloruro de oxalilo, o similares). Similarmente, II puede convertirse a un fluoruro de acilo durante la exposición a un agente de fluoración (tal como fluoruro cianúrico). La condensación del haluro de acilo (cloruro o fluoruro) con la amina III (típicamente llevada a cabo en presencia de una base tal como piridina o trietilamina en un solvente aprótico) puede entonces proporcionar la amida Ia. En casos donde R_{11}= H (esto es, III = NH_2Z), el producto inmediato de condensación de II y III (Ia, R_{11}= H) puede convertirse a Ib (R_{11}= alquilo) por tratamiento de Ia con un agente alquilante (haluro de alquilo, sulfonato de alquilo, o similares) en presencia de una base (carbonato de cesio, hidruro de sodio, o similares). Ia (R_{11} = H) puede convertirse a Ib (R_{11} = C(O)alquilo, CO_2alquilo) por tratamiento con una base fuerte (hidruro de sodio, diisopropil amida de litio, o similares) seguido por acilación con un reactivo acilante apropiado (un cloruro ácido, cloroformiato, o similares). Similarmente, la sulfonilación puede efectuarse por tratamiento con una base y haluro de sulfonilo para proporcionar Ib (R_{11} = SO_2arilo o SO_2alquilo). La arilación de Ia para dar Ib (R_{11} = arilo) también puede efectuarse por N-arilación catalizada por paladio de amidas (véase, por ejemplo, Yin, J.; Buchwald S. Org. Lett. 2000, 2,

1101-1104 y referencias citadas en la presente) o la arilación promovida por cobre de amidas con ácidos aril borónicos o arilsiloxanos (véase, por ejemplo, Lam, P. et al. Synlett 2000, 674-676).

El Esquema de reacción 2 ilustra varios métodos para la preparación del ácido carboxílico II intermediario. La cetona IV intermediaria puede reducirse al alcohol V por tratamiento con un agente reductor (típicamente un hidruro de metal tal como borohidruro de sodio en metanol o hidruro de litio y aluminio en éter de dietilo o THF). En un modo de preparación, el alcohol puede condensarse con ácido malónico para dar, después de la descarboxilación de un ácido dicarboxílico intermediario putativo, el intermediario deseado II (Jones et al. J. Am. Chem. Soc. 1948, 70, 2843; Beylin et al. Tetrahedron Lett. 1993, 34, 953-956.). El alcohol V también puede tratarse con un silil ceteno acetal, representado por VI. En casos donde R_9 = R_{10} = R_{50} = R_{51} = Me, VI puede obtenerse de fuentes comerciales. La condensación de V (J_2 = J_3 = enlace) con VI para dar el éster VII generalmente requiere la presencia de un ácido Lewis, tal como eterato de trifluoruro de boro, tetracloruro de titanio, o similares y se lleva a cabo mejor en un solvente aprótico, polar tal como diclorometano. La saponificación del éster VII a II puede llevarse a cabo con hidróxido de sodio o hidróxido de potasio en agua en presencia de co-solventes tal como metanol, THF, y/o DMSO. En los casos en donde R_9 = R_{10} = alquilo, la hidrólisis del éster VII se lleva a cabo mejor a temperatura elevada (generalmente 80°C) durante tiempos prolongados (> 5h).

Esquema de reacción 2

Preparación de ácidos carboxílicos II de las cetonas IV



La cetona IV también puede condensarse con un derivado del enolato del éster IX (R_{51} = alquilo), preparado por el tratamiento de IX con una base apropiada (diisopropil amida de litio, hexametildisilizano de litio o potasio o similares) a

baja temperatura (-78°C hasta 0°C), para dar el éster X. Un ácido carboxílico intermediario X (R_{51} = H) puede también prepararse al tratar primero un ácido carboxílico IX (R_{50} = H) con al menos dos equivalentes de una base fuerte (preferiblemente diisopropil amida de litio o dietil amida de litio) para generar un dianión de enediolato. La generación del enediolato se lleva a cabo preferiblemente a 0°C a 55°C. La condensación del enediolato preparado *in situ* con cetona IV puede entonces dar el hidroxi ácido X (R_{51} = H). En los casos en donde uno o ambos de J_2, J_3 = alquileno, el alcohol intermediario X pueden deshidratarse rápidamente para dar los intermediarios insaturados XI y/o XII. La deshidratación puede presentarse espontáneamente por exposición de X (J_2, J_3 = alquileno) a condiciones ácidas, tal como ácido acuoso o ácido Lewis (trifluoruro de boro, tetracloruro de titanio, o similares). Las olefinas intermediarias XI y XII pueden reducirse para dar el éster VII (R_{51} = alquilo) bajo hidrogenación catalítica (típicamente paladio en carbono en presencia de gas de hidrógeno), que puede saponificarse como se describe anteriormente para preparar el ácido carboxílico II. Alternativamente, en casos donde las olefinas XI y XII son ácidos carboxílicos (R_{51} = H), hidrogenación catalítica (típicamente paladio en carbono en presencia de gas de hidrógeno) puede proporcionar directamente el ácido carboxílico II. En casos donde la deshidratación del alcohol X

AR 455

a XI y/o XII no se presenta espontáneamente, X (R_{51} = H) puede reducirse al II. La reacción se lleva a cabo preferiblemente con un silano (típicamente trietilsilano) en presencia de un ácido prótico (típicamente ácido trifluoroacético). El éster X (R_{51} = alquilo) también puede reducirse al éster VII bajo las mismas condiciones empleadas para la conversión de X a II. El éster VII también puede hidrolizarse al ácido II bajo las condiciones descritas anteriormente.

La cetona IV también puede tratarse con silil ceteno acetal VI para proporcionar el hidroxi éster X (R_{51} = alquilo). La condensación se lleva a cabo mejor en presencia de un ácido Lewis (eterato de trifluoruro de boro, o similares) en diclorometano a 0°C. El hidroxi éster X puede aislarse, o, alternativamente, reducción *in situ* al éster VII puede llevarse a cabo. En casos donde cualesquiera de uno o más de R_1-R_4 = OH, adición de trietilsilano a la mezcla de reacción que contiene el hidroxi éster no X aislado puede dar el éster VII. Alternativamente, la adición de un ácido prótico fuerte (típicamente ácido trifluoroacético) y trietilsilano a la mezcla de reacción que contiene el hidroxi éster X no aislado puede proporcionar el éster VII. La conversión del éster VII al ácido carboxílico II puede entonces llevarse a cabo como se describe anteriormente.

La síntesis de ejemplos y derivados basados en xanteno hidroxilado se describe en el Esquema de reacción 3. La 3-

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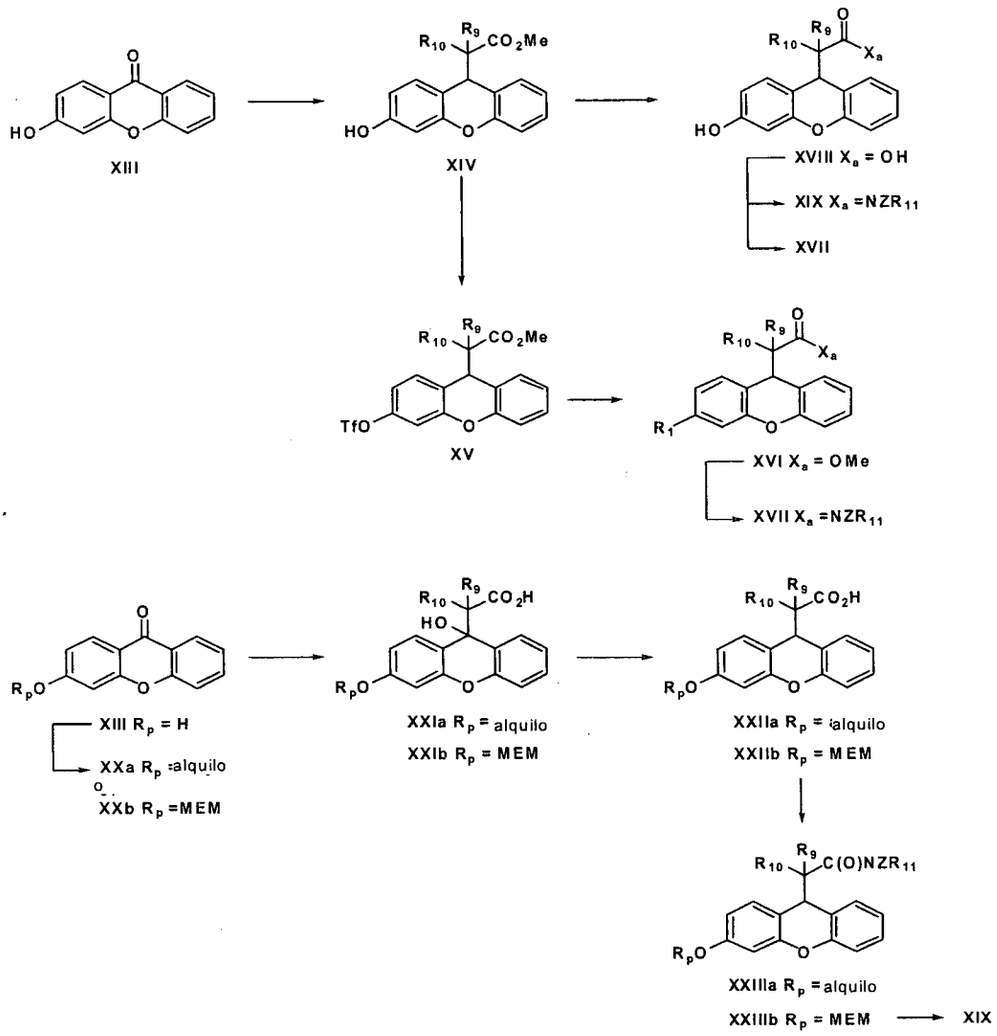
hidroxi-9H-xanten-9-ona XIII ("enlazador de Sieber", Sieber P. Tetrahedron Lett., 1987, 28, 6147-6150) puede convertirse al éster XIV por tratamiento con un silil ceteno acetal (por ejemplo, (1-metoxi-2-metilprop-1-eniloxi)trimetilsilano, donde R_9 = R_{10} = Me) en presencia de un ácido Lewis apropiado (preferiblemente eterato de trifluoruro de boro) en diclorometano a 0°C. La adición posterior de un agente reductor (preferiblemente trietilsilano) puede dar el éster de metilo XIV. El grupo de hidróxilo fenólico de XIV puede derivarse por un número de medios diferentes. El tratamiento de XIV con un reactivo triflante (anhídrido tríflico, $PhNTf_2$, o similares) en presencia de una base apropiada (trietilamina, piridina, o similares) puede dar un triflato de arilo XV que puede experimentar reacciones de unión cruzada mediadas por un metal. Por ejemplo, la unión de Suzuki puede efectuarse por tratamiento de XV con un ácido aril borónico o éster de aril boronato en presencia de un catalizador de paladio (tetraquis trifenilfosfina paladio, o similares) y una base acuosa (carbonato de potasio, carbonato de sodio, fosfato de potasio o similares) en un solvente apropiado o combinación de solventes (DMF, tolueno/etanol, 1,4-dioxano o similares) a temperatura elevada (típicamente 100°C) puede proporcionar un éster de metilo intermediario

arilado XVI. (R1 = arilo). El triflato también puede experimentar una variedad de otras reacciones de unión cruzada mediadas por un metal, conocidas por aquellos expertos en la técnica (véase, por ejemplo, de Meijere, A., & Diederich, F. (2004). Metal-Catalyzed Cross-Coupling Reactions. (2nd ed.): John Wiley & Sons). La saponificación del éster XVI bajo condiciones descritas anteriormente para la preparación de II a partir de VII, seguido por condensación bajo las condiciones descritas anteriormente para la preparación de Ia a partir de II puede dar los productos de xanteno XVII. El éster de fenol XIV también puede hidrolizarse al ácido carboxílico XVIII bajo condiciones descritas anteriormente para la preparación de VII a partir de II. La amida XIX puede entonces prepararse como se describe anteriormente para la preparación de Ia a partir de II. La amida XVII puede también prepararse a partir de la amida XIX por la conversión a un derivado de triflato como se describe anteriormente para la preparación de XV a partir de XIV seguido por la unión cruzada catalizada por paladio como se describe anteriormente para la preparación de XVI a partir de XV.

458

Esquema de reacción 3

Preparación de xantenos fenólicos y sus derivados



La 3-hidroxi-9H-xanten-9-ona ("enlazador de Sieber") (XIII) puede convertirse al éter de alquilo XXa o éter de (2-metoxietoxi)metilo (MEM) XXb correspondiente por tratamiento con una base apropiada (típicamente hidruro de sodio) en un solvente aprótico polar (típicamente DMF) en presencia de un haluro de alquilo (típicamente un haluro primario tal como yodometano) o MEM-

Patente de Invención

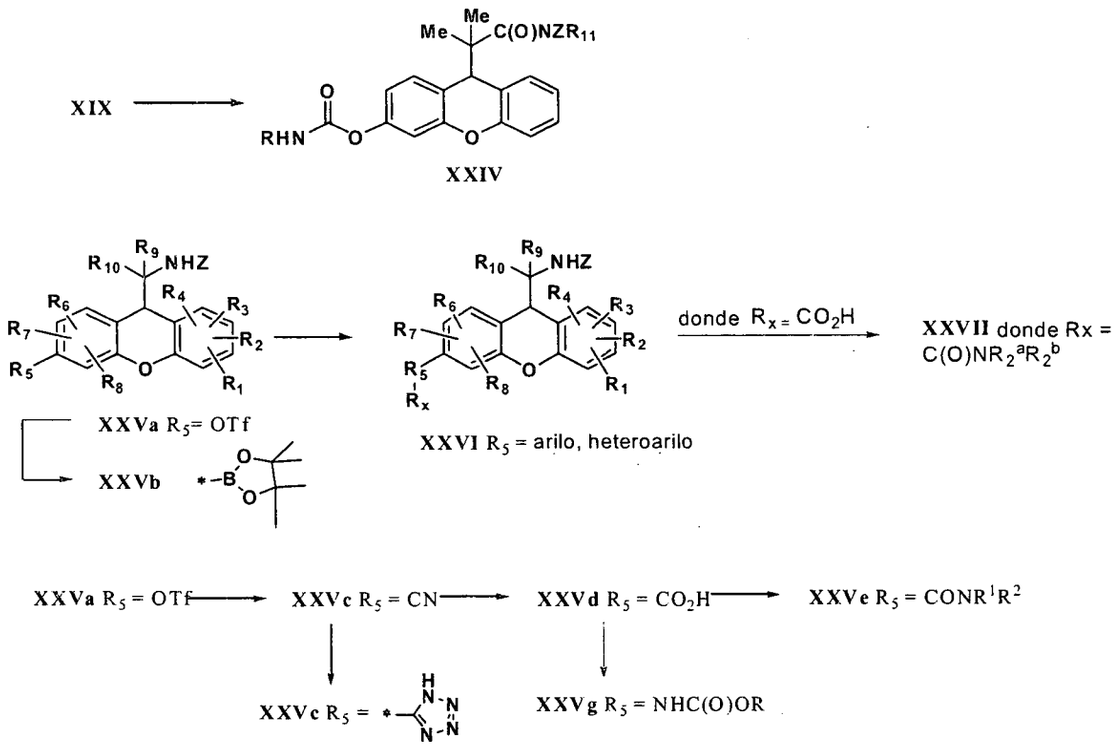
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Cl. Los ácidos hidroxi XXIa y XXIb pueden prepararse como se describe anteriormente para la preparación de X (R_{51} = H). La reducción como se describe anteriormente para la preparación de II directamente a partir de X puede entonces dar XXIIa o XXIIb, que puede convertirse a XXIIIa o XXIIIb bajo las condiciones descritas anteriormente para la preparación de 1a a partir de II. El XXIIIa puede convertirse en un fenol XIX por tratamiento con tiofenol o 2-aminotiofenol en presencia de una cantidad estequiométrica de carbonato de potasio en N-metil-pirrolidinona a alta temperatura (típicamente 200°C - 205°C en un reactor de microondas) (ver Chakraborti, et al. J. Org. Chem. 2002, 67, 6406-6414).

ESQUEMA DE REACCIÓN 4

Preparación de derivados de xanteno no fenólicos substituidos



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En una modalidad, los compuestos de los ejemplos representados por XIX puede convertirse a los compuestos de los ejemplos representados por XXIV (Esquema de reacción 4). De esta manera, el tratamiento de XIX con un alquilo o isocianato de arilo en presencia de una base no nucleofílica (preferiblemente N,N-diisopropiletil amina) en un solvente aprótico, polar (preferiblemente 1,4-dioxano), preferiblemente a temperatura ambiente puede proporcionar XXIV. El Intermediario XXV , donde R5 es triflato o nonoflato (ONf) puede convertirse al xanteno arilado XXVI por unión de Suzuki con un boronato de arilo apropiado. Por ejemplo, el tratamiento de XXV con cualquier ácido aril borónico, sal de trifluoroborato de arilo, o boronato de arilo (por ejemplo, boronato de aril pinacol) en presencia de un catalizador de paladio (0) (preferiblemente tetraquistrifenilfosfina paladio (0)), y una base (preferiblemente, carbonato de sodio acuoso, carbonato de potasio, fosfato de potasio, o similares) en un sistema de solventes típicamente empleado para reacciones de unión de Suzuki (tal como tolueno/etanol, agua/DMF, o similares) puede proporcionar XXVI. Alternativamente, XXV puede convertirse a un éster de boronato (por ejemplo, boronato de pinacol XXVb) por tratamiento con un catalizador de paladio (típicamente dicloruro de 1,1'-bis(difenilfosfino)ferroceno-paladio (II)) en presencia de una fuente de boro (preferiblemente bis(pinacolato)de diboro) en

presencia de una base (preferiblemente acetato de paladio). La conversión de XXVb a XXVI puede llevarse a cabo por unión cruzada con un haluro de arilo o heteroarilo bajo las condiciones de Suzuki como se describe anteriormente para la conversión de XXV a XXVI. Donde XXVI se adjunta con un grupo de ácido carboxílico, la conversión a una carboxamida (XXVII) puede efectuarse bajo cualquier número de las condiciones típicas para condensación deshidratada de aminas y ácidos carboxílicos, por ejemplo como se describe para la conversión de II a Ia. El triflato (o nonflato) XXVa también puede convertirse a nitrilos XXVc por métodos para cianación catalizada por paladio de haluros de arilo (Sundmeier, M. et al, Eur. J. Inorg. Chem. 2003, 3513). Por ejemplo, el tratamiento de XXVa con una fuente de cianuro (típicamente cianuro de zinc) en presencia de un catalizador de paladio (típicamente tetraquis trifenilfosfina paladio (0)) en un solvente polar (típicamente DMF) a temperatura elevada (típicamente 120°C) proporciona los nitrilos XXVc. Los nitrilos XXVc también pueden hidrolizarse para proporcionar los ácidos carboxílicos XXVd por tratamiento con peróxido de sodio en agua. La condensación de ácidos XXVd con aminas primarias o secundarias (como se describe para la conversión de II a Ia) puede proporcionar carboxamidas XXVe. Los nitrilos XXVc pueden convertirse a tetrazoles XXVf por condensación con una fuente de azida (preferiblemente azida de sodio) en

presencia de un ácido (preferiblemente cloruro de amonio o trimetilsilil azida u óxido de tributil estaño). Los ácidos carboxílicos XXVd también pueden convertirse a carbamatos XXVg por rearreglo de Curtius. De esta manera, la conversión de XXVd a una azida de acilo (típicamente efectuada por la exposición a una azida de difenilfosforilo), en presencia de una amina terciaria (típicamente trietilamina), con calentamiento, seguido por apagado con un alcohol, puede dar los carbamatos XXVg.

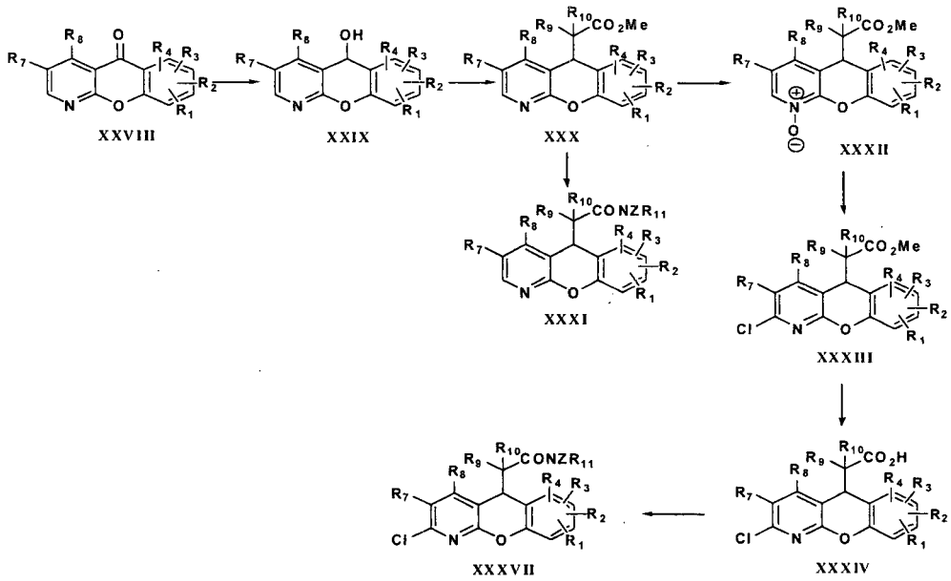
Los ejemplos basados en azaxanteno pueden prepararse como se ilustra en el Esquema de reacción 5. La 5H-cromen[2,3-b]piridin-5-ona XXVIII (comercialmente disponible o preparado en la manera descrita por Villani et al., J. Med. Chem. 1975, 18, 1) puede reducirse al alcohol correspondiente XXIX durante el tratamiento con borohidruro de sodio en metanol anhidro como se describe por Bristol, et al. (J. Med. Chem., 1981, 24, 1010-1013). El tratamiento de XXIX con el trimetil silil ceteno acetal de isobutirato de metilo como se describe anteriormente para la preparación de VII a partir de V puede dar el éster XXX. La hidrólisis del éster como se describe anteriormente para la preparación de II a partir de VII, seguido por amidación como se describe para la preparación de Ia a partir de II y III puede proporcionar las azaxanteno amidas XXXI. Alternativamente, la oxidación de XXX puede efectuarse bajo condiciones para la preparación de N-óxido de

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piridina (preferiblemente mCPBA en diclorometano) para dar el N-óxido XXXII, que puede entonces tratarse con un reactivo de cloración apropiado (preferiblemente oxicloruro de fósforo, $POCl_3$, en la ausencia de un co-solvente) para dar el cloroazaxanteno XXXIII. La saponificación de XXXIII al ácido carboxílico XXXIV puede efectuarse bajo condiciones descritas anteriormente para la preparación de VII a partir de II, preferiblemente en la ausencia de DMSO. La condensación de XXXIV con una amina ($NHR_{12}R_{13}$) a temperatura elevada (típicamente 130°C) puede proporcionar XXXVa (Esquema de reacción 6, $R_5 = NR_{12}R_{13}$). Alternativamente, la unión de Suzuki de XXXIV con un ácido aril borónico apropiado o boronato de arilo como se describe anteriormente para la preparación de XVI a partir de XV puede proporcionar XXXVb. XXXVa y XXXVb pueden convertirse a XXXVIa o XXXVIb, respectivamente, siguiendo las condiciones descritas anteriormente para la preparación de Ia a partir de II y III. El ácido carboxílico XXXIV también puede convertirse a la amida XXXVII como se describe anteriormente para la preparación de Ia a partir de II y III. La arilación como se describe anteriormente para la preparación de XVI a partir de XV puede proporcionar XXXVIb. Cualesquiera de los intermediarios racémicos XXX - XXXVII o compuestos de los ejemplos pueden separarse en enantiómeros sencillos, purificados por cualesquiera de varios métodos conocidos por aquellos expertos en la técnica.

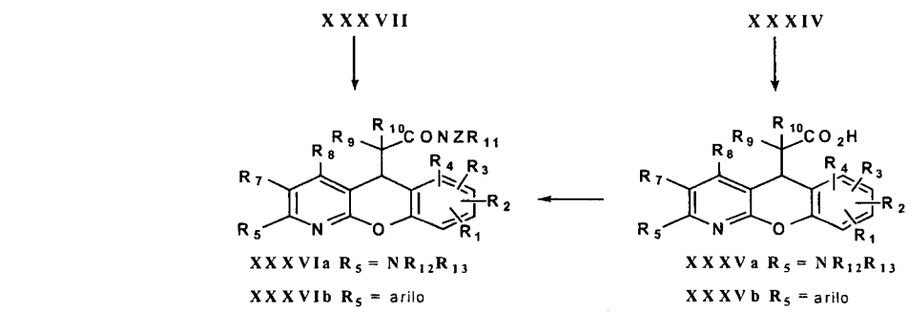
Esquema de reacción 5

Preparación de 5H-cromeno[2,3-b]piridinas



ESQUEMA DE REACCIÓN 6

Elaboración de 2-cloro-5H-cromeno[2,3-b]piridinas

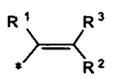
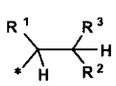


XXXVII ⟶ XXXVIc R_5 = • —≡— R

XXXVII ⟶ XXXVId R_5 = CN

XXXVII ⟶ XXXVIe R_5 = C(O)NR^1R^2

XXXVII ⟶ XXXVIf R_5 = C(O)CH_3

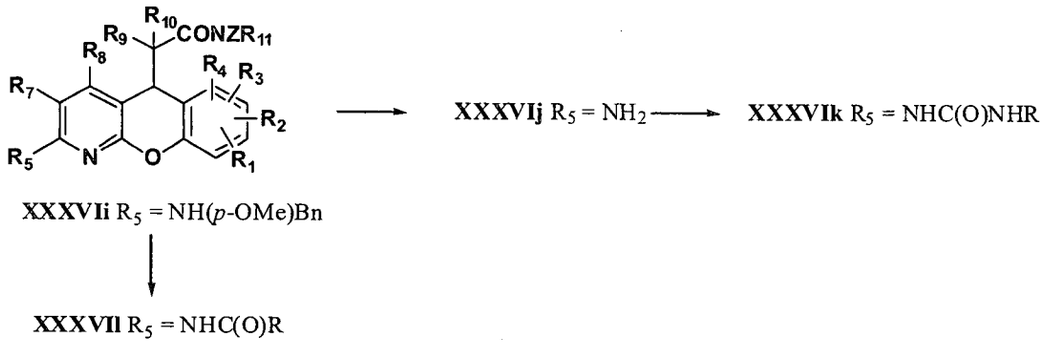
XXXVII ⟶ XXXVIg R_5 =  ⟶ XXXVIh R_5 = 

El cloruro XXXVII (Esquema de reacción 6) también puede experimentar uniones cruzadas de Sonagashira o Stevens-Castro con alquinos en presencia de un catalizador de paladio (preferiblemente bis(trifenilfosfina)-paladio (II(cloruro) con yoduro cuproso catalítico en presencia de una base amina secundaria impedida (preferiblemente diisopropilamina) para dar los alquinos XXXVIc. XXXVII también puede convertirse a nitrilos XXXVId, como se describe para la preparación de XXVc a partir de XXVa. XXXVII también puede convertirse a amidas XXXVIe en un procedimiento de dos etapas que involucra hidrólisis inicial por hidróxido (típicamente hidróxido de potasio) para dar un ácido carboxílico (R_5 = CO2H) que puede entonces condensarse con aminas primarias o secundarias como se describe para la preparación de Ia a partir de II para dar carboxamidas XXVIe. XXXVII también puede convertirse a las cetonas XXXVIf como se describe por Jean-Yves Legros et al (Tetrahedron 2001, 57, 2507). El tratamiento de XXXVII con alquenil boronatos (o sales de trifluoroborato) bajo condiciones descritas para la preparación de XXXVIb a partir de XXXVII pueden proporcionar los compuestos de ejemplo de alquenilo (XXXVIg). La hidrogenación de XXXVIg puede efectuarse con un catalizador de paladio (preferiblemente paladio en carbón vegetal) bajo una atmósfera de hidrógeno para proporcionar los correspondientes compuestos de alquilo XXXVIh.

456

Esquema de reacción 7

Preparación de 5H-cromeno[2,3-b]piridinas substituidas con amino, urea, y carbamoilo



Las 5H-cromeno[2,3-b]piridinas substituidas con amino, urea, y carbamoilo pueden prepararse como se muestra en el Esquema de reacción 7. De esta manera, calentando una solución de XXXVIi substituido con p-metoxi bencilamino (preparado como se describe anteriormente para la preparación de XXXVIa) en ácido trifluoroacético (preferiblemente a 50°C) puede proporcionar las aminas XXXVIj. Las aminas XXXVIj pueden convertirse a ureas XXXVIk al tratar primero con un reactivo carbonilante (tal como cloroformiato de fenilo) en presencia de una base (preferiblemente piridina) para proporcionar intermediarios carbamoilados (R5 = NHC(O)OPh) que, sin aislamiento, pueden entonces condensarse con aminas, con calentamiento (típicamente a 100°C). Las aminas XXXVIi también pueden convertirse a amidas XXXVIl por acilación con un reactivo acilante apropiado (haluro ácido, u otro

ácido carboxílico apropiadamente activado como se describe para la preparación de Ia a partir de II), seguido por segmentación del grupo p-metoxibencilo como se describe para la preparación de XXXVIj a partir de XXXVIi.

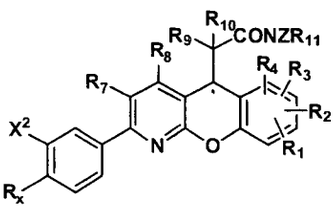
Las 2-(Para-fenil substituido)-5H-cromeno[2,3-b]piridinas pueden elaborarse además como se describe en el Esquema de reacción 8. Los fenoles XXXVIm (R_x = OH) pueden alquilarse bajo condiciones de Mitsunobu (Synthesis 1, 1981). De esta manera, el tratamiento de XXXVIm con un alcohol (RyOH) en presencia de una fosfina (preferiblemente, trifenilfosfina) y un diazodicarboxilato de alquilo (preferiblemente azodicarboxilato de diisopropilo o dietilazodicarboxilato) en tetrahidrofurano puede proporcionar éteres XXXVIn. Los tioéteres (por ejemplo, XXXVIo, R_x = SMe) puede oxidarse hasta los sulfóxidos o sulfonas (XXXVIp) por tratamiento con cualesquiera de una variedad de oxidantes, incluyendo ácido m-cloroperbenzoico. Los ácidos carboxílicos (XXXVIq) pueden convertirse a benzamidas (XXXVIr) usando muchos de la multitud de los métodos para la conversión de ácidos benzoicos a benzamidas. Preferiblemente, el tratamiento de XXVIq con reactivos activantes (típicamente HOBt en presencia de una carbodiimida tal como EDCI) en presencia de bases de amina terciaria (típicamente trietilamina o diisopropiletilamina) y aminas primarias o secundarias en

- 8[468

un solvente aprótico, polar (típicamente acetonitrilo o DMF) da las benzamidas XXXVIr. El aldehído XXXVIs puede convertirse al alcohol XXXVIt por la reducción con un agente reductor apropiado (borohidruro de sodio, o similares) o por tratamiento con un nucleófilo organometálico (alquilo o aril litio, reactivo Grignard, o similares). Similarmente, las cetonas XXXVIv pueden condensarse con nucleófilos organometálicos para proporcionar alcoholes terciarios XXXVIv.

Esquema de reacción 8

Elaboración de 5H-cromeno[2,3-b]piridinas fenil-substituidas



XXXVIm $R_x = OH$ **XXXVIo** $R_x = SMe$ **XXXVIq** $R_x = CO_2H$ **XXXVIs** $R_x = CHO$ **XXXVIu** $R_x = C(O)Me$

↓ ↓ ↓ ↓ ↓

XXXVIn $R_x = OR_y$ **XXXVIp** $R_x = S(O)_nMe$ donde = 1,2 **XXXVIr** $R_x = C(O)NR_2{}^aR_2{}^b$ **XXXVIt** $R_x = CH(OH)R$ **XXXVIv** $R_x = C(OH)R_2{}^aR_2{}^b$

El Esquema de reacción 9 ilustra un número de métodos clásicos para sintetizar intermediarios reactivos XXXVIII - XLIII que se usan entonces para formar los heterociclos XLIV y XLV ($NHR_{11}Z$). El Esquema de reacción 5, reacción (1) muestra condiciones típicas para bromación en alfa de una cetona. En este caso específico,

la bromación se presenta primero en la posición bencílica y luego en la posición substituida por R8 deseada. Usando el procedimiento de Chi et al (Org. Lett. 2003, 5, 411-414), la dibromación seguido por desbromación con acetona proporciona la alfa-bromocetona deseada XXXVIII.

El Esquema de reacción 5, reacción (2) es la misma transformación como la reacción (1) pero cuando la posición bencílica se substituye con R^4 y R^5, la bromación se presenta selectivamente o exclusivamente en la posición deseada para dar la estructura XXXIX.

El Esquema de reacción 5, reacción (3) es un resumen del método de Takano (Heterocycles 1989, 29, 1861-1864; véase también Zhao et al Bioorg. Med. Chem. Lett. 1998, 6, 2531-2539) que describe el uso de cupratos para abrir la epiclorohidrina para formar clorohidrinas. Deberá notarse que los reactivos de Grignard por sí mismos abren los epóxidos ya sea en presencia o ausencia de sales de cobre (véase, Mazzocchi et al Synth Commun. 1986, 309-312; Eur. J. Med. Chem. 1979, 14, 165-170). La oxidación de la clorohidrina usando periodinano de Dess-Martin u otros oxidantes apropiados, proporciona la clorometilcetona deseada XL.

Otro método para formar clorometilcetonas se muestra en el Esquema de reacción 5, reacción (4). La litiación

de los grupos metilo activados usan butil-litio seguido por reacción con cloroacetilcloruro (o cloroacetato de etilo, Khim. Geterot. Soed. 1986, 6, 802-809) proporciona directamente el intermediario de clorometilcetona XLI.

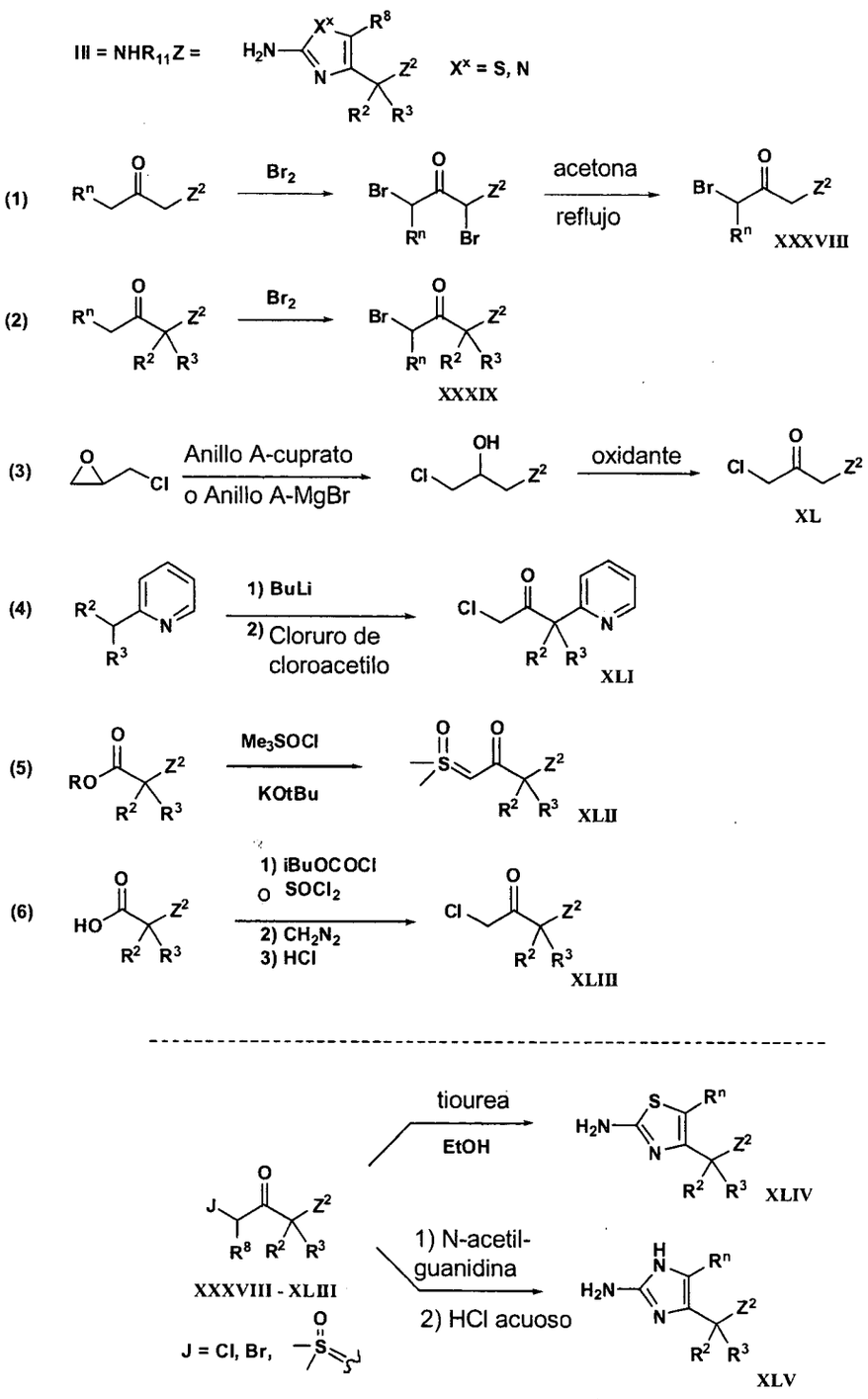
El Esquema de reacción 5, reacción (5) muestra el método de Nugent et al (J. Org. Chem. 2004, 69, 1629-1633) que usa metiluro de dimetilsulfoxonio para agregar nucleofílicamente a los ésteres que forma los iluros de β-ceto azufre reactivos XLII.

Por último, un procedimiento de homologación ácida ampliamente usado mostrado en el Esquema de reacción 5, reacción (6) involucra la conversión de un ácido carboxílico a un anhídrido mezclado (o cloruro ácido) seguido por tratamiento con diazometano y luego HCl para formar la clorometilcetona XLIII.

Los intermediarios reactivos XXXVIII - XLIII pueden tratarse con tiourea con o sin agregar ácido para proporciona los 2-aminotiazoles substituidos XLIV. La síntesis de los 2-aminoimidazoles substituidos XLV se realiza mejor usando el procedimiento de Little and Webber (J. Org. Chem. 1994, 59, 7299-7305) usando N-acetilguanidina como el nucleófilo seguido por hidrólisis ácida del grupo acetilo.

Esquema de reacción 9

Preparación de 2-aminotiazoles y 2-aminoimidazoles



Z^2 es un anillo cicloalquilo, cicloalquenilo, cicloheteroalquilo, arilo, o heteroarilo;

R^2 y R^3 son independientemente cada que se presentan hidrógeno, halógeno, hidroxi, alquilo, alquenilo, alquinilo, alcoxi, ciano, nitro, NR^eR^f, o CHO;

o R^2 y R^3 se combinan para formar =O o un enlace doble, en donde el enlace doble se substituye por hidrógeno, arilo, alquilo, alquenilo, alquinilo, alcoxi, amino, amino substituido, alcoxialquilo, alquilaminoalquilo, dialquilaminoalquilo, heteroarilo, cicloheteroalquilo, heteroarilalquilo, cicloheteroalquilalquilo, cicloalquilo, o cicloalquilalquilo;

R^e y R^f son independientemente cada que se presentan seleccionados de hidrógeno, arilo, alquilo, alquenilo, alquinilo, alcoxi, amino, amino substituido, alcoxialquilo, alquilaminoalquilo, dialquilaminoalquilo, heteroarilo, cicloheteroalquilo, heteroarilalquilo, cicloheteroalquilalquilo, cicloalquilo, y cicloalquilalquilo, con la condición de que R^e y R^f ambos no son alcoxi o amino;

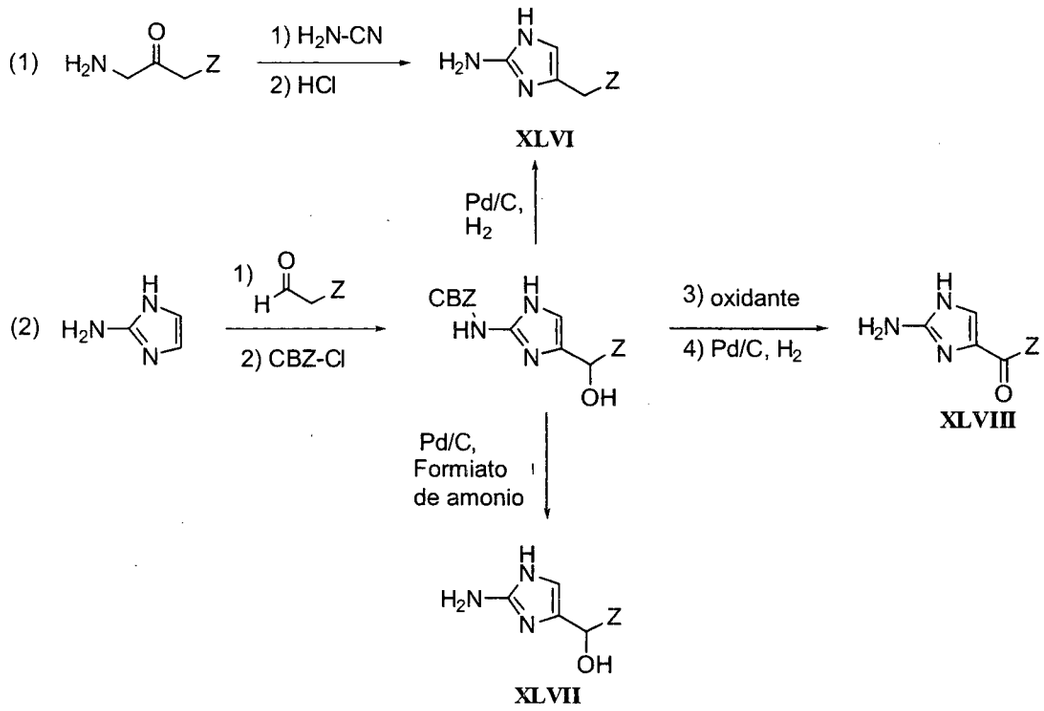
o R^e y R^f cada que se presentan pueden tomarse junto con el nitrógeno al cual se enlazan para formar un anillo heteroarilo o cicloheteroalquilo de 5, 6 ó 7 elementos que contiene 1, 2 ó 3 heteroátomos que pueden ser N, O, o S.

Otras dos síntesis de 2-aminoimidazoles se ilustran en el Esquema de reacción 10 a continuación. En el Esquema de

reacción 10, reacción (1), una aminometilcetona se condensa con cianamida para formar un intermediario de guanidinometilcetona que experimenta deshidratación durante el tratamiento con HCl (véase, Lancini and Lazzari, J. Het. Chem. 1966, 3, 152-154) para formar el compuesto XLVI. Las aminometil cetonas pueden sintetizarse a partir de los intermediarios reactivos XXXVIII-XLIII (Esquema de reacción 5) usando procedimientos estándar conocidos por aquellos expertos en la técnica.

Esquema de reacción 10

Síntesis Adicionales de 2-aminoimidazoles



El Esquema de reacción 10 (arriba) detalla el procedimiento de Horne et al (Tetrahedron. Lett. 1993, 34,

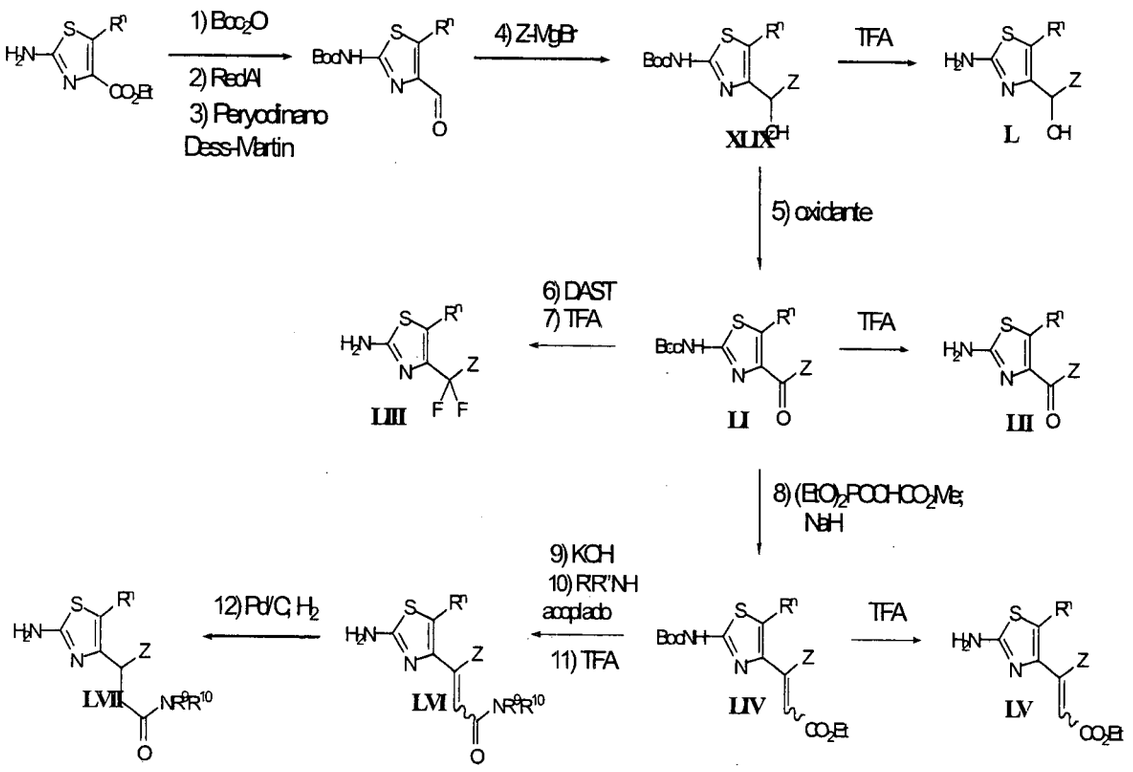
6981-6984) para hacer 2-aminoimidazoles substituidos. El 2-aminoimidazol comercialmente disponible reacciona con aldehídos para formar hidroxialquilaminoimidazoles que se protegen convenientemente *in situ* con un grupo CBZ *in situ* para facilitar la purificación. La hidrogenación catalítica de este intermediario bajo condiciones suaves, reduce primero el grupo CBZ para dar los hidroxialquilaminoimidazoles XLVIII. La hidrogenación prolongada bajo condiciones más fuertes reduce el grupo hidróxilo bencílico para dar el compuesto XLVI. Si el hidroxialquilaminoimidazol intermediario se oxida primero (usando periodinano de Dess-Martin por ejemplo) y luego se trata con bajo condiciones de hidrogenación suaves, se forma el compuesto 2-amino-4-cetoimidazol XLVIII.

El Esquema de reacción 11 ilustra varias otras transformaciones sintéticas para hacer 2-aminotiazoles substituidos. Partiendo del éster de 2-aminotiazol-4-carboxílico comercialmente disponible, el grupo amino se protegió usando anhídrido Boc y el éster se reduce con RedAl. La oxidación del alcohol con periodinano de Dess-Martin da el aldehído que puede experimentar reacciones con reactivos organometálicos tales como reactivos Grignard para dar el compuesto XLIX. La desprotección de TFA de XLIX da L que es fácil de unir a diferentes núcleos para hacer compuestos de la Fórmula I. Alternativamente,

la oxidación del intermediario XLIX da el compuesto ceto LI que puede desprotegerse para dar el compuesto LII, fluorado usando trifluoruro de azufre (dietilamino) (DAST) y desprotegiendo para dar el compuesto LIII, u homologado usando un procedimiento Horner-Wadsworth-Emmons para dar el éster α,β-insaturado LIV. El éster LIV puede desprotegerse con TFA para dar el compuesto LV, el éster se convierte usando procedimientos estándares a la amida LVI, y por último se reduce a la amida LVII.

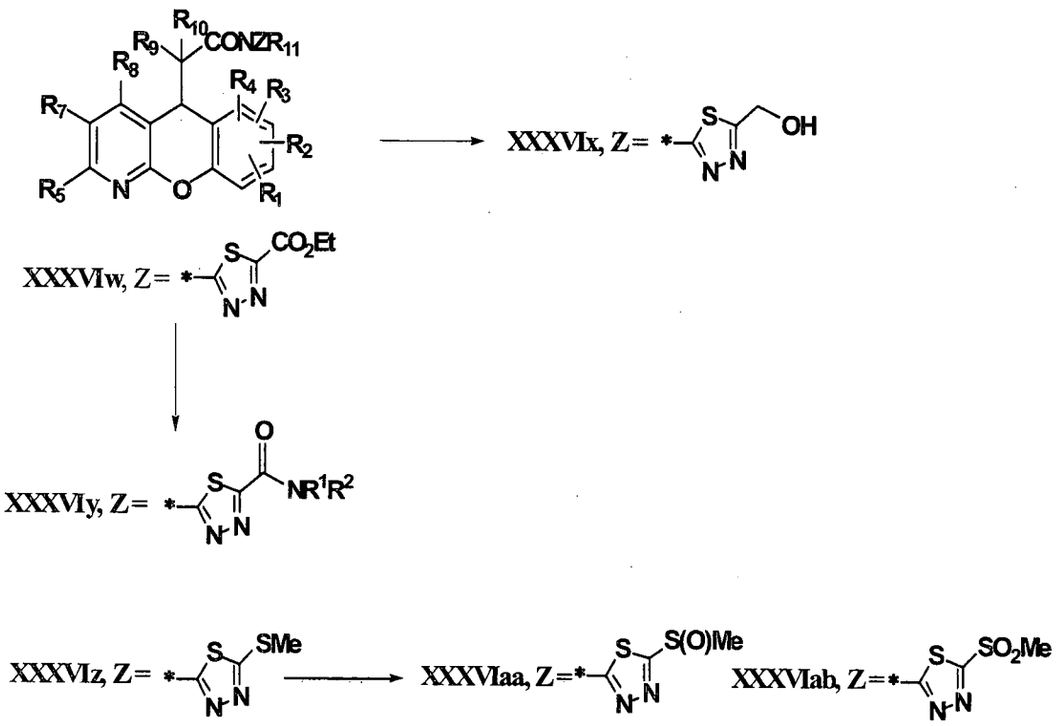
Esquema de reacción 11

Síntesis Adicional de 2-aminotiazoles



ESQUEMA DE REACCIÓN 12

Síntesis y Elaboración de 1,3,4-tiadiazoles



El Esquema de reacción 12 ilustra la preparación de algunos compuestos de los ejemplos en donde el grupo Z es un 1,3,4-tiadiazol 5-substituido. De esta manera, el éster XXXVIw puede reducirse por la acción de cualquier número de agentes reductores, tales como borohidruro de sodio, para dar el alcohol XXXVIx. Alternativamente, el éster XXXVIw también puede hidrolizarse a un ácido carboxílico (típicamente empleando hidróxido de sodio acuoso en metanol) que puede entonces experimentar la condensación con aminas primarias o secundarias bajo condiciones estándar

(tales como las descritas para la preparación de Ia a partir de II) para proporcionar las carboxamidas XXXVIy. Los compuestos de los ejemplos que contienen 5-alquiltio-1,3,4-tiadiazoles (XXXVIz) pueden oxidarse hasta los sulfóxidos (XXXVIaa) y/o sulfonas (XXVIab) bajo la acción de un oxidante apropiado, tal como m-CPBA.

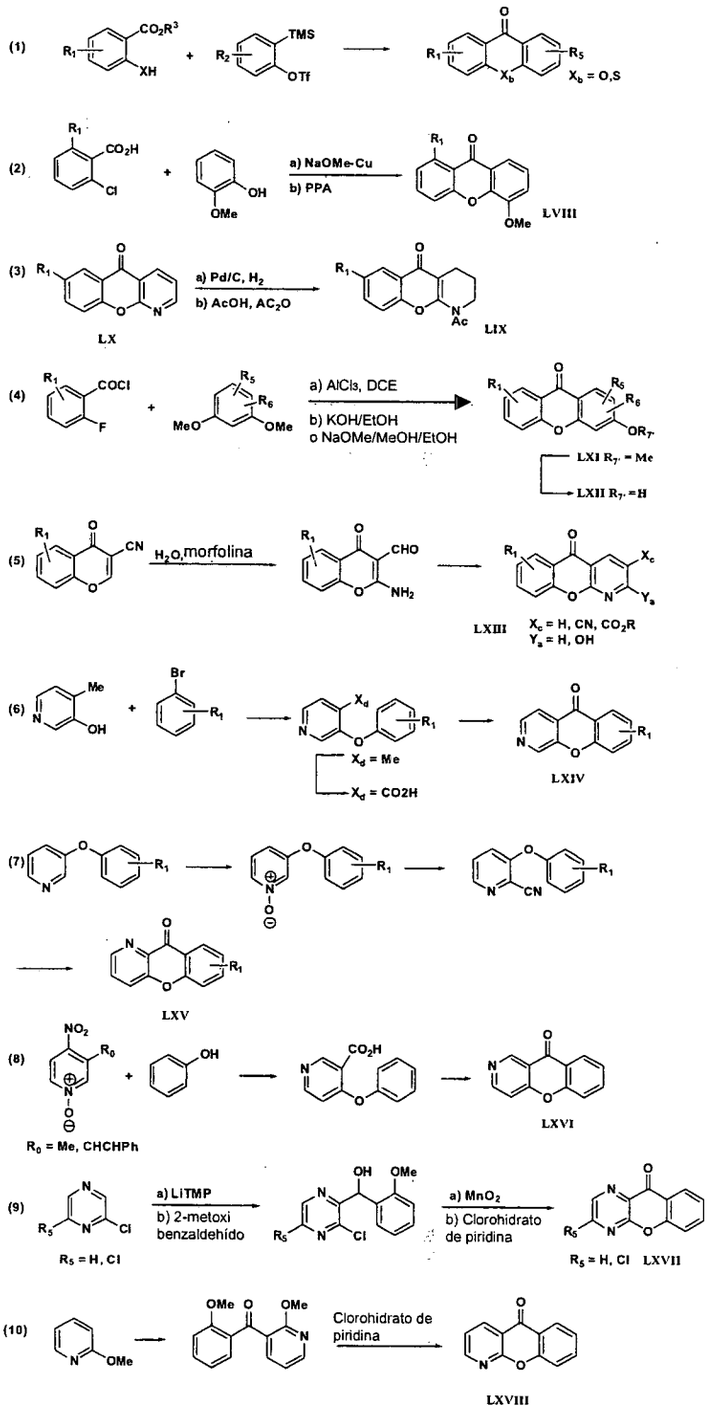
El Esquema de reacción 13 ilustra justo varias síntesis de cetonas IV que se han descrito en la literatura. El Esquema de reacción 13, reacción (1) muestra el método de Zhao and Larock (Organic Letters 2005, 7, 4273-4275) para la síntesis de un lote de xantonas y tioxantonas por la ciclización de unión en serie de arinos y salicilatos. El Esquema de reacción 13, secuencia de reacción (2) ilustra la preparación de xantonas LVIII por la condensación de Ullman de ácidos o-halobenzoicos y fenoles seguido por ciclización inducida por ácido polifosfórico, como se describe por Galt et al. (J. Med. Chem. 1989, 32, 2357-2362). Una variedad de xantonas substituidas con metilo, nitro, carboxi, y nitro pueden prepararse por un método similar (Pickert et al. Arch. Pharm. Pharm. Med. Chem. 1998, 331, 177-192). La química similar puede utilizarse para la preparación de los ácidos 9-oxo-9H-xanteno-4-acéticos variablemente substituidos como por

los procedimientos de Rewcastle et al. (J. Med. Chem. 1991, 34, 217-222 y J. Med. Chem. 1989, 32, 793). La 4-metoxixantona puede prepararse por el procedimiento de dos etapas descrito por Coelho et al. (Helv. Chim. Act. 2001, 84, 117-123). La 1-hidroxixantona pueden prepararse por la condensación del ácido salicíclico y resorcinol en presencia de cloruro de zinc (ibid). La 2-hidroxi y 3-hidroxixantona pueden prepararse siguiendo los métodos descritos por Lin et al. (J. Pharm. Sci. 1993, 82, 11) y Quillinan et al. (J. Pharm. Sci. 1965, 54, 633). El Esquema de reacción 13, secuencia de reacción (3) muestra la síntesis de 5H-[1]benzopirano[2,3-b]-1,2,3,4-tetrahidropiridin-5-onas LIX por la secuencia de dos etapas reportada por Pasutto et al. (Heterocycles 1985, 2293-2297). Las benzopiranopiridin-5-onas de partida LX pueden obtenerse por el método de Villani et al. (J. Med. Chem. 1975, 18, 1-8). El Esquema de reacción 13, secuencia de reacción (4) ilustra el método de Sato et al. (Chem. Pharm. Bull. 1990, 38, 1266-1277) que puede emplearse para la preparación de 3-metoxi y 3-hidroxi xantonas (LXI y LXII, respectivamente) por la acilación de Friedel-Crafts de éteres de resorcinol dimetilo con cloruros de o-fluoro benzoilo seguido por ciclización inducida por una base. Las 5H-[1]benzopirano[2,3-

b]piridin-5-onas LXIII (Esquema de reacción 13, secuencia de reacción (5)) pueden también prepararse a partir de 4-oxo-4H-1-benzopiran-3-carbonitrilos siguiendo los procedimientos descritos por Nohara et al. (J. Med. Chem. 1985, 28, 559-567). Las benzopiranopiridinas LXIV, LXV y LXVI (isómeros de benzopiranopiridin-5-onas LX) pueden prepararse por los métodos de Villani et al. (J. Med. Chem. 1975, 18, 1-8, Esquema de reacción 8, secuencias de reacción (6 - 8)). La benzopiranopiridina LXVI puede también prepararse a partir de (4-fluoro-3-piridil)-2-metoxifenilmetanona por el método de Marsais, et al. (J. Heterocycl. Chem. 1988, 25, 81-87) o de N,N-dietil-2-(piridina-4-iloxi)benzamida por el método de Familoni et al. (Syn. Lett. 1997, 9, 1081-1083). Las 10-oxo-10H-[1]benzopirano[2,3-b]pirazinas LXVII (Esquema de reacción 13, secuencia de reacción (9)) pueden prepararse por la secuencia de reacciones descrita por Turck et al. (Synthesis 1988, 11, 881-884 y J. Organometallic Chem. 1991, 412, 301-310). La 4-azaxantona LXVIII puede también prepararse como se muestra en el Esquema de reacción 8, reacción (10) (Trecourt, et al., J. Chem. Soc. Perkin Trans. 1990, 2409-2415).

Esquema de reacción 13

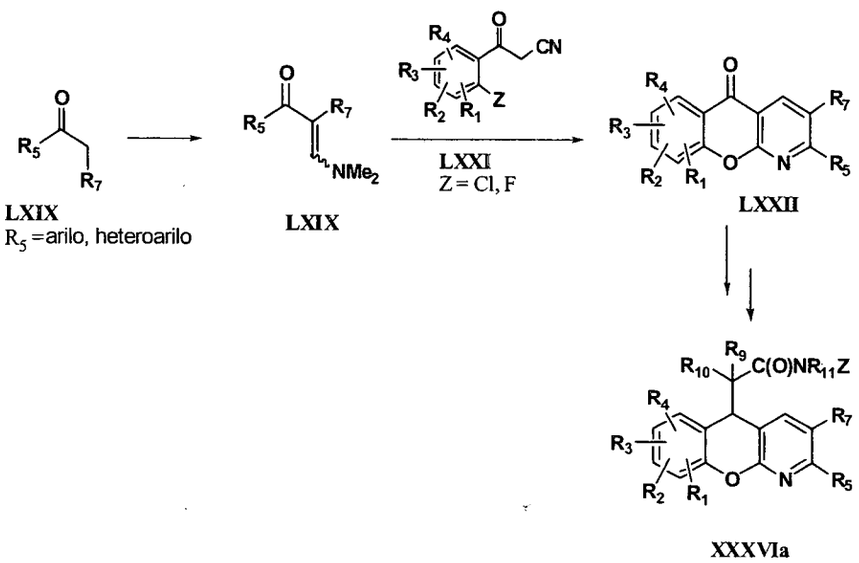
Preparación de cetonas IV



Una síntesis alternativa de los compuestos XXXVIa del ejemplo se describe en el Esquema de reacción 14. Las aril (o heteroaril) cetonas LXIX pueden convertirse a amidas de vinilo (LXX) por tratamiento con DMF dimetil acetal, típicamente al calentar una mezcla de los dos a reflujo durante la noche. Las cianoacetofenonas (LXXI) pueden adquirirse, o prepararse como se describe en la literatura (véase, por ejemplo, Ridge, David N. et al, J Med Chem 1979, 1385). Las cetonas LXXII pueden prepararse por condensación de LXX y LXXI en un solvente caliente (típicamente 120°C) (típicamente DMF o DMA) bajo condiciones ácidas (típicamente ácido acético). La elaboración del intermediario LXXII a los compuestos del título de la invención puede entonces llevarse a cabo como se describe en el Esquema de reacción 2 para la conversión de IV a II, y como se describe en el Esquema de reacción 1, para la conversión de II a Ia.

Esquema de reacción 14

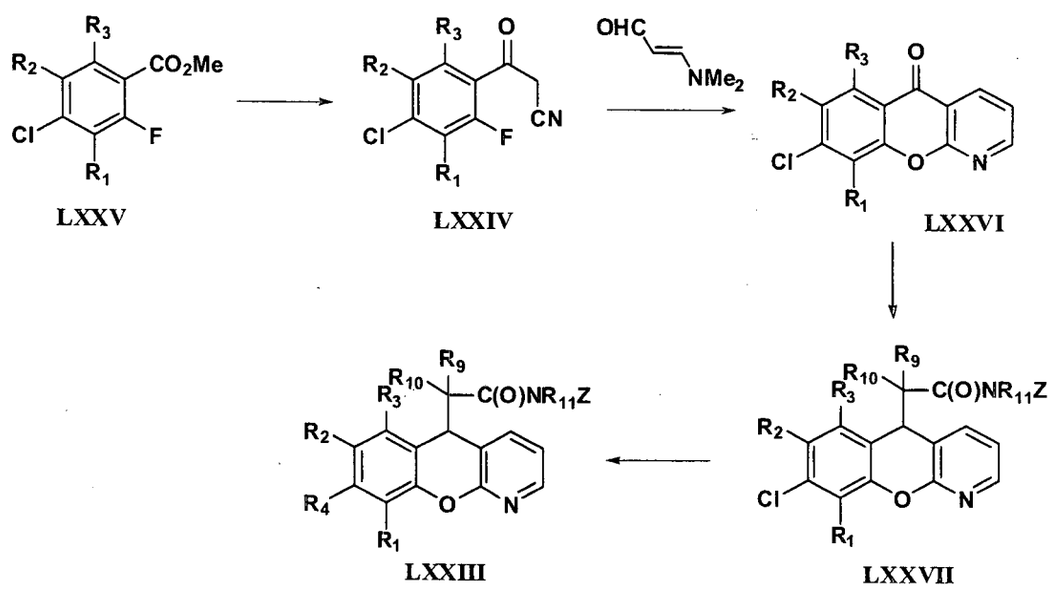
Preparation y Elaboración de 2-aril-5H-cromeno[2,3-b]piridina-5-onas



Otra síntesis de los compuestos de la invención (LXXIII) se describe en el Esquema de reacción 15. Las para-cloro-cianoacetofenonas LXXIV pueden prepararse como se describe para la preparación de LXXI. Alternativamente, LXXIV puede prepararse por el tratamiento de alquil-p-clorobenzoatos (LXXV) con el anión derivado del tratamiento de acetonitrilo con una base fuerte (preferiblemente LDA). La condensación de LXXIV con (E)-3-dimetilamino)acrilaldehído puede llevarse a cabo como se describe para la conversión de LXX a LXXII (Esquema de reacción 14) para proporcionar las cetonas LXXVI. LXXVI puede elaborarse para amidas LXXVII como se describe para la conversión de IV a II (Esquema de reacción 2) y II a Ia (Esquema de reacción 1). La conversión de LXXVII a LXXIII puede entonces llevarse a cabo como se describe para la preparación de XXXVb a partir de XXXIV, empleando un catalizador de paladio/ligando útil para la arilación de unión cruzada de cloruros de arilo (véase, por ejemplo, Littke, A.F.; Angew. Chem. IEE 2002, 4176). Los cloruros de arilo LXXVII también puede convertirse a LXXIII por medio de un éster de boronato, como se describe para la conversión de XXVa a XXVI por medio de XXVb (Esquema de reacción 4).

Esquema de reacción 15

Preparación y Elaboración de 8-cloro-5H-cromeno[2,3]b-piridin-5-onas



Definiciones

Las siguientes son definiciones de términos usados en esta especificación y reivindicaciones adjuntas. La definición inicial proporcionada para un grupo o término aquí, aplica para aquel grupo o término en toda la especificación y reivindicaciones, individualmente o como parte de otro grupo, a menos que se indique de otra forma.

El término "alquilo" solo o como parte de otros grupos hidrocarburos de cadena recta o ramificada que tienen 1 a 12 átomos de carbono, preferiblemente 1 a 8 átomos de carbono. Los grupos alquilo inferior, es decir, grupos alquilo de 1 a 4 átomos de carbono, son los más preferidos. Cuando aparecen

números en un subíndice después del símbolo "C", el subíndice define con más especificidad el número de átomos de carbono que un grupo particular puede contener. Por ejemplo, "alquilo C_{1-6}" se refiere a grupos alquilo de cadena recta o ramificada con uno a seis átomos de carbono, tales como metilo, etilo, n-propilo, isopropilo, n-butilo, t-butilo, n-pentilo, y ambos. El subíndice "0" se refiere a un enlace. Por consiguiente, el término hidroxi alquilo (C_{0-2}) o hidroxialquilo(C_{0-2}) incluye hidroxi, hidroximetilo e hidroxietilo.

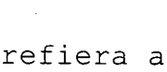
El "alquilo" incluye "alquilo substitudo" y "no substituido" en donde el alquilo puede substituirse con cualquiera de los substituyentes por el alquilo substituido que se describe a continuación.

El término "alquilo sustituido" se refiere a un grupo alquilo como se definió anteriormente que tiene uno, dos, o tres substituyentes seleccionados del grupo que consiste de halo (por ejemplo, trifluorometilo), alquenilo, alquenilo sustituido, alquinilo, nitro, ciano, oxo (=O), OR_a, SR_a, (=S), $-NR_aR_b$, $-N(alquilo)_3^+$, $-NR_aSO_2$, $-NR_aSO_2R_c$, $-SO_2R_c$, $-SO_2NR_aR_b$, $-SO_2NR_aC(=O)R_b$, SO_3H, $-PO(OH)_2$, $-C(=O)R_a$, $-CO_2R_a$, $-C(=O)NR_aR_b$, $-C(=O)(alquileno\ C_{1-4})NR_aR_b$, $-C(=O)NR_a(SO_2)R_b$, $-CO_2(alquilenoC_{1-4})NR_aR_b$, $-NR_aC(=O)R_b$, $-NR_aCO_2R_b$, $-NR_a(alquileno\ C_{1-4})CO_2R_b$, =N-OH, =N-O-alquilo, arilo, cicloalquilo, heterociclo, y/o heteroarilo, en donde R_a y R_b son los mismos o diferente y se seleccionan

independientemente de hidrógeno, alquilo, alquenilo, CO_2H, CO_2(alquilo), cicloalquiloC_{3-7}, fenilo, bencilo, feniletilo, naftilo, un heterociclo de cuatro a siete elementos, o un heteroarilo de cinco a seis elementos, o cuando se une al mismo átomo de nitrógeno puede unirse para formar un heterociclo o heteroarilo, y R_c se selecciona a partir de los mismos grupos como R_a y R_b pero no es hidrógeno. Cada grupo R_a y R_b cuando es diferente a hidrógeno, y cada grupo R_c opcionalmente tiene hasta tres substituyentes adicionales unidos a cualquier carbono disponible o átomo de nitrógeno de R_a, R_b y/o R_c, el(los) substituyente(s) son los mismos o diferentes y se selecciona independientemente del grupo que consiste de alquilo(C_{1-6}), alquenilo(C_{2-6}), hidroxi, halógeno, ciano, nitro, CF_3, O(alquiloC_{1-6}), OCF_3, C(=O)H, C(=O)(alquiloC_{1-6}), CO_2H, CO_2(alquiloC_{1-6}), $NHCO_2$(alquiloC_{1-6}), -S(alquiloC_{1-6}), $-NH_2$, NH(alquiloC_{1-6}), N(alquiloC_{1-6})$_2$, $N(CH_3)_3^+$, SO_2(alquiloC_{1-6}), C(=O)(alquilenoC$_{1-4}$)NH_2, C(=O)(alquilenoC$_{1-4}$)NH(alquilo), C(=O)(alquilenoC$_{1-4}$)N(alquilo C_{1-4})$_2$, cicloalquiloC_{3-7}, fenilo, bencilo, feniletilo, feniloxi, benciloxi, naftilo, un heterociclo de cuatro a siete elementos, o un heteroarilo de cinco a seis elementos. Cuando un alquilo sustituido se sustituye con un grupo arilo, heterociclo, cicloalquilo, o heteroarilo, los sistemas de anilla son como se definen posteriormente y

PCT/US 486

por consiguiente pueden tener cero, uno, dos o tres substituyentes, también como se define posteriormente y/o como se define para el alquilo substituido.

Un experto en la técnica entenderá que, cuando la designación "CO_2" se usa en la presente, esta se pretende que se refiera al grupo  .

Cuando el término "alquilo" se usa conjuntamente con otro grupo, tal como en "arilaquilo", esta conjunción define con más especificidad al menos uno de los substituyentes que el alquilo sustituido contendrá. Por ejemplo, "arilalquilo" se refiere a un grupo alquilo sustituido como se definió anteriormente en donde al menos uno de los substituyentes es un arilo, tal como bencilo. Por consiguiente, el término aril alquilo(C_{0-4}) incluye un alquilo inferior sustituido que tiene al menos un substituyente arilo y también incluye un arilo directamente unido a otro grupo, es decir, aril alquilo(C_0).

El término "alquenilo" (el cual incluye alquenilo substituido o no substituido) solo o como parte de otro grupo se refiere a grupos de hidrocarburo de cadena recta o ramificada que tiene 2 a 12 átomos de carbono y al menos un doble enlace. Los grupos alquenilo de 2 a 6 átomos de carbono y que tienen un doble enlace son más preferidos.

El término "alquinilo" (el cual incluye alquinilo substituido o no substituido) solo o como parte de otro grupo

NC 487

se refiere a grupos de hidrocarburos de cadena recta o ramificada que tienen 2 a 12 átomos de carbono y al menos un triple enlace. Los grupos alquinilo de 2 a 6 átomos de carbono y que tienen un triple enlace son más preferidos.

El término "alquileno" (el cual incluye alquileno substituido o no substituido) solo o como parte de otro grupo se refiere a grupos bivalentes de hidrocarburos de cadena recta o ramificada que tienen 1 a 12 átomos de carbono, preferiblemente 1 a 8 átomos de carbono, por ejemplo, $\{-CH_2-\}_n$, en donde n es 1 a 12, preferiblemente 1-8. Los grupos alquileno inferior, es decir, grupos alquileno de 1 a 4 átomos de carbono, son más preferidos. Los términos "alquenileno" y "alquinileno" se refieren a radicales bivalentes de grupos alquenilo y alquinilo, respectivamente, como se definió anteriormente.

Cuando se hace referencia a un grupo alquenilo, alquinilo, alquileno, alquenileno o alquinileno sustituido, estos grupos se sustituyen con uno a tres substituyentes como se definió anteriormente para grupos alquilo sustituidos.

El término "heteroalquileno" (el cual incluye heteroalquileno substituido o no substituido) solo o como parte de otro grupo se usa en la presente para referirse a grupos hidrocarburos de cadena recta o ramificada, bivalentes, saturados e insaturados, que tienen de 2 a 12 átomos de carbono, preferiblemente de 2 a 8 átomos de carbono, en donde

uno o dos átomos de carbono en la cadena recta se remplazan por heteroátomos seleccionados de -O-, -S-, -S(=O)-, $-SO_2-$, -NH-, y $-NHSO_2-$. Por consiguiente, el término "heteroalquileno" incluye grupos bivalentes de alcoxi, tioalquilo, y aminoalquilo, como se define posteriormente, así como también grupos alquileno y alquenileno que tienen una combinación de heteroátomos en la cadena alquilo. Como una ilustración, un "heteroalquileno" aquí puede comprender grupos tales como $-S-(CH_2)_{1-5}NH-CH_2-$, $-O-(CH_2)_{1-5}S(=O)-CH_2-$, $-NHSO_2-CH_2-$, $-CH_2-NH-$ y ambos. Preferiblemente, un heteroalquileno no tiene dos átomos adyacentes simultáneamente seleccionados de -O- y -S-. Cuando un subíndice se usa con el término heteroalquileno, por ejemplo, como en heteroalquilenoC_{2-3}, el subíndice se refiere al número de átomos de carbono en el grupo además de heteroátomos. Así, por ejemplo, un heteroalquilenoC_{1-2} puede incluir grupos tales como $-NH-CH_2-$, $-CH_2-NH-CH_2-$, $-CH_2-CH_2-NH-$, $-S-CH_2-$, $-CH_2-S-CH_2-$, $-O-CH_2-NH-CH_2-$, CH_2-O-CH_2, etc.

El término "heteroalquileno sustituido" se refiere a un grupo heteroalquileno como se definió anteriormente en donde al menos uno de los átomos de nitrógeno o carbono en la cadena heteroalquileno se enlaza a (o sustituido con) un grupo diferente del hidrógeno. Los átomos de carbono en la cadena heteroalquileno se pueden sustituir con un grupo seleccionado de aquellos citados anteriormente para grupos alquilo sustituidos, o con un grupo alquilo sustituido o alquilo

adicional. Los átomos de nitrógeno de la cadena heteralquileno se pueden sustituir con un grupo seleccionado de alquilo, alquenilo, alquinilo, ciano, y A_1-Q-A_2-R_{16}, en donde A_1 es un enlace, alquileno(C_{1-3}), o alquenileno(C_{2-3}); Q es un enlace, -C(=O)-, -C(=O)NR_d-, -(=S)NR_d-, -SO_2-, -SO_2NR_d-, -CO_2-, o-NR_dCO_2-; A_2 es un enlace, alquilenoC_{1-3}, alquenilenoC_{2-3}, -alquilenoC_{1-4}-NR_d-, alquilenoC_{1-4}-NR_dC(=O)-, alquilenoC_{1-4}-S-, alquileno C_{1-4}-SO_2-, o alquileno C_{1-4}-O-, en donde los grupos alquileno A_2 son de cadena recta o ramificada y opcionalmente sustituidos como se define en la presente por alquileno substituido; R_h es hidrógeno, alquilo, alquilo substituido, alquenilo, alquenilo substituido, arilo, heteroarilo, heterociclo, o cicloalquilo; y R_d se selecciona de hidrógeno, alquilo y alquilo sustituido como se define en la presente, siempre que, no obstante, R_h no sea hidrógeno cuando A_1, Q y A_2 sean cada uno enlaces. Cuando R_h es un arilo, heteroarilo, cicloalquilo, o heterociclo, estos anillos son, a su vez, opcionalmente sustituidos con uno a tres grupos como se define posteriormente en las definiciones para estos términos.

El término "alcoxi" se refiere a un grupo alquilo o alquilo sustituido como se definió anteriormente que tiene uno o dos átomos de oxígeno (-O-) en la cadena alquilo. Por ejemplo, el término "alcoxi" incluye los grupos -O-alquiloC_{1-12}, -(alquilenoC_{1-6})-O-alquiloC_{1-6}, -(alquilenoC_{1-4}-O-alquilenoC_{1-4})-O-alquiloC_{1-4}, y etcétera.

El término "tioalquilo" o "alquiltio" se refiere a un grupo alquilo o alquilo sustituido como se define que tiene uno o dos átomos de azufre en la cadena alquilo. Por ejemplo, el término "tioalquilo" o "alquiltio" incluye los grupos -S-alquiloC_{1-12}, -(S-alquilenoC_{1-6})-S-alquiloC_{1-6}, y etcétera.

Los términos "aminoalquilo" o "alquilamino" se refieren a un grupo alquilo o alquilo sustituido como se definió anteriormente que tiene uno o dos átomos de nitrógeno (-NR-) en la cadena alquilo. Por ejemplo, el término "aminoalquilo" incluye los grupos -NR-alquiloC_{1-12}, -NR-alquilenoC_{1-6}-NR-alquiloC_{1-6}, etc., (en donde R es preferiblemente hidrógeno pero puede incluir alquilo o alquilo sustituido como se definió anteriormente). Cuando un subíndice se usa con referencia a un alcoxi, tioalquilo o aminoalquilo, el subíndice se refiere a un número de átomos de carbono que el grupo puede contener además de heteroátomos. Así, por ejemplo, aminoalquiloC_{1-2} monovalente incluye los grupos $-CH_2-NH_2$, $-NH-CH_3$, $-(CH_2)_2-NH_2$, $-NH-CH_2-CH_3$, $-CH_2-NH_2-CH_3$, y $-N-(CH_3)_2$. Un aminoalquilo inferior comprende un aminoalquilo que tiene uno a cuatro átomos de carbono. "Amino" se refiere al grupo NH_2.

Los grupos alcoxi, tioalquilo, o aminoalquilo pueden ser monovalentes o bivalentes. Por "monovalente" se entiende que el grupo tiene una valencia (es decir, se puede combinar con otro grupo), de uno, y por "bivalente"

se entiende que el grupo tiene una valencia de dos. Así, por ejemplo, un alcoxi monovalente incluye grupos tales como -O-alquiloC_{1-12}, -alquilenoC_{1-6}-O-alquiloC_{1-6}, -alquilenoC_{1-4}-O-alquilenoC_{1-4}-O-alquiloC_{1-4}, mientras que un alcoxi bivalente incluye grupos tales como -O-alquilenoC_{1-12}-, -alquilenoC_{1-6}-O-alquilenoC_{1-6}-, -alquilenoC_{1-4}-O-alquilenoC_{1-4}-O-alquilenoC_{1-4}-, y ambos.

Se deberá entender que las selecciones para alcoxi, tioalquilo, y aminoalquilo se hará por un experto en el campo para proporcionar compuestos estables. Así, por ejemplo, en los compuestos de la fórmula I, cuando R_5, R_6, R_7 ó R_8 se enlanzan al átomo de nitrógeno (N*) del anillo B y se selecciona de un grupoalcoxi o alquiltio, los grupos alcoxi y alquiltio deberán tener al menos un átomo de carbono directamente enlazado al anillo B (a N*), con los átomos de oxígeno o azufre que tienen al menos un átomo lejos del átomo de nitrógeno.

El término "acilo" solo o como parte de otro grupo se refiere a un grupo carbonilo enlazado a un radical orgánico, más particularmente, el grupo C(=O)R_e, así como también los grupos bivalentes -C(=O)- o -C(=O)R_e-, los cuales se enlazan a radicales orgánicos o un anillo en los compuestos de la fórmula I. El grupo R_e se puede seleccionar de alquilo, alquenilo, alquinilo, aminoalquilo, alquilo sustituido, alquenilo sustituido, o

alquinilo sustituido, como se define aquí, o cuando sea apropiado, el grupo bivalente correspondiente, por ejemplo, alquileno, alquenileno, etc. Por consiguiente, en los compuestos de la fórmula I, cuando se describe que R_1 hasta R_8 puede ser "acilo", este se pretende que abarque una selección para R_1 hasta R_8 de -C(=O)- y también los grupos $-C(=O)R_e-$ o $-R_eC(=O)-$, en donde en este caso, el grupo R_e se seleccionará de grupos bivalentes, por ejemplo, alquileno, alquenileno, alquinileno, aminoalquilo bivalente, alquileno sustituido, alquenileno sustituido, o alquinileno sustituido.

El término "alcoxicarbonilo" solo o como parte de otro grupo se refiere a un grupo

carboxi $(-\overset{O}{\overset{\|}{C}}-O- \text{ o } -O-\overset{O}{\overset{\|}{C}}-)$ enlazado a un radical orgánico (CO_2R_e), así como también los grupos bivalentes $-CO_2-$, $-CO_2R_e-$ los cuales se enlazan a radicales orgánicos en compuestos de la fórmula (I), en donde R_e es como se definió anteriormente para acilo. El radical orgánico al cual el grupo carboxi se une, puede ser monovalente (por ejemplo, $-CO_2$-alquilo o -OC(=O)alquilo), o bivalente (por ejemplo, $-CO_2$-alquileno, -OC(=O)alquileno, etc.). Por consiguiente, "alcoxicarbonilo", se pretende que abarque los grupos $-CO_2R_e-$ o $-R_eCO_2-$, en donde en este ejemplo, el grupo R_e se seleccionará de los grupos bivalentes, por ejemplo, alquileno, alquenileno, alquinileno,

aminoalquilo bivalente, alquileno sustituido, alquenileno sustituido, o alquinileno sustituido.

El término "amida" o "amidilo" solo o como parte de otro grupo se refiere al grupo $C(=O)NR_aR_b$ (u otros grupos R con objeto de que R_a o R_b se liguen a un átomo N), en donde los grupos R_a y R_b se definen como se citó anteriormente en la definición para grupos alquilo sustituidos.

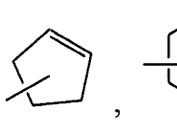
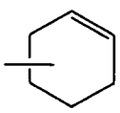
El término "sulfonilo" solo o como parte de otro grupo se refiere a un grupo sulfóxido enlazado a un radical orgánico en los compuestos de la fórmula (I), más particularmente, el grupo monovalente $S(O)_{1-2}-R_e$, o el grupo bivalente $-S(O)_{1-2}-$ se enlaza a los radicales orgánicos en los compuestos de la fórmula I. Por consiguiente, en los compuestos de la fórmula I, "sulfonilo", se propone que abarque $-S(=O)-$ o $-SO_2-$ así como también los grupos $-S(=O)R_e-$, $-R_eS(=O)-$, $-SO_2R_e-$, o $-R_eSO_2-$, en donde en este ejemplo, el grupo R_e se seleccionará de aquellos descritos anteriormente para los grupos acilo y alcoxicarbonilo.

El término "sulfonamidilo" solo o como parte de otro grupo se refiere al grupo $-S(O)_2NR_aR_b$, (u otro grupo R con objeto de que R_a o R_b se liguen a un átomo N), en donde R_a y R_b son como se definieron anteriormente para grupos alquilo substituidos. Adicionalmente, el grupo sulfonamidilo puede ser bivalente, en este caso uno de los grupos R_a y R_b será un enlace. Por consiguiente, en los compuestos de la fórmula I, sulfonamidilo se pretende que signifique que $-S(O)_2NR_a-$.

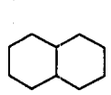
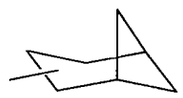
El término "cicloalquilo" solo o como parte de otro grupo se refiere a un grupo hidrocarburo cíclico parcialmente saturado o completamente saturado que contiene desde 3 hasta 9 anillos, preferiblemente 3 hasta 8 carbonos por anillo. En consecuencia, el término "cicloalquilo" se intenta para incluir un anillo de cicloalquenilo (por ejemplo, ciclohexenilo). El término "cicloalquilo" incluye tales anillos que tienen cero, uno, dos o tres substituyentes seleccionados del grupo que consiste de halógeno, trifluorometilo, trifluorometoxi, alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, nitro, ciano, oxo (=O), OR_a, SR_a, (=S), $-NR_aR_b$, $-N(alquilo)_3^+$, $-NR_aSO_2$, $-NR_aSO_2R_c$, $-SO_2R_c$, $-SO_2NR_aR_b$, $-SO_2NR_aC(=O)R_b$, SO_3H, $-PO(OH)_2$, $-C(=O)R_a$, $-CO_2R_a$, $-C(=O)NR_aR_b$, $-C(=O)(alquilenoC_{1-4})NR_aR_b$, $-C(=O)NR_a(SO_2)R_b$, $-CO_2(alquilenoC_{1-4})NR_aR_b$, $-NR_aC(=O)R_b$, $-NR_aCO_2R_b$, $-NR_a(alquilenoC_{1-4})CO_2R_b$, =N-OH, =N-O-alquilo, arilo, cicloalquilo, heterociclo, y/o heteroarilo, en donde R_a, R_b y R_c son como se definieron anteriormente para grupos alquilo sustituidos, y también son a su vez opcionalmente sustituidos como se mencionó anteriormente en la definición para grupos alquilo sustituidos. El término "cicloalquilo" también incluye tales anillos que tienen un segundo anillo fusionado a este (por ejemplo, incluyendo anillos benzo, heterociclo, o heteroarilo) o que tienen un puente de carbono-carbono de 3 a 4 átomos de carbono. Cuando un cicloalquilo está sustituido con un anillo adicional (o tiene un segundo anillo fusionado a este), el anillo a su vez está opcionalmente sustituido con uno a dos de $alquilo(C_{1-4})$, $alquenilo(C_{2-4})$, halógeno, hidroxi, ciano, nitro, CF_3, $O(alquiloC_{1-4})$,

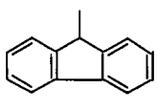
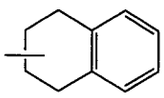
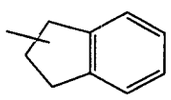
OCF_3, C(=O)H, C(=O)(alquilo C_{1-4}), CO_2H, CO_2(alquiloC_{1-4}), $NHCO_2$(alquiloC_{1-4}), -S(alquiloC_{1-4}), $-NH_2$, NH(alquiloC_{1-4}), N(alquiloC_{1-4})$_2$, N(alquiloC_{1-4})$_3^+$, SO_2(alquiloC_{1-4}), C(=O)(alquilenoC_{1-4})NH_2, C(=O)(alquilenoC_{1-4})NH(alquilo), y/o C(=O)(alquilenoC_{1-4})N(alquiloC_{1-4})$_2$.

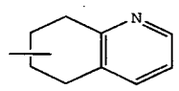
Por consiguiente, en los compuestos de la fórmula (I), el término "cicloalquilo" incluye ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, etc., así como también los siguientes sistemas de anillo,

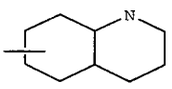
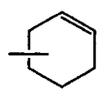

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y similares, los cuales opcionalmente se pueden sustituir en cualquiera de los átomos disponibles del(los) anillo(s). Los grupos cicloalquilo preferidos incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, 
y

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El término "halo" o "halógeno" solo o como parte de otro grupo se refiere a cloro, bromo, fluoro y yodo.

El término "haloalquilo" solo o como parte de otro grupo significa un alquilo sustituido que tiene uno o más substituyentes halo. Por ejemplo, "haloalquilo" incluye mono,

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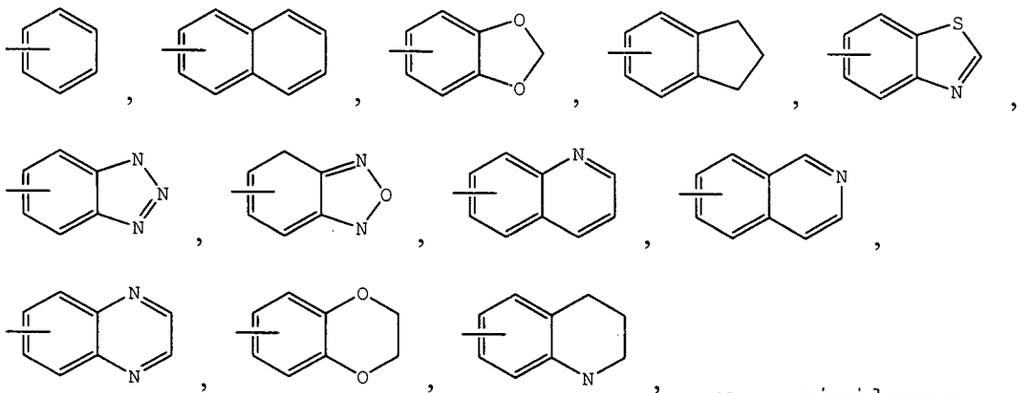
bi, y trifluorometilo.

El término "haloalcoxi" solo o como parte de otro grupo significa un grupo alcoxi que tiene uno o más substituyentes halo. Por ejemplo, "haloalcoxi" incluye OCF_3.

El término "arilo" solo o como parte de otro grupo se refiere a fenilo, bifenilo, 1-naftilo y 2-naftilo. El término "arilo" incluye los anillos que tienen cero, uno, dos o tres substituyentes seleccionados del grupo que consiste de halógeno, trifluorometilo, trifluorometoxi, alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, nitro, ciano, OR_a, SR_a, (=S), $-NR_aR_b$, $-N(alquilo)_3^+$, $-NR_aSO_2$, $-NR_aSO_2R_c$, $-SO_2R_c$-$SO_2NR_aR_b$, $-SO_2NR_aC(=O)R_b$, SO_3H, $-PO(OH)_2$, $-C(=O)R_a$, $-CO_2R_a$, $-C(=O)NR_aR_b$, $-C(=O)(alquilenoC_{1-4})NR_aR_b$, $-C(=O)NR_a(SO_2)R_b$, $-CO_2(alquilenoC_{1-4})NR_aR_b$, $-NR_aC(=O)R_b$, $-NR_aCO_2R_b$, $-NR_a$(alquileno C_{1-4})CO_2R_b, arilo, cicloalquilo, heterociclo, y/o heteroarilo, en donde R_a, R_b y R_c son como se definieron anteriormente para grupos alquilo sustituidos, y también a su vez son opcionalmente sustituidos como se mencionó anteriormente o cualquiera de los substituyentes para el alquilo establecido anteriormente. Adicionalmente, dos substituyentes unidos a un arilo, particularmente un grupo fenilo, pueden unirse para formar un anillo adicional tal como un anillo espiro o fusionado, por ejemplo, ciclopentilo o ciclohexilo, o heteroarilo o heterociclo fusionado. Cuando un arilo está sustituido con un anillo adicional (o tiene un segundo anillo fusionado a éste), el

anillo a su vez está opcionalmente sustituido con uno a dos de alquilo(C_{1-4}), alquenilo(C_{2-4}), halógeno, hidroxi, ciano, nitro, CF_3, O(alquiloC_{1-4}), OCF_3, C(=O)H, C(=O)(alquilo C_{1-4}), CO_2H, CO_2(alquiloC_{1-4}), $NHCO_2$(alquiloC_{1-4}), -S(alquiloC_{1-4}), $-NH_2$, NH(alquiloC_{1-4}), N(alquiloC_{1-4})$_2$, N(alquiloC_{1-4})$_3^+$, SO_2(alquiloC_{1-4}), C(=O)(alquilenoC$_{1-4}$)NH_2, C(=O)(alquilenoC$_{1-4}$)NH(alquilo), y/o C(=O)(alquilenoC$_{1-4}$)N(alquilo C_{1-4})$_2$.

Así, los ejemplos de grupos arilo incluyen:



y similares, los cuales opcionalmente se pueden sustituir en cualquier átomo de nitrógeno o carbono disponible. Un grupo arilo preferido es fenilo opcionalmente sustituido.

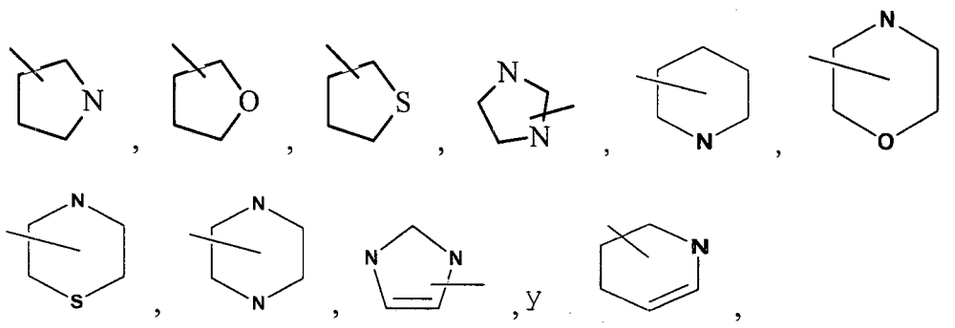
Los términos "heterociclo" o "heterocíclico" o "cicloheteroalquilo" solos o como parte de otro grupo se refieren a grupos monocíclicos de 3 a 7 elementos no aromáticos substituidos o no substituidos, grupos bicíclicos de 7 a 11 elementos, y grupos tricíclicos de 10 a 15 elementos, en los cuales al menos uno de los anillos tiene al menos un heteroátomo (O, S o N) (también referido

como cicloheteroalquilo o heterocicloalquilo). Cada anillo del grupo heterociclo que contiene un heteroátomo puede contener uno o dos átomos de azufre u oxígeno y/o uno a cuatro átomos de nitrógeno con la condición de que el número total de heteroátomos en cada anillo sea cuatro o menos, y adicionalmente con la condición de que el anillo contenga al menos un átomo de carbono. Los anillos fusionados que completan los grupos bicíclicos y tricíclicos pueden contener solamente átomos de carbono y pueden estar saturados, parcialmente saturados, o insaturados. El nitrógeno y los átomos de azufre se pueden oxidar opcionalmente y los átomos de nitrógeno se pueden cuaternizar opcionalmente. El grupo heterociclo se puede unir a cualquier átomo de carbono o nitrógeno disponible. El anillo heterociclo puede contener cero, uno, dos o tres substituyentes seleccionados de halógeno, trifluorometilo, trifluorometoxi, alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, nitro, ciano, oxo(=O), OR_a, SR_a, (=S), $-NR_aR_b$, $-N(alquilo)_3^+$, $-NR_aSO_2$, $-NR_aSO_2R_c$, $-SO_2R_c$-$SO_2NR_aR_b$, $-SO_2NR_aC(=O)R_b$, SO_3H, $-PO(OH)_2$, $-C(=O)R_a$, $-CO_2R_a$, $-C(=O)NR_aR_b$, $-C(=O)(alquilenoC_{1-4})NR_aR_b$, $-C(=O)NR_a(SO_2)R_b$, $-CO_2(alquilenoC_{1-4})NR_aR_b$, $-NR_aC(=O)R_b$, $-NR_aCO_2R_b$, $-NR_a(alquilenoC_{1-4})CO_2R_b$, =N-OH, =N-O-alquilo, arilo, cicloalquilo, heterociclo, y/o heteroarilo, en donde R_a, R_b y R_c son como se definieron anteriormente para

grupos alquilo sustituidos, y también a su vez son opcionalmente sustituidos como se mencionó anteriormente. Cuando un heterociclo está sustituido con un anillo adicional, el anillo a su vez está opcionalmente sustituido con uno a dos de alquilo(C_{1-4}), alquenilo(C_{2-4}), halógeno, hidroxi, ciano, nitro, CF_3, O(alquiloC_{1-4}), OCF_3, C(=O)H, C(=O)(alquiloC_{1-4}), CO_2H, CO_2(alquiloC_{1-4}), $NHCO_2$(alquiloC_{1-4}), -S(alquiloC_{1-4}), $-NH_2$, NH(alquiloC_{1-4}), N(alquiloC_{1-4})$_2$, N(alquiloC_{1-4})$_3^+$, SO_2(alquilo C_{1-4}), C(=O)(alquilenoC$_{1-4}$)NH_2, C(=O)(alquilenoC$_{1-4}$)NH(alquilo), y/o C(=O)(alquilenoC$_{1-4}$)N(alquiloC_{1-4})$_2$.

Los grupos monocíclicos ejemplares incluyen azetidinilo, pirrolidinilo, oxetanilo, imidazolinilo, oxazolidinilo, isoxazolinilo, tiazolidinilo, isotiazolidinilo, tetrahidrofuranilo, piperidinilo, piperazinilo, 2-oxopiperazinilo, 2-oxopiperidinilo, 2-oxopirrolidinilo, 2-oxoazepinilo, azepinilo, 4-piperidonilo, tetrahidropiranilo, morfolinilo, tiamorfolinilo, sulfóxido de tiamorfolinilo, tiamorfolinil sulfona, 1,3-dioxolano y tetrahidro-1,1-dioxotienilo y similares. Los grupos heterociclos bicíclicos ejemplares incluyen quinuclidinilo.

Los grupos heterociclos preferidos en los compuestos de la fórmula (I) incluyen



los cuales se pueden sustituir opcionalmente.

El término "heteroarilo" solo o como parte de otro grupo se refiere a grupos monocíclicos de 5 ó 6 elementos aromáticos sustituidos y no sustituidos, grupos bicíclicos de 9 ó 10 elementos y grupos tricíclicos de 11 a 14 elementos los cuales tienen al menos un heteroátomo (O, S o N) en al menos uno de los anillos. Cada anillo del grupo heteroarilo que contiene un heteroátomo puede contener uno o dos átomos de oxígeno o azufre y/o desde uno a cuatro átomos de nitrógeno siempre que el número total de heteroátomos en cada anillo sea cuatro o menos y cada anillo tiene al menos un átomo de carbono. Los anillos fusionados que completan los grupos bicíclicos y tricíclicos pueden contener solamente átomos de carbono y pueden estar saturados, parcialmente saturados o insaturados. Los átomos de nitrógeno y azufre se pueden oxidar opcionalmente y los átomos de nitrógeno se pueden cuaternizar opcionalmente. Los grupos heteroarilo los cuales son bicíclicos o tricíclicos deben incluir al menos un anillo completamente aromático pero el otro anillo o los anillos

fusionados pueden ser aromáticos o no aromáticos. El grupo heteroarilo se puede unir a cualquier átomo de carbono o nitrógeno disponible de cualquier anillo. El sistema de anillo heteroarilo puede contener cero, uno, dos o tres substituyentes seleccionados del grupo que consiste de halógeno, trifluorometilo, trifluorometoxi, alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, nitro, ciano, OR_a, SR_a, (=S), $-NR_aR_b$, $-N(alquilo)_3^+$, $-NR_aSO_2$, $-NR_aSO_2R_c$, $-SO_2R_c-SO_2NR_aR_b$, $-SO_2NR_aC(=O)R_b$, SO_3H, $-PO(OH)_2$, $-C(=O)R_a$, $-CO_2R_a$, $-C(=O)NR_aR_b$, $-C(=O)(alquilenoC_{1-4})NR_aR_b$, $-C(=O)NR_a(SO_2)R_b$, $-CO_2(alquilenoC_{1-4})NR_aR_b$, oxo(=O), $-NR_aC(=O)R_b$, $-NR_aCO_2R_b$, $-NR_a(alquileno\ C_{1-4})CO_2R_b$, arilo, cicloalquilo, heterociclo, y/o heteroarilo, en donde R_a, R_b y R_c son como se definieron anteriormente para grupos alquilo sustituidos, y también a su vez son opcionalmente sustituidos como se mencionó anteriormente. Cuando un heteroarilo está sustituido con un anillo adicional, el anillo a su vez está opcionalmente sustituido con uno a dos de $alquilo(C_{1-4})$, $alquenilo(C_{2-4})$, halógeno, hidroxi, ciano, nitro, CF_3, $O(alquiloC_{1-4})$, OCF_3, $C(=O)H$, $C(=O)(alquiloC_{1-4})$, CO_2H, $CO_2(alquiloC_{1-4})$, $NHCO_2(alquiloC_{1-4})$, $-S(alquiloC_{1-4})$, $-NH_2$, $NH(alquiloC_{1-4})$, $N(alquiloC_{1-4})_2$, $N(alquilo\ C_{1-4})_3^+$, $SO_2(alquiloC_{1-4})$, $C(=O)(alquilenoC_{1-4})NH_2$, $C(=O)(alquilenoC_{1-4})NH(alquilo)$, y/o $C(=O)(alquilenoC_{1-4})N(alquiloC_{1-4})_2$.

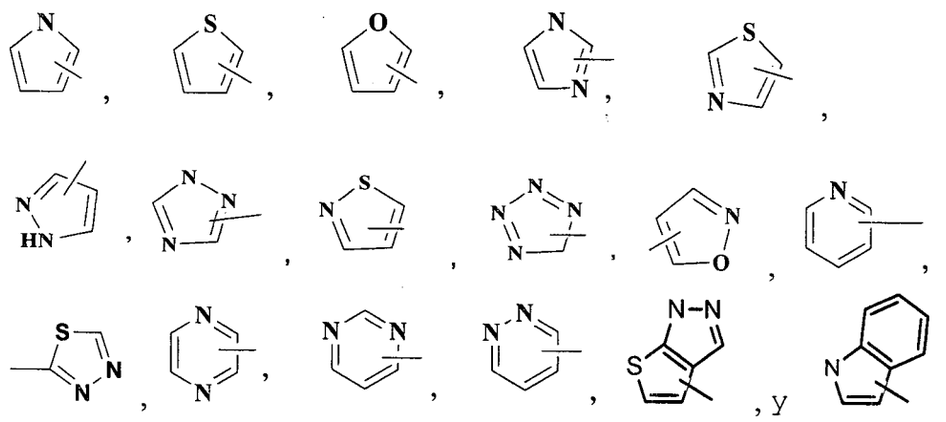
Los grupos heteroarilo monocíclicos ejemplares incluyen pirrolilo,

pirazolilo, pirazolinilo, imidazolilo, oxazolilo, isoxazolilo, tiazolilo, tiadiazolilo, isotiazolilo, furanilo, tienilo, oxadiazolilo, piridilo, pirazinilo, pirimidinilo, piridazinilo, triazinilo y similares.

Los grupos heteroarilo bicíclicos ejemplares incluyen indolilo, benzotiazolilo, benzodioxolilo, benzoxazolilo, benzotienilo, quinolinilo, tetrahidroisoquinolinilo, isoquinolinilo, bencimidazolilo, benzopiranilo, indolizinilo, benzofuranilo, cromonilo, cumarinilo, benzopiranilo, cinolinilo, quinoxalinilo, indazolilo, pirrolopiridilo, furopiridinilo, dihidroisoindolilo, tetrahidroquinolinilo y similares.

Los grupos heteroarilo tricíclicos ejemplares incluyen carbazolilo, bencidolilo, fenantrolinilo, acridinilo, fenantridinilo, xantenilo y similares.

En los compuestos de la fórmula (I), los grupos heteroarilo preferidos incluyen



y similares, los cuales se pueden sustituir opcionalmente en cualquier átomo de carbono o nitrógeno.

A menos que se indique de otra manera, cuando se hace

referencia a un arilo específicamente nombrado (por ejemplo, fenilo), cicloalquilo (por ejemplo, ciclohexilo), heterociclo (por ejemplo, pirrolidinilo) o heteroarilo (por ejemplo, imidazolilo), a menos que se indique específicamente de otra manera la referencia se propone para incluir anillos que tienen 0 a 3, preferiblemente 0-2 substituyentes seleccionados de aquellos citados anteriormente para los grupos arilo, cicloalquilo, heterociclo y/o heteroarilo como sea apropiado.

El término "heteroátomos" incluirá oxígeno, azufre y nitrógeno.

El término "carbocíclico" significa un anillo monocíclico o bicíclico saturado o insaturado en el cual todos los átomos de todos los anillos son carbonos. Por consiguiente, el término incluye anillos cicloalquilo y arilo. El anillo carbocíclico se puede sustituir en el caso de que los substituyentes se seleccionen de aquellos descritos anteriormente para grupos cicloalquilo y arilo.

Cuando el término "insaturado" se usa en la presente para referirse a un anillo o grupo, el anillo o grupo puede estar completamente insaturado o parcialmente insaturado.

A través de la especificación, los grupos y substituyentes de los mismos pueden elegirse por alguien experto en el campo para proporcionar porciones estables y compuestos útiles como compuestos farmacéuticamente aceptables y/o compuestos intermediarios útiles para hacer los compuestos

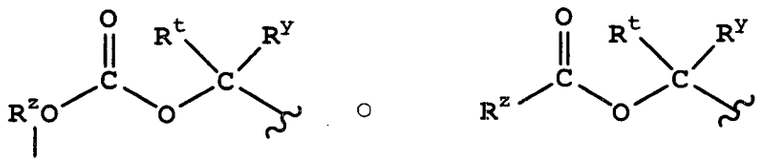
farmacéuticamente aceptables.

El término "profármaco" significa un compuesto el cual, durante la administración a un sujeto, se somete a conversión química por el proceso metabólico o químico para proporcionar un compuesto de la fórmula (I) y/o una sal y/o solvato del mismo. Por ejemplo, los compuestos que contienen un grupo carboxi pueden formar ésteres fisiológicamente hidrolizables los cuales sirven como profármacos que se hidrolizan en el cuerpo para producir los compuestos de la fórmula I per se. Los profármacos preferiblemente se administran oralmente, puesto que la hidrólisis en muchos casos ocurre principalmente bajo la influencia de las enzimas digestivas. La administración parenteral se puede usar donde el éster per se es activo, o en aquellos casos donde la hidrólisis ocurre en la sangre. Los ejemplos de ésteres fisiológicamente hidrolizables de los compuestos de la fórmula (I) incluye alquilbenciloC$_{1-6}$, 4-metoxibencilo, indanilo, ftalilo, metoximetilo, alcanoiloxiC$_{1-6}$-alquiloC$_{1-6}$, por ejemplo acetoximetilo, pivaloiloximetilo o propioniloximetilo, alcoxicarboniloxiC$_{1-6}$-alquiloC$_{1-6}$, por ejemplo metoxicarbonilo-oximetilo o etoxicarboniloximetilo, gliciloximetilo, fenilgliciloximetilo, (5-metil-2-oxo-1,3-dioxolen-4-il)-metilo y otros ésteres fisiológicamente hidrolizables bien conocidos, usados, por ejemplo, en las técnicas de penicilina y cefalosporina. Los ésteres se pueden preparar por técnicas

convencionales conocidas en la técnica.

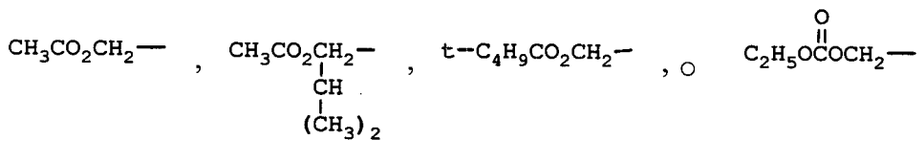
Los ejemplos del profármaco éster incluyen los siguientes grupos:

(1-alcanoiloxi)alquilo tales como,

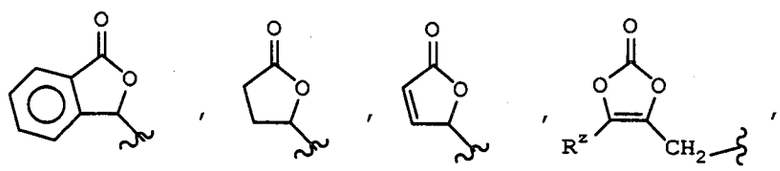


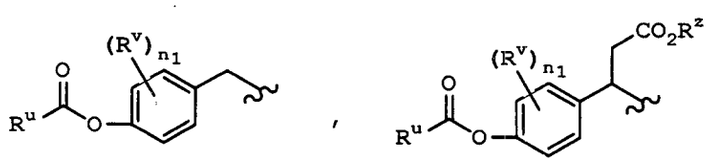
en donde R^z, R^t y R^y son H, alquilo, arilo o arilalquilo; sin embargo, R^zO no puede ser HO.

Los ejemplos de tales profármacos de ésteres incluyen



Otros ejemplos de los profármacos de ésteres adecuados incluyen





en donde R^z puede ser H, alquilo (tal como metilo o t-butilo), arilalquilo (tal como bencilo) o arilo (tal como fenilo); R^v es H, alquilo, halógeno o alcoxi, R^u es alquilo, arilo, arilalquilo o alcoxilo y n_1 es 0, 1 ó 2.

Para los ejemplos adicionales de los derivados de profármaco, véase:

a) Design of Prodrugs, editado por H. Bundgaard, (Elsevier, 1985) y Methods in Enzymology, Vol. 112, p. 309-396, editado por K. Widder, et al. (Acamedic Press, 1985);

b) A Textbook of Drug Design and Development, editado por Krosgaard-Larsen y H. Bundgaard, Capítulo 5, "Design and Application of Prodrugs", por H. Bundgaard, p. 113-191 (1991); y

c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992).

El término "tautómero" se refiere a compuestos de la fórmula (I) y sales de los mismos que pueden existir en su forma tautómerica, en la cual los átomos de hidrógeno se transportan a otras partes de las moléculas y los enlaces químicos entre los átomos de las moléculas se rearreglan consecuentemente. Se deberá entender que todas las formas tautómericas, con respecto a como pueden existir, se incluyen dentro de la invención.

Los términos "sal" y "sales" farmacéuticamente aceptables se refiere a sales básicas formadas con bases orgánicas e inorgánicas. Tales sales incluyen sales de amonio, sales de metales alcalinos, tales como sales de litio, sodio y potasio (las cuales se prefieren); sales de metales alcalinotérreos, tales como sales de calcio y magnesio; sales con bases orgánicas, tales como sales de tipo amina (por ejemplo, sal de diciclohexilamina, benzatina, N-

metil-D-glucamina y sales de hidrabamina); y sales con aminoácidos tipo arginina, lisina y similares; y zwitteriones, los llamados "sales internas". Las sales farmacéuticamente aceptables no tóxicas se prefieren, a través de otras sales también son útiles, por ejemplo, en el aislamiento o purificación del producto.

El término "sal" y "sales" farmacéuticamente aceptables también incluye sales de adición ácida. Estas se forman, por ejemplo, con ácidos inorgánicos fuertes, tales como ácidos minerales, por ejemplo ácido sulfúrico, ácido fosfórico o un ácido hidrohalico tal como HCl o HBr, con ácido carboxílicos orgánicos fuertes, tales como ácidos alcancarboxílicos de 1 hasta 4 átomos de carbonos los cuales son substituidos o no substituidos, por ejemplo, por halógeno, por ejemplo ácido acético, tal como ácidos dicarboxílicos saturados o no saturados, por ejemplo ácido oxalico, malónico, succínico, maleico, fumárico, ftálico o tereftálico, tales como ácidos hidroxicarboxílicos, por ejemplo, ácido ascórbico, glicólico, láctico, málico, tartárico o cítrico, tal como aminoácidos (por ejemplo, ácido aspártico o glutámico o lisina o arginina), o ácido benzoico, o con ácidos sulfónicos orgánicos, tales como alquilo (C_1-C_4) o ácidos arilsulfónicos los cuales son substituidos o no substituidos, por ejemplo por halógeno, por ejemplo, ácido metansulfónico y ácido p-toluensulfónico.

Todos los estereoisómeros de los compuestos de la presente invención se contemplan, ya sea mezclados o en una forma pura o

substancialmente pura. Los compuestos de la presente invención pueden tener centros asimétricos en cualquiera de los átomos de carbono incluyendo cualquiera de uno o los substituyentes R. Consecuentemente, los compuestos de la fórmula I pueden existir en formas enantioméricas o diastereoméricas o en mezclas de los mismos. Los procesos para la preparación pueden utilizar racematos, enantiómeros o diastereómeros como materiales de partida. Cuando los productos diastereoméricos o enantioméricos se prepararon, estos pueden separarse por métodos convencionales por ejemplo, cristalización cromatográfica o fraccionada.

Los compuestos inventivos pueden ser en la forma libre o solvato (por ejemplo, hidrato).

Combinaciones

Donde se desea, los compuestos de la estructura I pueden usarse en combinación con uno o más de otros tipos de agentes terapéuticos tales como inmunodepresores, agentes anticancerígenos, agentes anti-virales, agentes antiinflamatorios, agentes antifúngicos, antibióticos, agentes de hiperproliferación anti-vascular, agentes anti-depresivos, agentes hipolipidémicos o agentes reductores de lípido o agentes moduladores de lípidos, agentes antidiabéticos, agentes anti-obesidad, agentes antihipertensores, inhibidores de la agregación de plaquetas, y/o agentes anti-osteoporosis, que pueden adminsitrarse oralmente en la misma forma de dosis, en una forma de dosis oral separada o por inyección.

Los inmunodepresores que pueden emplearse opcionalmente en combinación con compuestos de la fórmula I de la invención incluyen ciclosporinas, por ejemplo ciclosporina A, micofenolato, interferon-beta, desoxispergolina, FK-506 o Ant.-IL-2.

Los agentes anti-cáncer que pueden emplearse opcionalmente en combinación con compuestos de la fórmula I de la invención incluyen azatiprina, 5-fluorouracilo, ciclofosfamida, cisplatina, metotrexato, tiotepa, carboplatina, y similares.

Los agentes anti-virales que pueden emplearse opcionalmente en combinación con compuestos de la fórmula I de la invención incluyen abacavir, aciclovir, ganciclovir, zidanocina, vidarabina, y similares.

Los agentes antiinflamatorios que pueden emplearse opcionalmente en combinación con compuestos de la fórmula I de la invención incluyen fármacos antiinflamatorios no esteroidales (NSAIDs) tales como ibuprofeno, inhibidores cox-2 tales como celecoxib, rofecoxib, aspirina, naproxeno, cetoprofeno, diclofenaco sódico, indometacina, piroxicam, esteroides tales como prednisona, dexametasona, hidrocortisona, diacetato de triamcinolona, compuestos de oro, tales como tiomalato de oro sodio, inhibidores de TNF-α tales como tenidap, anticuerpos anti-TNF o receptor TNF soluble, y rapamicina (sirolimús o Rapamune) o derivados de los mismos,

infliximab (Remicade® Centocor, Inc.). CTLA-4Ig, LEA29Y, anticuerpos tales como anti-ICAM-3, receptor anti-IL-2 (Anti-Tac), anti-CD45RB, anti-CD2, anti-CD3 (OKT-3), anti-CD4, anti-CD80, anti-CD86, anticuerpo monoclonal OKT3, agentes que bloquean la interacción entre CD40 y CD154 (a.k.a. "gp39"), tales como anticuerpos específicos para CD40 y/o CD154, proteínas de fusión tales como etanercept, proteínas de fusión construidas de CD40 y/o CD154gp39 (por ejemplo, CD40Ig y CD8gp39), inhibidores, tales como inhibidores de transubicación nuclear, de función NF-kappa B, tales como desoxiespergualina (DSG).

Los agentes antifúngicos que pueden emplearse opcionalmente en combinación con compuestos de la fórmula I de la invención incluyen fluconazol, miconazol, anfotericina B, y similares.

Los antibióticos que pueden emplearse opcionalmente en combinación con compuestos de la fórmula I de la invención incluyen penicilina, tetraciclina, amoxicilina, ampicilina, eritromicina, doxiciclina, vancomicina, minociclina, clindamicina o cefalexina.

Los agentes de hiperproliferación anti-vascular que pueden emplearse opcionalmente con compuestos de la fórmula I de la invención incluyen metotrexato, leflunomida, FK506 (tacrolimús, Prograf).

El agente hipolipidémico o agente que reduce los lípidos

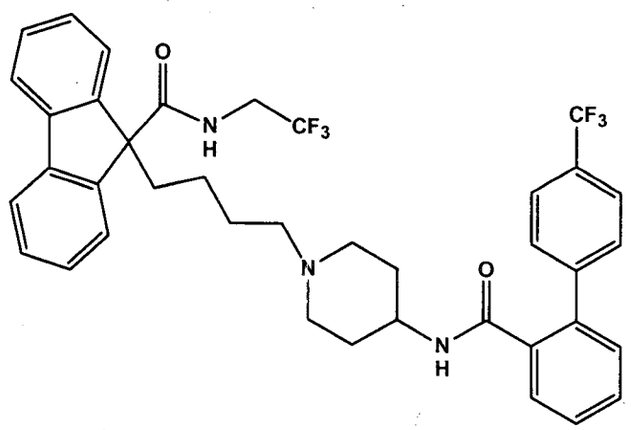
o agentes que modulan los lípidos que pueden emplearse opcionalmente en combinación con los compuestos de formula I de la invención pueden incluir 1, 2, 3 ó más inhibidores de MTP, inhibidores de la HMG CoA reductasa, inhibidores de la escualeno sintetasa, derivados de ácido fíbrico, inhibidores ACAT, inhibidores de lipoxigenasa, inhibidores de la absorción del colesterol, inhibidores del cotransporte de ácido ileal Na^+/biliar, sobre-reguladores de la actividad del receptor LDL, agentes de captura del ácido biliar, y/o ácido nicotínico y derivados de los mismos.

Los inhibidores de MTP empleados en la presente incluyen los inhibidores de MTP descritos en la Patente E.U.A. No. 5,595,872, Patente E.U.A. No. 5,739,135, Patente E.U.A. No. 5,712,279, Patente E.U.A. No. 5,760,246, Patente E.U.A. No. 5,827,875, Patente E.U.A. No. 5,885,983 y Solicitud E.U.A. No. de Serie 09/175,180 presentada el 20 de octubre 1998, ahora Patente E.U.A. No. 5,962,440. Se prefieren cada uno de los inhibidores MTP descritos en cada una de las patentes y solicitudes anteriores.

Todas las Patentes E.U.A. y solicitudes se incorporan en la presente para referencia.

La mayoría de los inhibidores de MTP a emplearse de conformidad con la presente invención incluyen los inhibidores de MTP preferidos como se establece en las Patentes E.U.A. Nos. 5,739,135 y 5,712,279, y Patente E.U.A. No. 5,760,246.

El inhibidor de MTP más preferido es 9-[4-[4-[[2-(2,2,2-trifluoroetoxi)benzoil]amino]-1-piperidinil]butil]-N-(2,2,2-trifluoroetil)-9H-fluoreno-9-carboxamida



El agente hipolipidémico puede ser un inhibidor de HMG CoA reductasa el cual incluye, pero no se limita a, compuestos de mevastatina y relacionados como se describen en la Patente E.U.A. No. 3,983,140, compuestos de lovastatina (mevinolina) y relacionados como se describen en la Patente E.U.A. No. 4,231,938, compuestos de pravastatina y relacionados tales como los que describen en la Patente E.U.A. No. 4,346,227, compuestos de simvastatina y relacionados como se describen en las Patentes E.U.A. Nos. 4,448,784 y 4,450,171. Otros inhibidores de HMG CoA reductasa que puede emplearse en la presente incluyen, pero no se limitan a, fluvastatina, descrita en la Patente E.U.A. No. 5,354,772, cerivastatina descrita en las Patentes E.U.A. Nos. 5,006,530 y 5,177,080, atorvastatina descrita en las Patentes E.U.A. Nos. 4,681,893, 5,273,995, 5,385,929 y 5,686,104, itavastatina (Nisvastatina

Nissan/Sankyo's (NK-104)) descrita en la Patente E.U.A. No. 5,011,930, visastatina de Shionogi-Astra/Zeneca (ZD-4522) descrita en la Patente E.U.A. No. 5,260,440, y compuestos de estatina relacionados descritos en la Patente E.U.A. No. 5,753,675, análogos de pirazol de los derivados de mevalonolactona como se describen en la Patente E.U.A. No. 4,613,610, análogos de indeno de los derivados de mevalonolactona como se describen en Solicitud PCT WO 86/03488, 6-[2-(substituido-pirrol-1-il)-alquilo)piran-2-onas y derivados de los mismos como se describen en la Patente E.U.A. No. 4,647,576, Searle SC-45355 (un derivado de ácido pentanedoico 3-substituido) dicloroacetato, análogos de imidazol de mavalonolactona como se describen en la Solicitud PCT WO 86/07054, derivados de ácido 3-carboxi-2-hidroxi-propano-fósfonico como se describen en la Patente Francesa No. 2,596,393, pirrol 2,3-disubstituido, derivados de furano y tiofeno como se describen en la solicitud de patente europea No. 0221025, análogos de naftilo de mevalonolactona como se describen en la Patente E.U.A. No. 4,686,237, octahidronaftalenos tales como los que se describen en la Patente E.U.A. No. 4,499,289, análogos ceto de mevinolina (lovastatina) como se describen en la solicitud de patente europea No. 0142146 A2, y derivados de quinolina y piridina descritos en la Patente E.U.A. No. 5,506,219 y 5,691,322.

Además, los compuestos de ácido fosfínico útiles en

inhibir la HMG CoA reductasa adecuada para uso en la presente se describen en la GB 2205837.

Los inhibidores de sintetasa escualeno adecuados para uso en la presente incluyen, pero no se limitan a, α-fosfono-sulfonatos descritos en la Patente E.U.A. No. 5,712,396, aquellos descritos por Biller et al., J. Med. Chem., Vol. 31, No. 10, pp. 1869-1871 (1988), incluyendo (fosfonil-metil)fosfonato de isoprenoide así como otros inhibidores de sintetasa escualeno conocidos, por ejemplo, como se describen en la Patente E.U.A. No. 4,871,721 y 4,924,024 y en Biller, S.A., Neuenschwander, K., Ponpipom, M.M., and Poulter, C.D., Current Pharmaceutical Design, Vol. 2, pp. 1-40 (1996).

Además, otros inhibidores de sintetasa escualeno adecuados para uso en la presente incluyen el pirofosfato de terpeno descrito por P. Ortiz de Montellano et al., J. Med. Chem., 1977, 20, 243-249, el análogo A de difosfato de farnesilo y análogos de pirofosfato de preescualeno (PSQ-PP) como los descritos por Corey and Volante, J. Am. Chem. Soc., 98, 1291-1293 (1976), fosfinilfosfonatos reportados por McHPLCd, R.W. et al., J. Am. Chem. Soc., 1987, 109, 5544 (1987), y ciclopropanos reportados por Capson, T.L., PhD dissertation, Dept. Med. Chem. U. of Utah, Abstract, Table of Contents, pp. 16, 17, 40-43, 48-51, Summary (June, 1987).

Otros agentes hipolipidémicos adecuados para uso en la presente incluyen, pero no se limitan a, derivados de ácido

fíbrico, tales como fenofibrato, gemfibrozilo, clofibrato, bezafibrato, ciprofibrato, clinofibrato y similares, probucol, y compuestos relacionados como se describen en la Patente E.U.A. No. 3,674,836, probucol y gemfibrozilo se prefieren, agentes de captura de ácido biliar tales como colestiramina, colestipol y DEAE-Sephadex (Secholex®, Policexide®) y colestagel (Sankyo/Geltex), así como lipostabil (Rhone-Poulenc), Eisai E-5050 (un derivados de etanolamina N-substituido), imanixilo (HOE-402), tetrahidrolipstatina (THL), istigmastanilfos-forilcolina (SPC, Roche), aminociclodextrina (Tanabe Seiyoku), Ajinomoto AJ-814 (derivado de azuleno), melinamida (Sumitomo), Sandoz 58-035, American Cyanamid CL-277,082 y CL-283,546 (derivados de urea disubstituidos), ácido nicotínico (niacin), acipimox, acifran, neomicina, ácido p-aminosalicíclico, aspirina, derivados de poli(dialquilmetilamina) tales como los que se describen en la Patente E.U.A. No. 4,759,923, cloruro de poli(dialildimetilamonio) de amina cuaternaria y ionenos tales como los que se describen en la Patente E.U.A. No. 4,027,009, y otros agentes reductores del colesterol en el suero conocidos.

El agente hipolipidémico puede ser un inhibidor ACAT tal como se describe en, Drugs of the Future, 24, 9-15 (1999), (Avasimibe); "The ACAT inhibitor, C1-1011 is effective in the prevention and regression of aortic fatty streak area in

hamsters", Nicolosi et al., Atherosclerosis (Shannon, Irel). 137(1), 77-85 (1998), "The pharmacological profile of FCE 27677: a novel ACAT inhibitor con potent hypolipidemic activity mediated by selective suppression of the hepatic secretion of ApoB100-containing lipoprotein", Ghiselli, Giancarlo, Cardiovasc. Drug Rev. (1998), 16(1), 16-30; "RP 73163: a bioavailable alkylsulfinyl-diphenylimidazole ACAT inhibitor", Smith, C., et al, Bioorg. Med. Chem. Lett. 6(1), 47-50 (1996); "ACAT inhibitors: physiologic mechanisms for hypolipidemic and anti-atherosclerotic activities in experimental animals", Krause et al, Editor(s): Ruffolo, Robert R., Jr.; Hollinger, Mannfred A., Inflammation: Mediators Pathways 173-98 (1995), Publisher: CRC, Boca Raton, Fla.; "ACAT inhibitors: potential anti-atherosclerotic agents", Sliskovic et al, Curr. Med. Chem. 1(3), 204-25 1994); "Inhibitors of acyl-CoA:cholesterol O-acyl transferase (ACAT) as hypocholesterolemic agents. 6. The first water-soluble ACAT inhibitor with lipid-regulating activity. Inhibitors of acyl-CoA:cholesterol acyltransferase (ACAT). 7. Development of a series of substituido N-phenyl-N'-[(1-phenylciclopentyl)metil]ureas with enhanced hypocholesterolemic activity", Stout et al, Chemtracts: Org. Chem. 8(6), 359-62 (1995), or TS-962 (acetamida, N-[2,6-bis(1-metiletil)fenil]-2-(tetradeciltio)-)(Taisho Pharmaceutical Co. Ltd).

El agente hipolipidémico puede ser un subregulador de la actividad del receptor LD2 tal como MD-700 (1(3H)-isobenzofuranona, 3-(13-hidroxi-10-oxotetradecil)-5,7-dimetoxi) (Taisho Pharmaceutical Co. Ltd) y LY295427 (colestan-3-ol, 4-(2-propenil)-, (3a,4a,5a)-) (Eli Lilly).

El agente hipolipidémico puede ser un inhibidor de la absorción de colesterol preferiblemente Schering-Plough's ezetimibe (SCH58235) y SCH48461 así como aquellos descritos en Atherosclerosis 115, 45-63 (1995) and J. Med. Chem. 41, 973 (1998).

El agente hipolipidémico puede ser un inhibidor del cotransportador de ácido ileal Na+/biliar tal como se describe en Drugs of the Future, 24, 425-430 (1999).

El agente modulador de lípidos puede ser un inhibidor de la proteína de transferencia de éster de colesterol (CETP) tal como CP 529,414 de Pfizer (torcetrapib) (WO/0038722 y EP 818448) y SC-744 y SC-795 de Pharmacia.

El inhibidor de liasa de citrato ATP que puede emplearse en la combinación de la invención puede incluir, por ejemplo, aquellos descritos en la Patente E.U.A. No. 5,447,954.

Los agentes hipolipidémicos preferidos son pravastatina, lovastatina, simvastatina, atorvastatina, fluvastatina, cerivastatina, itavastatina y visastatina y ZD-4522.

Las patentes de E.U.A. mencionadas arriba se incorporan en la presente para referencia. Las cantidades y dosis

empleadas deberán indicarse en el Physicians' Desk Reference y/o en las patentes establecidas anteriormente.

Los compuestos de fórmula I de la invención deberán emplearse en una relación de peso con respecto al agente hipolipidémico (como se presentaron), dentro del intervalo de alrededor de 500:1 hasta alrededor de 1:500, preferiblemente de alrededor de 100:1 hasta alrededor de 1:100.

La dosis administrada deberá ajustarse cuidadosamente de conformidad a la edad, peso y condición del paciente, así como la ruta de administración, forma de dosis y regimen y el resultado deseado.

Las dosis y formulaciones para el agente hipolipidémico serán como se describe en diversas patentes y solicitudes descritas anteriormente.

Las dosis y formulaciones para el otro agente hipolipidémico deberán emplearse donde sea aplicable, deberá ser como se establece en la última edición del Physicians' Desk Reference.

Para la administración oral, un resultado satisfactorio pueden obtenerse empleando el inhibidor MTP en una cantidad dentro del intervalo de alrededor de 0.01 mg hasta alrededor de 500 mg y preferiblemente de alrededor de 0.1 mg hasta alrededor de 100 mg, una hasta cuatro veces diariamente.

Una forma de dosis oral preferida, tal como tabletas o cápsulas, deberán contener el inhibidor MTP en una cantidad de

alrededor de 1 hasta alrededor de 500 mg, preferiblemente de alrededor de 2 hasta alrededor de 400 mg, y más preferiblemente de alrededor de 5 hasta alrededor de 250 mg, una hasta cuatro veces diariamente.

Para la administración oral, un resultado satisfactorio pueden obtenerse empleando un inhibidor de HMG CoA reductasa, por ejemplo, pravastatina, lovastatina, simvastatina, atorvastatina, fluvastatina o cerivastatina en dosis empleadas como se indica en el Physicians' Desk Reference, tal como en una cantidad dentro del intervalo de alrededor de 1 hasta 2000 mg, y preferiblemente de alrededor de 4 hasta alrededor de 200 mg.

El inhibidor de sintetasa de escualeno puede emplearse en dosis en una cantidad dentro del intervalo de alrededor de 10 mg hasta alrededor de 2000 mg y preferiblemente de alrededor de 25 mg hasta alrededor de 200 mg.

Una forma de dosis oral preferida, tal como tabletas o cápsulas, deberá contener el inhibidor de HMG CoA reductasa en una cantidad de alrededor de 0.1 hasta alrededor de 100 mg, preferiblemente de alrededor de 0.5 hasta alrededor de 80 mg, y más preferiblemente de alrededor de 1 hasta alrededor de 40 mg.

Una forma de dosis oral preferida, tal como tabletas o cápsulas deberán contener el inhibidor de sintetasa de escualeno en una cantidad de alrededor de 10 hasta alrededor

de 500 mg, preferiblemente de alrededor de 25 hasta alrededor de 200 mg.

El agente hipolipidémico puede también ser un inhibidor de lipoxigenasa incluyendo un inhibidor de 15-lipoxigenasa (15-LO) tales como derivados de benzimidazol como se describen en la WO 97/12615, inhibidores de 15-LO como se describen en la WO 97/12613, isotiazolonas como se describen en la WO 96/38144, e inhibidores de 15-LO como se describe por Sendobry et al "Attenuation of diet-induced aterosclerosis in rabbits with a highly selective 15-lipoxygenasa inhibitor lacking significant antioxidant properties", Brit. J. Pharmacology 120, 1199-1206 (1997), y Cornicelli et al, "15-Lipoxygenase and its Inhibition: A Novel Therapeutic Target for Vascular Disease", Current Pharmaceutical Design, 5, 11-20 (1999).

Los compuestos de fórmula I y el agente hipolipidémico pueden emplearse juntos en la misma forma de dosis oral o en la forma de dosis oral separadas quen se toman al mismo tiempo.

Las composiciones descritas anteriormente pueden administrarse en las formas de dosis como se describe anteriormente en dosis sencillas o divididas de una hasta cuatro veces diariamente. Puede ser predecible que inicie un paciente en una combinación de dosis baja y se trabaje gradualmente hasta una combinación de dosis alta.

El agente hipolipidémico preferido es pravastatina,

simvastatina, lovastatina, atorvastatina, fluvastatina o cerivastatina así como niacina y/o colestagel.

El otro agente antidiabético que pueden emplearse opcionalmente en combinación con el compuesto de la fórmula I puede ser 1, 2, 3 o más agentes antidiabéticos o agentes antihiperglicémicos incluyendo secretagogos de insulina o sensibilizadores de insulina, u otros agentes antidiabéticos preferiblemente que tienen un mecanismo de accción diferente de los compuestos de fórmula I de la invención, los cuales pueden incluir biguanidas, sulfonil ureas, inhibidores de glucosidasa, agonistas de PPAR γ, tales como tiazolidindionas, inhibidores aP2, inhibidores de peptidasa IV de dipeptidilo (DP4), inhibidores de SGTL2, y/o meglitinides, así como insulina, y/o péptido-1 tipo glucagon (GLP-1).

El otro agente antidiabético puede ser un agente antihiperglicémico oral preferiblemente una biguanida tal como metformina o fenformina o sales de los mismos, preferiblemente metformina HCl.

Donde el agente antidiabético es una biguanida, los compuestos de la estructura I deberán emplearse en una relación de peso con respecto a la biguanida dentro del intervalo de alrededor de 0.001:1 hasta alrededor de 10:1, preferiblemente de alrededor de 0.01:1 hasta alrededor de 5:1.

El otro agente antidiabético puede también ser preferiblemente una sulfonil urea tal como gliburida (también

conocida como glibenclamida), glimepirida (descrita en la Patente E.U.A. No. 4,379,785), glipizida, gliclazida o clorpropamida, otras sulfonilureas conocidas u otros agentes antiperglicemicos los cuales actúan en el canal dependiente de ATP de las células β, con gliburida y glipizida siendo preferidas, las cuales pueden administrarse en la misma forma o en dosis orales separadas.

Los compuestos de la estructura I deberán emplearse en una relación de peso con respcto a la sulfonil urea en el intervalo de alrededor de 0.01:1 hasta alrededor de 100:1, preferiblemente de alrededor de 0.02:1 hasta alrededor de 5:1.

El agente antidiabético oral puede también ser un inhibidor de glucosidasa tal como acarbosa (descrita en la Patente E.U.A. No. 4,904,769) o miglitol (descrito en la Patente E.U.A. No. 4,639,436), el cual puede administrarse en la misma forma o en dosis orales separadas.

Los compuestos de la estructura I deberán emplearse en una relación en peso con respecto al inhibidor de glucosidasa dentro del intervalo de alrededor de 0.01:1 hasta alrededor de 100:1, preferiblemente de alrededor de 0.05:1 hasta alrededor de 10:1.

Los compuestos de la estructura I pueden emplearse en combinación con un agonista PPAR γ tal como un agente anti-diabético oral de tiazolidindiona u otros sensibilizadores de insulina (el cual tiene un efecto de sensibilidad de insulina

en pacientes NIDDM) tal como troglitazona (Warner-Lambert Rezulin®, descrita en la Patente E.U.A. No. 4,572,912), rosiglitazona (SKB), pioglitazona (Takeda), Mitsubishi MCC-555 (descrita en la Patente E.U.A. No. 5,594,016), Glaxo-Wellcome GL-262570 (farglitazar), englitazona (CP-68722, Pfizer) o darglitazona (CP-86325, Pfizer, isaglitazona (MIT/J&J), JTT-501 (reglitazar) (JPNT/P&U), L-895645 (Merck), R-119702 (rivoglitazona) (Sankyo/WL), NN-2344 (balaglitazona) (Dr. Reddy/NN), o YM-440 ((Z)-1,4-bis-4-[(3,5-dioxo-1,2,4-oxadiazolidin-2-il-metil)]-fenoxibut-2-eno) (Yamanouchi), preferiblemente rosiglitazona y pioglitazona.

Los compuestos de la estructura I deberán emplearse en una relación en peso con respecto a la tiazolidindiona en una cantidad dentro del intervalo de alrededor de 0.01:1 hasta alrededor de 100:1, preferiblemente de alrededor de 0.05 hasta alrededor de 10:1.

La sulfonil urea y tiazolidindiona en cantidades de menos de alrededor de 150 mg del agente antidiabético oral pueden incorporarse en una sola tableta con los compuestos de la estructura I.

Los compuestos de la estructura I también pueden emplearse en combinación con un agente antihiperglicémico tal como insulina o con péptido-1 tipo glucagón (GLP-1) tal como GLP-1(1-36) amida, GLP-1(7-36) amida, GLP-1(7-37) (como se describe en Patente E.U.A. No. 5,614,492 a favor de Habener,

la descripción de lo cual se incorpora en la presente para referencia), así como AC2993 (exenatida) (Amylin) y LY-315902 (péptido I de tipo 8-37—glucagón (humano), N-[3-(1H-imidazol-4-il)-1-oxopropil]-26-L-arginina-34-[N6-(1-oxooctil)-L-lisina]-) (Lilly), el cual puede administrarse por medio de inyección, o por dispositivos intranasales, de inhalación, transdérmicos o bucales.

En donde se presenta, la metformina, las sulfonil ureas, tales como gliburida, glimepirida, glipirida, glipizida, clorpropamida y gliclazida y los inhibidores de glucosidasa acarbosa o miglitol o insulina (inyectable, pulmonar, bucal, u oral) pueden emplearse en formulaciones como se describen arriba y en cantidades y dosis como se indica en el Physicians' Desk Reference (PDR).

En donde se presenta, la metformina o sal del mismo puede emplearse en cantidades dentro del intervalo de alrededor de 500 hasta alrededor de 2000 mg por día la cual puede administrarse en dosis sencillas o divididas una hasta cuatro veces diariamente.

En donde se presenta, el agente anti-diabético de tiazolidindiona puede emplearse en cantidades dentro del intervalo de alrededor de 0.01 hasta alrededor de 2000 mg/día el cual puede administrarse en dosis sencillas o divididas una hasta cuatros veces por día.

En donde se presenta, la insulina puede emplearse en las

formulaciones, cantidades y dosis como se describe por el Physicians' Desk Reference.

En donde se presentan, los péptidos GLP-1 pueden administrarse en formulaciones bucales orales, por administración nasal o parenteral como se describe en las Patentes E.U.A. Nos. 5,346,701 (TheraTech), 5,614,492 and 5,631,224 la cuales se incorporan en la presente para referencia.

El otro agente antidiabético puede también ser un agonista PPAR α/γ dual tal como AR-HO39242 (tesaglitazar) (Astra/Zeneca), GW-409544 (Glaxo-Wellcome), KRP297 (benzamida, 5-[(2,4-dioxo-5-tiazolidinil)metil]-2-metoxi-N-[[4-(trifluorometil)fenil]metil]- (Kyorin Merck) así como aquellos descritos por Murakami et al, "A Novel Insulin Sensitizer Acts As a Coligand for Peroxisome Proliferation-Activated Receptor Alpha (PPAR alpha) and PPAR gamma. Effect on PPAR alpha Activation on Abnormal Lipid Metabolism in Liver of Zucker Fatty Rats", Diabetes 47, 1841-1847 (1998).

El agente antidiabético puede ser un inhibidor de SGLT2 tal como se describe en la solicitud E.U.A. No. de Serie 09/679,027, presentada el 4 de Octubre de 2000, empleando dosis establecidas en la presente. Son preferidos los compuestos designados como se prefiere en la solicitud anterior.

El agente antidiabético puede ser un inhibidor aP2 tal

como se describe en la Solicitud E.U.A. No. de Serie 09/391,053, presentada el 7 de septiembre de 1999, y en la Solicitud E.U.A. No. de Serie 09/519,079, presentada el 6 de marzo de 2000, empleando dosis establecidas en la presente. Son preferidos los compuestos designados como se prefiere en la solicitud anterior.

El agente antidiabético puede ser un inhibidor DP4 tal como el descrito en Solicitud E.U.A. No. de Serie 09/788,173 presentada el 16 de febrero 2001, WO99/38501, WO99/46272, WO99/67279 (PROBIODRUG), WO99/67278 (PROBIODRUG), WO99/61431 (PROBIODRUG), NVP-DPP728A (1-[[[2-[(5-cianopiridin-2-il)amino]etil]amino]acetil]-2-ciano-(S)-pirrolidina) (Novartis) (preferido) como se describe por Hughes et al, *Biochemistry*, 38(36), 11597-11603, (1999), TSL-225 (ácido triptofil-1,2,3,4-tetrahidro-isoquinolin-3-carboxílico (descrito por Yamada et al, *Bioorg. & Med. Chem. Lett.* 8 1537-1540 (1998), 2-cianopirrolididas y 4-cianopirrolididas como se describe por Ashworth et al, *Bioorg. & Med. Chem. Lett.*, Vol. 6, No. 22, pp 1163-1166 y 2745-2748 (1996) empleando dosis como se establece en las referencias anterior.

La meglitinida que puede opcionalmente emplearse en combinación con el compuesto de la fórmula I de la invención puede ser repaglinida, nateglinida (Novartis) o KAD1229 (mitiglinida) (PF/Kissei), siendo preferida la repaglinida.

El compuesto de la fórmula I se empleará en una relación

en peso con respecto a la meglitinida, agonista PPAR γ, agonista PPAR α/γ dual, inhibidor aP2, inhibidor DP4 o inhibidor SGLT2 dentro del intervalo desde alrededor de 0.01:1 hasta alrededor de 100:1, preferiblemente desde alrededor de 0.05 hasta alrededor de 10:1.

El otro tipo de agente terapéutico que puede emplearse opcionalmente con un compuesto de la fórmula I puede ser 1, 2, 3 o más de un agente anti-obesidad incluyendo un agonista adrenérgico beta 3, un inhibidor de lipasa, un inhibidor de la reabsorción de serotonina (y dopamina), un inhibidor aP2, un agonista del receptor de tiroides y/o un agente anorexígeno.

El agonista adrenérgico beta 3 que puede emplearse opcionalmente en combinación con un compuesto de la fórmula I puede ser AJ9677 (rafabegron) (Takeda/Dainippon), L750355 (bencensulfonamida, N-[4-[2-[[(2S)-3-[(6-amino-3-piridinil)oxi]-2-hidroxipropil]amino]etil]fenil]-4-(1-metiletil)-) (Merck), o CP331684 (ácido 4-[2-[[2-(6-aminopiridin-3-il)-2(R)-hidroxietil]-amino]ethoxi]fenil]acético) (Pfizer) u otros agonistas beta 3 conocidos como se describe en Patentes E.U.A. Nos. 5,541,204, 5,770,615, 5,491,134, 5,776,983 y 5,488,064, con AJ9677, L750,355 (bencensulfonamida, N-[4-[2-[[(2S)-3-[(6-amino-3-piridinil)oxi]-2-hidroxipropil]amino]etil]fenil]-4-(1-metiletil)-) y siendo preferido el CP331684.

El inhibidor de lipasa que puede emplearse opcionalmente

en combinación con un compuesto de la fórmula I puede ser orlistat o ATL-962 (Alizyme), siendo preferido el orlistat.

El inhibidor de reabsorción de serotonina (y dopamina) que puede emplearse opcionalmente en combinación con un compuesto de la fórmula I puede ser sibutramina, topiramato (Johnson & Johnson) o axocina (Regeneron), siendo preferidos la sibutramina y topiramato.

El agonista del receptor de tiroides que puede emplearse opcionalmente en combinación con un compuesto de la fórmula I puede ser un ligando del receptor de tiroides como se describe en WO97/21993 (U. Cal SF), WO99/00353 (KaroBio), WO00/039077 (KaroBio), y Solicitud Provisional E.U.A. 60/183,223 presentada el 17 de febrero 2000, siendo preferidos los compuestos de las solicitudes de KaroBio y la Solicitud Provisional E.U.A. anterior.

El agente anorexígeno que puede emplearse opcionalmente en combinación con un compuesto de la fórmula I puede ser dexanfetamina, fentermina, fenilpropanolamina o mazindol, siendo preferida la dexanfetamina.

Los diversos agentes anti-obesidad descritos anteriormente pueden emplearse en la misma forma de dosis con el compuesto de la fórmula I o en diferentes formas de dosis, en dosis y regímenes cómo se conoce generalmente en la técnica o en el PDR.

Los agentes antihipertensores que pueden emplearse en

combinación con el compuesto de la fórmula I de la invención incluyen inhibidores de ACE, antagonistas del receptor de angiotensina II, inhibidores de NEP/ACE, así como bloqueadores del canal de calcio, bloqueadores adrenérgicos β y otros tipos de agentes antihipertensores incluyendo diuréticos.

Los inhibidores de enzima convertidora de la angiotensina que pueden emplearse en la presente incluyen aquellos que contienen una porción mercapto (-S-) tal como derivados de prolina substituida, tales como cualesquiera de aquellos descritos en Patente E.U.A. No. 4,046,889 para Ondetti et al mencionado anteriormente, siendo preferido el captoprilo, esto es, 1-[(2S)-3-mercapto-2-metilpropionil]-L-prolina, y derivados de mercaptoacilo de prolinas substituidas tales como cualesquiera de aquellos descritos en Patente E.U.A. No. 4,316,906, siendo preferido el zofenoprilo.

Otros ejemplos de inhibidores ACE que contienen mercapto que pueden emplearse en la presente incluyen rentiaprilo (fentiaprilo, Santen) descrito en Clin. Exp. Pharmacol. Physiol. 10:131 (1983); así como pivoprilo y YS980.

Otros ejemplos de inhibidores de enzima convertidora de la angiotensina que pueden emplearse en la presente incluyen cualesquiera de aquellos descritos en Patente E.U.A. No. 4,374,829 mencionada anteriormente, siendo preferido la N-(1-etoxicarbonil-3-fenilpropil)-L-alanil-L-prolina, esto es, enalaprilo, cualesquiera de los ácidos o sales amino o imino

substituidas con fosfato descritas en la Patente E.U.A. No. 4,452,790 siendo preferido la (S)-1-[6-amino-2-[[hidroxi-(4-fenilbutil)fosfinil]oxi]-1-oxohexil]-L-prolina o (ceronaprilo), fosfinilalcanoil prolinas descritas en Patente E.U.A. No. 4,168,267 mencionada anteriormente siendo preferido el fosinoprilo, cualesquiera de las prolinas substituidas con fosfinilalcanoil descritas en Patente E.U.A. No. 4,337,201, y los fosfonamidatos descritos en Patente E.U.A. No. 4,432,971 descritos anteriormente.

Otros ejemplos de inhibidores ACE que pueden emplearse en la presente incluyen Beecham BRL 36,378 como se describe en las Solicitudes de Patente Europea Nos. 80822 y 60668; Chugai MC-838 descrito en C.A. 102:72588v y *Jap. J. Pharmacol.* 40:373 (1986); Ciba-Geigy CGS 14824 (ácido 3-([1-etoxicarbonil-3-fenil-(1S)-propil]amino)-2,3,4,5-tetrahidro-2-oxo-1-(3S)-benzazepin-1 acético HCl) descrito en Patente U.K. No. 2103614 y CGS 16,617 (ácido 3(S)-[[(1S)-5-amino-1-carboxipentil]amino]-2,3,4,5-tetrahidro-2-oxo-1H-1-benzazepina-1-etanoico) descrito en Patente E.U.A. No. 4,473,575; cetaprilo (alaceprilo, Dainippon) descrito en Eur. Therap. Res. 39:671 (1986); 40:543 (1986); ramiprilo (Hoechst) descrito en Patente Europea No. 79-022 y *Curr. Ther. Res.* 40:74 (1986); Ru 44570 (Hoechst) descrito en *Arzneimittelforschung* 34:1254 (1985), cilazaprilo (Hoffman-LaRoche) descrito en *J. Cardiovasc. Pharmacol.* 9:39 (1987); R

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31-2201 (Hoffman-LaRoche) descrito en *FEBS Lett.* 165:201 (1984); lisinoprilo (Merck), indalaprilo (delaprilo) descrito en Patente E.U.A. No. 4,385,051; indolaprilo (Schering) descrito en *J. Cardiovasc. Pharmacol.* 5:643, 655 (1983), espirapril (Schering) descrito en *Acta. Pharmacol. Toxicol.* 59 (Supp. 5):173 (1986); perindoprilo (Servier) descrito en *Eur. J. Clin. Pharmacol.* 31:519 (1987); quinaprilo (Warner-Lambert) descrito en Patente E.U.A. No. 4,344,949 y CI925 (Warner-Lambert) (HCl del ácido [3S-[2[R(*)R(*)]]3R(*)]-2-[2-[[1-(etoxi-carbonil)-3-fenilpropil]amino]-1-oxopropil]-1,2,3,4-tetrahidro-6,7-dimetoxi-3-isoquinolincarboxílico) descrito en *Pharmacologist* 26:243, 266 (1984), WY-44221 (Wyeth) descrito en *J. Med. Chem.* 26:394 (1983).

Los inhibidores ACE preferidos son captoprilo, fosinoprilo, enalaprilo, lisinoprilo, quinaprilo, benazeprilo, fentiaprilo, ramiprilo y moexiprilo.

Lso inhibidores de NEP/ACE también pueden emplease en la presente porque los mismos poseen actividad inhibidora de endopeptidasa neutral (NEP) y actividad inhibidora de enzima convertidora de angiotensina (ACE). Los ejemplos de inhibidores de NEP/ACE adecuados para uso en la presente incluyen aquellos descritos en la Patente E.U.A. Nos. 5,362,727, 5,366,973, 5,225,401, 4,722,810, 5,223,516, 4,749,688, Patente E.U.A. No. 5,552,397, Patente E.U.A. No. 5,504,080, Patente E.U.A. No. 5,612,359, Patente E.U.A. No.

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5,525,723, Solicitud de Patente Europea 0599444, 0481522, 0599444, 0595610, Solicitud de Patente Europea 0534363A2, 534396 y 534492, y Solicitud de Patente Europea 0629627A2.

Se prefieren aquellos inhibidores de NEP/ACE y dosis de los mismso que se designan como preferidos en las patentes/solicitudes anteriores cuyas patentes E.U.A. se incorporan en la presente para referencia; más preferidos son omapatrilat (ácido [S-(R*,R*)]-hexahidro-6-[(2-mercapto-1-oxo-3-fenilpropil)amino]-2,2-dimetil-7-oxo-1H-azepin-1-acético (gemopatrilat)) y CGS 30440.

En antagonista del receptor II de angiotensina (también referida en la presente como antagonista de la angiotensina II o antagonista AII) adecuada para su uso en la presente incluye, pero no se limitan a, irbesartan, losartan, valsartan, candesartan, telmisartan, tasosartan o eprosartan, siendo preferidos el irbesartan, losartan o valsartan.

Una forma de dosis oral preferida, tal como tabletas o cápsulas, contendrán el inhibidor de ACE o antagonista AII en una cantidad dentro del intervalo desde alrededor de 0.1 hasta alrededor de 500 mg, preferiblemente desde alrededor de 5 hasta alrededor de 200 mg y más preferiblemente desde alrededor de 10 hasta alrededor de 150 mg.

Para administración parenteral, el inhibidor de ACE, antagonista de la angiotensina II o inhibidor de NEP/ACE se empleará en una cantidad dentro del intervalo desde alrededor

de 0.005 mg/kg hasta alrededor de 10 mg/kg y preferiblemente desde alrededor de 0.01 mg/kg hasta alrededor de 1 mg/kg.

Donde un fármaco es para administrarse intravenosamente, se formulará en vehículos convencionales, tal como agua destilada, solución salina, solución Ringer u otros portadors convencionales.

Se apreciará que las dosis preferidas del inhibidor ACE y el antagonista AII así como otros antihipertensores descritos en la presente serán como se establecen en la última edición del Physicians' Desk Reference (PDR).

Otros ejemplos de agentes de antihipertensión preferidos adecuados para su uso en la presente incluyen omapatrilat (Vanlev®) beslato de amlodipina (Norvasc®), HCl de prazosina (Minipress®), verapamilo, nifedipina, nadolol, diltiazem, felodipina, nisoldipina, isradipina, nicardipina, atenolol, carvedilol, sotalol, terazosina, doxazosina, propranolol, y HCl de clonidina (Catapres®).

Los diuréticos que pueden emplearse en combinación con compuestos de la fórmula I incluyen hidroclorotiazida, torasemida, furosemida, espironolactono, e indapamida.

Los agentes antiplaquetas que pueden emplearse en combinación con compuestos de la fórmula I de la invención incluyen aspirina, clopidogrel, ticlopidina, dipiridamol, abciximab, tirofiban, eptifibatida, anagrelida, y ifetroban,

siendo preferidos clopidogrel y aspirina.

Los agentes antiplaquetas pueden emplearse en cantidades como se indica en la PDR. Ifetroban puede emplearse en cantidades como se establece en la Patente E.U.A. No. 5,100,889.

Los agentes antiosteoporosis adecuados para usarse en la presente en combinación con los compuestos de la fórmula I de la invención incluyen la hormona paratiroidea o bisfosfonatos, tal como MK-217 (alendronato) (Fosamax®).

Las dosis empleadas para los fármacos anteriores serán como se establecen en la Physicians' Desk Reference.

Formulaciones farmacéuticas

La composición farmacéutica de la invención incluye un portador, adyuvante o vehículo farmacéuticamente aceptable, que puede ser administrado a un sujeto, junto con un compuesto de la presente invención, y el cual no destruye la actividad farmacológica del mismo. Los portadores, adyuvantes y vehículos farmacéuticamente aceptables que pueden usarse en las composiciones farmacéuticas de la presente invención incluyen, pero no se limitan a, lo siguiente: intercambiadores de iones, alúmina, estearato de aluminio, lecitina, sistemas de administración de fármacos auto-emulsificante ("SEDDS") tal como succinato de d(-tocoferol polietilenglicol 1000), tensoactivos usados en forma de dosis farmacéutica tal como Tweens u otras matrices de administración polimérica similar,

hur535

proteínas de suero tales como la albúmina de suero humana, substancias amortiguadoras tales como fosfatos, glicina, ácido sórbico, sorbato de potasio, mezclas parciales de glicéridos de ácidos grasos vegetales saturados, agua, sales o electrolitos, tales como sulfato de protamina, fosfato ácido de disodio, fosfato ácido de potasio, cloruro de sodio, sales de zinc, sílice coloidal, trisilicato de magnesio, polivinil pirrolidona, substancias de base celulosa, polietilen glicol, carboximetilcelulosa de sodio, poliacrilatos, ceras, polímeros de bloque de polietileno-polioxipropileno, polietilen glicol y grasa de lana. Las ciclodextrinas tales como la α-, β- y γ-ciclodextrina, o derivados químicamente modificados tales como hidroxialquil ciclodextrinas, incluyendo 2- y 3-hidroxipropil-β-ciclodextrinas, u otros derivados solubilizables se pueden también usar para aumentar la administración de los compuestos de la presente invención.

Las composiciones de la presente invención pueden contener otros agentes terapéuticos como se describen abajo, y se pueden formular por ejemplo, al emplear vehículos o diluyentes sólidos o líquidos convencionales, así como aditivos farmacéuticos de un tipo adecuado para el modo deseado de administración (por ejemplo, excipientes, aglutinantes, conservadores, estabilizadores, sabores, etc.) según las técnicas tales como aquellas bien conocidas en la técnica de la formulación farmacéutica.

538

Los compuestos de la invención se pueden administrar por cualquier medio adecuado, por ejemplo oralmente, tal como en forma de tabletas, cápsulas, gránulos o polvos; sublingualmente, bucalmente, parenteralmente, tal como por técnicas de infusión o inyección subcutánea, intravenosa, intramuscular o intraesternal (por ejemplo como soluciones o suspensiones acuosas o no acuosas estériles inyectables); nasalmente tal como por un rocío por inhalación; tópicamente, tal como en forma de una crema o ungüento; o rectalmente tal como en forma de supositorios; en formulaciones de dosis unitaria que contienen vehículos o diluyentes no tóxicos farmacéuticamente aceptables. Los compuestos de la invención pueden por ejemplo, administrarse en una forma adecuada para la liberación inmediata o liberación prolongada. La liberación inmediata o liberación prolongada se puede alcanzar por el uso de composiciones farmacéuticas adecuadas incluyendo los compuestos de la invención, o particularmente en el caso de la liberación prolongada, por el uso de dispositivos tales como implantes subcutáneos o bombas osmóticas. Los compuestos actuales también se pueden administrar por liposomas.

Las composiciones ejemplares para administración oral, incluyen suspensiones que pueden contener por ejemplo, celulosa microcristalina para impartir volumen, ácido algínico o alginato de sodio como un agente de suspensión,

537

metil celulosa como un mejorador de la viscosidad, y agentes edulcorantes y saborizantes, tales como aquellos conocidos en la técnica; y tabletas de liberación inmediata que pueden contener por ejemplo, celulosa microcristalina, fosfato de dicalcio, almidón, estearato de magnesio, y/o lactosa y/u otros excipientes, aglutinantes, agentes de dilución, desintegrantes, diluyentes, lubricantes tales como aquellos que se conocen en la técnica. Los compuestos actuales también se pueden suministrar a través de la cavidad oral por administración sublingual y/o bucal. Las tabletas moldeadas, tabletas comprimidas o tabletas liofilizadas son formas ejemplares que se pueden usar. Las composiciones ejemplares incluyen aquellas que formulan los compuestos de la invención con diluyentes de disolución rápida tales como manitol, lactosa, sacarosa, y/o ciclodextrinas. También se pueden incluir en tales formulaciones excipientes de alto peso molecular tales como celulosas (avicel) o polietilen glicoles (PEG). Tales formulaciones pueden también incluir un excipiente para ayudar a la adhesión de la mucosa tal como hidroxi propil celulosa (HPC), hidroxi propil metil celulosa (HPMC), carboxi metil celulosa sódica (SCMC), copolímero de anhídrido maléico (por ejemplo Gantrez), y agentes para controlar la liberación tal como el copolímero poliacrílico (por ejemplo Carbopol 934). También se pueden agregar lubricantes, agentes mejoradores del flujo,

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saborizantes, agentes colorantes y estabilizadores para facilidad de fabricación y uso.

Las composiciones ejemplares para administración por aerosol nasal o inhalación, incluyen soluciones salinas que pueden contener por ejemplo alcohol bencílico u otros conservadores adecuados, promotores de la absorción para aumentar la biodisponibilidad, y/u otros agentes solubilizantes o dispersantes tales como aquellos conocidos en la técnica.

Las composiciones ejemplares para administración parenteral incluyen soluciones inyectables o suspensiones que pueden contener por ejemplo, diluyentes o solventes parenteralmente aceptables, adecuados no tóxicos, tal como el manitol, 1,3-butanodiol, agua, solución de Ringer, una solución de cloruro de sodio isotónica, u otros agentes de suspensión y humectantes o dispersantes adecuados, incluyendo mono o diglicéridos sintéticos, y ácidos grasos incluyendo ácido oleico. El término "parenteral" como se usa en la presente, incluye técnicas de inyección o infusión, subcutáneas, intracutáneas, intravenosas, intramusculares, intraarticulares, intraarterianas, intrasinoviales, intraesternales, intratecales, intralesionales e intracraneales.

Las composiciones ejemplares para administración rectal incluyen supositorios que pueden contener por ejemplo, un

539

excipiente adecuado no irritante tal como manteca de cacao, ésteres de glicéridos sintéticos o polietilen glicoles, que son sólidos a temperaturas ordinarias, pero que se licuan y/o disuelven en la cavidad rectal para liberar el fármaco.

Las composiciones ejemplares para administración tópica incluyen un portador tópico tal como Plastibase (aceite mineral gelificado con polietileno).

La cantidad efectiva de un compuesto de la presente invención, se puede determinar por alguien con experiencia ordinaria en la técnica, e incluye cantidades ejemplares de dosis para un humano adulto desde alrededor de 0.1 hasta 500 mg/kg de peso corporal de compuesto activo por día, o entre 5 y 2000 mg por día el cual puede administrarse en una dosis simple o en forma de dosis divididas individuales tales como de 1 a 5 veces por día. Se entenderá que el nivel de dosis específico y la frecuencia de dosis para algún sujeto en particular, puede variar y dependerá de una diversidad de factores incluyendo la actividad del compuesto específico empleado, la estabilidad metabólica y longitud de acción de ese compuesto, la especie, edad, peso corporal, salud general, sexo y dieta del sujeto, el modo y tiempo de administración, tasa de excreción, combinación de fármacos, y severidad de una condición en particular. Los sujetos preferidos para tratamiento incluyen animales, más preferiblemente especies animales tales como humanos, y

animales domésticos tales como perros, gatos y similares.

Una cápsula típica para administración oral contiene compuestos de la estructura I (250 mg), lactosa (75 mg) y estearato de magnesio (15 mg). La mezcla se pasa a través de una tamiz de malla 60 y se empaca en una cápsula de gelatina No. 1.

Una preparación inyectable típica se produce al colocar asepticamente 250 mg de los compuestos de la estructura I en un vial, asepticamente secado por congelación y sellado. Para su uso, los contenidos del vial se mezclan con 2 mL de solución salina fisiológica, para producir una preparación inyectable.

Los compuestos de los ejemplos son inhibidores de la actividad de AP-1 y/o compiten con ligandos conocidos del receptor de glucocorticoide.

Los ensayos idénticos y/o similares se describen en la Solicitud Provisional copendiente No. 60/396,907, presentada el 18 de julio de 2002 la cual se incorpora en su totalidad en la presente para referencia.

Ensayos

Ensayos de Enlace de GR

Ensayo de Enlace del Receptor Glucocorticoide (I)[a]

Con objeto de evaluar la afinidad de los compuestos de prueba para el receptor glucocorticoide humano, se usó un kit comercialmente disponible (Kit de Ensayo de Competidor del

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Receptor Glucocorticoide, Invitrogen Parte # 2893). Brevemente, el receptor glucocorticoide de longitud completa humano purificado (2 nM) se mezcló con el glucocorticoide fluorescentemente etiquetado (1 nM Fluormone GS Red) en presencia o ausencia del compuesto de prueba. Después de dos horas de incubación a temperatura ambiente en la oscuridad, la polarización fluorescente (FP) de las muestras se midió. La FP de la mezcla del receptor, sonda fluorescente (esto es, Fluormone GS Red) y dexametasona 5μM representan la fluorescencia de respaldo o el 100% de inhibición, mientras que la FP de la mezcla sin dexametasona (pero en presencia del vehículo) se tomó para ser el 100% enlazado. El porcentaje de inhibición de los compuestos de prueba se comparan entonces con la muestra con dexametasona 5μM y se extra como el % de actividad de enlace relativa con dexametasona siendo del 100% y sin inhibición es 0%. Los compuestos de prueba se analizaron en el intervalo de concentración desde 8.5E-05μM a 5μM.

Ensayo de Enlace del Receptor Glucocorticoide (II)[b]

Con objeto de medir el enlace de los compuestos en el receptor glucocorticoide, se usó un kit comercialmente disponible (kit de ensayo de competidor del Receptor Glucocorticoide, PanVera Co., Madison, WI, P2816). Brevemente, el lisado celular que contiene el receptor glucocorticoide de longitud completa humano recombinantemente expresado se mezcló con un

glucocorticoide fluorescentemente etiquetado (4nM FITC-dexametasona) más o menos la molécula de prueba. Después de una hora a temperatura ambiente, la polarización por fluorescencia (FP) de las muestras se midieron. La FP de la mezcla de receptor, sonda fluorescente (esto es FITC-dexametasona) y 1mM dexametasona representa la fluorescencia de respaldo o el 100% de inhibición, mientras que la FP de la mezcla sin dexametasona se tomó para ser 100% de enlace. El porcentaje de inhibición de las moléculas de prueba se comparan entonces con la muestra con 1mM dexametasona y se expresa como el % de actividad de enlace relativa con dexametasona siendo del 100% y sin inhibición es 0%. Las moléculas de prueba se analizaron en el intervalo de concentración desde 0.1nM a 40 mM.

Ensayo de Trans-represión Celular

Para medir la capacidad de las moléculas de prueba para inhibir la actividad de transcripción inducida por AP-1, se utiliza una célula A549 que se transfectó establemente con un plásmido que contiene 7x sitios de enlace AP-1 ADN (plásmido pAP-1-Luc, Stratagene Co. La Jolla, CA) seguido por el gen para luciferasa. Las células se activaron con 10ng/ml de ácido forbol mirístico (PMA) más o menos las moléculas de prueba por 7 horas. Después de 7 horas se agregó un reactivo de luciferasa para medir la actividad enzimática de luciferasa en

la célula. Después de una incubación de 10 minutos del reactivo de luciferasa con células, se midió la luminiscencia en un contador de luminiscencia TopCount. Se calculó la represión de la actividad de AP-1 como el porcentaje de reducción en la señal inducida por PMA sólo. Las moléculas de prueba se analizaron en el intervalo de concentración desde 0.1nM hasta 40 μM. Los EC50 se determinaron usando métodos de configuración de curva estándar tales como Excel fit (Microsoft Co.). Un EC50 es la concentración de molécula de prueba a la cual hay un 50% de represión de la inhibición máxima de transcripción, esto es, una reducción del 50% de la actividad de AP-1. En la ausencia de un EC50 el % de inhibición máxima es la inhibición de AP-1 en una concentración del compuesto de 10 micromolar.

Otros reporteros y líneas celulares también pueden usarse en el ensayo de trans-represión celular. Un ensayo similar se realiza en el cual se mide la actividad NF-κB. El plásmido que contiene sitios de enlace NF-κB ADN se usan, tales como pNF-kB-Luc, (Stratagene, LaJolla CA), y PMA u otros estímulos, tales como TNF-α o lipopolisacárido, se usan para activar la trayectoria NF-κB. Pueden usarse ensayos NF-κB similares al que se describe en Yamamoto K., et al., J. Biol. Chem., Dec 29, 270(52):31315-20 (1995).

Los ensayos de trans-represión celular descritos anteriormente pueden usarse para medir la trans-represión por

cualquier NHR. Alguien de habilidad en la técnica entenderá que los ensatos pueden requerir la adición de los componentes, tales como un estímulo (por ejemplo PMA, lipopolisacárido, TNF-α, etc.) que inducirán la transcripción mediada por AP-1 o NF-κB.

Adicionalmente, la trans-represión mediada por AR puede medirse por el ensayo descrito en Palvimo. J.J. et al., J. Biol. Chem., 27 septiembre, 271 (39): 24151-6 (1996) y la trans-represión mediada por PR puede medirse por el ensayo descrito en Kalkhoven E., et al. J. Biol. Chem., 15 marzo, 271 (11): 6217-24 (1996).

Abreviaturas

Las siguientes abreviaturas es emplean en las siguientes Preparaciones y Ejemplos:

F = fenilo

Bn = bencilo

t-Bu = butilo terciario

Me = metilo

Et = etilo

TMS = trimetilsililo

$TMSN_3$ = azida de trimetilsililo

TBS = terc-butildimetilsililo

FMOC = fluorenilmetoxicarbonilo

Boc = terc-butoxicarbonilo

Cbz = carbobenciloxi o carbobenzoxi o benciloxicarbonilo

THF = tetrahidrofurano

Et_2O = éter de dietilo

hex = hexanos

EtOAc = acetato de etilo

DMF = dimetil formamida

MeOH = metanol

EtOH = etanol

i-PrOH = isopropanol

DMSO = sulfóxido de dimetilo

DME = 1,2 dimetoxietano

DCE = 1,2 dicloroetano

HMPA = triamida hexametil fosfórica

HOAc o AcOH = ácido acético

TFA = ácido trifluoroacético

TFAA = anhídrido trifluoroacético

$i\text{-}Pr_2NEt$ = diisopropiletilamina

Et_3N = trietilamina

NMM = N-metil morfolina

DMAP = 4-dimetilaminopiridina

$NaBH_4$ = borohidruro de sodio

$NaBH(OAc)_3$ = triacetoxiborohidruro de sodio

DIBALH = hidruro de diisobutil aluminio

LAH o $LiAlH_4$ = hidruro de litio y aluminio

n-BuLi = n-butil-litio

LDA = diisopropilamida de litio

Pd/C = paladio sobre carbono

PtO_2 = óxido de platino

KOH = hidróxido de potasio

NaOH = hidróxido de sodio

LiOH = hidróxido de litio

K_2CO_3 = carbonato de potasio

$NaHCO_3$ = bicarbonato de sodio

DBU = 1,8-diazabiciclo[5.4.0]undec-7-eno

EDC (o EDC.HCl) o EDCI (o EDCI.HCl) o EDAC = clorohidrato de 3-etil-3'-(dimetilamino)propil-carbodiimida (o clorohidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida)

HOBT o HOBT.H_2O = hidrato de 1-hidroxibenzotriazol

HOAT = 1-Hidroxi-7-azabenzotriazol

Reactivo BOP = hexafluorofosfato de benzotriazol-1-iloxi-tris(dimetilamino) fosfonio

$NaN(TMS)_2$ = hexametildisilazida de sodio o bis(trimetilsilil)amida de sodio

Ph_3P = trifenilfosfina

$Pd(OAc)_2$ = Acetato de paladio

$(Ph_3P)_4Pd^o$ = tetraquis trifenilfosfina paladio

DEAD = azodicarboxilato de dietilo

DIAD = azodicarboxilato de diisopropilo

Cbz-Cl = cloroformiato de bencilo

CAN = nitrato de amonio cérico

SAX = Intercambiador de anión fuerte

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SCX = Intercambiador de catión fuerte

Ar = argón

N_2 = nitrógeno

min = minuto(s)

h o hr = hora(s)

L = litro

mL = mililitro

mL = microlitro

g = gramo(s)

mg = miligramo(s)

mol = moles

mmol = milimol(es)

meq = miliequivalente

TA = temperatura ambiente

sat o sat'd = saturado

ac. = acuoso

TLC = cromatografía de capa delgada

HPLC = cromatografía líquida de alta resolución

HPLC de fase inversa = cromatografía líquida de alta resolución de fase inversa, usando una columna YMC ODS S5 y eluyentes DE un solvente A binario/solvente B

Solvente A = 10% MeOH - 90% H_2O - 0.1% TFA

Solvente B = 90% MeOH - 10% H_2O - 0.1% TFA

CL/EM = cromatografía líquida de alta resolución/espectrometría de masa

EM o Espectro de masa = espectrometría de masa

RMN = resonancia magnetica nuclear

Datos espectrales RMN: s = singlete; d = doblete; m = multiplete; amp. = amplio; t = triplete

pf = punto de fusión.

Ejemplos

Los siguientes Ejemplos ilustran modalidades de los compuestos inventivos y materiales de partida, y no se pretende que limiten el alcance de las reivindicaciones.

Preparaciones

Las preparaciones establecidas anteriormente son para la síntesis de reactivos que no se obtuvieron de fuentes comerciales y se emplearon para la preparación de compuestos de la fórmula I de la invención. Todos los compuestos quirales en las tablas y esquemas de reacción son racémicos a menos que se especifique de otra manera.

La cromatografía líquida de alta resolución preparativa de fase inversa ("HPLC") se realizó con Cromatógrafos para líquidos Shimadzu 8A usando columnas YMC S5 ODS (20 x 100, 20 x 250, o 30 x 250 milimetros ("mm")). La elución de gradiente se realizó con metanol ("MeOH")/mezclas de agua en la presencia de ácido trifluoroacético 0.1% ("TFA").

Método de HPLC analítica Empleado en Caracterización de Ejemplos

La HPLC analítica se realizó en cromatógrafos para

líquidos Shimadzu LC10AS usando los siguientes métodos:

Método A (Usado en todos los casos, a menos que se indique de otra manera):

Gradiente lineal de 0 hasta 100% solvente B durante 4 minutos ("min"), con 1 minuto ("min") de espera a 100% B.

Visualización Ultravioleta ("UV") en 220 nanómetros ("nm")

Columna: YMC S5 ODS Ballistic 4.6 x 50 mm

Relación de flujo: 4 mililitros ("mL")/min

Solvente A: 0.2% ácido fosfórico, 90% agua, 10% metanol

Solvente B: 0.2% ácido fosfórico, 90% metanol, 10% agua.

Método B:

Columna: Phenomenex Luna C18(2), 4.6 x 50 mm x 5 um

Fase Móvil: (A) 10:90 metanol: agua; (B) 90:10 metanol: agua

Solución amortiguadora: 0.1% TFA

Intervalo de gradiente: 0-100% B

Tiempo de gradiente: 4 min

Relación de flujo: 4 mL/min

Tiempo de análisis: 5 min

Detección:

Detector 1: UV a 220 nm

Detector 2: EM (ESI+)

Detector 3: ELSD

Método C:

Columna: Waters SunFire C18, 4.6 x 50 mm x 5 um

Fase Móvil: (A) 10:90 metanol: agua; (B) 90:10 metanol: agua

Solución amortiguadora: 0.1% TFA

Intervalo de gradiente: 0-100% B

Tiempo de gradiente: 4 min

Relación de flujo: 4 mL/min

Tiempo de análisis: 5 min

Detección:

Detector 1: UV a 220 nm

Detector 2: EM (ESI+)

Detector 3: ELSD

Método D:

Gradiente lineal de 0 hasta 100% solvente B durante 4 min, con 1 min de espera a 100% B.

Visualización UV a 220 nm

Columna: YMC CombiScreen ODS-A S5 4.6 x 50 mm

Relación de flujo: 4 mL/min

Solvente A: 0.2% ácido fosfórico, 90% agua, 10% metanol

Solvente B: 0.2% ácido fosfórico, 90% metanol, 10% agua.

Método E:

Gradiente lineal de 0 hasta 100% solvente B durante 2 min, con 1 min de espera a 100% B.

Visualización UV a 254 nm

Columna: YMC S5 ODS Ballistic 4.6 x 50 mm

Relación de flujo: 4 mL/min

Solvente A: 0.2% ácido fosfórico, 90% agua, 10% metanol

Solvente B: 0.2% ácido fosfórico, 90% metanol, 10% agua.

Método F:

Gradiente lineal de 0 hasta 100% solvente B durante 2 min, con 1 min de espera a 100% B.

UV visualización a 254 nm

Columna: Phenomenex Luna C18 4.6 x 30 mm

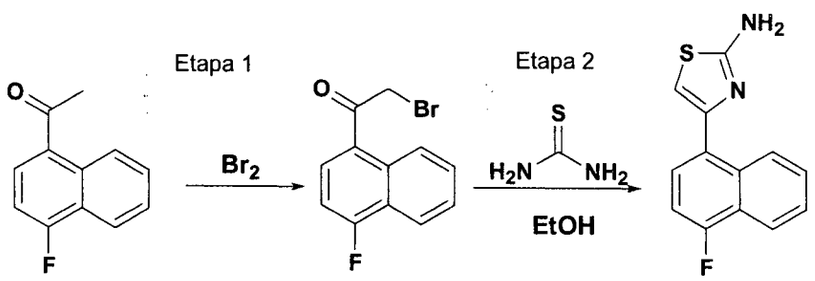
Relación de flujo: 5 mL/min

Solvente A: 0.1% TFA, 90% agua, 10% metanol

Solvente B: 0.1% TFA, 90% metanol, 10% agua.

Preparación 1

4-(4-Fluoro-naftalen-1-il)-tiazol-2-ilamina



Etapa 1

A una solución de 4'-fluoro-1'-acetonaftona (28.69 millimoles ("mmol"), 5.4 gramos ("g")) en 1,4-dioxano (18.0 mL) a 0°C se le agregó bromo (35.13 mmol, 5.61 g). Después de 3 horas ("h" o "hr") a temperatura ambiente ("ta") la mezcla de reacción se concentró *in vacuo* para dar 7.66 g (Rendimiento

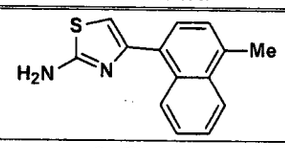
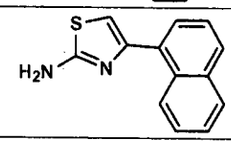
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("Y"): 100%) del producto de la etapa 1.

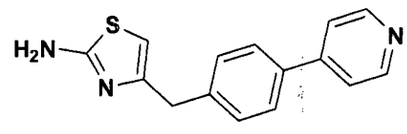
Etapa 2

A una solución del producto de la etapa 1 (28.69 mmol, 7.66 g) en alcohol etílico ("EtOH") (20 mL) a temperatura ambiente se agregó tiourea (36.13 mmol, 2.75 g). Después de 1 hora a temperatura ambiente se formó un precipitado. A la mezcla de reacción se le agregó agua (100 mL) y el sólido se colectó por filtración al vacío. El sólido se lavó luego con agua (3 x 100 mL) y diclorometano (3 x 100 mL), luego se secó *in vacuo* para dar 5.5 g (Y: 75%) del compuesto del título. Espectrometría de masa ("EM") (E+) m/z: 245 (MH^+).

Los siguientes compuestos se prepararon de la misma forma que el producto de la Preparación 1:

Preparación No.	Estructura
2	
3	

Preparación 4



(a) A una solución de 4-bromofenilacetona comercialmente disponible (25 g, 117 mmol) en 30 mL de ácido acético y 15 mL de

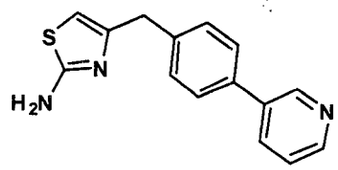
48% HBr se agregó una solución de bromo (40 g, 217 mmol) en 50 mL de ácido acético. Después de 4 hr, se agregó acetona (150 mL) y la mezcla de reacción se agitó durante 3 d. La reacción se concentró por evaporador rotatorio, se diluyó con salmuera, y se extrajo 2 x DCM. Los extractos DCM se secaron sobre $MgSO_4$. La solución se filtró, concentró por evaporador rotatorio, y se procesó por cromatografía en SiO_2 usando DCM para dar 20.8 g (98%) de un aceite obscuro 4a. ^{1}H-RMN (400 MHz, $CDCl_3$): δ 7.49 (d, 2H), 7.12 (d, 2H), 3.94 (s, 2H), 3.92 (s, 2H).

(b) A una solución de 4a (116 mmol) en 200 mL de EtOH se le agregó tiourea (9.0 g, 118 mmol) todo a la vez. La reacción se calentó a reflujo durante 4 hr. La reacción se concentró por evaporador rotatorio y el residuo sin refinar se disolvió en EtOAc y se extrajo 3 x 1N HCl. Los extractos acuosos se basificaron con 1N NaOH y luego se extrajeron 2 x EtOAC. Los extractos EtOAc se secaron sobre $MgSO_4$, y el sólido se trituró en 10% hexanos en EtOAc. El sólido se colectó y se secó *in vacuo* para dar 18 g (57%) de 6b puro. EM encontrado: $(M+H)^+$ = 270.

(c) Se carga un matraz con 4b (8.07 g, 30 mmol), ácido 4-piridinborónico (6.1 g, 50 mmol), tetraquis(trifenilfosfina)paladio (0) (3.5 g, 3.0 mmol), 30 mL de 2M K_2CO_3, y 200 mL de DMF. La mezcla de reacción se desgasificó al burbujear nitrógeno durante 15 min luego se calentó a 100°C durante la noche. La mezcla de reacción se

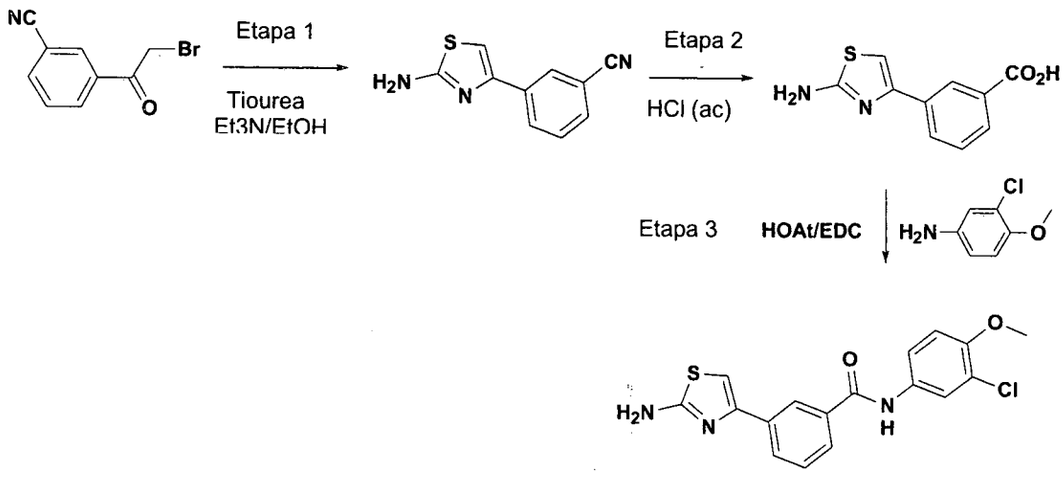
diluyó en EtOAc y se extrajo 3 x 1N HCl. Los extractos acuosos se basificaron con 1N NaOH y luego se permitieron reposar en el refrigerador durante 2 hr. El sólido se colectó y se secó *in vacuo* para dar 5.4 g (68%) de 4c puro. EM encontrado: (M+H)+ = 268.

Preparación 5



El compuesto del título se preparó a partir del bromuro intermediario 4b de la misma forma que 4c substituyendo el ácido 3-piridilborónico por ácido 4-piridilborónico. EM (E-) m/z: 268 (M+H); ^{1}H-RMN (400 MHz, $CDCl_3$): δ 8.80 (s, 1 H), 8.51 (dd, 1 H), 8.13 (dd, 1 H), 7.62 (d, 2 H), 7.53 (dd, 1 H), 7.40 (d, 2 H), 6.15 (s, 1 H), 3.89 (s, 2 H).

Preparación 6



Etapa 1

A una solución de 3-(2-bromoacetil)benzonitrilo (15.0 g, 66.6 mmol) (preparada en la forma descrita en Tanaka et al., J. Med. Chem. 1998, 41, 2390-2410), en EtOH (220 mL) se le agregó trietilamina ("TEA") (9.3 mL, 66.6 mmol) y tiourea (6.6 g, 86.6 mmol) y la reacción se agitó a temperatura ambiente durante la noche. Después de 20 h, la reacción se concentró *in vacuo* y el residuo se dividió entre agua y EtOAc. La capa acuosa se lavó con EtOAc (3x). Los extractos orgánicos combinados se lavaron con bicarbonato de sodio saturado ("sat.") ("$NaHCO_3$"), se secaron sobre $MgSO_4$, filtraron, y concentraron por evaporador rotatorio. El sólido resultante se recristalizó de EtOAc y hexano para dar 7.78 g del sólido amarillo pálido en un primer lote y 1.87 g de un segundo lote (72% de rendimiento combinado). EM encontrado: $(M+H)^+$ = 202. ^{1}H-RMN (DMSO) δ 8.21 s (1H), 8.14 (dd, 1H), 7.72 (dd, 1H), 7.60 (t ap., 1H), 7.27 (s, 1H), 7.19 (s, 2H).

Etapa 2

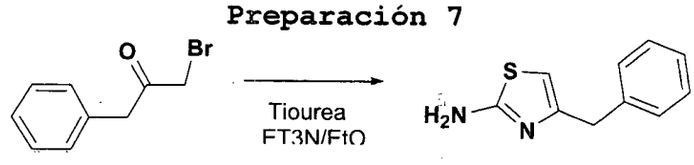
El producto de la Etapa 1 (6.73 g, 33.5 mmol) se suspendió en 110 mL de HCl concentrado y se puso a reflujo mientras se agitaba durante 4 hr. La solución homogénea se enfrió en un baño de hielo para formar cristales que se filtraron, lavaron con agua y secaron *in vacuo* para dar 6.89 g del producto deseado (94% de rendimiento). EM encontrado: (M+H)+ = 221.

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Etapa 3

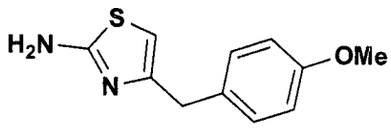
A una solución del producto de la etapa 2 (6.89 g, 31.3 mmol) en DMF (100 mL) se le agregó trietilamina (8.8 mL, 63 mmol), 1-hidroxi-7-azabenzotriazol ("HOAt") (4.26 g, 31.3 mmol), y clorohidrato de 3-etil-3'-(dimetilamino)propil-carbodiimida (o clorohidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida) ("EDC") (6.0 g, 31.3 mmol). Después de agitar 25 min, una solución de 3-cloro-4-anisidina (5.92 g, 37.6 mmol) en 50 mL DMF y 8.8 mL trietilamina se agregó todo a la vez a temperatura ambiente. Después de agitar durante 24 h, la reacción se concentró por evaporador rotatorio, se extrajo de una solución de cloruro de sodio saturado ("salmuera") con EtOAc. Los orgánicos combinados se secaron sobre $MgSO_4$ hasta producir producto sin refinar. El producto sin refinar se concentró *in vacuo*, se disolvió en una cantidad mínima de EtOAc y se trituró con hexano. El sólido resultante se filtró y la trituración se repitió dos veces para dar un total de 5.7 g (51% de rendimiento) del producto sin refinar. EM encontrado: $(M+H)^+$ = 360. ^{1}H-RMN (DMSO) δ 10.3 (s, 1H), 8.35 (s, 1H), 8.00 (d, 1H), 7.95 (d, 1H), 7.80 (d, 1H), 7.69 (d, 1H), 7.52 (t, 1H), 7.16 (m, 4H), 3.85 (s, 3H).

Preparación 7



A una solución de 1-bromo-3-fenil-2-propanona (2.2 g, 10 mmol) (preparada en la forma descrita en Choi et al., Org. Lett. 2003, vol. 5, no. 4, 411-414), en EtOH (100 mL) se agregó tiourea (1.0 g, 13 mmol) y la reacción se agitó a reflujo durante la noche. Después de 20 h, la reacción se concentró *in vacuo* y dividió entre agua y acetato de etilo ("EtOAc"). La capa acuosa se lavó con EtOAC (3x). Los extractos orgánicos combinados se secaron sobre sulfato de magnesio ("$MgSO_4$"), filtraron, y concentraron por evaporador rotatorio. El sólido resultante se purificó por cromatografía en gel de sílice usando 10% MeOH/EtOAc como el eluyente para dar 2.1 g del sólido amarillo pálido (95% de rendimiento). EM encontrado: (M+H)+ = 191. Resonancia magnética nuclear de protón ("^{1}H-RMN") en cloroformo ("$CDCl_3$") δ 7.2-7.35 m (5H), 6.01 (s, 1H), 4.8-5.3 (s a., 2H), 3.86 (s, 2H). Datos espectrales RMN: s = singlete; d = doblete; m = multiplete; a. = amplio; t = triplete.

Preparación 8



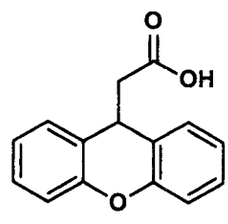
(a) Aplicando el método de Mazzocchi et al (Synth. Commun. 1986, 309-312) un cuprato se preparó a partir de bromuro de 4-metoxifenilmagnesio (20 mmol, 40 mL de solución THF 0.5 M) y CuBr (574 mg, 2.0 mmol) en 50 mL de éter anhidro.

El cuprato se trató con epiclorohidrina (1.94 g, 21 mmol) y se agitó a -40°C durante 20 hr. La reacción se apagó con agua, se extrajo 2 x Et_2O, y los extractos etéreos se secaron sobre $MgSO_4$. La solución se filtró, concentró por evaporador rotatorio, y procesó por cromatografía en SiO_2 usando 25% EtOAc en hexanos para dar 888 mg (22%) de la clorohidrina 5a como un aceite amarillo. ^{1}H-RMN (400 MHz, $CDCl_3$): δ 7.18 (d, 2H), 6.88 (d, 2H), 4.0 (m, 1H), 3.82 (s, 3H), 3.65 (dd, 1H), 3.52 (dd, 1H), 2.83 (d, 2H).

(b) El alcohol intermediario 8a (888 mg, 4.44 mmol) se recibió en diclorometano (40 mL) y se trató con periodinano de Dess-Martin (1.88 g, 4.44 mmol). La reacción se dejó calentar a temperatura ambiente y se completó por TLC observando después de 4 hr. La mezcla de reacción se concentró por evaporación rotatoria y el residuo sin refinar se purificó sobre SiO_2 (diclorometano como eluyente) para dar 762 mg (86% Y) de clorometilcetona 8b.

(c) Este intermediario se recibó en 15 mL de EtOH y se trató con una solución de tiourea (302 mg, 3.82 mmol) en 5 mL de EtOH. La reacción se concentró *in vacuo* y un sólido se formó en el reposo para dar 8c puro, 208 mg (80%) como un sólido amarillo. EM encontrado: (M+H)+ = 221.

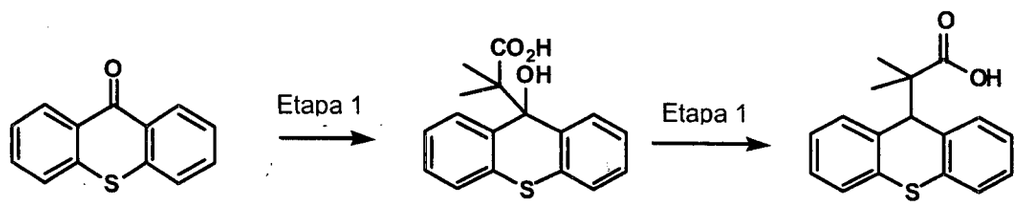
Preparación 9



Una mezcla de 9-hidroxi xanteno (3.96 g, 20 mmol) y ácido

malónico (2.6 g, 25 mmol) en piridina seca se agitó bajo nitrógeno a 65°C, volviéndose homogénea después de 20 min a esa temperatura. Después de calentar 2 h a 65°C, la solución se calentó a 95°C, y se calentó a esa temperatura durante 4.5 h adicionales. La solución se vació luego en HCl acuoso 1N, dando un aceite el cual se solidificó durante 1 h. El sólido se colectó y se lavó con agua, luego se dividió entre NaOH acuoso 1N y diclorometano. La capa acuosa se acidificó con HCl concentrado, luego se lavó con acetato de etilo. La capa orgánica se secó (sulfato de sodio) y concentró para dar el producto (2.48 g, Y = 50%) como un sólido blanco opaco/rosa pálido. EM (E-) m/z: 239 (M-H); Tiempo de retención de CL: 3.39 min.

Preparación 10



Etapa 1

A una solución de diisopropilamina (9.28 mL, 66.16 mmol) en THF seco (70 mL) a -30°C se agregó n-butil litio (1.6 M en hexanos, 41.4 mL) gota a gota. La solución resultante se calentó a 0°C y una solución de ácido isobutírico (3.06 mL, 33.1 mmol) en THF (10 mL) se agregó luego gota a gota. La mezcla se calentó a 55°C durante 1.5 h, luego se enfrió a

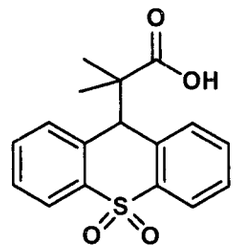
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temperatura ambiente y se agregó en porciones por medio de cánula a tioxanten-9-ona (5.0 g, 23.58 mmol) en THF (100 mL) a 0°C. El baño de hielo se removió y la mezcla de reacción se agitó a temperatura ambiente durante 2 h, luego se dividió entre acetato de etilo y HCl 1N. La capa orgánica se lavó con NaOH acuoso 1N. La capa acuosa básica se acidificó a un pH 2 con la adición gota a gota de HCl concentrado, luego se lavó con acetato de etilo. La capa orgánica se secó (sulfato de sodio) y concentró para dar el producto sin refinar (3.5 g), el cual se usó directamente en la siguiente etapa sin purificación adicional. EM (E+) m/z: 301 (M+H); Tiempo de retención CL: 3.44 min.

Etapa 2

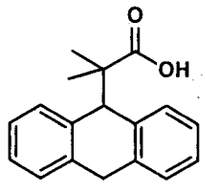
A una solución del producto de la etapa 1 (3.5 g, 11.7 mmol) en diclorometano (40 mL) a 0°C se agregó eterato de trifluoruro de boro (2.6 mL, 20.4 mmol) seguido por trietilsilano (3.4 mL, 21.3 mmol). La solución resultante se dejó calentar a temperatura ambiente durante 1 h. Después de 2 h a temperatura ambiente, la mezcla de reacción se dividió entre diclorometano y NaOH acuoso 1N. La capa acuosa se acidificó a un pH 2 con la adición gota a gota de HCl concentrado, luego se lavó con acetato de etilo. La capa orgánica se secó (sulfato de sodio) y concentró, luego se purificó por cromatografía de columna por desorción súbita (sílice, 1:1 acetato de etilo: hexanos, producto Rf = 0.6) para dar el producto (0.7 g) como un sólido amarillo pálido. Tiempo de retención CL: 3.83 min.

Preparación 11



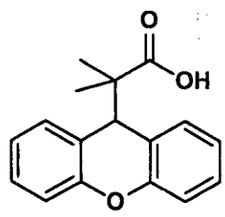
A una solución del producto de la Preparación 9 (100 mg, 0.352 mmol) en ácido acético glacial (4 mL) a 0°C se le agregó peróxido de hidrógeno (4 mL). La solución se dejó que aumente de temperatura, y se agitó durante 2 h. A la mezcla de reacción se le agregó dihidrato del tungstato de sodio (30 mg, 0.10 mmol). Después de agitar otras 12 h a temperatura ambiente, la mezcla de reacción se dividió entre acetato de etilo y agua. La capa orgánica se lavó secuencialmente con una solución saturada de sulfito de sodio acuoso y agua, luego se secó sobre sulfato de sodio y se concentró para dar el producto (95 mg, 85% de rendimiento) como un sólido blanco. Tiempo de retención CL: 2.69 min.

Preparación 12



El compuesto del título se preparó de la misma forma como el compuesto del título de la Preparación 10, reemplazando la tioxanten-9-ona con antrona.

Preparación 13



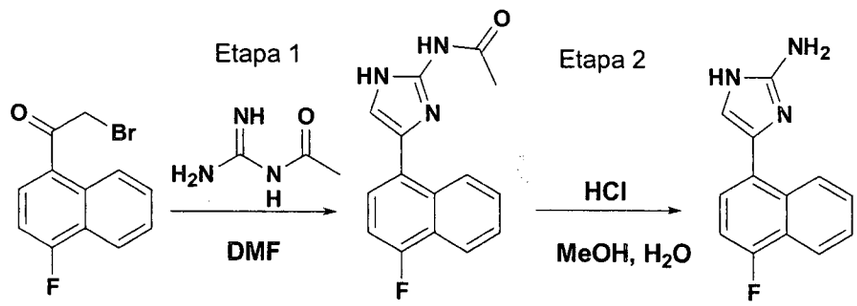
El compuesto del título se preparó de la misma forma como el compuesto del título de la Preparación 10, reemplazando la tioxanten-9-ona con 9H-xanten-9-ona.

La preparación alternativa del compuesto del título es como sigue: A una solución de 9-hidroxi xanteno (250 mg, 1.26 mmol) en diclorometano (11 mL) a °C bajo nitrógeno se agregó tetracloruro de titanio (1.0M en diclorometano, 1.26 mL) gota a gota para dar una mezcla opaca, amarilla. Después de 5 min a 0°C, metil trimetilsilil dimetilceteno acetal (MTDKA) (0.64 mL, 3.15 mmol) se agregó gota a gota, dando un solución de tono café. Después de 30 min a 0°C, agua (3 mL) se agregó y la mezcla se agitó durante 10 min, volviéndose amarilla con la formación de un precipitado. La mezcla se filtró sobre Celite, y la capa orgánica se separó, luego se lavó con bicarbonato de sodio acuoso saturado, se secó sobre sulfato de sodio, y se concentró. La purificación del residuo por cromatografía de columna por desorción súbita (5% acetato de etilo en hexanos) proporcionó el compuesto del título (178 mg). Tiempo de retención CL: 3.89 min.

563

Preparación 14

4-[1-(4-Fluoro)naftil]aminoimidazol



Etapa 1

A una solución del producto de la Preparación 1, etapa 1 (18.73 mmol, 5.0 g) en DMF (15 mL) a temperatura ambiente se agregó 1-acetilguanidina (57.43 mmol, 5.80 g). Después de 5 horas a temperatura ambiente, la mezcla de reacción se diluyó con agua (100 mL) y se extrajo con acetato de etilo (3 x 100 mL). Las fases orgánicas se concentraron *in vacuo* y el residuo se procesó por cromatografía en gel de sílice (eluyendo con 5% metanol en diclorometano) para dar 2.0 g (Y: 39%) del producto de la etapa 1. EM (E+) m/z: 270 (MH^+).

Etapa 2

A una solución del producto de la etapa 1 (7.43 mmol, 2.0 g) en metanol (17 mL) se le agregó agua (8.5 mL) y 12 N HCl (12.0 mL). Después de 1 hora a reflujo la mezcla de reacción se concentró *in vacuo* a aproximadamente 15 mL. La solución resultante se purificó luego y neutralizó por intercambio de cationes SPE para dar 1.66 g (Y: 99%) del compuesto del título 2a. EM (E+) m/z: 228 (MH^+).

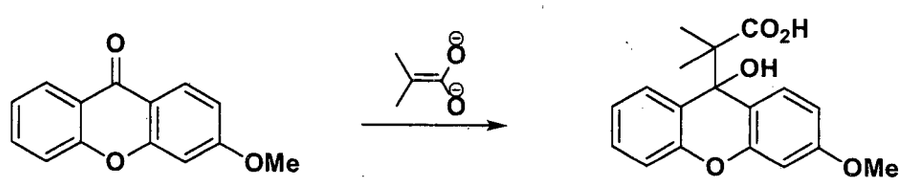
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Preparación 15



Etapa 1

A una solución de 3-hidroxi-9-H-xantenona ("enlazador de Sieber") (20.4 g, 96.2 mmol) en DMF (475 mL) se agregó yoduro de metilo (18.0 mL, 287 mmol) seguido por NaH (60% p/p en aceite mineral, 7.68 g, 192 mmol). La mezcla se dejó agitar a temperatura ambiente durante 2.5 h, luego se dividió entre acetato de etilo (750 mL) y HCl 1N (300 mL). La capa acuosa se extrajo nuevamente con 2 porciones de acetato de etilo. La capa orgánica combinada se lavó secuencialmente con agua (500 mL), bicarbonato de sodio saturado, y salmuera, luego se secó sobre sulfato de sodio y se concentró. El sólido sin refinar se recristalizó a partir de EtOH y una segunda cosecha de cristales se obtuvo por re-cristalización del licor madre para dar 20.21 g (93% de rendimiento) de 15a como agujas. EM m/z: 227 (M+H); Tiempo de retención CL: 3.38 min.

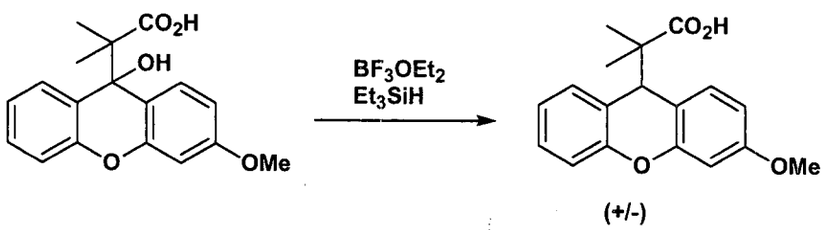


Etapa 2

A una solución de diisopropil amina (6.63 mL, 47.25 mmol)

565

en THF seco (35 mL) a -30°C se agregó nBuLi (1.6 M/hexanos, 29.6 ml) gota a gota. La solución se calentó a 0°C. Una solución de ácido isobutírico (2.19 mL, 23.63 mmol) en THF (10 mL) se le agregó luego gota a gota. La solución se calentó a 55°C durante 1.5 h, luego se enfrió a temperatura ambiente y se agregó en porciones por medio de cánula a la cetona 15a (3.56 g, 15.75 mmol) en THF (30 mL) a 0°C. La solución se dejó calentar lentamente a temperatura ambiente. Después de 2 h, la CL indica el 70% de completado. La mezcla de reacción se dividió entre acetato de etilo y HCl acuoso 1N. La capa orgánica se lavó con NaOH acuoso 1N. La capa acuosa básica se acidificó a 0°C con la adición gota a gota de HCl concentrado hasta un pH = 2. La capa acuosa ácida se lavó con acetato de etilo, y la capa orgánica se secó sobre sulfato de sodio y se concentró para dar el producto alcohol (4.45 g, 90% de rendimiento). EM m/z: 297 (M-OH); Tiempo de retención CL: 3.22 min.



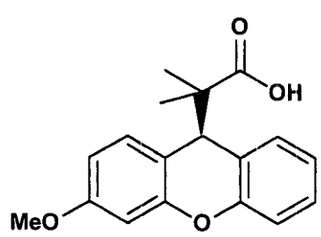
Etapa 3

A una solución de 15b (2.81 g, 8.95 mmol) en diclorometano (35 mL) a 0°C se agregó eterato dietil trifluoruro de boro (2.27 mL, 17.9 mmol) seguido por

trietilsilano (2.86 mL, 17.9 mmol). La solución se dejó calentar a temperatura ambiente durante 1 h. La reacción se completó después de 2 h a temperatura ambiente como se indica por HPLC. La continuación de la reacción más allá de 2 h llevó a un aumento gradual en la producción de un producto derivado de descarboxilación. La mezcla de reacción se dividió entre diclorometano y NaOH acuoso 1N. La capa acuosa se acidificó a un pH 2 con la adición gota a gota de HCl concentrado, luego se lavó con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio y se concentró para dar el producto como un sólido (1.81 g, 68% de rendimiento). EM m/z: 321 (M+Na); Tiempo de retención CL: 3.64 min

PREPARACIÓN 16

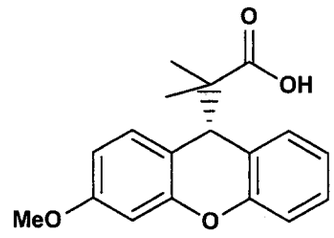
El ácido carboxílico racémico de la Preparación 15 se resolvió por HPLC quiral (Chiralpak AD, 1:1 etanol: metanol, 0.05% TFA, isocrático) para proporcionar los enantiómeros puros 16a, 16b.



16a.

Primero en eluir de HPLC quiral preparativa. HPLC quiral analítica (Chiralpak AD, 4.6 x 250 mm, 1:1 etanol: metanol, isocrático, 0.5 mL/min) tiempo de retención = 6.41 min, >99.9%

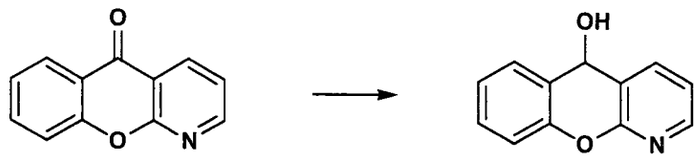
ee.



16b.

Segundo en eluir de HPLC quiral preparativa. HPLC quiral analítica (Chiralpak AD, 4.6 x 250 mm, 1:1 etanol: metanol, isocrático, 0.5 mL/min) tiempo de retención = 10.3 min, >99% ee. El análisis cristalográfico de rayos X de la sal derivada de 16b y (R)(+)-alfa-metilbencilamina probó que 16b va a ser el enantiómero R.

Preparación 17

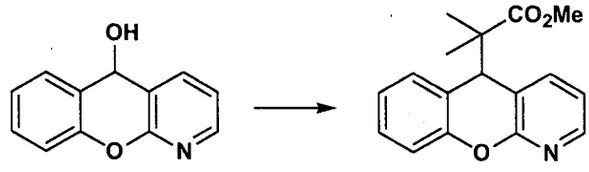


Etapa 1

A una suspensión de 1-azaxantona (adquirida o preparada por el método de Villani et al,. J. Med. Chem. 1975, 18, 1-8.) (18.5 g, 94 mmol) en MeOH (650 mL) a 0°C se le agregó borohidruro de sodio (4.26 g, 113 mmo) en porciones durante 10 min. La mezcla de reacción se dejó calentar a temperatura ambiente, y se agitó 15 h. El análisis HPLC de la mezcla de reacción indicó dos picos, uno correspondiente al alcohol, el otro correspondiente a 9-metoxi-1-azaxanteno el cual se genera

563

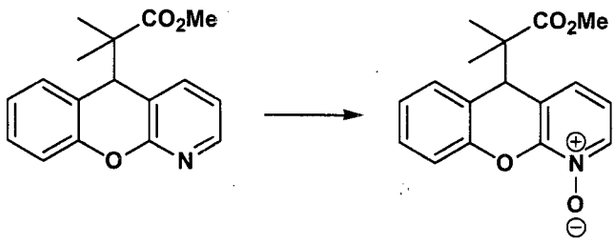
probablemente bajo las condiciones de Análisis CL. La solución amarilla pálida se concentró luego a un tercer volumen y se vació en salmuera fría (500 mL). Esta mezcla se lavó con cloroformo (2 x 300 mL). Las capas orgánicas combinadas se secaron sobre sulfato de sodio y se concentraron para dar un sólido amarillento 17a (17.80 g, 95% de rendimiento) el cual se usó directamente en la siguiente etapa sin purificación adicional. EM (E+) m/z: 200 (M+H); Tiempo de retención CL: 2.01 min., 2.46 min.



Etapa 2

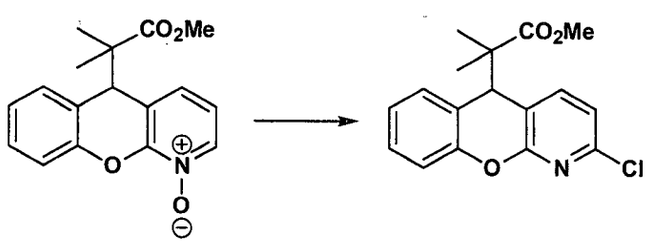
A una suspensión de 17a (17.80 g, 89 mmol) en diclorometano (475 mL) a 0°C se le agregó tetracloruro de titanio (1.0 M en diclorometano, 89 mL) gota a gota. La suspensión color canela resultante se agita 10 min a 0°C (agitación mecánica recomendada) antes de agregar (1-metoxi-2-metilprop-1-eniloxi)trimetilsilano (36 mL, 173 mmol) a la mezcla gota a gota. La solución homogénea, oscura, resultante, se dejó agitar 1 h a 0°C, luego se apagó con la adición de bicarbonato de sodio acuoso saturado, dando evolución de gas y formación de un precipitado blanco. La mezcla se

filtró sobre Celite, y la capa orgánica resultante del filtrado se separó, secó sobre sulfato de sodio, y se concentró para dar un sólido (17b) (22.3 g, 89% de rendimiento) el cual se usó directamente en la siguiente etapa sin purificación adicional. EM (E+) m/z: 284 (M+H); Tiempo de retención CL: 3.04 min.



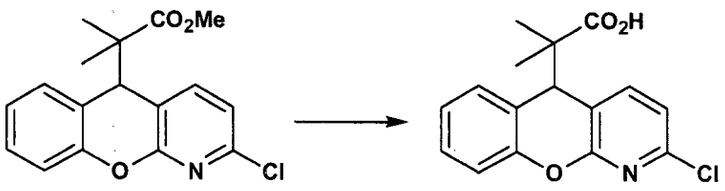
Etapa 3

A una solución de 17b (21.2 g, 74.9 mmol) en diclorometano a temperatura ambiente se le agregó mCPBA (que contiene 30% de ácido m-clorobenzóico) (53 g). Después de 2 h, la mezcla de reacción se lavó secuencialmente con 10% sulfito de sodio acuoso (500 mL), NaOH acuoso 1N (200 mL), y agua (200 mL). La capa orgánica se secó sobre sulfato de sodio, y se concentró para proporcionar el compuesto del título (17c) como un sólido amorfo (21.63 g, 97% de rendimiento) el cual se usó directamente en la siguiente etapa sin purificación adicional. EM (E+) m/z: 300 (M+H); Tiempo de retención CL: 2.25 min.



Etapa 4

Una solución de 17c (21.15 g, 71.0 mmol) en oxicloruro de fosforo (150 mL) se calentó durante 30 min a 90°C. El solvente se removió luego por destilación al vacío bulbo a bulbo. El sólido residual se disolvió en diclorometano (250 mL) y se transfirió en porciones a una cubeta de 1L que contiene hielo (3/4 del total). El carbonato de sodio sólido se agregó en porciones con agitación vigorosa (evolución de gas) a la mezcla espesa resultante hasta que alcanza un pH 6. La emulsión resultante se dejó que reposara durante la noche en un embudo separador. La capa orgánica se removió, se secó (sulfato de sodio), y se concentró para dar el sólido sin refinar 17d 17.37g (77% de rendimiento sin refinar). Este sólido se puede recristalizarse hasta alta pureza de metanol o tomar directamente en la siguiente etapa sin purificación adicional. EM (E+) m/z: 318 (M+H); Tiempo de retención CL: 3.37 min.



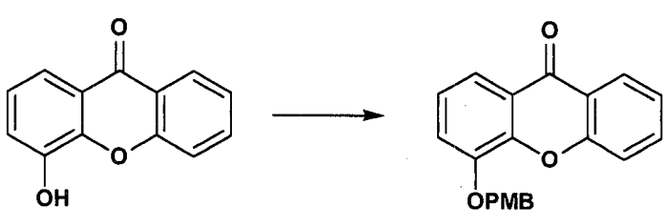
Etapa 5

A una solución de 17d (16.08 g, 50.7 mmol) en THF (240 mL) y metanol (400 mL) se le agregó una solución de KOH (28.46 g, 507 mmol) en agua (320 mL). La solución resultante se calentó a

- 000571

reflujo (65°C) 10 h, luego se concentró bajo presión reducida hasta alrededor de 2/3 de volumen. La solución resultante se acidificó a un pH 5 con la adición gota a gota de HCl 12N, luego se lavó con acetato de etilo (2 x 300 mL). Las capas orgánicas combinadas se secaron (sulfato de sodio) y se concentraron. El ácido carboxílico sin refinar (12.6 g) se disolvió en acetato de etilo tibio (600 mL) y se trató con bencilamina (9.2 mL, 48 mmol). La solución se dejó enfriar gradualmente a temperatura ambiente, y se dejó reposar durante 3 h. El precipitado se colectó y se lavó (éter de dietilo), luego se dividió entre acetato de etilo (350 mL) y HCl acuoso 1N (200 mL). La capa orgánica se secó sobre sulfato de magnesio y se concentró para proporcionar 17e como un sólido (8.53 g, 43% de rendimiento durante dos etapas). EM (E+) m/z: 304 (M+H); Tiempo de retención CL: 3.19 min.

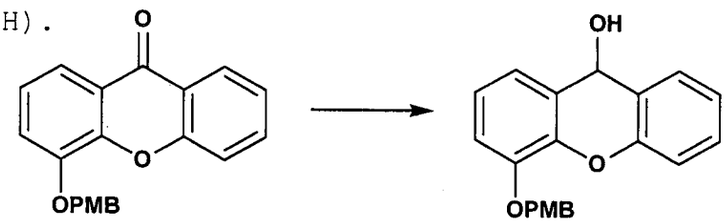
Preparación 18



Etapa 1

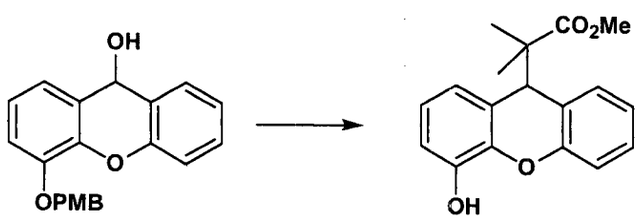
A una solución de 4-hidroxi-9H-9-xantenona (Maybridge) (512 mg, 2.42 mmol) y cloruro de 4-metoxi bencilo (0.393 mL, 2.90 mmol) en DMF (15 mL) se le agregó hidruro de sodio (60 % en p en aceite mineral, 145 mg, 3.63 mmol), dando un color

rojo oscuro y evolución de gas. Después de 3 h a temperatura ambiente, la mezcla de reacción se dividió entre acetato de etilo y HCl acuoso 1N. La capa orgánica se lavó secuencialmente con agua, bicarbonato de sodio acuoso saturado y salmuera, luego se secó sobre sulfato de sodio y se concentró. El residuo sin refinar se purificó por cromatografía de columna por desorción súbita (sílice, 30% acetona en hexanos) para dar el producto 18a (420 mg). EM (E+) m/z: 333 (M+H).



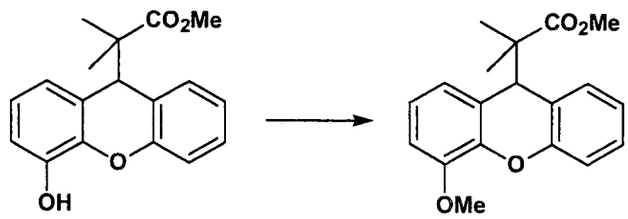
Etapa 2

Una solución de 18a (197 mg, 0.59 mmol) en THF (6 mL) a 0°C bajo nitrógeno se trató con hidruro de aluminio y litio (1.0M en éter de dietilo, 0.59 mL). Después de 30 min a 0°C, agua (aprox. 2 mL) se agregó gota a gota a la mezcla. Después de agitar durante 5 min a 0°C, la mezcla se filtró sobre una almohadilla de Celite y sulfato de sodio, luego se concentró para dar el 18b (183 mg, 93%). EM (E+) m/z: 317 (M-OH); Tiempo de retención CL: 3.88 min.



Etapa 3

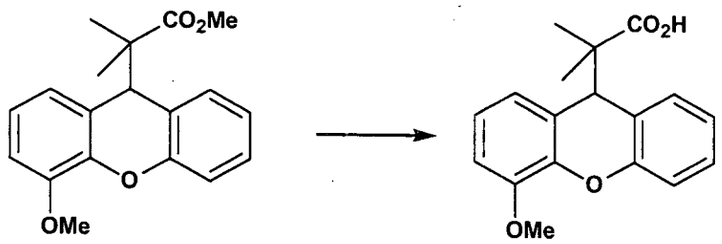
A una solución de 18b (181 mg, 0.54 mmol) en diclorometano (5 mL) a 0°C se le agregó tetracloruro de titanio (1.0M en diclorometano, 0.54 mL) gota a gota para dar una solución roja oscura, brillante, que se vuelve opaca durante el curso de 10 min a 0°C. El (1-metoxi-2-metilprop-1-eniloxi)trimetilsilano (0.219 mL, 1.08 mmol) se agregó luego gota a gota, dando una solución roja oscura, transparente. Después de 20 min a 0°C, la reacción se apagó con la adición de agua (1 mL), volviéndose la mezcla incolora, con la formación de un precipitado. La mezcla se filtró sobre Celite. La capa orgánica se separó y se lavó con bicarbonato de sodio acuoso saturado, se secó sobre sulfato de sodio, y se concentró. El residuo se purificó por cromatografía de columna por desorción súbita (sílice, 10-20% acetato de etilo en hexanos) para dar el producto 18c como la tercera fracción eluida (110 mg, 68%). EM (E-) m/z: 297 (M-H); Tiempo de retención CL: 3.29 min.



Etapa 4

Una mezcla de 18c (32 mg, 0.11 mmol), yoduro de metilo (0.014 mL, 0.22 mmol) y carbonato de cesio (42 mg, 0.13 mmol)

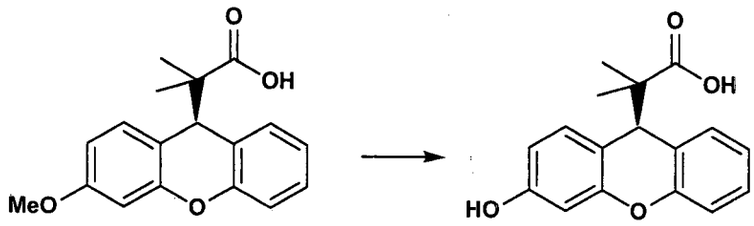
en DMF (1 mL) se calentó a 60°C durante 6 h. La mezcla de reacción se dividió luego entre acetato de etilo y agua. La capa orgánica se lavó secuencialmente con agua, bicarbonato de sodio acuoso saturado, y salmuera, luego se secó sobre sulfato de sodio y se concentró. El intermediario 18d (28 mg, 82%) se usó en la siguiente etapa sin purificación adicional. EM (ES+) m/z: 335 (M+Na); Tiempo de retención CL: 3.57 min.



Etapa 5

El intermediario 18e se obtuvo de 18d de la misma forma descrita anteriormente para la preparación del compuesto del título de 17e a partir de 17d. EM (ES-) m/z: 297 (M-H); Tiempo de retención CL: 3.29 min.

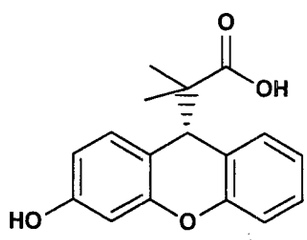
Preparación 19



El producto de la Preparación 16a (600 mg, 2.01 mmol) se dividió uniformemente en 3 recipientes de reacción de microondas. A cada recipiente de reacción se le agregó 1-metil-2-pirrolidinona (4 mL), 2-aminotiofenol (92 mg, 0.74

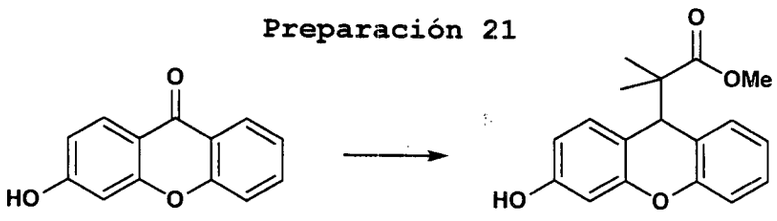
mmol) y carbonato de potasio (102 mg, 0.74 mmol). Cada mezcla se calentó por microondas a 205°C durante 1.5 h. Las mezclas de reacción se combinaron y dividieron entre acetato de etilo y agua. La capa orgánica se extrajo con acuoso hidróxido de sodio 1N. Las capas acuosas combinadas se acidificaron aproximadamente a un pH 2.0, luego se extrajeron con acetato de etilo (3x). Las capas orgánicas combinadas se lavaron con HCl acuoso 1N, luego se secaron sobre sulfato de sodio y se concentraron. La purificación del residuo por HPLC preparativa proporcionó el producto como un sólido amorfo (400 mg, 70%). EM (ES-) m/z: 283 (M-H); Tiempo de retención CL: 3.16 min.

Preparación 20



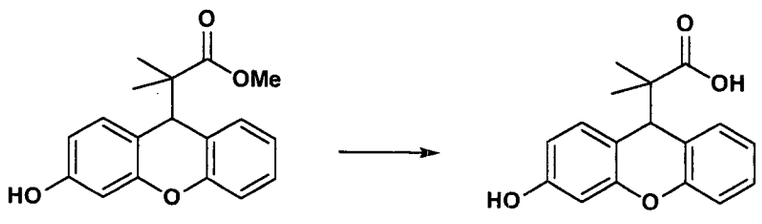
El compuesto del título se preparó a partir del producto de la Preparación 16b siguiendo el procedimiento descrito anteriormente para la preparación del compuesto del título de la Preparación 19. EM (ES-) m/z: 283 (M-H); Tiempo de retención CL: 3.16 min.

Preparación 21



Etapa 1

A una suspensión de 3-hidroxi-9-H-xantenona ("Enlazador de Sieber") (1.0 g, 4.72 mmol) en diclorometano (10 mL) a 0°C bajo nitrógeno se le agregó eterato de trifluoruro de boro (1.8 mL, 14.15 mmol) gota a gota durante 10 min. Después de agitar 10 min a 0°C, se agregó 1-metoxi-2-metilprop-1-eniloxi)trimetilsilano (2.88 mL, 14.15 mmol) gota a gota a la suspensión, dando una solución café oscura transparente durante la adición, la cual se agitó otras 2 h a 0°C. Otra porción de eterato de trifluoruro de boro (1.8 mL, 14.15 mmol) se agregó luego a la mezcla de reacción, seguido por trietilsilano (2.26 mL, 14.15 mmol). La mezcla de reacción se dejó calentar lentamente a temperatura ambiente, y se agitó 15 h. Una solución acuosa saturada de bicarbonato de sodio se agregó a la mezcla de reacción, la cual se extrajo luego con diclorometano. La fase orgánica se lavó con otra porción de bicarbonato de sodio saturado, luego se secó sobre sulfato de sodio y se concentró. El material sin refinar se purificó al pasar a través de una columna corta de gel de sílice (30-50% acetato de etilo en hexanos) para dar el producto 21a (1.2g, 85% de rendimiento) como un sólido amarillo pálido. EM (ES-) m/z: 297 (M-H); Tiempo de retención CL: 3.42 min.

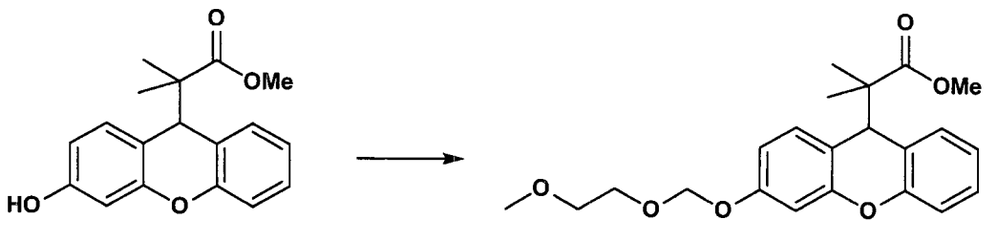


Etapa 2

Una suspensión de 21a (133 mg, 0.45 mmol) en metanol (1

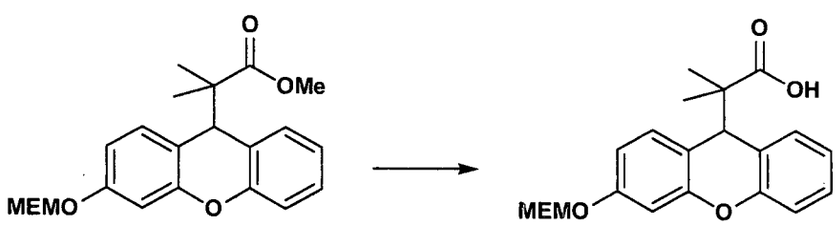
mL), agua (2 mL), DMSO (1 mL) y KOH acuoso 4N (1.13 mL) se calentó a 100°C durante 3 h. La mezcla de reacción se dividió luego entre acetato de etilo y HCl 1N. La capa orgánica se secó sobre sulfato de sodio, y se concentró para dar el producto 21b (124 mg, 97% de rendimiento). Tiempo de retención CL: 3.15 min.

Preparación 22



Etapa 1

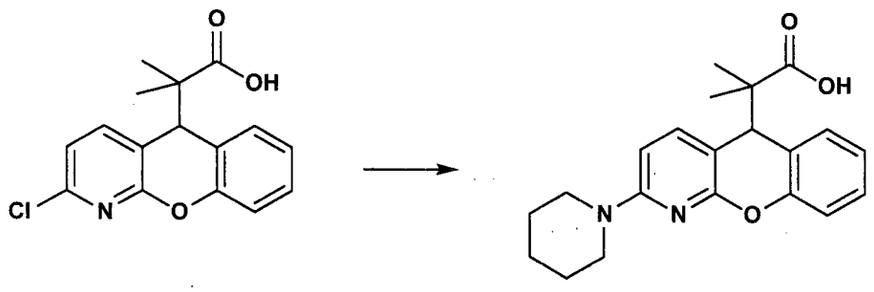
A una solución de 21a (490 mg, 1.64 mmol) en THF (15 mL) a 0°C se le agregó cloruro de 2-metoxietoximetilo (MEM) (0.282 mL, 2.47 mmol), seguido por hidruro de sodio (60% p/p en aceite mineral, 85 mg). Después de 1.3 h, la mezcla de reacción se dividió entre acetato de etilo y HCl 1N. La capa orgánica se lavó secuencialmente con bicarbonato de sodio acuoso saturado y salmuera, luego se secó sobre sulfato de sodio y se concentró para dar 667 mg (ca. 99%) del producto sin refinar 22a como un aceite el cual se tomó directamente en la siguiente etapa sin purificación adicional. Tiempo de retención CL: 3.83 min.



Etapa 2

Una mezcla de 22a sin refinar (ca. 1.64 mmol) en metanol (4 mL), DMSO (3.5 mL), y KOH 4N (4.1 mL) se agitó a 100°C durante 3 h, luego se dividió entre acetato de etilo y HCl 1N. La capa orgánica se secó sobre sulfato de sodio y se concentró. La cromatografía de columna por desorción súbita (sílice, 50-60% acetato de etilo en hexanos) proporcionó el producto 22b (428 mg, 70% durante dos etapas) como un aceite amarillo pálido. Tiempo de retención CL: 3.61 min.

Preparación 23

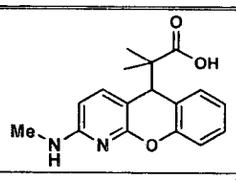
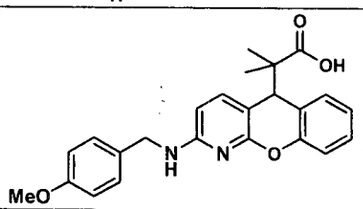
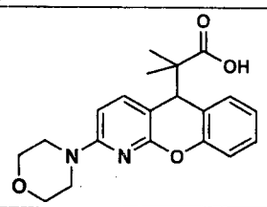
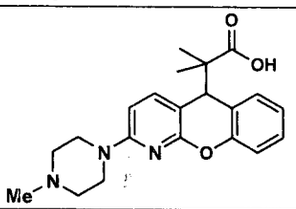
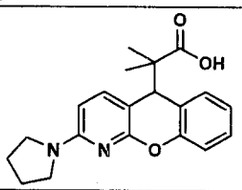
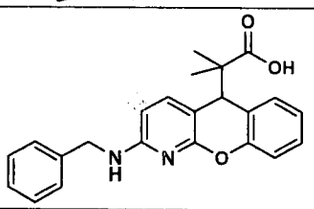


Una solución del producto de la Preparación 17e (1.0g, 3.30 mmol) en piperidina (15 mL) en un tubo sellado se calentó a 150°C durante 4 h. La mayoría de la piperidina se removió luego *in vacuo* para obtener un sólido, el cual se suspendió en una solución 1:1 de éter de dietilo en hexanos. Esta suspensión se lavó con una solución de hidróxido de sodio 1N. La capa acuosa se lavó dos veces con 1:1 éter de dietilo en hexanos, luego se acidificó a un pH 3.0 con la adición gota a gota de HCl concentrado y se extrajo con acetato de etilo. La capa acuosa se lavó dos veces con acetato de etilo. Las capas de acetato de etilo combinadas se secaron sobre sulfato de sodio y se concentraron para dar un sólido

amarillo (1.10 g, 95% de rendimiento). EM (ES+) m/z: 353 (M+H); Tiempo de retención CL: 3.71 min.

Preparaciones 24 hasta 29

Los siguientes compuestos se prepararon de la misma forma como el producto de la Preparación 23.

No.de Preparación	Estructura
24	
25	
26	
27	
28	
29	

- 000531

Preparación 30

El producto de la Preparación 17 (17e) se resolvió en enantiómeros puros por cromatografía de fluido supercrítico quiral (SFC).

Condiciones Preparatorias A:

Columna: Chiralcel OJ 250 X 30 mm ID; 10 um

Temperatura: Ambiente

Fase Móvil: CO_2/MeOH/TFA = 85:15:0.1

Relación de flujo: 65 mL/min

Volumen de inyección: 1.2 mL

Detección UV: 220 nm

Condiciones preparatorias B:

Columna: Chiralpak AD-H (3x25cm, 5µm)

Presión BPR: 100 bars

Temperatura: 35°C

Fase Móvil: CO_2/MeOH = 88:12

Relación de flujo: 150 mL/min

Detección UV: 220 nm

Programa de Inyección: Inyección almacenada (4.20 min/por ciclo)

Volumen de inyección: 2.20mL

Preparación Muestra: 20,000 mg/450 mL MeOH = 46.7 mg/mL

Condiciones analíticas:

Columna: Chiralpak OJ 250 X 4.6 mm ID; 10 um

001531

Temperatura: Ambiente

Fase Móvil: Hex/IPA/TFA = 80:20:0.1

Relación de flujo: 1.0 mL/min

Volumen de inyección: 3~15 ml

Detección UV: 290 nm

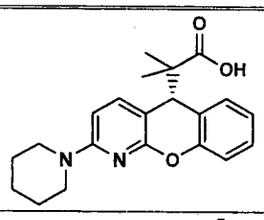
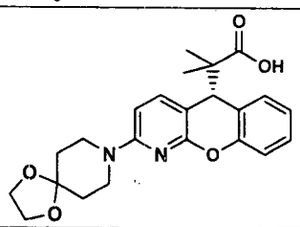
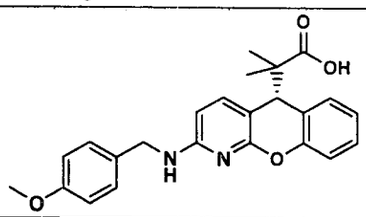
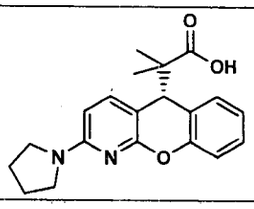
Tiempo de retención (min): TR_1: 5.349 TR2: 8.231

El primer pico que eluyó bajo las condiciones preparatorias (SFC) (Condiciones preparatorias A) descritas anteriormente también se eluye primero bajo las condiciones CL quiral analíticas antes mencionadas. Una muestra del primer material de elución (30a) se co-cristalizó con (R)-(+)-alfa-metilbencilamina. Una determinación de la estructura de cristal de rayos X del material cristalino así obtenido probó que 30a es de la estereoquímica absoluta 'R'. El segundo enantiómero de elución (30b) de "Condiciones preparatorias A" se dedujo así que va a ser de la estereoquímica absoluta 'S'. Las condiciones de separación SFC para 17e se optimizaron además como se describe anteriormente ("Condiciones preparatorias B"), en este caso el enantiómero 'S' (30b) eluye primero, mientras el enantiómero 'R' (30a) eluye en segundo lugar (confirmado por la comparación de cromatógrafos de compuestos homoquirales obtenidos de ambos métodos preparatorios (A y B) bajo las condiciones analíticas descritas anteriormente.

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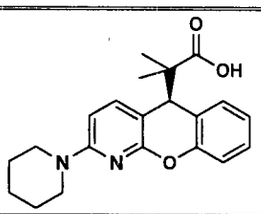
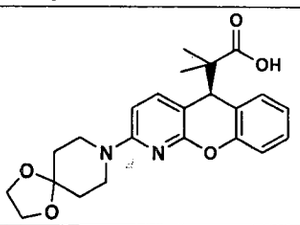
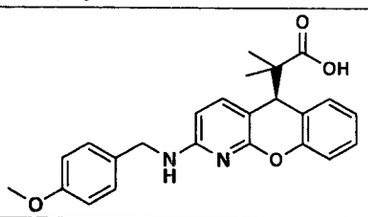
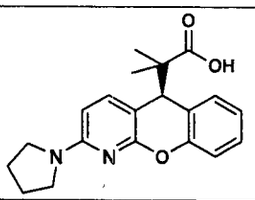
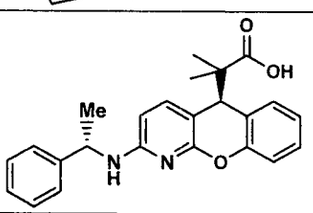
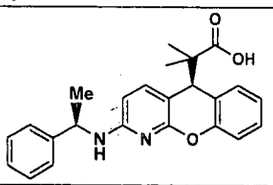
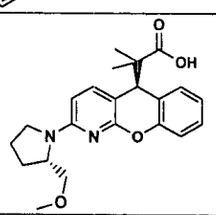
Preparaciones 31 hasta 34

Los siguientes compuestos se prepararon a partir de 30a de la misma forma descrita anteriormente para la preparación de los compuestos del título de las Preparaciones 23 hasta 29.

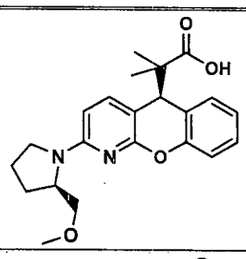
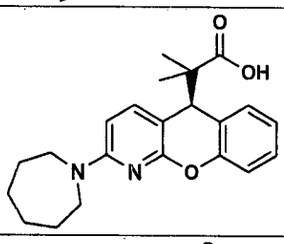
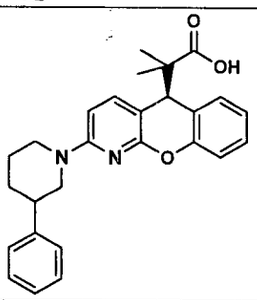
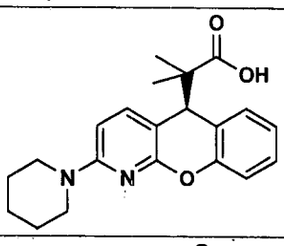
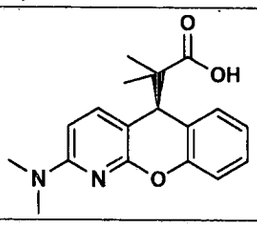
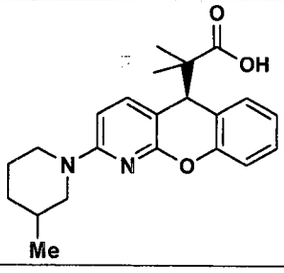
No. de Preparación	Estructura
31	
32	
33	
34	

Preparaciones 35 hasta 47

Los siguientes compuestos se prepararon a partir de 30b de la misma forma descrita anteriormente para la preparación de los compuestos del título de las Preparaciones 23 hasta 29.

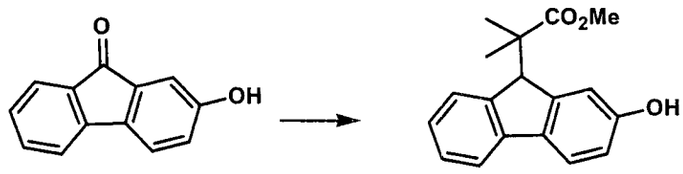
No. de Preparación	Estructura
35	
36	
37	
38	
39	
40	
41	

584

No. de Preparación	Estructura
42	
43	
44	
45	
46	
47	

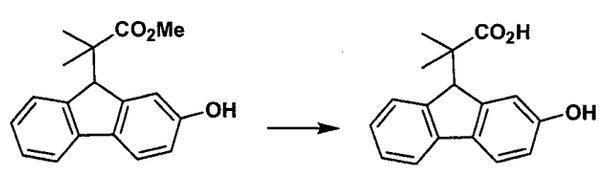
- 492585

Preparación 48



Etapa 1

A una suspensión color rojo herrumbre de 2-hidroxifluorenona (303 mg, 1.54 mmol) en diclorometano a 0°C se le agregó eterato de trifluoruro de boro (0.392 mL, 3.09 mmol) gota a gota, dando una suspensión de tono café. Después de 10 min a 0°C, 1-metoxi-2-metilprop-1-eniloxi)trimetilsilano (0.627 mL, 3.09 mmol) se agregó gota a gota, dando una solución transparente, color canela. Después de 80 min a 0°C, se agregó ácido trifluoroacético (1.1 mL), seguido por trietilsilano (0.494 mL, 3.09 mmol). La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante la noche. El bicarbonato de sodio acuoso saturado se agregó lentamente a la mezcla de reacción con agitación. La capa orgánica se removió, se secó sobre sulfato de sodio, y se concentró para dar 48a (452 mg, 99%) como una espuma. El material sin refinar se usó directamente en la siguiente etapa sin purificación adicional. EM (E+) m/z: 305 (M+Na); Tiempo de retención CL: 3.55 min.



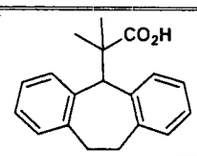
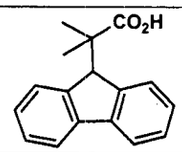
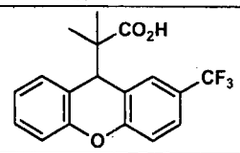
000536

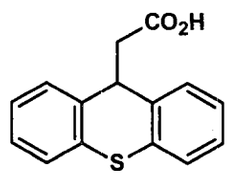
Etapa 2

El producto (48b) se obtuvo en la forma descrita anteriormente para la preparación de 22b. EM (E+) m/z: 286 ($M+H_2O$); EM (E-) m/z: 267 (M-H); Tiempo de retención CL: 3.32 min.

Preparaciones 49 hasta 51

Los siguientes compuestos se prepararon en la forma descrita para la preparación del compuesto del título de la Preparación 10, reemplazando la tioxanten-9-ona con ya sea dibenzosuberona, 9-fluorenona, o 2-trifluorometilxanten-9-ona.

No. de Preparación	Estructura
49	
50	
51	

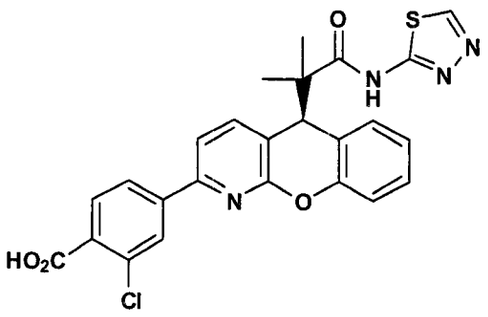


El compuesto del título se preparó en la forma descrita anteriormente para la preparación del compuesto del título de

587

la Preparación 9, como se describe por Jones et al. (J. Am. Chem. Soc., 1948, 70, 2843).

Preparación 53



Etapa 1

A una solución de ácido (S)-2-(2-cloro-5H-cromeno[2,3-b]piridin-5-il)-2-metilpropanóico (30b, 10 g, 32.9 mmol) en acetonitrilo (200 ml) se agregó trietilamina (22.94 ml, 165 mmol), O-(7-AZABENZOTRIAZOL-1-IL)-N,N,N',N'-TETRAMETILURONIO PF6 (HATU) (16.27 g, 42.8 mmol) y 1,3,4-tiadiazol-2-amina (9.99 g, 99 mmol). La mezcla resultante se calentó a 80°C durante 12 h. La mezcla de reacción se concentró luego *in vacuo* y el residuo se dividió entre EtOAc y HCl 1N. La capa orgánica obtenida se lavó con $NaHCO_3$ saturado, salmuera, luego se secó (Na_2SO_4) y se concentró para dar un sólido. El sólido se disolvió en EtOH (400 mL) con calentamiento suave. Se agrega HCl 1N (~200 mL) en porciones. El sólido se colectó y se lavó con agua, se secó en bomba de vacío durante la

noche para dar 10g (79%) de (S)-2-(2-cloro-5H-cromeno[2,3-b]piridin-5-il)-2-metil-N-(1,3,4-tiadiazol-2-il)propanamida (53a). EM (E+) m/z: 387 (M+H); Tiempo de retención CL: 3.12 min.

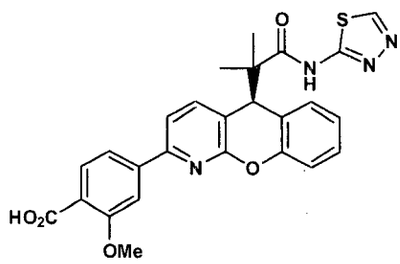
Etapa 2

A una solución de (S)-2-(2-cloro-5H-cromeno[2,3-b]piridin-5-il)-2-metil-N-(1,3,4-tiadiazol-2-il)propanamida (53a) (1 g, 2.58 mmol) en DMF (40 mL) se le agregó ácido 4-borono-2-clorobenzóico (1.036 g, 5.17 mmol) (sin refinar de 68106-008) y Ortofosfato de Potasio (5.17 mL, 10.34 mmol). Se burbujea argón durante 10 min. y luego se agregó paladio tetraquis-(trifenilfosfina) (0.209 g, 0.181 mmol). Se mantiene burbujeando argón durante otros 5 min. El recipiente de reacción se selló y se calentó a 90°C durante 4 h. Se filtró, luego se lavó con EtOAc. El HCl 1N se agregó a un pH ~ 2.0, y luego se extrajo con EtOAc (3x). Las capas orgánicas combinadas se lavaron con base (1N NaOH, 3x), y luego la solución base se acidificó a un pH ~2.0, se extrajo con EtOAc (3x), se secó (Na_2SO_4), y se concentró.

Se vuelve a purificar por la misma secuencia anterior, esto es, se disuelve en EtOAc, se lava con NaOH 1N, y luego se hace ácida a un pH ~2.0, se extrae con EtOAc, se seca (Na_2SO_4), y se concentra. EM (E+) m/z: 507 (M+H); Tiempo de

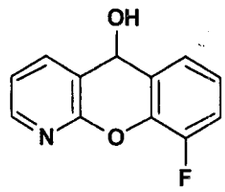
retención CL: 3.51 min.

Preparación 54



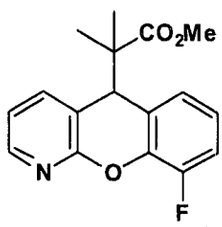
El compuesto del título se preparó a partir del producto de 53a de la misma forma como se describió anteriormente para la preparación del compuesto del título de la Preparación 53. EM (E+) m/z: 503.2 (M+H); Tiempo de retención CL: 3.30 min.

Preparación 55



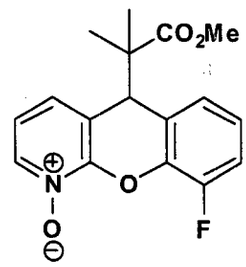
Etapa 1

El compuesto del título (55a) se preparó a partir de 9-fluoro-5H-cromeno[2,3-b]piridin-5-ona de la misma forma como se describe anteriormente para la preparación del compuesto del título de la Preparación 17a. La 9-fluoro-5H-cromeno[2,3-b]piridin-5-ona se preparó siguiendo el método de Villani et al. (J. Med. Chem. 1975, 18, 1-8), substituyendo el fenol con 2-fluorofenol.



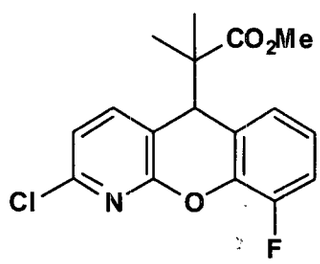
Etapa 2

El compuesto del título (55b) se preparó a partir de 55a de la misma forma descrita anteriormente para la preparación de 17b a partir de 17a. EM (E+) m/z: 302 (M+H); Tiempo de retención CL: 2.96 min.



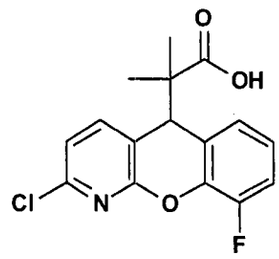
Etapa 3

El compuesto del título (55c) se preparó a partir de 55b de la misma forma descrita anteriormente para la preparación de 17c a partir del 17b. EM (E+) m/z: 318 (M+H); Tiempo de retención CL: 2.13 min.



Etapa 4

El compuesto del título (55d) se preparó a partir de 55c de la misma forma descrita anteriormente para la preparación de 17d a partir de 17c. EM (E+) m/z: 336 (M+H); Tiempo de retención CL: 3.26 min.



Etapa 5

El compuesto del título (55e) se preparó a partir de 55d de la misma forma como se describe anteriormente para la preparación del compuesto del título de la Preparación 17e a partir de 17d. EM (E+) m/z: 322 (M+H); Tiempo de retención CL: 3.11 min.

Preparación 56

El producto de la Preparación 55 (55e) se resolvió en enantiómeros puros (56a y 56b) por cromatografía de fluido supercrítico quiral (SFC).

Condiciones preparatorias:

Columna Preparatoria: Chiralcel OJ-H (3x25cm, 5µm)

Presión BPR: 100 baria

Temperatura: 35°C

Relación de flujo: 70 mL/min

Fase Móvil: CO_2/[IPA:ACN 1:1 p 0.1% TFA] (90/10)

Longitud de Onda del detector: 212 nm

Programa de separación: Inyección en secuencia

Inyección: 0.25 mL/(100.0 mg/mL) con tiempo del ciclo de 7.5 minutos

Preparación muestra: 2g / 20 mL ACN/MeOH (1:1 v/v)

Condiciones analíticas:

Columna Analítica: Chiralcel OJ-H (0.46x25cm, 5µm)

Presión BPR: 100 baria

Temperatura: 35°C

Relación de flujo: 2.0 mL/min

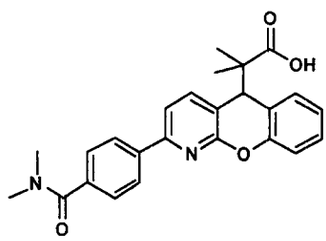
Fase Móvil: CO_2/[IPA: ACN 1:1 p 0.1% TFA] (90/10)

longitud de onda del detector: 212 nm

Tiempo de retención (min): TR_1: 7.43 TR2: 8.81.

El primer compuesto que eluye bajo las condiciones preparatorias (56a) también eluyó con el tiempo de retención anterior bajo las condiciones analíticas descritas anteriormente.

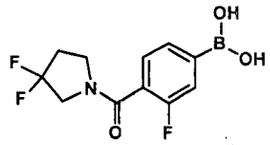
Preparación 57



Una solución de DMF (50 mL) de 17e (10367, pagina 107, Preparación 17) (1.45 g, 4.77 mmol), ácido 4-(N,N-dimetilaminocarbonil)fenil borónico (Combi-Blocks Inc., 1.35 g, 1.5 eq.), $Pd(Ph_3P)_4$ (0.67 g, 0.12 eq.) y una solución 2 M de K_3PO_4 (12 mL, 5 eq.) se desgasificó por ciclo de relleno de N_2 al vacío dos veces luego se calentó a 100°C bajo N_2 durante 5 h. Después de enfriar a temperatura ambiente, el material sin refinar se vació en HCl 1 N y se extrajo con acetato de

etilo. La fase de acetato de etilo se lavó con agua y salmuera, se secó sobre $MgSO_4$ y filtró. El filtrado se concentró para dar el producto esperado como un cristal de agujas blancas (1.59 g, 80% de rendimiento). EM (ES+) m/z: 417 (M+H); Tiempo de retención CL: 3.79 min (HPLC analítica Método D).

Preparación 58



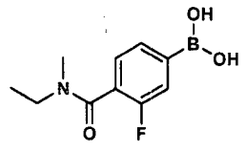
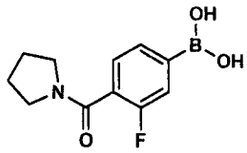
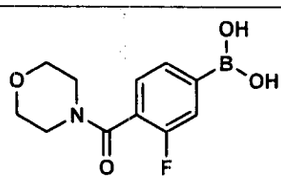
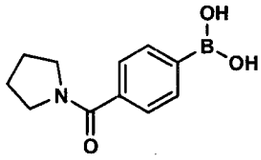
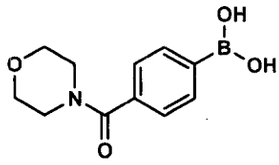
Una solución DMF (6 mL) de ácido 4-borono-2-fluorobenzóico (Combi-Bocks Inc., 1 g, 5.44 mmol), sal de clorohidrato de 3,3-difluoropirrolidina (Matrix Scientific, 1 g, 1.3 eq.), DIPEA (2.85 mL, 3 eq.) y HATU (2.163 g, 1 eq.) se agitó a temperatura ambiente durante 1 h. El material sin refinar se vació en HCl 1 N (16 mL) y se extrajo con acetato de etilo (40 mL). La fase acuosa se neutralizó a un pH 7 con NaOH sólido luego K_2CO_3, y se extrajo con acetato de etilo. Los extractos de acetato de etilo combinados se secaron sobre $MgSO_4$ y se concentraron para dar un aceite café espeso. Después de la adición de aproximadamente volumenes iguales de agua, los cristales de agujas blancas se precipitaron lentamente. El sólido se colectó por filtración y se lavó con una cantidad pequeña de éter para dar el producto esperado (0.7811 g). El filtrado se purificó por HPLC de fase inversa

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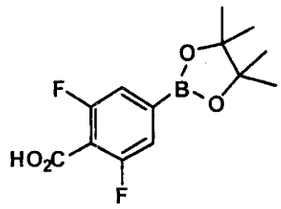
preparativa (usando cromatógrafos para líquidos Shimadzu 10A y columna Waters Sunfire S10 30 x 250 mm) para dar 0.5632 g adicionales del producto esperado. El rendimiento total fue 1.3443 g (91%). EM (ES+) m/z: 274 (M+H); Tiempo de retención CL: 2.68 min (Método HPLC analítica D).

Preparaciones 59 hasta 63

Usando procedimiento análogo a la Preparación 58, los siguientes intermediarios se prepararon por acopladores entre aminas y ácidos borónicos comercialmente disponibles.

No. de Preparación	Estructura
59	
60	
61	
62	
63	

Preparación 64

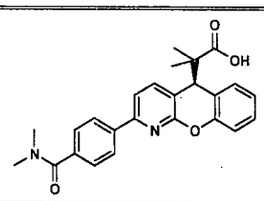
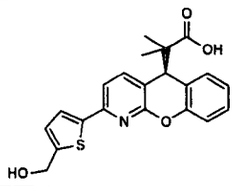


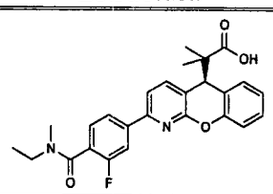
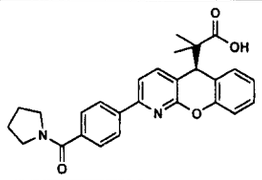
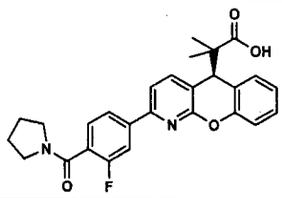
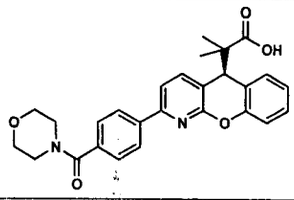
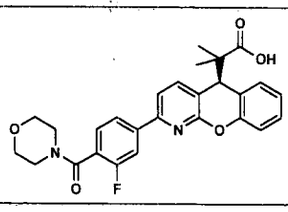
Una solución de dioxano (16.5 mL) de ácido 4-bromo-2,6-difluorobenzóico (0.4 g, 1.6 mmol), 4,4,4',4',5,5,5',5'-octametil-2,2'-bi(1,3,2-dioxaborolano) (0.5 g, 2.0 mmol), $PdCl_2$(dppf) (0.12 g, 0.17 mmol) y acetato de potasio (0.49 g, 4.9 mmol) se colocó en un vial sellado y desgasificó por ciclo de relleno de N_2 al vacío dos veces. La mezcla se calentó a 80°C durante 21 h, se enfrió a temperatura ambiente y filtró a través de un lecho corto de gel de sílice. El filtrado se concentró y purificó por cromatografía de columna por desorción súbita (cartucho de gel de sílice ISCO 12 g, 20-100% acetato de etilo-hexanos) para dar el producto esperado como un aceite café (0.11 g, 19%). EM (ES-) m/z: 283 (M-H); Tiempo de retención CL: 1.48 min (HPLC analítica Método D).

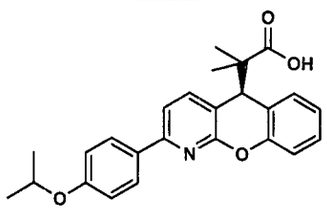
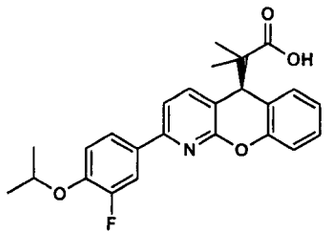
Preparaciones 65 hasta 73

Siguiendo el procedimiento análogo a la Preparación 57, los siguientes compuestos intermedios se prepararon por launión de Suzuki entre los ácidos borónicos (comercialmente disponibles o preparados en las preparaciones 58-63 y 30b.

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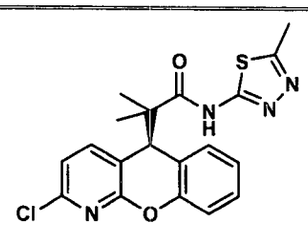
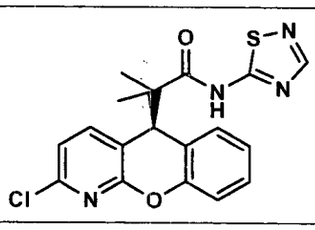
No. de Preparación	Estructura
65	
66	

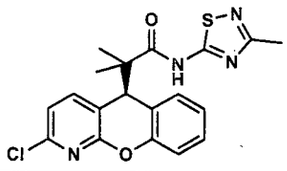
No. de Preparación	Estructura
67	
68	
69	
70	
71	

No. de Preparación	Estructura
72	
73	

Preparaciones 74 hasta 76

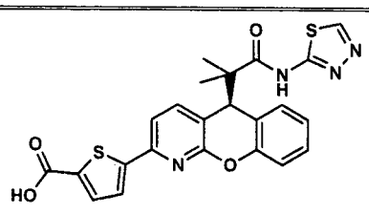
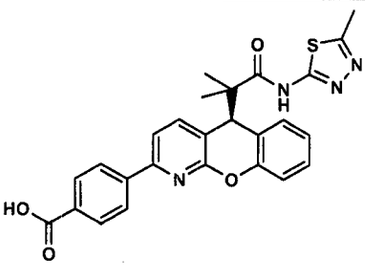
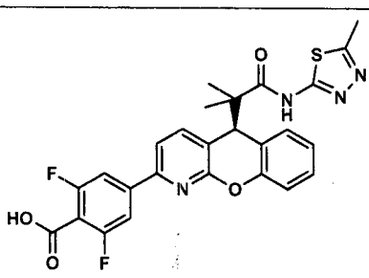
Siguiendo procedimientos análogos al producto de la primera etapa de la Preparación 53 (53a), los siguientes intermediarios se prepararon por reacción entre amino azoles comercialmente disponibles y el enantiómero 'S' de la Preparación (30b).

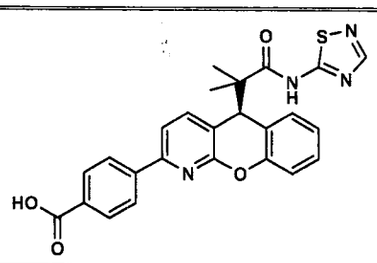
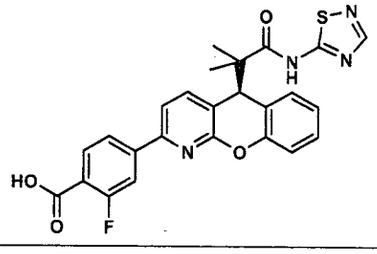
No. de Preparación	Estructura
74	
75	

No. de Preparación	Estructura
76	

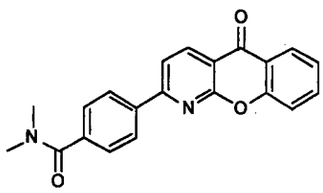
Preparaciones 77 hasta 81

Siguiendo el procedimiento análogo a la Preparación 57, los siguientes intermediarios se prepararon por enlazadores de Suzuki entre ácidos borónicos (comercialmente disponibles o preparados en Preparaciones 58 hasta 64) e intermediarios de Preparaciones 53a, 58 hasta 64.

No. de Preparación	Estructura
77	
78	
79	

No. de Preparación	Estructura
80	
81	

Preparación 82



Etapa 1

Una mezcla de ácido 4-acetilbenzóico (10.0 g, 60.9 mmol), solución acuosa al 40% de dimetilamina (8.24 g, 73.1 mmol), EDC (14.0 g, 73.1 mmol), HOBT (11.2 g, 73.1 mmol) y DIEA (21.3 mL, 122 mmol) en CH_3CN (150 mL) se agitó a temperatura ambiente durante 15 h y se concentró. El residuo se disolvió en acetato de etilo (600 mL), se lavó con agua (2x80 mL), salmuera (80 mL), se secó ($MgSO_4$) y se concentró para proporcionar 4-acetil-N,N-dimetilbenzamida (9.80 g, 84%). EM

(E+) m/z: 191 (M+H); tiempo de retención HPLC: 0.88 min (HPLC analítica Método F).

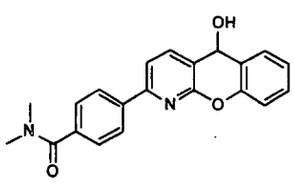
Etapa 2

Una mezcla de 4-acetil-N,N-dimetilbenzamida (9.80 g, 51.2 mmol) y DMF dimetil acetal (60 mL) se calentó a reflujo durante 15 h, se enfrió a temperatura ambiente y se concentró. El residuo se recristalizó a partir de acetato de etilo para dar (E)-4-(3-(dimetilamino)acriloil)-N,N-dimetilbenzamida como un sólido café (8.80 g, 70%). EM (E+) m/z: 247 (M+H).

Etapa 3

Una mezcla de (E)-4-(3-(dimetilamino)acriloil)-N,N-dimetilbenzamida (4.0 g, 16.3 mmol), 3-(2-fluorofenil)-3-oxopropanonitrilo (3.44 g, 21.1 mmol) y ácido acético (4.65 mL, 81.0 mmol) en DMF (40 mL) se calentó a 120°C. Después de 48 h a 120°C, la mezcla se enfrió a temperatura ambiente, se diluyó con acetato de etilo (600 mL), se lavó con $NaHCO_3$ saturado (80 mL), agua (80 mL) y salmuera (80 mL), se secó ($MgSO_4$) y se concentró. El residuo se trató con MeOH y filtró para proporcionar el producto esperado como un sólido café (2.70 g, 48%). EM (E+) m/z: 345 (M+H); tiempo de retención HPLC: 1.67 min (HPLC analítica Método F).

Preparación 83

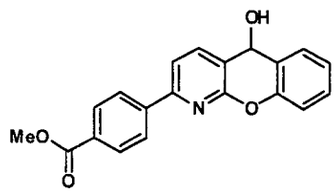


El borohidruro de sodio (1.48 g, 39.2 mmol) se agregó a

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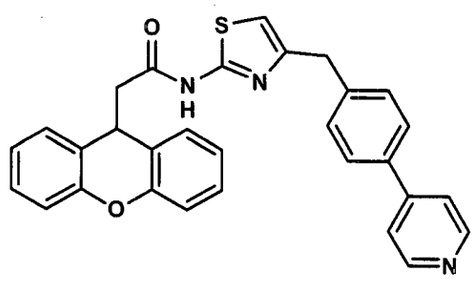
una solución del producto de la Preparación 82 (2.70 g, 7.84 mmol) en MeOH (160 mL) y diclorometano (40 mL) a 0°C. Después de 2 h a esta temperatura, la mezcla se apagó con $NaHCO_3$ saturado (40 mL). Los solventes orgánicos se evaporaron *in vacuo*. El residuo acuoso se extrajo con diclorometano (3 x 100 mL). Los extractos orgánicos combinados se lavaron con agua (30 mL), salmuera (30 mL), se secaron ($MgSO_4$) y se concentraron para proporcionar el producto esperado (1.80 g, 66%). EM (ES+) m/z: 347 (M+H).

Preparación 84



Siguiendo el procedimiento de las Etapas 2 y 3 de la Preparación 82, y Preparación 83, el compuesto del título se preparó a partir de 4-acetilbenzoato de metilo. EM (ES+) m/z: 334 (M+H).

EJEMPLO 1

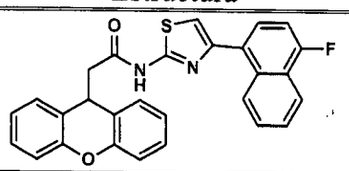
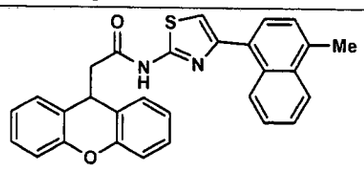
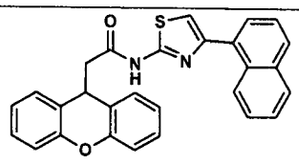


A una solución del producto de la Preparación 9 (34 mg,

0.14 mmol) en DMF (1.2 mL) se agregó secuencialmente trietilamina (0.049 mL, 0.35 mmol), HOAt (23 mg, 0.17 mmol), EDC (33 mg, 0.17 mmol), y el producto de la Preparación 4 (42 mg, 0.16 mmol). La mezcla resultante se calentó a 85°C durante 16 h, se filtró a través de un filtro de punta de jeringa de 0.45 micrones, y se purificó por HPLC preparativa. El producto (30 mg, Y = 35%) se obtuvo como un sólido blanco, sal de TFA. EM (E+) m/z: 490 (M+H); Tiempo de retención CL: 3.24 min.

Ejemplos 2 hasta 4

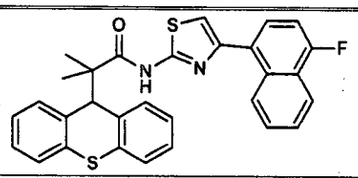
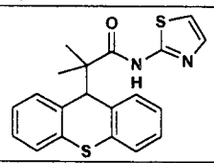
Los siguientes Ejemplos 2 hasta 4 se prepararon de la misma forma como se describió para la preparación del compuesto del título del Ejemplo 1 usando aminas de las Preparaciones 1 hasta 3.

Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
2		3.872	467
3		3.935	463
4		3.785	449.00

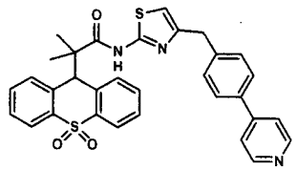
Ejemplos 5 hasta 9

Los siguientes Ejemplos 5 hasta 9 se prepararon de la misma forma

como se describió para la preparación del compuesto del título del Ejemplo 1 usando el producto de ácido carboxílico de la Preparación 10 y aminas de las Preparaciones 1 hasta 4 y 2-aminotiazol.

Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
8		3.37	511
9		3.87	365

EJEMPLO 10

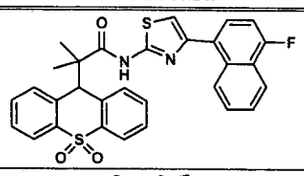
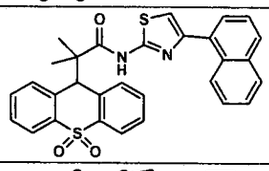
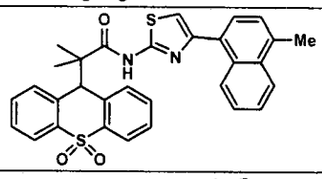
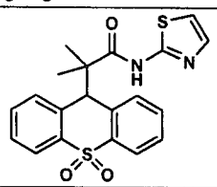


A una solución del producto de la Preparación 11 (90 mg, 0.29 mmol) en acetonitrilo (4 mL) se le agregaron HOAt (46 mg, 0.34 mmol) y EDC (66 mg, 0.34 mmol). La solución resultante se agitó a temperatura ambiente durante 1 h, luego se trató con trietilamina (0.1 mL) y el producto de la Preparación 4 (84 mg, 0.31 mmol) y se calentó en un recipiente sellado a presión a 140°C durante 1.5 h. La solución se concentró luego y purificó por HPLC. El producto así obtenido se liofilizó a partir de agua/acetonitrilo para dar el compuesto del título (45 mg) como una sal de TFA sólida blanca. EM (E+) m/z: 566 (M+H); Tiempo de retención CL: 2.89 min.

604

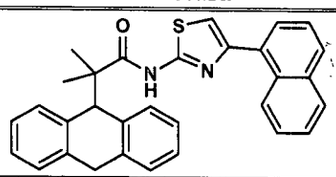
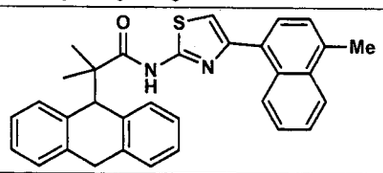
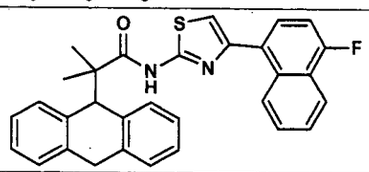
Ejemplos 11 hasta 14

Los siguientes Ejemplos 11 hasta 14 se prepararon de la misma forma como se describió para la preparación del compuesto del título del Ejemplo 10 usando aminas de las Preparaciones 1 hasta 3 ó 2-aminotiazol.

Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
11		3.592	543
12		3.512	525
13		3.68	539
14		3.04	399

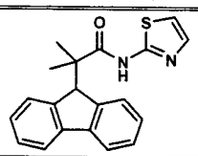
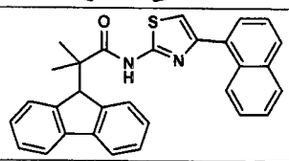
Ejemplos 15 hasta 17

Los siguientes Ejemplos 15 hasta 17 se prepararon de la misma forma como se describió para la preparación del compuesto del título del Ejemplo 10 usando el producto de la Preparación 12 y aminas de las Preparaciones 1 hasta 3.

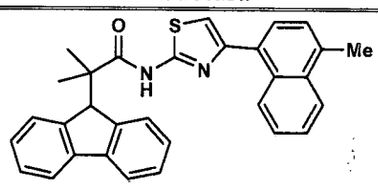
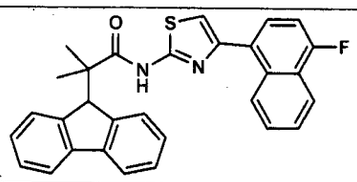
Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
15		3.18	475
16		3.42	489
17		3.31	493

Ejemplos 18 hasta 21

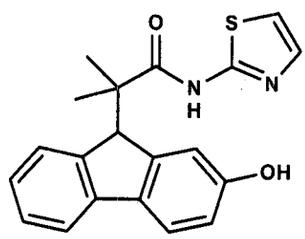
Los siguientes Ejemplos 18 hasta 21 se prepararon de la misma forma como se describió para la preparación del compuesto del título del Ejemplo 18 usando el producto de la Preparación 50, las aminas de las Preparaciones 1 hasta 3 ó 2-aminotiazol.

Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
18		4.11	335
19		3.18	461

606

Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
20		3.41	475
21		3.30	479

Ejemplo 22

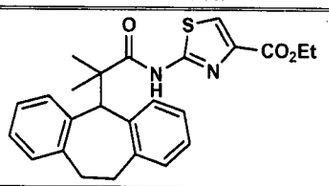
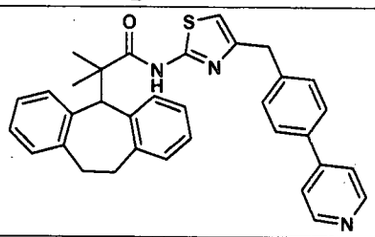
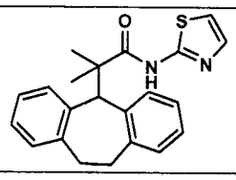


(+/-)

El compuesto del título se preparó en la forma descrita para la preparación del compuesto del título del Ejemplo 10, usando el producto de la Preparación 48b. EM (E+) m/z: 351 (M+H); Tiempo de retención CL: 3.33 min.

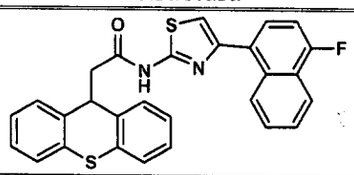
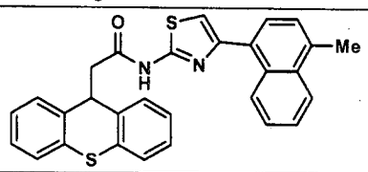
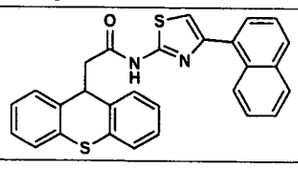
Ejemplos 23 hasta 25

Los siguientes Ejemplos 23 hasta 25 se prepararon de la misma forma como se describió para la preparación del compuesto del título del Ejemplo 10 usando el producto de la Preparación 49 y ya sea la amina de las Preparaciones 2 o 4, o 2-aminotiazol.

Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
23		4.213	435.16
24		3.527	530.16
25		3.937	363.25

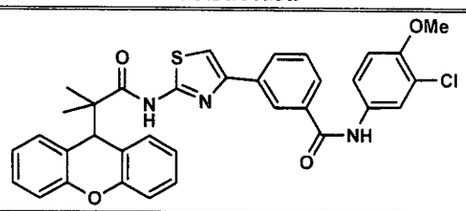
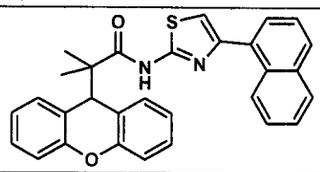
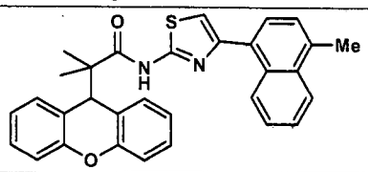
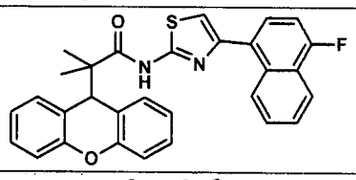
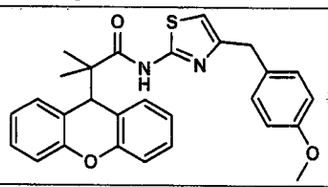
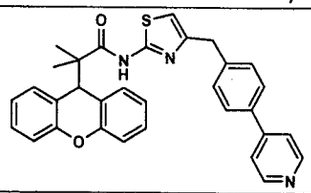
Ejemplos 26 hasta 28

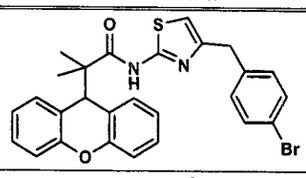
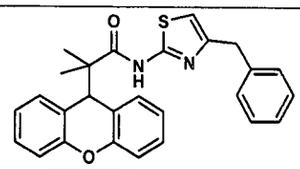
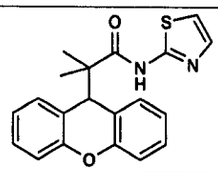
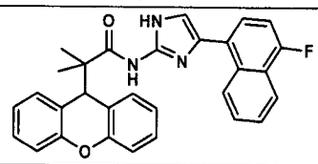
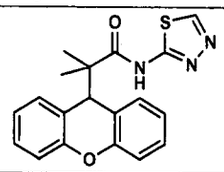
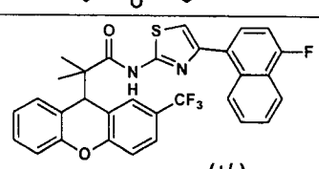
Los siguientes Ejemplos 26 hasta 28 se prepararon de la misma forma como se describió para la preparación del compuesto del título del Ejemplo 10 usando el producto de la Preparación 52 y aminas de las Preparaciones 1 hasta 3.

Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
26		3.885	483
27		3.945	479
28		3.822	465

Ejemplos 29 hasta 40

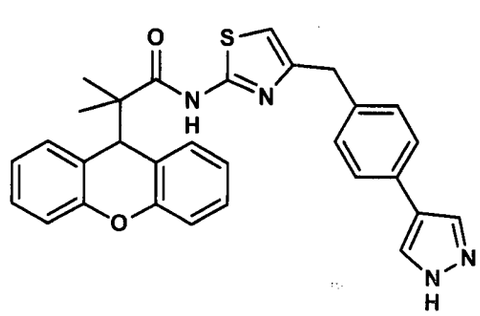
Los siguientes Ejemplos 29 hasta 40 se prepararon de la misma forma como se describió para la preparación del compuesto del título del Ejemplo 10 usando los ácidos carboxílicos de la Preparación 13 o Preparación 51 y ya sea aminas comercialmente disponible o aminas de las Preparaciones 1 hasta 7, 4b, o 14.

Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
29		3.825	610.06
30		3.13	477
31		3.39	491
32		3.28	495
33		4.22	471
34		3.37	518

Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
35		5.34	521
36		4.44	441
37		4.14	351
38		3.87	478
39		3.53	*
40	 (+/-)	4.65	563

*observado m/e 350 (electrorrociado de iones negativos)

Ejemplo 41



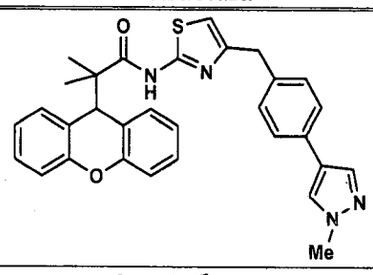
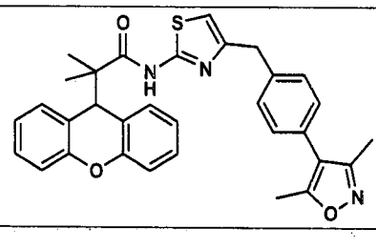
El compuesto del título del Ejemplo 35 (25 mg, 0.048 mmol) y

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4,4,5,5-tetrametil-2-[1H-pirazol-4-il]-1,3,2-dioxaborolano (19 mg, 0.098 mmol) se disolvieron en DMF (2 mL) en un recipiente de reacción de microondas. El fosfato de potasio acuoso (2.0M, 0.1 mL) se agregó y la mezcla se purgó con gas de nitrógeno durante 5 min. El tetraquis (trifenilfosfin)paladio (21 mg, 0.018 mmol) se agregó luego a la mezcla la cual se calentó en un reactor de microondas Smith a 150°C durante 30 min. La mezcla de reacción se filtró luego sobre Celite, lavando con acetato de etilo. El filtrado se dividió entre acetato de etilo y agua, y la capa orgánica se removió, se secó sobre sulfato de sodio, y se concentró. La purificación del material sin refinar por HPLC preparativa proporcionó el compuesto del título (18 mg, 75% de rendimiento). EM (E+) m/z: 507 (M+H); Tiempo de retención CL: 4.66 min.

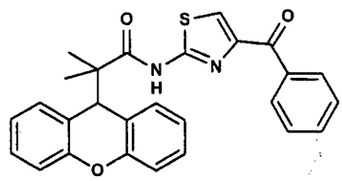
Ejemplos 42 hasta 43

Los siguientes Ejemplos 42 y 43 se prepararon de la misma forma que el compuesto del título del Ejemplo 41 usando boronatos o ácidos borónicos comercialmente disponibles.

Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
42		4.80	521
43		4.68	536

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Ejemplo 44



(a) A una solución de 1-fenil-1,2-propandiona comercialmente disponible (3.3 g, 27.3 mmol) en 30 mL se le agregó una solución de bromo (34.7 g, 217 mmol) en 5 mL de $CHCl_3$ gota a gota. La reacción se calentó a reflujo durante 12 hr. La reacción se diluyó con agua y se extrajo 2 x $CHCl_3$. Los extractos $CHCl_3$ se secaron sobre $MgSO_4$, filtraron, y se concentraron por evaporador rotatorio para dar 5.0 g (100%) de un sólido oscuro 45a. ^{1}H-RMN (400 MHz, $CDCl_3$): δ 8.03 (d, 2H), 7.68 (t, 1H), 7.53 (dd, 2H), 4.4 (s, 2H).

(b) A una solución de 45a (1.5 g, 6.6 mmol) en 25 mL de EtOH se le agregó tiourea (0.55 g, 7.2 mmol) todo a la vez. La reacción se calentó a reflujo durante 4 hr. La reacción se diluyó con agua y se extrajo 2 x EtOAc. Los extractos EtOAc se secaron sobre $MgSO_4$, filtraron, y se concentraron por evaporador rotatorio para dar 1.28 g (89%) de 46b. EM encontrado: (M+H)+ = 205.

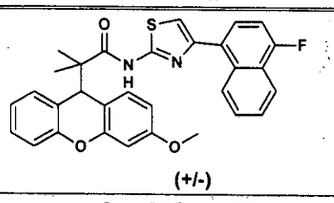
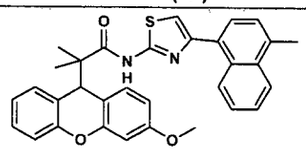
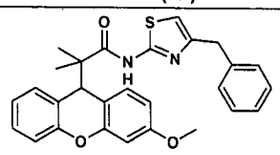
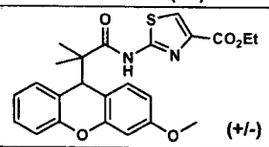
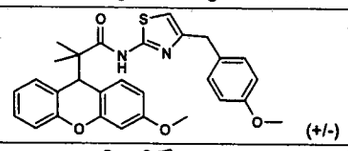
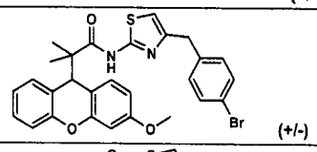
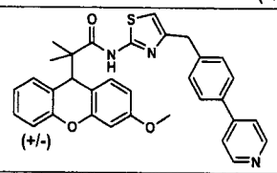
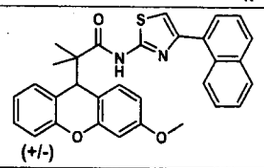
(c) El compuesto del título se preparó de la misma forma como se describió para la preparación del compuesto del título del Ejemplo 10 usando el ácido carboxílico de la Preparación 12 y la amina de 45b. EM (E+) m/z: 455 (M+H); Tiempo de retención CL: 4.79 min.

Ejemplos 45 hasta 52

Los siguientes Ejemplos 45 hasta 52 se prepararon de la misma forma como se describió para la preparación del compuesto del título del

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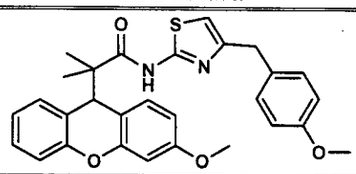
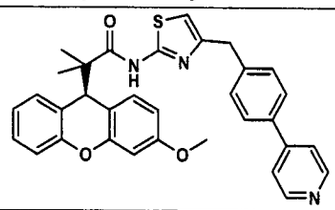
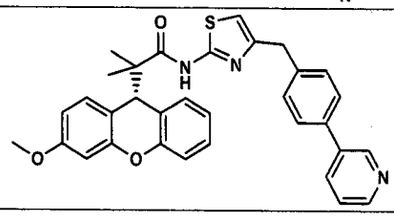
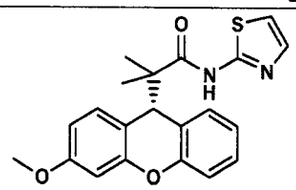
Ejemplo 10 usando el ácido carboxílico de la Preparación 15 y ya sea aminas comercialmente disponibles o aminas de las Preparaciones 1 hasta 4, 7, 8, o 4b.

Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
45		4.57	525
46		4.70	521
47		4.25	472
48		4.02	453
49		4.22	501
50		4.59	549, 551
51		3.60	548
52		4.43	507

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Ejemplos 53 hasta 56

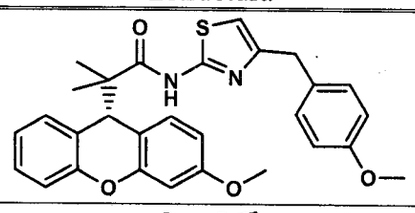
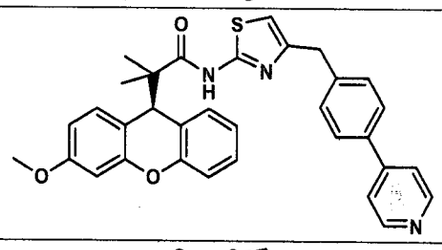
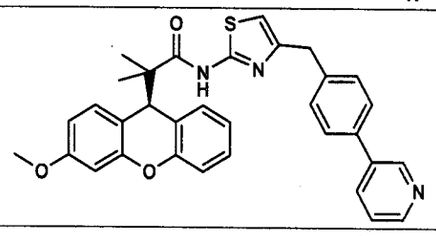
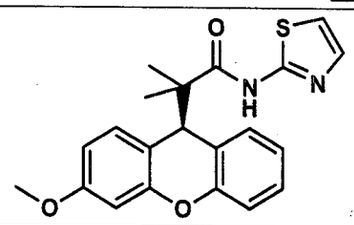
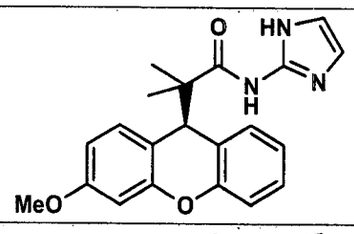
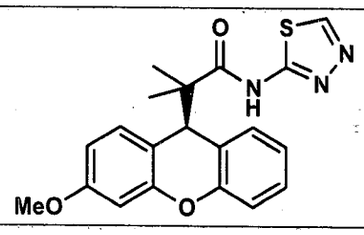
Los siguientes Ejemplos 53 hasta 56 se prepararon a partir del ácido carboxílico del enantiómero R de la Preparación 16 y 2-amino tiazol o aminas de las Preparaciones 8, 4, y 5 de la misma forma como se describió para la preparación de los compuestos del título de los Ejemplos 45 hasta 52.

Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
53		4.23	501
54		3.60	548
55		3.83	548.3
56		3.82	381

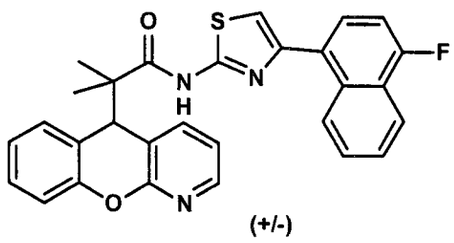
Ejemplos 57 hasta 62

Los siguientes Ejemplos 57 hasta 62 se prepararon a partir del ácido carboxílico del enantiómero S de la Preparación 16 y aminas de las Preparaciones 4, 5, y 8 o

aminas comercialmente disponibles de la misma forma como se describió para la preparación de los compuestos del título de los Ejemplos 45 hasta 52.

Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
57		4.23	501
58		3.59	548
59		3.83	548
60		3.81	381
61		2.79	364
62		3.58	382

Ejemplo 63



(+/-)

Etapa 1

A una solución del producto de la Preparación 17b (1.0 g, 3.72 mmol) en metanol (30 mL) y THF (15 mL) se le agregó una solución acuosa 4N de hidróxido de potasio (9.3 mL). La mezcla resultante se calentó a 80°C durante 16 h, luego se hace ácida hasta alrededor de pH 2.0 con la adición gota a gota de HCl concentrado. La mezcla se extrajo con acetato de etilo. La capa orgánica se removió, se secó sobre sulfato de sodio, luego se concentró para dar el ácido carboxílico 65a como un sólido (990 mg, 99%). EM (E+) m/z: 270 (M+H); Tiempo de retención CL: 2.84 min.

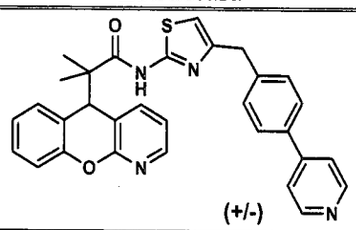
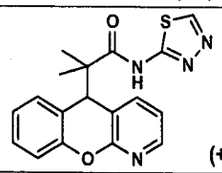
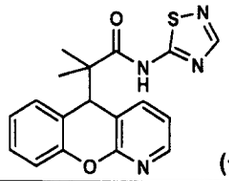
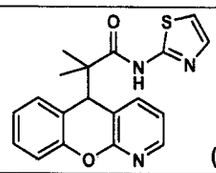
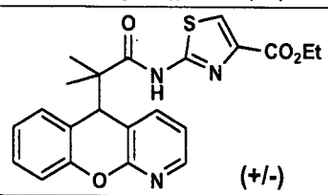
Etapa 2

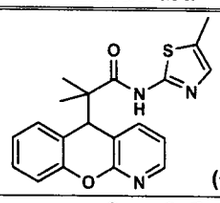
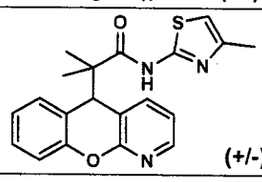
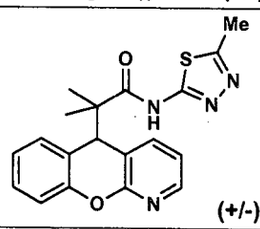
Una mezcla del producto de la etapa 1 (20 mg, 0.052 mmol), trietilamina (0.022 mL, 0.16 mmol), hidrato de HOBT (8.4 mg, 0.062 mmol) y EDC (12.0 mg, 0.062 mmol) en acetonitrilo (0.6 mL) se calentó durante 4 h a 80°C. La purificación por HPLC preparativa proporcionó el producto, el cual se liofilizó para dar un sólido incoloro. EM (E+) m/z: 496 (M+H); Tiempo de retención CL: 4.17 min.

616

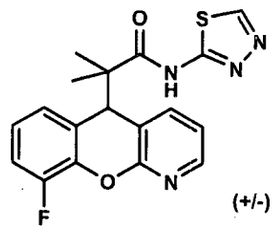
Ejemplos 64 hasta 71

Los siguientes Ejemplos 64 hasta 71 se prepararon ya sea en la forma descrita anteriormente para la preparación del compuesto del título del Ejemplo 63 o en la forma descrita para la preparación de los compuestos del título de los Ejemplos 45 hasta 52 usando el ácido carboxílico del Ejemplo 63, Etapa 1, y ya sea aminas comercialmente disponibles o aminas preparadas como se describió en la sección de Preparaciones.

Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
64		2.99	519
65		2.81	353
66		3.07	353
67		3.11	352
68		3.50	424

Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
69	 (+/-)	3.30	366
70	 (+/-)	3.26	366
71	 (+/-)	3.02	367

Ejemplo 72

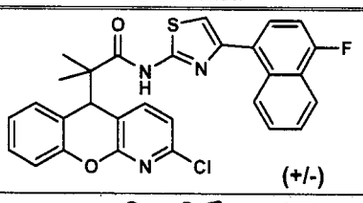
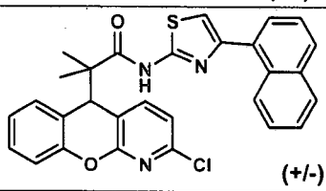
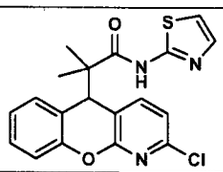
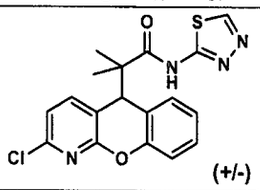

(+/-)

El compuesto del título se preparó a partir del compuesto del título de la Preparación 55b de la misma forma descrita anteriormente para la preparación de los Ejemplos 63 hasta 71. EM (E+) m/z: 371 (M+H); Tiempo de retención CL: 2.51 min.

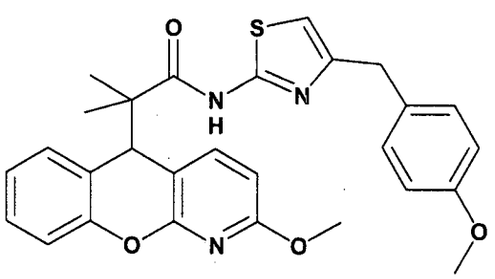
Ejemplos 73 hasta 76

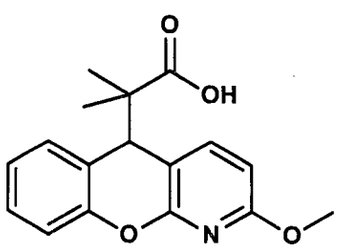
Los siguientes Ejemplos 73 hasta 76 se prepararon de la misma forma descrita para la preparación de los compuestos del título de los Ejemplos 45 hasta 52 del producto de la Preparación 17e y aminas obtenidas de fuentes comerciales o

las preparaciones descritas anteriormente.

Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
73		4.31	530
74		4.23	512
75		3.48	386
76		3.37	387

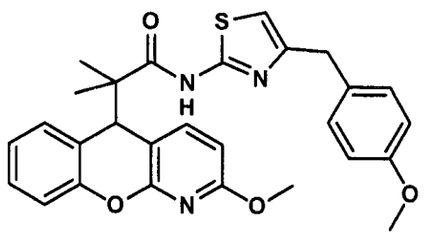
Ejemplo 77





Etapa 1

Una mezcla del compuesto del título de la Preparación 17e (150 mg, 0.50 mmol) en metanol (3 mL) y metóxido de sodio en metanol (25% p/p, 1.23 mL) se calentó por microondas a 140°C durante 40 min, luego se hace ácida con la adición de HCl concentrado. La suspensión resultante se dividió entre diclorometano y agua, y la capa orgánica se removió, se secó sobre sulfato de sodio, y se concentró para dar el producto de la etapa 1 (120 mg, 80%), el cual se usó en la siguiente etapa sin purificación adicional. Tiempo de retención CL: 3.23 min.



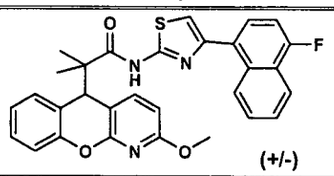
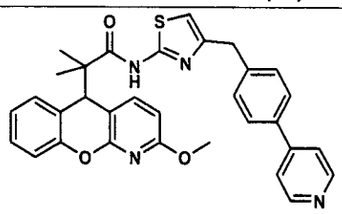
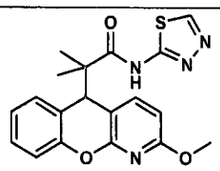
Etapa 2

El compuesto del título se preparó a partir del producto de la etapa 1 y la amina de la Preparación 8 de la misma forma descrita para la preparación de los compuestos del título de 47 hasta 54. EM (E+) m/z: 502 (M+H); Tiempo de retención CL: 4.06 min.

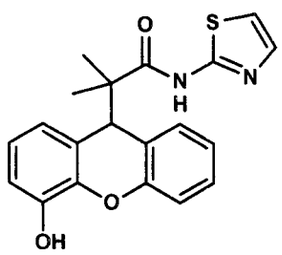
Ejemplos 78 hasta 80

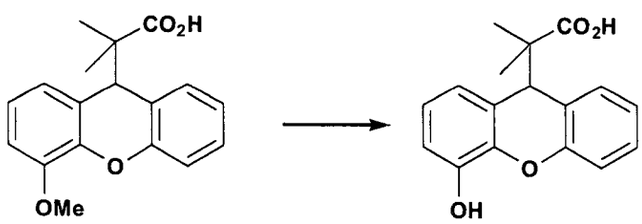
Los siguientes Ejemplos 78 hasta 80 se prepararon en la forma descrita anteriormente para la preparación del compuesto del título del Ejemplo 77, reemplazando las aminas de la Preparación 1 y de la Preparación 4 por la amina de la

Preparación 8 o 2-amino-1,3,4-tiadiazol.

Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
78		4.29	526
79		3.20	549
80		3.16	383

Ejemplo 81



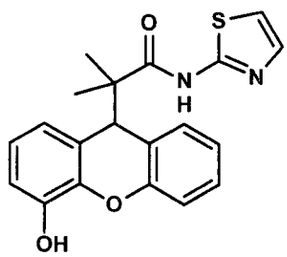


80a

007621

Etapa 1

Una mezcla del ácido 18e (50 mg, 0.17 mmol), tiofenol (0.019 mL, 0.18 mmol), y carbonato de potasio (25 mg, 0.18 mmol) en 1-metil-2-pirrolidinona (NMP) (1.5 mL) se calentó por microondas a 205°C durante 70 min. Otra porción de tiofenol (0.01 mL) y carbonato de potasio (12 mg) se agregó, y la mezcla se calentó por microondas otros 30 min a 205°C. La mezcla de reacción se dividió luego entre acetato de etilo y HCl 0.5N. La capa orgánica se removió y se secó sobre sulfato de sodio, se concentró, y purificó por HPLC preparativa para dar el producto de la etapa 1 (80a) como un sólido amorfo (32 mg, 66%). EM (ES-) m/z: 283 (M-H); Tiempo de retención CL: 3.02 min.



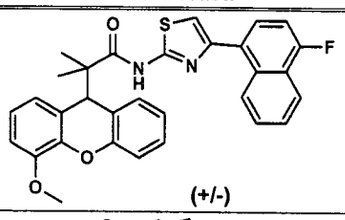
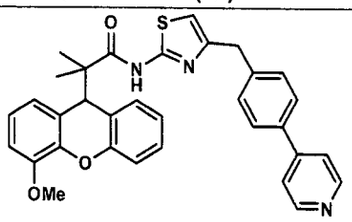
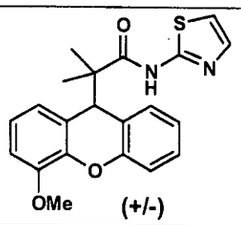
Etapa 2

Una solución del producto de la etapa 1 (19 mg, 0.07 mmol), trietilamina (0.024 mL, 0.175 mmol), y HOAt (11 mg, 0.08 mmol) en acetonitrilo (1 mL) se agitó a 65°C durante 35 min. El 2-aminotiazol (8 mg, 0.077 mmol) se agregó luego a la mezcla de reacción, la cual se calentó a 140°C durante 1 h. La purificación de la mezcla de reacción por HPLC preparativa dio el compuesto del título (11 mg). EM (ES+) m/z: 367 (M+H); Tiempo de retención CL: 3.26 min.

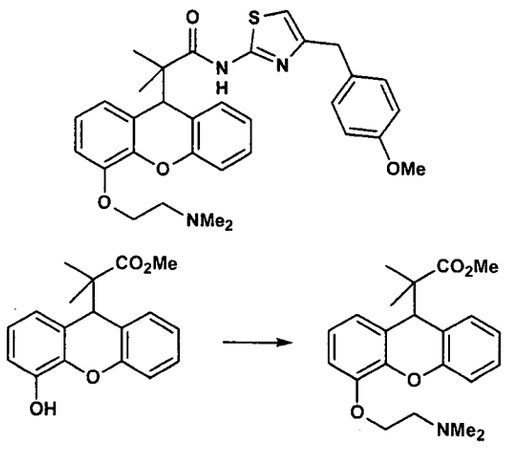
- 006622

Ejemplos 82 hasta 84

Los siguientes Ejemplos 82 hasta 84 se prepararon a partir de 18e de la misma forma descrita anteriormente para las preparaciones de los compuestos del título de los Ejemplos 76, 79 y 81.

Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
82	 (+/-)	4.35	525
83	 (+/-)	3.38	548
84	 (+/-)	3.50	NA

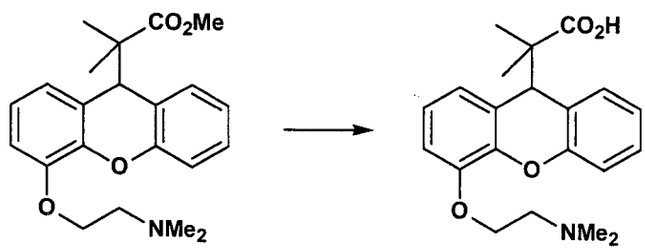
Ejemplo 85



- 000623

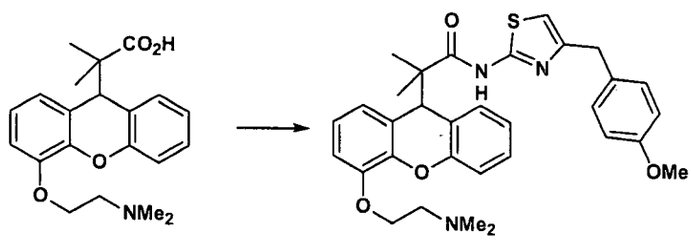
Etapa 1

A una solución del compuesto del título de la Preparación 18c (32 mg, 0.11 mmol) en DMF (1.1 mL) se le agregó cloruro de 2-(dimetilamino)etilo en la forma del clorhidrato (17 mg, 0.12 mmol), seguido por hidruro de sodio (60% p/p en aceite mineral, 9 mg). La mezcla se calentó a 80°C durante 35 min. El solvente se removió luego *in vacuo*, y el material sin refinar se usó directamente en la siguiente etapa sin purificación adicional. EM (ES+) m/z: 370 (M+H); Tiempo de retención CL: 2.54 min.



Etapa 2

Una mezcla del producto de la etapa 1 (0.11 mmol), metanol (2 mL), THF (1 mL), y KOH acuoso 4N (1.1 mL) se calentó a 80°C durante 14 h. La mezcla de reacción se acidificó con HCl concentrado, luego se concentró y purificó por HPLC preparativa para dar el producto de la etapa 2 (12 mg). EM (ES+) m/z: 356 (M+H); Tiempo de retención CL: 2.33 min.

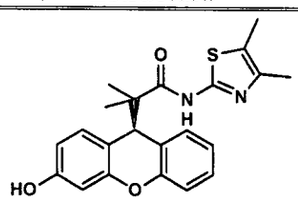
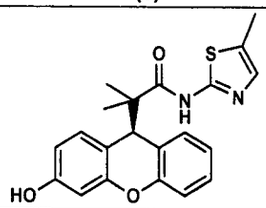
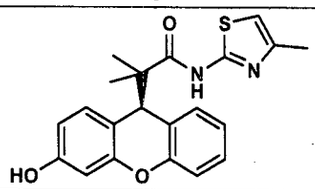
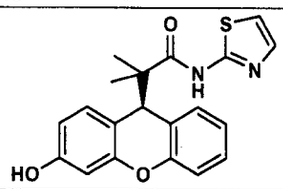


Etapa 3

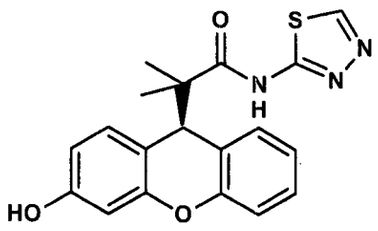
El compuesto del título se preparó a partir del producto de la etapa 2 de la misma forma como se describió para la preparación del compuesto del título del Ejemplo 57. EM (ES+) m/z: 558 (M+H); Tiempo de retención CL: 3.27 min.

Ejemplos 86 hasta 89

Los siguientes Ejemplos 86 hasta 89 se prepararon a partir del compuesto del título de la Preparación 19 y aminas comercialmente disponibles de la misma forma como se describe anteriormente para la preparación del compuesto del título del Ejemplo 81.

Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
86	 (S)	3.59	395
87		3.47	379
88		3.45	379
89		3.33	365

Ejemplo 90

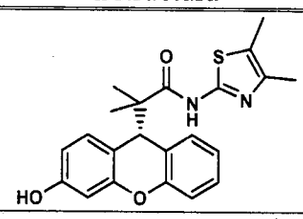
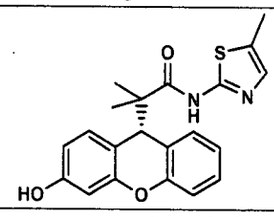
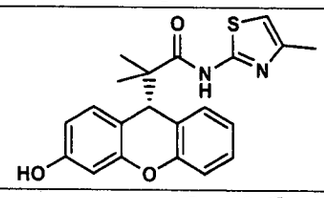
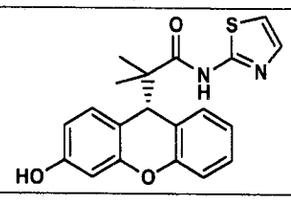


A una solución del producto de la Preparación 19 (30 mg, 0.11 mmol) en diclorometano (0.5 mL) se le agregaron secuencialmente piridina (0.019 mL, 0.23 mmol), 4-dimetilaminopiridina (1 mg, catalítico), y clorotrimetilsilano (0.029 mL, 0.23 mmol). Después de 4.5 h a temperatura ambiente, se agregaron N,N-dimetilformamida (0.01 mL) seguido por cloruro de oxalilo (0.01 mL, 0.11 mmol) a la mezcla de reacción. Después de 1.5 h adicionales a temperatura ambiente, se agregó piridina (0.044 mL, 0.55 mmol) a la mezcla de reacción, seguido por 2-amino-1,3,4-tiadiazol (12 mg, 0.12 mmol). La reacción se dejó reposar a temperatura ambiente 10 min, luego se concentró y purificó por cromatografía de capa delgada preparativa (0.5 mm sílice, 100 cm x 200 cm, 7% metanol en diclorometano) para dar el compuesto del título (15 mg, 37%) como un sólido incoloro. EM (ES+) m/z: 368 (M+H); Tiempo de retención CL: 3.10 min.

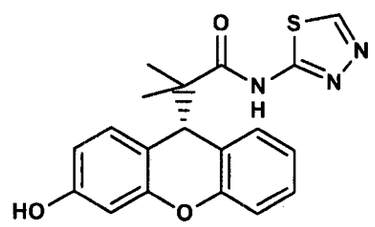
Ejemplos 91 hasta 94

Los siguientes Ejemplos 90 hasta 93 se prepararon a

partir del compuesto del título de la Preparación 20 y aminas comercialmente disponibles de la misma forma como se describe anteriormente para la preparación de los compuestos del título del Ejemplo 85 hasta 88.

Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
91		3.60	395
92		3.46	379
93		3.45	379
94		3.33	365

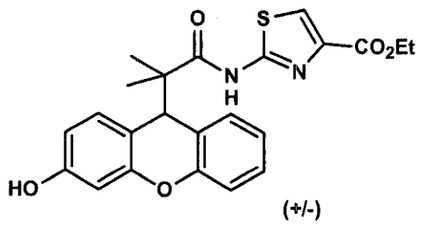
EJEMPLO 95



El compuesto del título se preparó a partir del producto de la Preparación 20 de la misma forma descrita anteriormente

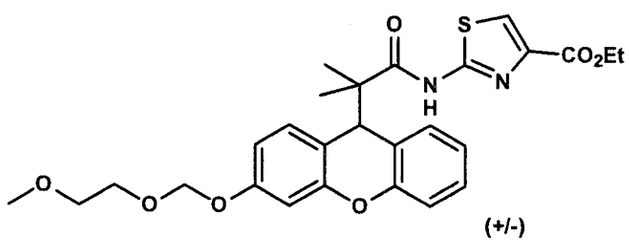
para la preparación del compuesto del título del Ejemplo 90. EM (ES+) m/z: 368 (M+H); Tiempo de retención CL: 3.10 min.

Ejemplo 96



El compuesto del título se preparó a partir del producto de la Preparación 21b de la misma forma descrita anteriormente para la preparación del compuesto del título del Ejemplo 81, Etapa 1, substituyendo 2-aminotiazol-4-carboxilato de etilo por 2-aminotiazol. EM (ES+) m/z: 439 (M+H); Tiempo de retención CL: 3.65 min.

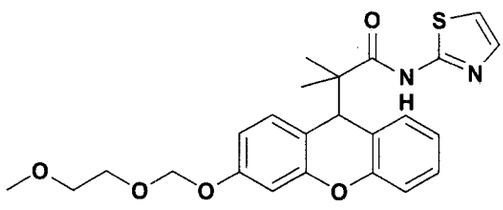
Ejemplo 97



Una mezcla del producto de la Preparación 22b (109 mg, 0.29 mmol), trietilamina (0.101 mL, 0.73 mmol), EDC (67 mg, 0.35 mmol), y HOAt (48 mg, 0.35 mmol) en acetonitrilo (3.0 mL) se agitó 12 h a temperatura ambiente. El 2-aminotiazol-4-carboxilato de etilo (55 mg, 0.32 mmol) se agregó a la mezcla, la cual se calentó en un tubo sellado a 140°C durante 1.5 h. La mezcla de reacción se concentró *in vacuo* y el residuo se

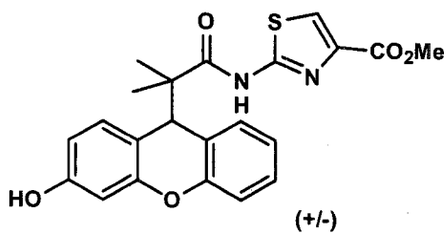
dividió entre acetato de etilo (30 mL) y HCl 1N (20 mL). La capa orgánica se lavó secuencialmente con bicarbonato de sodio acuoso saturado y salmuera, luego se secó sobre sulfato de sodio y se concentró. La cromatografía de columna por desorción súbita (sílice, 50% acetato de etilo en hexanos) proporcionó el compuesto del título (94 mg, 62% de rendimiento) como una espuma. EM (ES+) m/z: 527 (M+H); Tiempo de retención CL: 4.00 min.

Ejemplo 98



El compuesto del título se preparó a partir del producto de la Preparación 22b de la misma forma como se describe anteriormente para la preparación del compuesto del título del Ejemplo 97, substituyendo el 2-amino tiazol por 2-aminotiazol-4-carboxilato de etilo. EM (ES+) m/z: 455 (M+H); Tiempo de retención CL: 3.68 min.

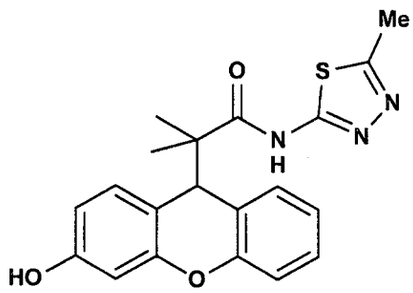
Ejemplo 99

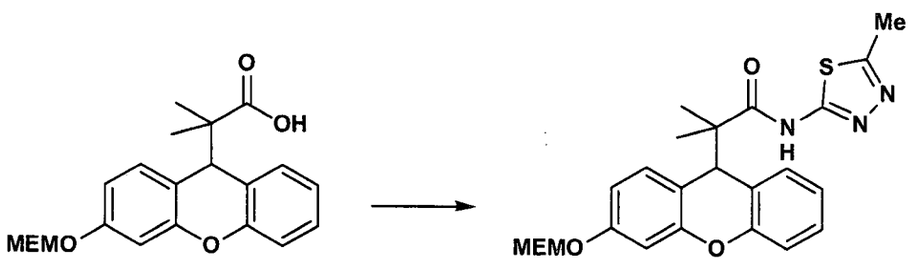


A una solución del compuesto del título del Ejemplo 97

(42 mg, 0.08 mmol) en metanol seco (0.8 mL) se le agregó ácido alcanforsulfónico (5.5 mg, 0.024 mmol). La solución se calentó a 70°C durante 24 h, luego se concentró *in vacuo*. El residuo se dividió entre acetato de etilo y bicarbonato de sodio acuoso saturado. La capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio, luego se concentró para dar un sólido pegajoso (22 mg, 65% de rendimiento). EM (ES+) m/z: 425 (M+H); Tiempo de retención CL: 3.47 min.

Ejemplo 100



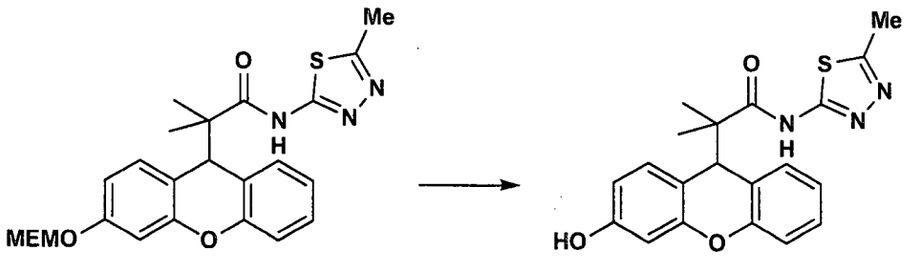


(MEMO = metoxietoximetoxi)

Etapa 1

El producto 100a se preparó a partir de la misma forma como se describió anteriormente para la preparación del compuesto del título del Ejemplo 97, substituyendo el 5-metil-2-amino-1,3,4-tiadiazol por 2-aminotiazol-4-carboxilato de

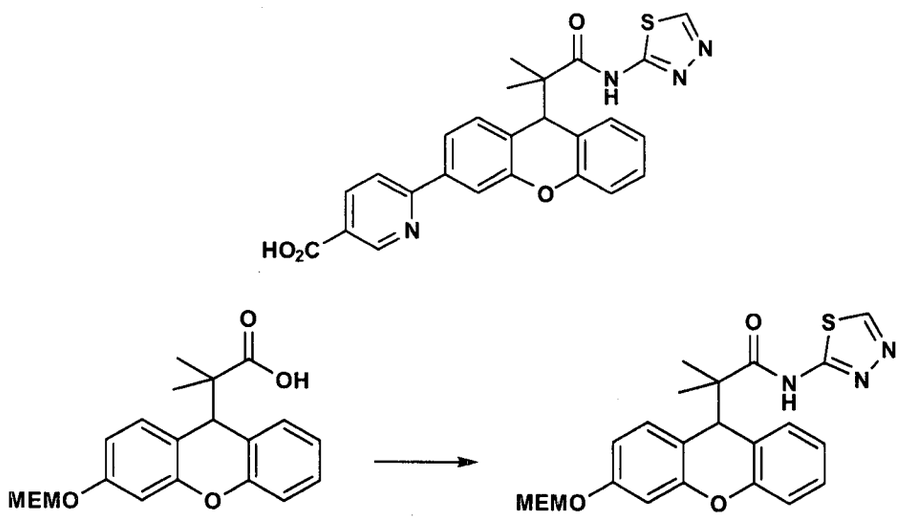
etilo. EM (ES+) m/z: 470 (M+H); Tiempo de retención CL: 3.82 min.



Etapa 2

El compuesto del título se preparó de la misma forma como se describió anteriormente para la preparación del compuesto del título del Ejemplo 99. EM (ES+) m/z: 382 (M+H); Tiempo de retención CL: 3.32 min.

Ejemplo 101

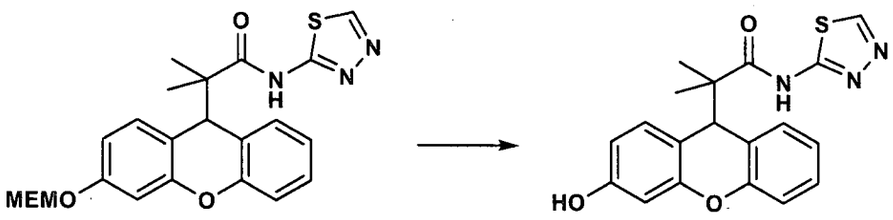


(MEMO=metoxietoximetoxi)

Etapa 1

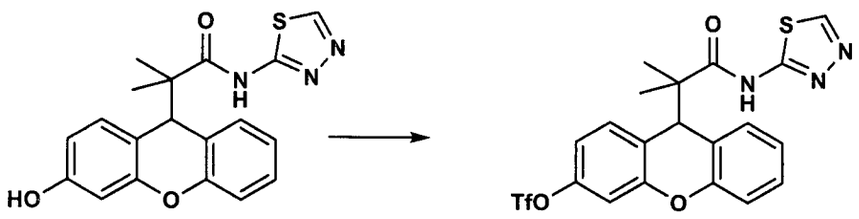
El producto de la etapa 1 se preparó en la forma descrita

anteriormente para la preparación del producto de la etapa 1 del Ejemplo 100.



Etapa 2

El producto de la etapa 2 se preparó en la forma descrita anteriormente para la preparación del producto de la etapa 2 del Ejemplo 100.

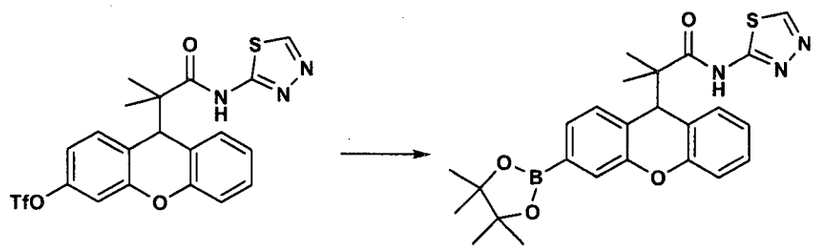


Etapa 3

A una solución del producto de la etapa 2 (200 mg, 0.545 mmol) en diclorometano (5 mL) a 0°C bajo nitrógeno se le agregó trietilamina (0.182 mL, 1.31 mmol) seguido por 1,1,1-trifluoro-N-fenil-N-(trifluorometilsulfonil)metansulfonamida (292 mg, 0.817 mmol). La mezcla de reacción se dejó agitar a 0°C durante 2.5 h, luego se dividió entre diclorometano y solución de bicarbonato de sodio acuoso saturado. La capa orgánica se secó sobre sulfato de sodio y se concentró. La purificación por cromatografía de columna por desorción súbita (40 g sílice, 50% acetato de etilo en hexanos) proporcionó el

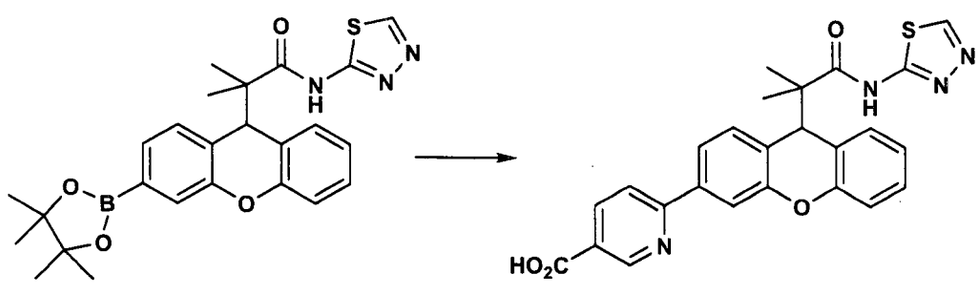
- 607632

producto de la etapa 3 (150 mg, Y = 55%) como un sólido blanco. EM (ES+) m/z: 500 (M+H); Tiempo de retención CL: 3.99 min.



Etapa 4

A una solución del producto de la etapa 3 (160 mg, 0.32 mmol) en 1,4-dioxano (3 mL) se agregaron secuencialmente el complejo de diclorometano - dicloruro de 1,1'-bis(difenilfosfino)ferroceno-paladio(II) (24 mg, 0.03 mmol), bis(pinacolato)diboro (120 mg, 0.47 mmol), y acetato de potasio (96 mg, 0.98 mmol). Una corriente de gas de nitrógeno se sopló a través de la mezcla de reacción durante 15 min, la cual se calentó luego a 80°C durante 5 h. La mezcla de reacción se concentró *in vacuo*, y el residuo se purificó por cromatografía de columna por desorción súbita (12 g silica, 20% hasta 50% acetato de etilo en hexanos) para proporcionar el producto de la etapa 4 (120 mg, Y = 79%) como un aceite amarillo. EM (ES+) m/z: 478 (M+H); Tiempo de retención CL: 4.07 min.

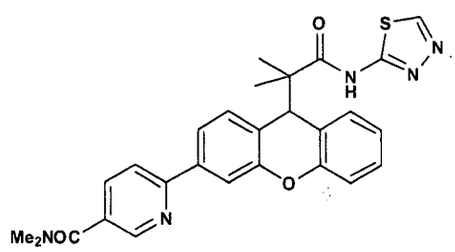


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Etapa 5

A una solución de ácido 6-cloronicotínico (7.4 mg, 0.047 mmol) en DMF (1 mL) se agregó el producto de la etapa 4 (15 mg, 0.031 mmol), seguido por fosfato de potasio acuoso (2.0 M, 0.1 mL) y tetraquis(trifenilfosfina)paladio(0) (10 mg, 0.009 mmol). Una corriente de gas de nitrógeno se burbujeó a través de la mezcla durante 15 min, la cual se calentó luego a 100°C durante 2 h. La mezcla de reacción se purificó por HPLC preparativa para dar el compuesto del título como una sal de TFA la cual se liofilizó de acetonitrilo/agua para dar un polvo blanco (3.1 mg, Y = 21%). EM (ES+) m/z: 473 (M+H); Tiempo de retención CL: 3.55 min.

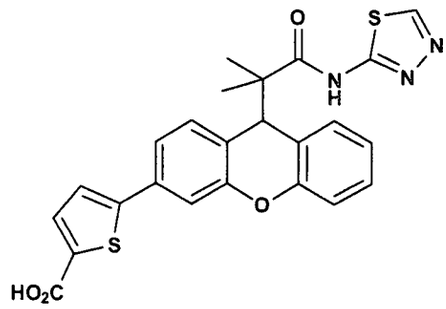
Ejemplo 102



Una mezcla del compuesto del título del Ejemplo 101 (10 mg, 0.021 mmol), monohidrato de HOBT (4.3 mg, 0.032 mmol), EDCI (6.12 mg, 0.032 mmol), trietilamina (0.1 mL) y clorohidrato de dimetilamina (3.43 mg, 0.042 mmol) en acetonitrilo (1 mL) se calentó a 80°C durante 12 h. La mezcla de reacción se purificó luego por HPLC preparativa para dar el compuesto del título, el cual se liofilizó de acetonitrilo/agua para dar un polvo blanco (4 mg, Y = 38%). EM

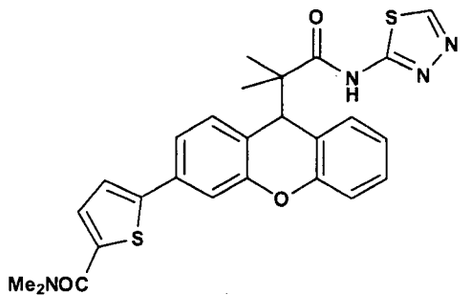
(ES+) m/z: 500 (M+H); Tiempo de retención CL: 3.26 min.

Ejemplo 103



A una solución del producto del Ejemplo 101, Etapa 4 (45 mg, 0.094 mmol) y ácido 5-bromotiofen-2-carboxílico (38 mg, 0.188 mmol) en DMF (9 mL) y agua (0.1 mL) se agregaron tetraquis(trifenilfofina)paladio(0) (10 mg, 0.009 mmol) y hexahidrato de hidróxido bario (89 mg, 0.28 mmol). El gas nitrógeno se burbujeó a través de la mezcla durante 10 min, la cual se calentó luego a 100°C durante 14 h. La purificación por HPLC preparativa proporcionó el compuesto del título (3 mg, Y = 7%) como un polvo blanco. EM (ES+) m/z: 478 (M+H); Tiempo de retención CL: 3.75 min.

Ejemplo 104



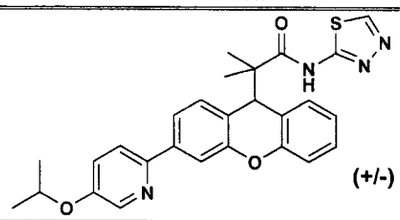
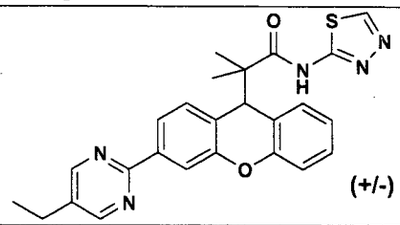
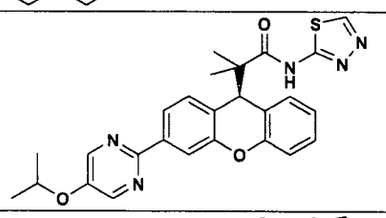
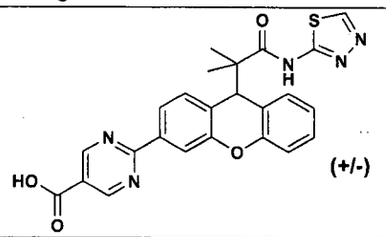
El compuesto del título se preparó a partir del compuesto del título del Ejemplo 103 en la forma descrita para la

635

preparación del compuesto del título del Ejemplo 102 del Ejemplo 101. EM (ES+) m/z: 505 (M+H); Tiempo de retención CL: 3.62 min.

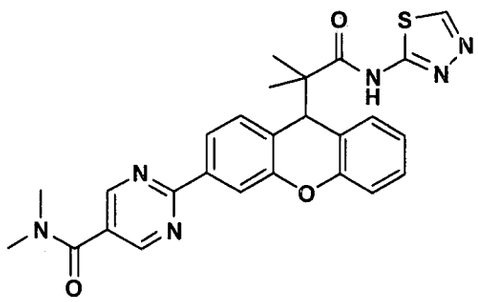
Ejemplos 105 hasta 108

Los siguientes Ejemplos 105 hasta 108 se prepararon de la misma forma descrita anteriormente para la preparación del compuesto del título del Ejemplo 103 usando el producto del Ejemplo 101, etapa 4 o el compuesto del título del Ejemplo 90 y haluros comercialmente disponibles en lugar de ácido bromotiofeno-2-carboxílico.

Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
105		3.71	487
106		3.85	458
107		3.74	487
108		3.75	474

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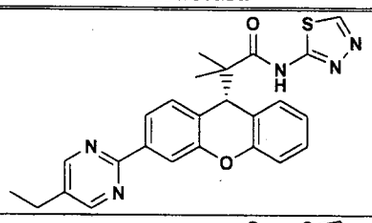
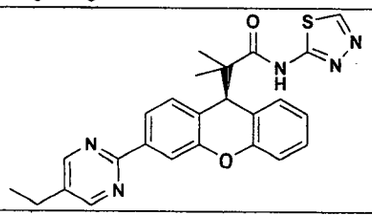
Ejemplo 109



El compuesto del título se preparó a partir del compuesto del título del Ejemplo 108 de la misma forma descrita anteriormente para la preparación del compuesto del título del Ejemplo 104 a partir del compuesto del título del Ejemplo 103. EM (ES+) m/z: 501 (M+H); Tiempo de retención CL: 3.42 min.

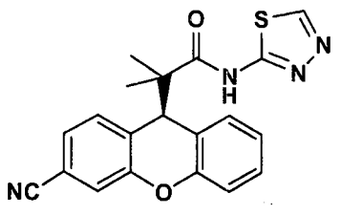
Ejemplos 110 hasta 111

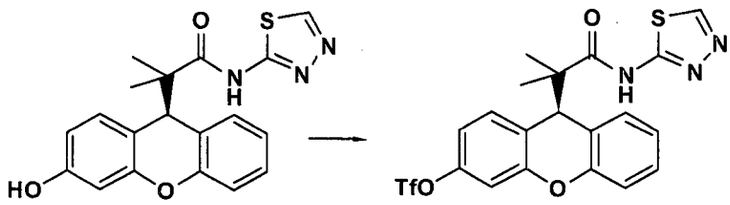
Los siguientes Ejemplos 110 hasta 111 se prepararon de la misma forma descrita anteriormente para la preparación del compuesto del título del Ejemplo 106 usando los compuestos del título del Ejemplo 95 y Ejemplo 90.

Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
110		3.92	458
111		3.92	458

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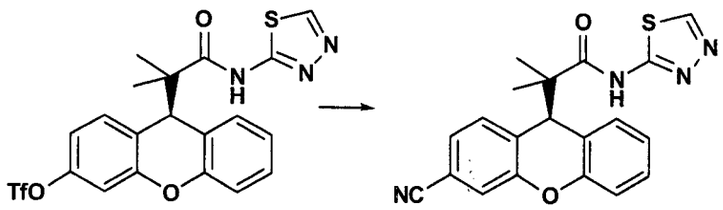
EJEMPLO 112





Etapa 1

El producto de la etapa 1 se preparó a partir del compuesto del título del Ejemplo 90 de la misma forma como se describe anteriormente para la preparación del producto de la etapa 3 del Ejemplo 101.

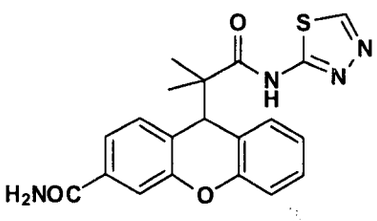


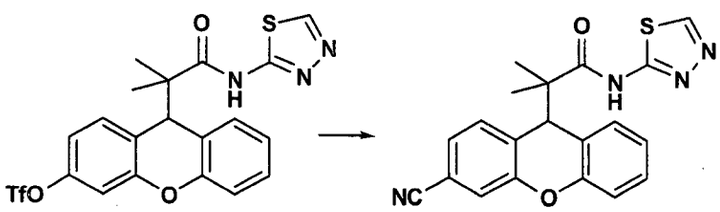
Etapa 2

Una solución del producto de la etapa 1 (25 mg, 0.05 mmol) en DMF (0.3 mL) se desgasificó al pasar a través de una corriente de nitrógeno durante 5 min. El cianuro de zinc (12 mg, 0.1 mmol) y tetraquis(trifenilfosfin)paladio(0) (12 mg, 0.05 mmol) se agregaron luego y la mezcla se desgasificó duranto otros 5 min, luego se calentó a 120°C durante 2 h en un vial sellado. La mezcla se filtró a

través de un filtro de punta de jeringa (0.45 micrones, PTFE), luego se purificó por HPLC preparativa para dar el producto como un sólido blanco. EM (ES+) m/z: 375; Tiempo de retención CL: 3.40 min.

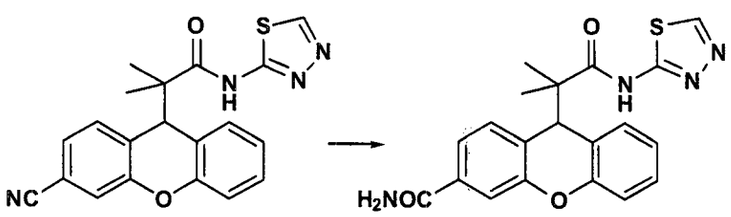
Ejemplo 113





Etapa 1

El producto de la etapa 1 se obtuvo del producto de la etapa 3 del Ejemplo 101 de la misma forma descrita anteriormente para la preparación del compuesto del título del Ejemplo 112. EM (ES+) m/z: 375; Tiempo de retención CL: 3.40 min.

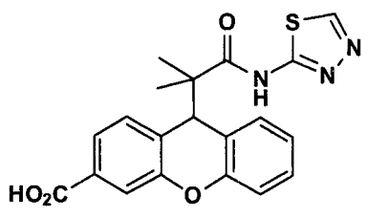


Etapa 2

A una suspensión del producto de la etapa 1 (10 mg, 0.0266 mmol) en agua (2 mL) se le agregó peróxido de sodio (12

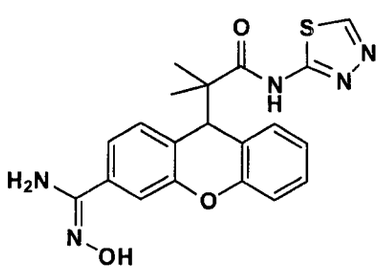
mg, 0.16 mmol). La mezcla se calentó a 70°C durante 1h, luego se hace ácida a un pH ~5 con la adición gota a gota de HCl 6 N y se purificó por HPLC preparativa. El material así obtenido se liofilizó del acetonitrilo/agua para dar el compuesto del título como un polvo blanco, sal de TFA (4 mg, Y = 29%). EM (ES+) m/z: 395 (M+H); Tiempo de retención CL: 2.89 min.

Ejemplo 114



A una suspensión del producto de la etapa 1 del Ejemplo 113 (10 mg, 0.027 mmol) en agua (2 mL) se le agregó peróxido de sodio (30 mg, 0.38 mmol). La mezcla se calentó a 100°C durante 16 h. Otra porción de peróxido de sodio (30 mg, 0.38 mmol) se le agregó luego y la mezcla se calentó a 100°C durante otras 3 h, luego se purificó por HPLC preparativa para dar el compuesto del título como un polvo blanco (3 mg, Y = 28%). EM (ES+) m/z: 396 (M+H); Tiempo de retención CL: 3.36 min.

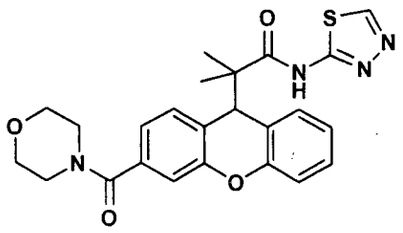
Ejemplo 115



Una mezcla del producto del Ejemplo 113, etapa 1 (40

mg, 0.106 mmol), clorohidrato de hidroxilamina (30 mg, 0.426 mmol) y carbonato de potasio (59 mg, 0.426 mmol) en etanol (5 mL) y agua (1 mL) se calentó a reflujo durante la noche. La HPLC preparativa proporcionó el producto (28 mg, Y = 65%). EM (ES+) m/z: 410 (M+H); Tiempo de retención CL: 2.29 min.

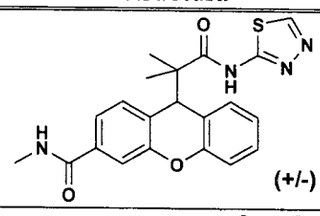
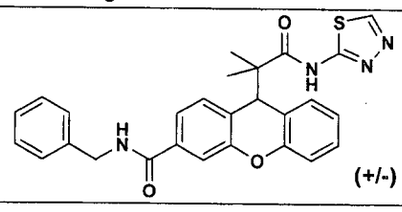
EJEMPLO 116



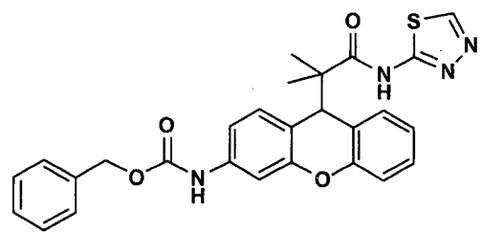
Una solución del compuesto del título del Ejemplo 114 (5 mg, 0.013 mmol) en acetonitrilo (2 mL) se trató con monohidrato de HOBT (3 mg, 0.019 mmol), EDCI (4 mg, 0.019 mmol), piridina (0.1 mL) y morfolina (0.003 mL, 0.025 mmol). La solución resultante se calentó a 60°C durante 14 h, luego se purificó por HPLC preparativa para dar el compuesto del título (4.7 mg, Y = 78%) como un sólido blanco. EM (ES+) m/z: 465 (M+H); Tiempo de retención CL: 3.07 min.

Ejemplos 117 hasta 118

Los siguientes Ejemplos 117 hasta 118 se prepararon de la misma forma descrita anteriormente para la preparación del compuesto del título del Ejemplo 116.

Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
117		2.96	409
118		3.49	485

EJEMPLO 119

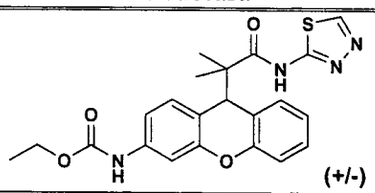
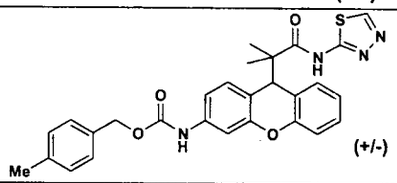
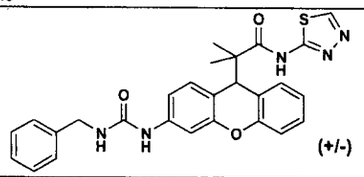
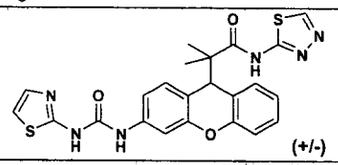
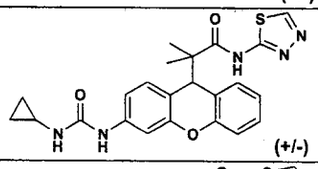
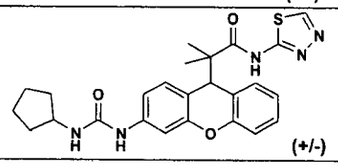


A una solución del compuesto del título del Ejemplo 114 (25 mg, 0.06 mmol) en tolueno (3 mL) se le agregaron trietilamina (0.025 mL, 0.18 mmol) y azida de difenil fosforilo (0.026 mL, 0.12 mmol). La solución resultante se puso a reflujo durante 30 min, luego se enfrió a temperatura ambiente. El alcohol de bencilo (0.019 mL, 0.18 mmol) se agregó luego a la mezcla de reacción, se puso a reflujo durante otras 5 h. El solvente se removió *in vacuo* y el residuo resultante se purificó por HPLC preparativa para proporcionar el producto, el cual se liofilizó del acetonitrilo/agua para dar el compuesto del título (19 mg, Y = 43%) como un polvo blanco. EM (ES+) m/z: 501 (M+H); Tiempo de

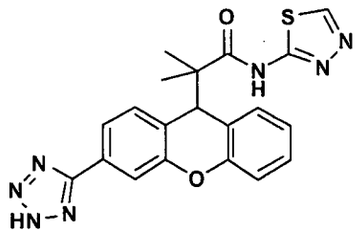
retención CL: 3.79 min.

Ejemplos 120 hasta 125

Los siguientes Ejemplos 120 hasta 125 se prepararon de la misma forma descrita anteriormente para la preparación del compuesto del título del Ejemplo 119, substituyendo el alcohol de bencilo con alcoholes y aminas comercialmente disponibles.

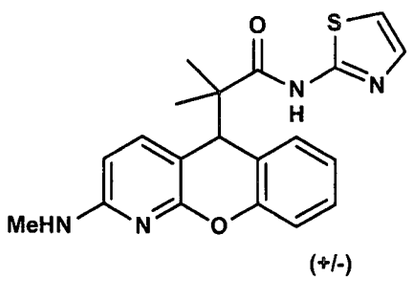
Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
120		3.71	487
121		2.92	515
122		3.49	500
123		3.47	493
124		3.17	450
125		3.51	478

Ejemplo 126



A una solución del producto del Ejemplo 113, etapa 1 (10 mg, 0.027 mmol) en DMF (1 mL) se le agregó azida de sodio (18 mg, 0.27 mmol) y cloruro de amonio (53.5 mg, 0.27 mmol). La mezcla se calentó a 120°C durante 6 h. Después de enfriar, la mezcla se purificó por HPLC preparativa para dar el producto el cual se liofilizó a partir del acetonitrilo/agua para proporcionar el compuesto del título (6 mg, Y = 53%) como un polvo blanco. EM (ES+) m/z: 420 (M+H); Tiempo de retención CL: 3.14 min.

Ejemplo 127

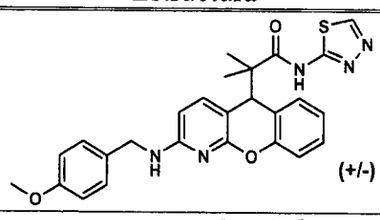
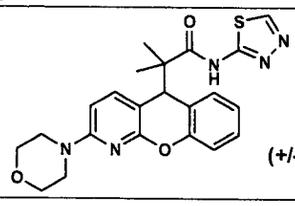


El compuesto del título se preparó a partir del producto de la Preparación 24 de la misma forma descrita anteriormente para la preparación del compuesto del título del Ejemplo 67. EM (ES+) m/z: 381 (M+H); Tiempo de retención CL: 3.07 min.

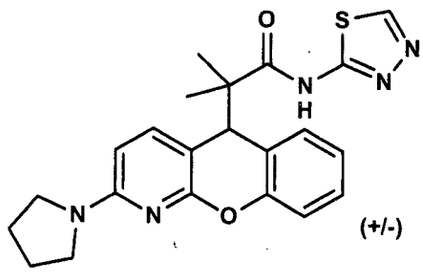
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Ejemplos 128 hasta 129

Los siguientes Ejemplos 128 hasta 129 se prepararon de la misma forma descrita anteriormente para la preparación del compuesto del título del Ejemplo 127 usando compuestos de las Preparaciones 25 y 26 y 2-amino-1,3,4-tiadiazol en lugar de 2-aminotiazol.

Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
128		3.55	488
129		3.19	438

Ejemplo 130



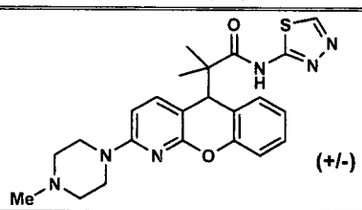
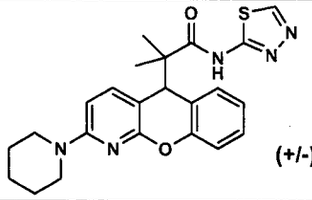
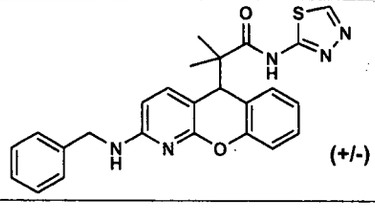
A una solución del producto de la Preparación 28 (100 mg, 0.297 mmol) en acetonitrilo (3.0 mL) se le agregó hexafluoro fosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (HATU) (226 mg, 0.594 mmol), seguido por trietilamina (0.2 mL) y 2-amino-1,3,4-tiadiazol (60 mg, 0.594

- 000645

mmol). La solución se calentó a 80°C durante 16 h, luego se concentró *in vacuo* y purificó por HPLC preparativa para dar el producto como un sólido (120 mg, 76%). EM (ES+) m/z: 422 (M+H); Tiempo de retención CL: 3.38 min.

Ejemplo 131 hasta 133

Los siguientes Ejemplos 131 hasta 133 se prepararon a partir de los compuestos de las Preparaciones 23, 27 y 29 en la forma descrita anteriormente para la preparación del compuesto del título del Ejemplo 130.

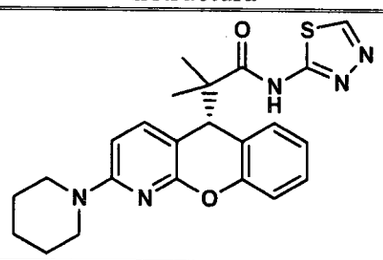
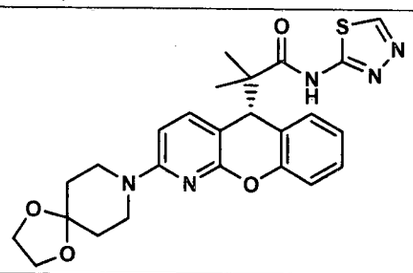
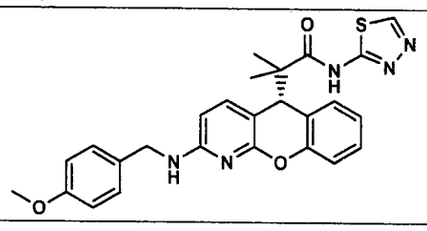
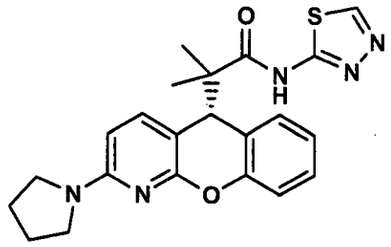
Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
131		2.20	451
132		3.70	4.36
133		3.51	456

Ejemplos 134 hasta 137

Los siguientes Ejemplos 134 hasta 137 se prepararon a partir de los compuestos de las Preparaciones 31 hasta 34 en la forma descrita anteriormente para la preparación de

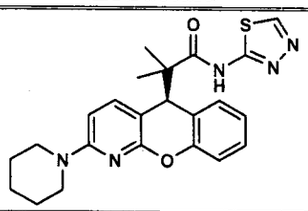
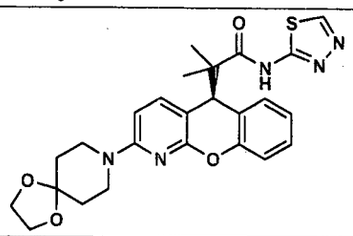
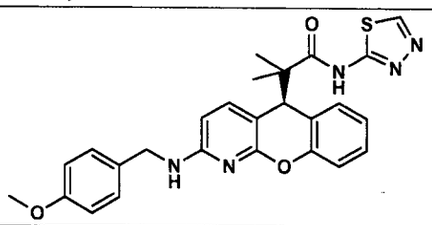
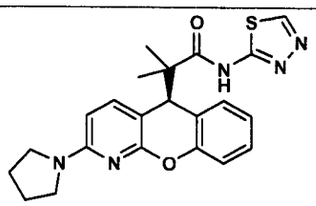
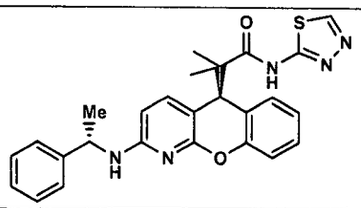
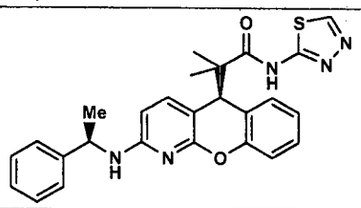
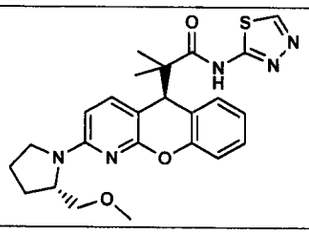
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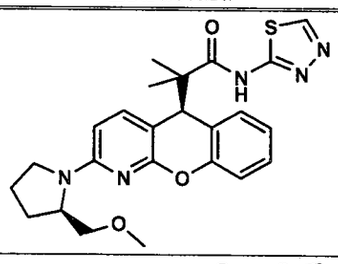
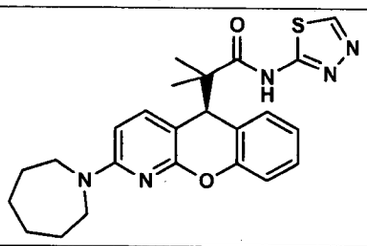
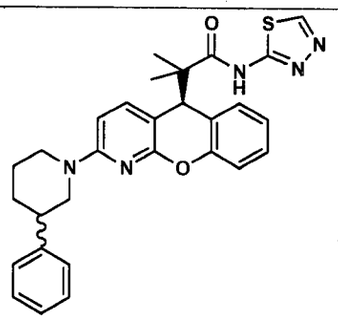
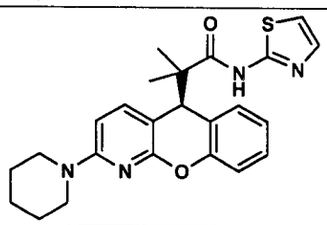
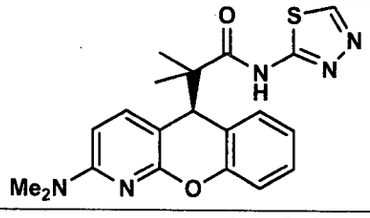
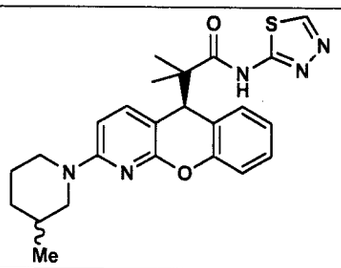
los compuestos del título de los Ejemplos 130 hasta 133.

Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
134		3.70	436
135		3.42	494
136		3.51	488
137		3.41	422

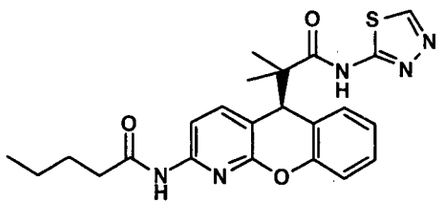
Ejemplos 138 hasta 150

Los siguientes Ejemplos 138 hasta 150 se prepararon a partir de los compuestos de las Preparaciones 35 hasta 47 en la forma descrita anteriormente para la preparación de los compuestos del título de los Ejemplos 130 hasta 137.

Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
138		3.73	436
139		3.43	494
140		3.51	488
141		3.41	422
142		3.60	470
143		3.60	472
144		3.52	466

Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
145		3.50	466
146		3.83	450, 448
147		4.15	512
148		3.86	435, 433
149		3.22	394, 396
150		3.92	448, 450

Ejemplo 151



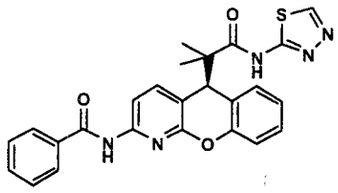
Etapa 1

A una solución del compuesto del título del Ejemplo 140 (20 mg, 0.04 mmol) en DMF (0.4 mL) se le agregaron trietilamina (0.028 mL, 0.2 mmol) y cloruro de butirilo (0.042 mL, 0.4 mmol), seguido por N,N-dimetilaminopiridina (5 mg, 0.04 mmol). La mezcla se calentó a 80°C durante 30 min, luego se dividió entre acetato de etilo y HCl acuoso 1N. La capa orgánica se lavó con bicarbonato de sodio acuoso saturado y salmuera, luego se secó sobre sulfato de sodio y se concentró. EM (ES+) m/z: 558 (M+H); Tiempo de retención CL: 3.62 min. El material sin refinar (140a) se usó directamente en la siguiente etapa sin purificación adicional.

Etapa 2

El producto de la etapa 1 (140a) se disolvió en TFA (1 mL) y se calentó a 50°C durante 12 h. El solvente se removió *in vacuo*, y el residuo se purificó por HPLC preparativa para dar el producto (7 mg, 40% de rendimiento durante dos etapas) como un sólido blanco opaco. EM (ES+) m/z: 438 (M+H); Tiempo de retención CL: 3.24 min.

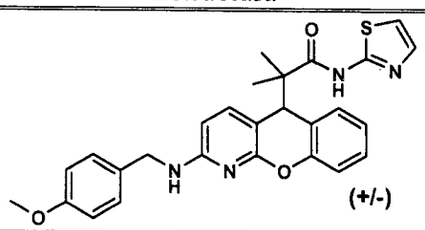
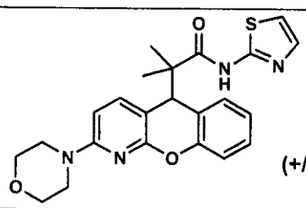
Ejemplo 152

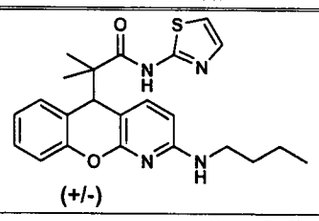
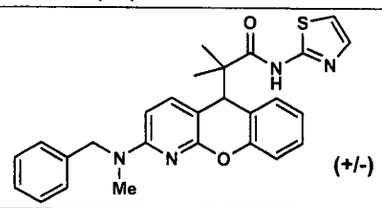
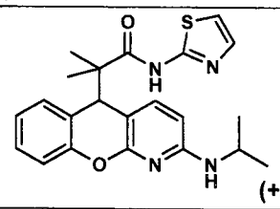


El compuesto del título se preparó a partir del compuesto del título del Ejemplo 140 en una forma similar como se describe anteriormente para la preparación del compuesto del título del Ejemplo 151. EM (ES+) m/z: 472 (M+H); Tiempo de retención CL: 3.48 min.

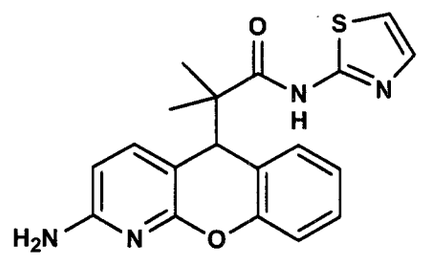
Ejemplos 153 hasta 157

Los siguientes Ejemplos 153 hasta 157 se prepararon de la misma forma descrita anteriormente para las preparaciones de los compuestos del título de las Preparaciones 23 hasta 29, usando el compuesto del título del Ejemplo 75 en lugar del producto de la Preparación 17e.

Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
153		3.70	487
154		3.39	435

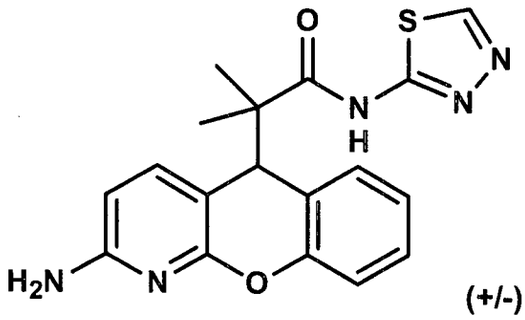
Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
155	 (+/-)	4.00	423
156	 (+/-)	4.39	471
157	 (+/-)	3.47	409

Ejemplo 158


(+/-)

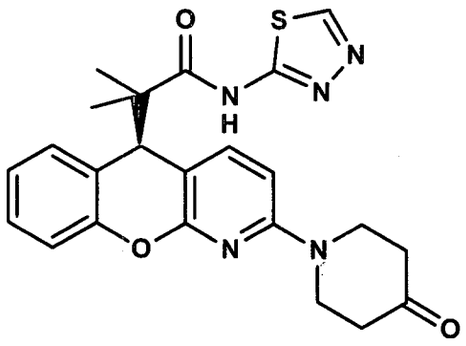
Una solución del compuesto del título del Ejemplo 153 (10 mg, 0.021 mmol) en ácido trifluoroacético (1 mL) se calentó a 50°C durante 0.5 h. El solvente se removió *in vacuo* y el residuo se purificó por HPLC preparativa para dar el producto (8.5 mg, 86%) como un sólido. EM (ES+) m/z: 365; Tiempo de retención CL: 2.79 min.

EJEMPLO 159



El compuesto del título se preparó a partir del compuesto del título del Ejemplo 128 en la forma descrita anteriormente para la preparación del compuesto del título del Ejemplo 158. EM (ES+) m/z: 368 (M+H); Tiempo de retención CL: 2.50 min.

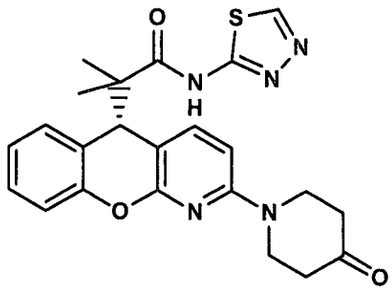
Ejemplo 160



Una solución del compuesto del título del Ejemplo 135 (11 mg, 0.022 mmol) en THF (0.6 mL) y HCl 1N (0.5 mL) se agitó a temperatura ambiente durante 15 h. El producto (2 mg, 20%) se aisló por HPLC preparativa. EM (ES+) m/z: 464 (M+MeOH-OH); Tiempo de retención CL: 3.10 min.

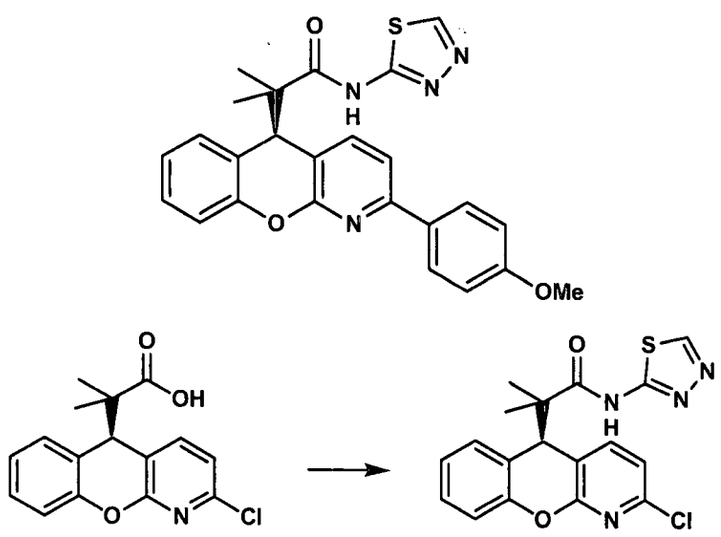
653

Ejemplo 161



El compuesto del título se preparó a partir del compuesto del título del Ejemplo 139 en la forma descrita anteriormente para la preparación del compuesto del título del Ejemplo 160. EM (ES+) m/z: 464 (M+MeOH-OH); Tiempo de retención CL: 3.10 min.

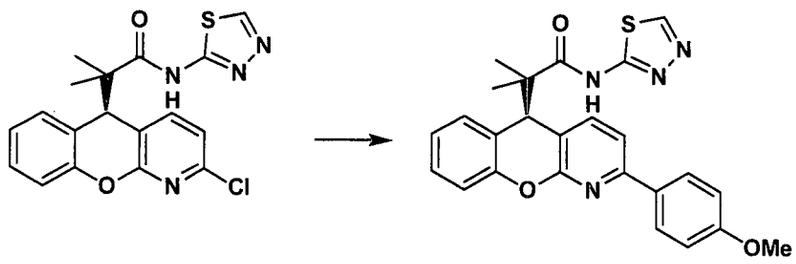
Ejemplo 162



Etapa 1

El producto de la etapa 1 (162a) se preparó a partir del isómero R de la Preparación 30 (30a) de la misma forma descrita anteriormente para la preparación del compuesto del

título del Ejemplo 76.



Etapa 2

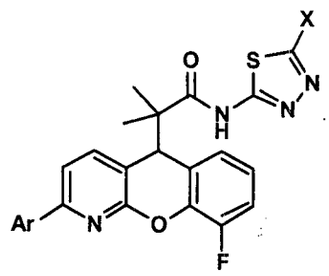
El ácido 4-metoxifenil borónico (24 mg, 0.156 mmol) y 134a (30 mg, 0.078 mmol) se combinaron en un recipiente de reacción de microondas y se recibieron en DMF (1 mL) y fosfato de potasio acuoso 2M (0.2 mL). El gas de nitrógeno se burbujeó a través de la solución durante 5 min, punto en el cual se agregó tetraquis(trifenilfosfina)paladio(0) (10 mg, 0.009 mmol). La mezcla se calentó por microondas durante 30 min a 100°C, luego se purificó por HPLC preparativa para dar el compuesto del título (21.2 mg, 60%) como un sólido blanco. EM (ES+) m/z: 459 (M+H); Tiempo de retención CL: 3.65 min.

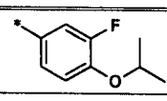
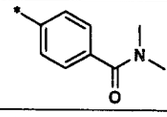
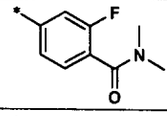
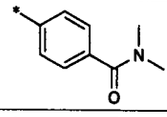
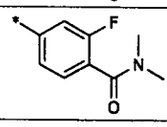
Ejemplos 163 hasta 167

Los siguientes Ejemplos 163 hasta 167 se prepararon a partir del compuesto del título de la Preparación 55e de la misma forma que la preparación del compuesto del título del Ejemplo 162, usando 2-amino-1,3,4-tiadiazol o 2-amino-5-metil-1,3,4-tiadiazol en la primera etapa y ácidos borónicos comercialmente disponibles en lugar de ácido 4-metoxifenil

655

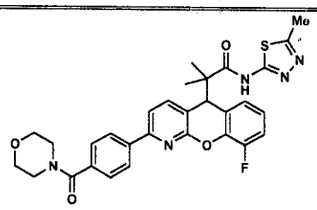
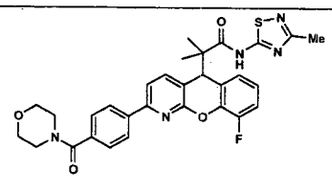
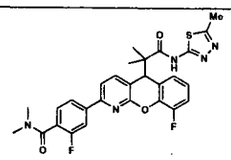
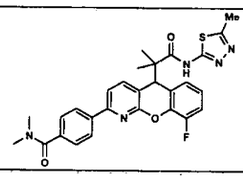
borónico en la segunda etapa.



Ejemplo No.	X	Ar	Tr (min)	M/z $(MH)^+$
163	H		3.90	523
164	H		3.20	518
165	H		3.25	536
166	Me		3.31	532
167	Me		3.40	550

Ejemplos 163ª hasta 166ª

Los siguientes Ejemplos 163ª hasta 166ª se prepararon a partir del compuesto del título de la Preparación 56a de la misma forma como la preparación del compuesto del título del Ejemplo 162, usando 2-amino-1,3,4-tiadiazol o 2-amino-5-metil-1,3,4-tiadiazol o 5-amino-3-metil-1,2,4-tiadiazol en la primera etapa y ácidos borónicos comercialmente disponibles en lugar de ácido 4-metoxifenil borónico en la segunda etapa.

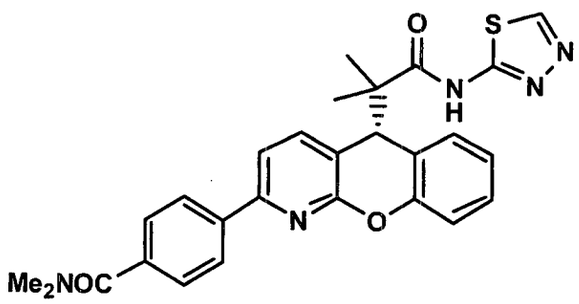
Ejemplo No.	Estructura	Tr (min)	M/z $(MH)^+$
163[a]		3.31	574
164[a]		3.40	574
165[a]		3.38	550
166[a]		3.33	532

163[a]: ^{1}H RMN (400 MHz, CLOROFORMO-D) δ ppm 1.25 (d, J=13.85 Hz, 6 H) 2.77 (s, 3 H) 3.44 - 3.93 (m, 8 H) 4.65 (s, 1 H) 6.91 (d, J=7.81 Hz, 1 H) 7.00 - 7.07 (m, 1 H) 7.11 - 7.18 (m, 1 H) 7.53 (d, J=8.06 Hz, 2 H) 7.59 (d, J=7.81 Hz, 1 H) 7.70 (d, J=7.81 Hz, 1 H) 8.11 (d, J=8.31 Hz, 2 H).

164[a]: ^{1}H RMN (400 MHz, CLOROFORMO-D) δ ppm 1.24 (d, J=6.04 Hz, 6 H) 2.59 (s, 3 H) 3.42 - 3.93 (m, 8 H) 4.62 (s, 1 H) 6.89 (d, J=7.81 Hz, 1 H) 6.99 - 7.06 (m, 1 H) 7.12 - 7.18 (m, 1 H) 7.50 - 7.64 (m, 4 H) 8.11 (d, J=8.31 Hz, 2 H).

165ª: ^{1}H RMN (400 MHz, CLOROFORMO-D) δ ppm 1.25 (d, J=12.59 Hz, 6 H) 2.78 (s, 3 H) 3.00 (d, J=1.26 Hz, 3 H) 3.19 (s, 3 H) 4.70 (s, 1 H) 6.94 (d, J=7.81 Hz, 1 H) 7.00 - 7.07 (m, 1 H) 7.11 - 7.18 (m, 1 H) 7.51 (t, J=7.30 Hz, 1 H) 7.57 (d, J=7.81 Hz, 1 H) 7.74 (d, J=7.81 Hz, 1 H) 7.88 (d, J=9.57 Hz, 2 H).

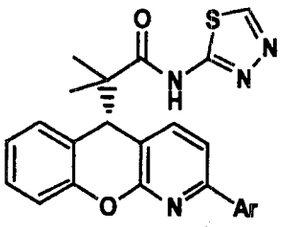
Ejemplo 168

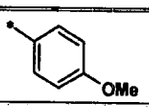
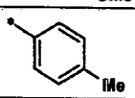
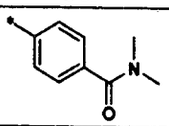
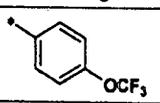
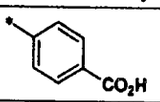
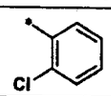
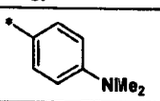
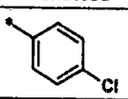
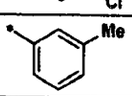
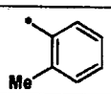
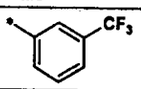


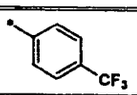
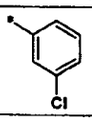
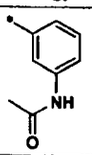
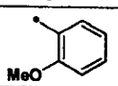
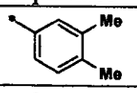
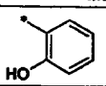
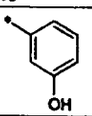
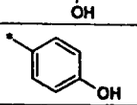
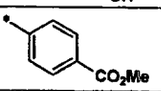
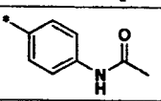
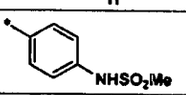
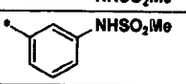
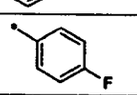
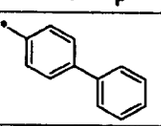
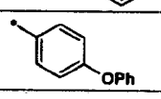
El compuesto del título se preparó a partir del compuesto del título del Ejemplo 162 Etapa 1 (162a) en la forma descrita anteriormente para la preparación de los compuestos del título del Ejemplo 162. EM (ES+) m/z: 500 (M+H); Tiempo de retención CL: 3.22 min.

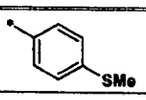
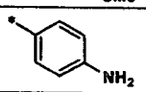
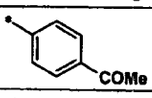
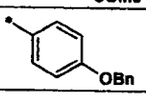
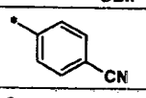
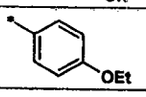
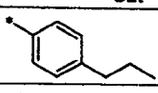
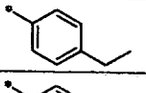
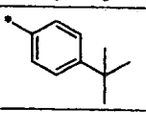
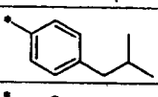
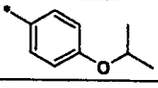
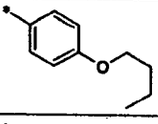
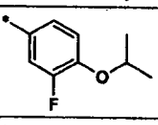
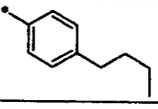
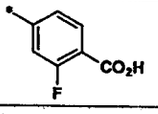
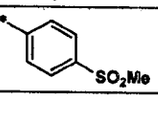
Ejemplos 169 hasta 237

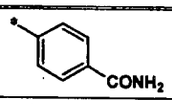
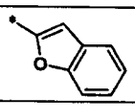
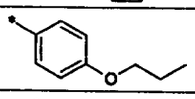
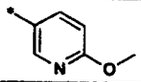
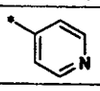
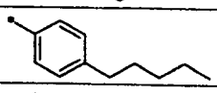
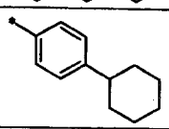
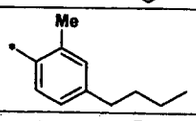
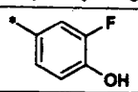
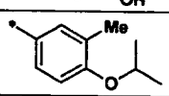
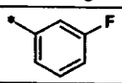
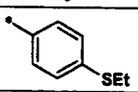
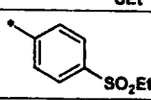
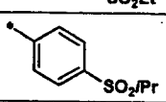
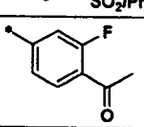
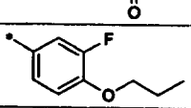
Los siguientes Ejemplos 169 hasta 237 se prepararon del producto de la Preparación 53a en la forma descrita anteriormente para la preparación del compuesto del título del Ejemplo 162 del 162a, usando ácido borónicos comercialmente disponibles.



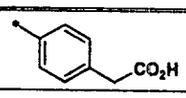
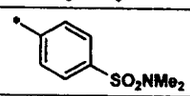
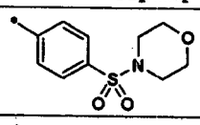
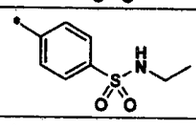
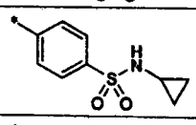
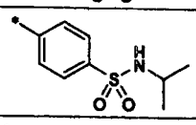
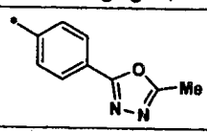
Ejemplo No.	Ar	Tr (min)	EM de Iones observado
169		3.65	459
170		3.81	443
171	Ph	3.06	429
172		3.22	500
173		4.03	513
174		3.42	473
175		3.65*	463
176		3.03*	472
177	1-naftilo	3.84**	479
178		3.96**	463
179		3.84**	443
180		3.67**	443
181		4.02**	497

Ejemplo No.	Ar	Tr (min)	EM de Iones observado
182		4.00**	497
183		3.98**	463
184		3.33**	486
185		3.60**	459
186	2-naftilo	4.02**	479
187	3-piridilo	2.41**	430
188		3.97**	457
189		3.84**	445
190		3.35**	445
191		3.31**	445
192		3.73**	487
193		3.30**	486
194		3.23**	522
195		3.25**	522
196		3.72**	447
197		4.11**	505
198		4.08**	521

Ejemplo No.	Ar	Tr (min)	EM de Iones observado
199		3.85**	475
200		2.69**	444
201		3.51**	471
202		4.06**	535
203		3.52**	454
204		3.81**	473
205		4.11**	471
206		3.94**	457
207		4.15**	485
208		4.22**	485
209		3.89**	487
210		4.12**	501
211		3.92	505
212		4.28	485
213		3.43	491
214		3.16	507

Ejemplo No.	Ar	Tr (min)	EM de Iones observado
215		3.06	472
216		3.94	469
217		4.02	487
218		3.50	460
219		2.38	430
220		4.44	499
221		4.47	511
222		4.28	499
223		3.35	463
224		4.12	501
225		3.72	447
226		4.01	489
227		3.26	521
228		3.39	535
229		3.63	489
230		4.01	505

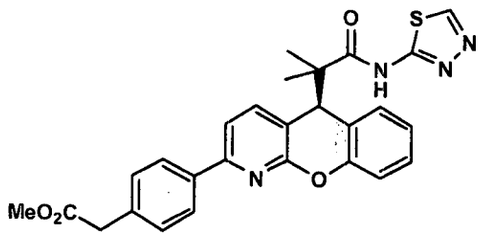
652

Ejemplo No.	Ar	Tr (min)	EM de Iones observado
231		3.33	487
232		3.34	536
233		3.35	578
234		3.27	536
235		3.31	548
236		3.40	550
237		3.46	511

** HPLC analítica Método B

** HPLC analítica Método C

Ejemplo 238



A una solución del compuesto del título del Ejemplo 231 (11 mg, 0.023 mmol) en benceno (0.3 mL) y metanol (0.3 mL) a temperatura ambiente se le agregó trimetilsilil diazometano (0.037 mL, 0.2 mmol). La mezcla de reacción se dejó reposar a

Patente de Invención

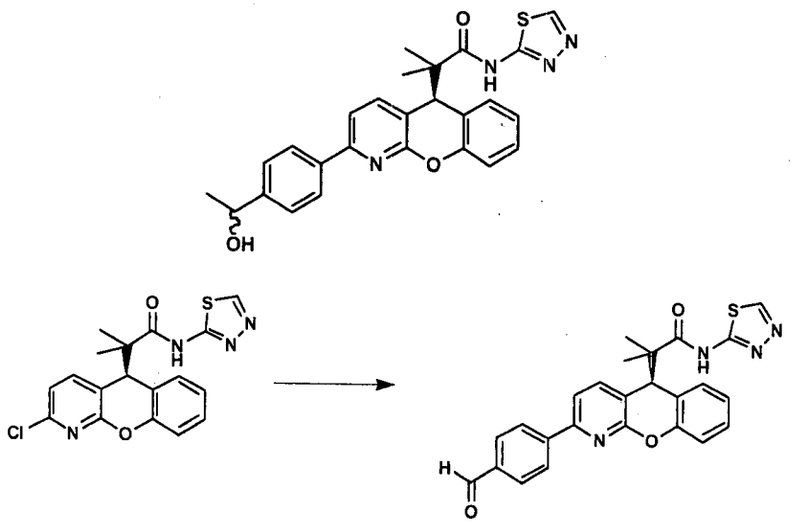
09/20345

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663

temperatura ambiente durante 30 min, luego se apagó con la adición de 2 gotas de ácido acético glacial. La mezcla de reacción se concentró, y purificó por TLC preparativa (0.5 mm sílice, 100 cm x 100 cm, 40% acetato de etilo en hexanos). Lo más bajo de las dos bandas se aisló, dando el compuesto del título (6 mg, Y = 52%) como un sólido incoloro. EM (ES+) m/z: 501; Tiempo de retención CL: 3.50 min. ^{1}H RMN (400 MHz, CLOROFORMO-D) δ ppm 1.23 (s, 3 H) 1.25 (s, 3 H) 3.67 (s, 2 H) 3.69 (s, 3 H) 4.71 (s, 1 H) 6.99 - 7.05 (m, 1 H) 7.19 (d, J=7.63 Hz, 1 H) 7.28 - 7.33 (m, 2 H) 7.37 (d, J=8.14 Hz, 2 H) 7.48 (d, J=8.14 Hz, 1 H) 7.67 (d, J=7.63 Hz, 1 H) 7.98 (d, J=8.14 Hz, 2 H) 8.88 (s, 1 H).

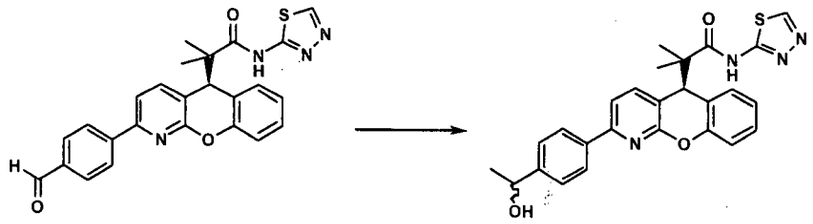
Ejemplo 239



Etapa 1

El producto de la etapa 1 se preparó en la forma descrita anteriormente para la preparación de los compuestos del título de los Ejemplos 169 hasta 237. EM (ES+) m/z: 457; Tiempo de

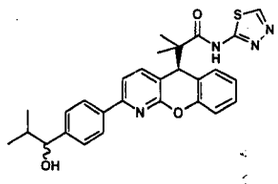
retención CL: 3.44 min.



Etapa 2

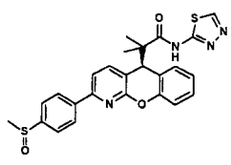
A una solución del producto de la etapa 1 (20 mg, 0.044 mmol) en THF (1 mL) se le agregó bromuro de metilmagnesio (3M en éter de dietilo, 0.04 mL) gota a gota. La mezcla de reacción se agitó a temperatura ambiente durante 1 h, luego se apagó con la adición de metanol, se concentró, y purificó por HPLC preparativa para proporcionar el compuesto del título como una mezcla de diaestereoisómeros co-eluidos (16 mg, Y = 77%). EM (ES+) m/z: 473; Tiempo de retención CL: 3.34 min.

Ejemplo 239



El compuesto del título se obtuvo del producto de la etapa 1 del Ejemplo 239 en la forma descrita para la preparación del compuesto del título del Ejemplo 239. EM (ES+) m/z: 501; Tiempo de retención CL: 3.65 min.

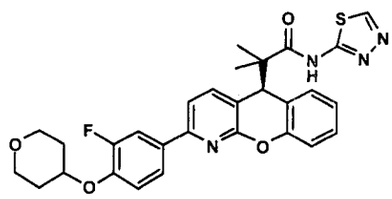
Ejemplo 241



A una solución del compuesto del título del Ejemplo 199 (20 mg,

0.042 mmol) en diclorometano (1 mL) a 0°C se le agregó ácido m-cloroperbenzóico (que contiene ~30% ácido 3-clorobenzóico, 10 mg, 0.042 mmol). Después de 5 min a 0°C, el solvente se removió y se intercambió con metanol. Esta solución se purificó por HPLC preparativa para proporcionar el producto, el cual se liofilizó a partir del acetonitrilo/agua para dar el compuesto del título (10 mg, Y = 39%) como un polvo blanco. EM (ES+) m/z: 491; Tiempo de retención CL: 3.08 min.

Ejemplo 242

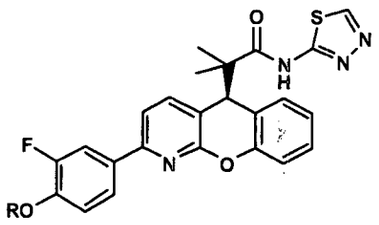


El compuesto del título del Ejemplo 223 (21 mg, 0.045 mmol) se hizo azeotrópico hasta secarse a partir del tolueno, luego se disolvió en THF (0.5 mL). A esta solución se le agregaron secuencialmente tetrahidro-4H-piran-4-ol (0.0065 mL, 0.068 mmol), trifenil fosfina (18 mg, 0.068 mmol), y diisopropildiazodicarboxilato (DIAD) (0.013 mL, 0.068 mmol). La mezcla de reacción se dejó agitar a temperatura ambiente durante 3 h 20 min, luego se concentró y purificó por TLC preparativa (sílice, 0.5 mm, 100 cm x 100 cm, 50% acetato de etilo en hexanos) para dar el compuesto del título (11 mg, Y = 45%) como un polvo blanco. EM (ES+) m/z: 547; Tiempo de retención CL: 3.69 min. ^{1}H RMN (500 MHz, Solvente) δ ppm 1.09 (s, 3 H) 1.17 (s, 3 H) 1.68 - 1.75 (m, 1 H) 1.76 - 1.83 (m, 1 H) 2.04 - 2.20 (m, 2 H) 3.39 - 3.49 (m, 2 H) 3.96 (dd, J=11.68, 3.71 Hz, 1 H) 4.04 (dd, J=11.68, 3.71 Hz, 1 H) 4.48 (s, 1 H) 4.77 - 4.86 (m, 1 H) 7.00 - 7.05 (m,

2 H) 7.14 (d, J=7.15 Hz, 1 H) 7.24 - 7.26 (m, 3 H) 7.29 (d, J=7.70 Hz, 1 H) 7.43 (d, J=8.25 Hz, 1 H) 7.64 - 7.68 (m, 1 H) 7.82 (dd, J=11.96, 2.06 Hz, 1 H) 8.33 (s, 1 H).

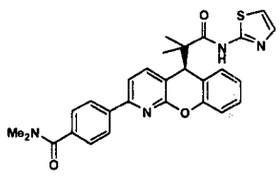
Ejemplos 243 hasta 244

Los siguientes Ejemplos 243 hasta 244 se prepararon en la forma descrita anteriormente para la preparación del compuesto del título del Ejemplo 242.



Ejemplo No.	R	Tr (min)	EM de Iones observado
243	Ciclohexilo	4.20	545
244	ciclopentilo	4.13	531

Ejemplo 245



Etapa 1

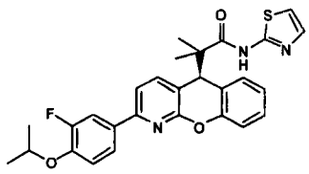
Una corriente de gas de nitrógeno se burbujeó a través de mezcla del compuesto del título de la Preparación 30b (40 mg, 0.13 mmol), ácido 4-(dimetilcarbamoil)fenilborónico (50 mg, 0.26 mmol), fosfato de potasio (2.0 M, 0.36 mL) y tetraquis(trifenilfosfin)paladio(0) (15 mg, 0.014 mmol) durante 10 min. La mezcla se calentó luego a 100°C durante 2 h, luego se filtró a través de un filtro de punta de jeringa (0.45 micrones, PTFE), y

se purificó por HPLC preparativa para dar el producto (245a, ácido (S)-2-(2-(4-(dimetilcarbamoil)fenil)-5H-cromeno[2,3-b]piridina-5-il)-2-metilpropanóico, 43 mg, 79% de rendimiento) como un polvo blanco. EM (ES+) m/z: 417; Tiempo de retención CL: 3.29 min.

Etapa 2

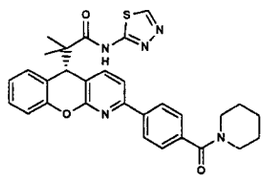
El compuesto del título (245b) se preparó a partir de 245a en una forma similar como se describe anteriormente para la preparación de los Ejemplos 73 hasta 76. EM (ES+) m/z: 499; Tiempo de retención CL: 3.42 min.

Ejemplo 246



El compuesto del título se preparó en la forma descrita anteriormente para la preparación del compuesto del título del Ejemplo 246. EM (ES+) m/z: 504; Tiempo de retención CL: 4.07 min. ^{1}H RMN (400 MHz, CLOROFORMO-D) δ ppm 1.15 (s, 3 H) 1.17 (s, 3 H) 1.38 (d, J=6.10 Hz, 6 H) 4.57 (s, 1 H) 4.58 - 4.66 (m, 1 H) 7.17 (d, J=7.12 Hz, 1 H) 7.26 - 7.32 (m, 2 H) 7.37 (d, J=8.14 Hz, 1 H) 7.40 (d, J=3.56 Hz, 1 H) 7.58 (d, J=8.14 Hz, 1 H) 7.72 (d, J=9.66 Hz, 1 H) 7.77 (dd, J=12.46, 2.29 Hz, 1 H).

Ejemplo 247



Una solución del compuesto del título del Ejemplo 174 (31

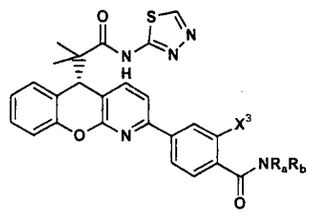
663

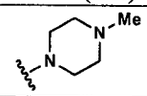
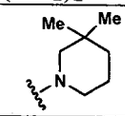
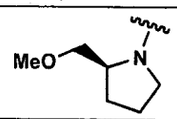
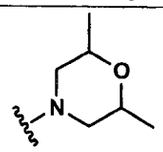
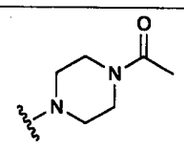
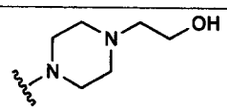
mg, 0.066 mmol), trietilamina (0.028 mL, 0.20 mmol), monohidrato de HOBT (12 mg, 0.086 mmol), EDC (16 mg, 0.086 mmol) y piperidina (0.013 mL, 0.132 mmol) en acetonitrilo (0.5 mL) se calentó durante 12 h a 45°C. La purificación por HPLC preparativa dio el compuesto del título (15 mg, 35%), el cual se liofilizó a partir del acetonitrilo/agua para dar un sólido blanco, amorfo. EM (ES+) m/z: 540; Tiempo de retención CL: 3.57 min.

^{1}H RMN (400 MHz, CLOROFORMO-D) δ ppm 1.24 (s, 3 H) 1.26 (s, 3 H) 1.52 (s, 2 H) 1.68 (s, 4 H) 3.35 (s, 2 H) 3.73 (s, 2 H) 4.71 (s, 1 H) 6.98 - 7.10 (m, 1 H) 7.19 (d, J=7.12 Hz, 1 H) 7.30 (d, J=2.54 Hz, 2 H) 7.49 (t, J=8.39 Hz, 3 H) 7.69 (d, J=7.63 Hz, 1 H) 8.04 (d, J=8.14 Hz, 2 H) 8.88 (s, 1 H).

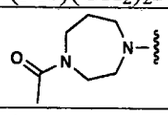
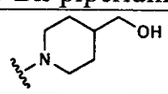
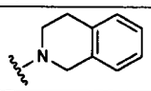
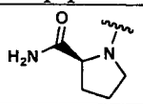
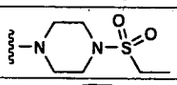
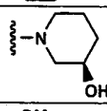
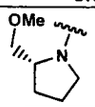
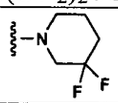
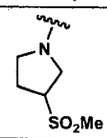
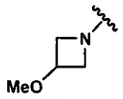
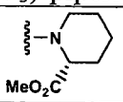
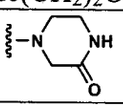
Ejemplos 248 hasta 361

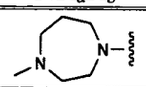
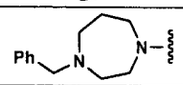
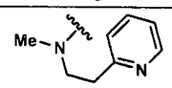
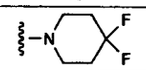
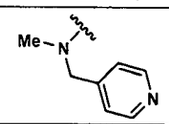
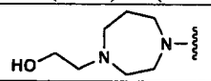
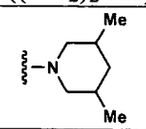
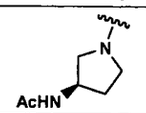
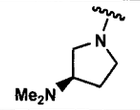
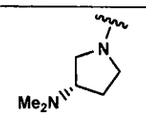
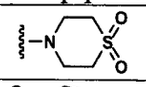
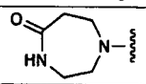
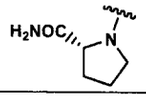
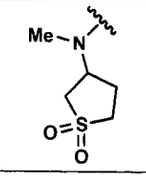
Los siguientes Ejemplos 248 hasta 362 se prepararon a partir de los compuestos del título de los Ejemplos 174 y 213, y las Preparaciones 53 y 54 en una forma similar a aquellas descritas para la preparación del compuesto del título del Ejemplo 247.

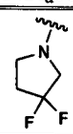
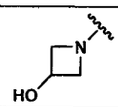
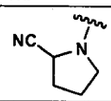
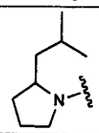
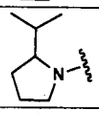
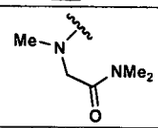
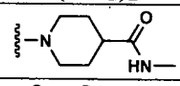
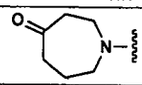
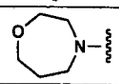
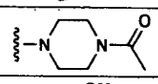
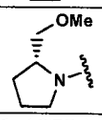
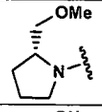
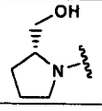


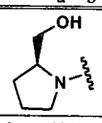
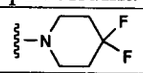
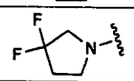
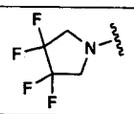
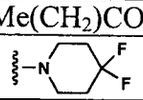
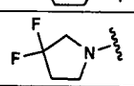
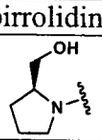
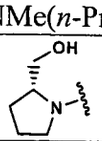
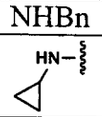
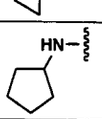
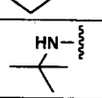
Ejemplo No.	NR_aR_b	X^3	Tr (min)	M/z $(MH)^+$
248	NEt_2	H	3.66	542
249	piperidina	F	3.66	558
250	NMe_2	F	3.30	518
251	NMeEt	H	3.38*	514
252	pirrolidina	H	3.42*	526
253	NHMe	F	3.16	504
254	NMe(*n*-Pr)	H	3.53*	528
255	NMe(Bn)	H	3.73*	576
256		H	2.66*	555
257	morfolina	H	3.21*	542
258	NMe(*i*-Pr)	H	3.50*	528
259	NEt2	F	3.56	546
260	NMe2	Cl	3.41	534
261	piperidina	H	3.57	540
262	NEt_2	Ome	3.51	558
263	NEt_2	Cl	3.67	562
264	Piperidina	Cl	3.58	575
265	Piperidina	Ome	3.58	570
266	Piperidina	F	3.66	558
267	$NMe(CH_2)_2CN$	H	3.08*	539
268	4-Me-piperidina	H	3.73*	554
269	4-OH-piperidina	H	3.11*	556
270	$NMe(CH_2)_2CH(CH_3)_2$	H	3.80*	556
271		H	3.81*	568
272		H	3.49*	570
273		H	3.49*	570
274		H	3.04*	583
275		H	3.30*	584

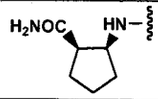
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Ejemplo No.	NR_aR_b	X^3	Tr (min)	M/z $(MH)^+$
276	$N(Me)(CH_2)_2Ph$	H	3.75*	590
277		H	3.05*	597
278	4-Bn-piperidina	H	4.04*	630
279		H	3.19*	570
280		H	3.80*	588
281	4-Ph-piperidina	H	3.92*	616
282		H	3.03*	569
283		H	3.19*	633
284		H	3.17*	556
285		H	3.48*	570
286	$NMe(CH_2)_2SO_2Me$	H	3.03*	592
287		H	3.49*	576
288		H	3.00*	604
289		H	3.30*	542
290	4-(CF_3)-piperidina	H	3.71*	608
291		H	3.59*	598
292	NMe(*n*-Bu)	H	3.67*	542
293	$NMeCH_2CO_2Me$	H	3.22*	558
294	$NMe(CH_2)_2OH$	H	3.02*	530
295	$NMe(CH_2)_2Ome$	H	3.27*	544
296		H	2.91*	555

Ejemplo No.	NR_aR_b	X^3	Tr (min)	M/z $(MH)^+$
297		H	2.56*	569
298		H	2.80*	645
299		H	2.67*	591
300		H	3.53*	576
301		H	2.66*	577
302	$NMe(CH_2)_2O(t\text{-}Bu)$	H	3.70*	586
303		H	2.58*	599
304	$N((CH_2)_2OH)_2$	H	2.90*	560
305		H	3.90*	568
306		H	3.05*	583
307		H	2.58*	569
308		H	2.58*	570
309	4-OMe-piperidina	H	3.39*	570
310		H	2.99*	590
311		H	2.95*	569
312		H	3.03*	569
313		H	3.04*	604

Ejemplo No.	NR_aR_b	X^3	Tr (min)	M/z $(MH)^+$
314		H	3.46*	562
315		H	3.08*	528
316		H	3.23*	551
317		H	3.94*	582
318		H	3.83*	568
319		H	3.03*	571
320	$NEt(CH_2)_2OH$	H	3.16*	544
321		H	3.08*	597
322		H	3.14*	568
323		H	3.23*	556
324		F	3.12	601
325		F	3.58	588
326	$NMe(CH_2)_2CN$	F	3.14	557
327	morfolina	F	3.27	560
328	morfolina	Cl	3.39	576
329	NMe(*i*-Pr)	F	3.57	546
330		Cl	3.70	604
331		H	3.25	556

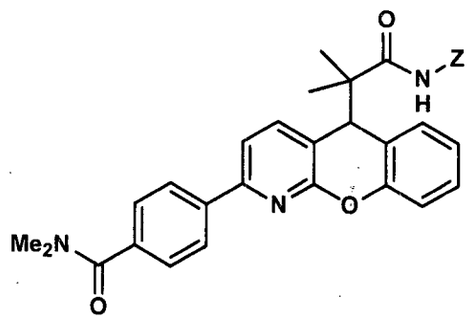
Ejemplo No.	NR_aR_b	X^3	Tr (min)	M/z $(MH)^+$
332		H	3.25	556
333	pirrolidina	F	3.44	544
334		F	3.61	594
335		F	3.51	580
336	NEtMe	F	3.47	532
337		F	3.69	616
338	$NMe(CH_2)CO_2H$	H	3.06	544
339		Cl	3.69	610
340		Cl	3.59	596
341	pirrolidina	Cl	3.57	560
342		F	3.30	574
343	NMe(*n*-Pr)	F	3.60	546
344		F	3.30	574
345	NMeEt	Cl	3.49	548
346	NMe(*n*-Pr)	Cl	3.69	562
347	NMe_2	Ome	3.24	530
348	NHMe	H	3.17	486
349	NHBn	H	XX*	XX
350		H	3.35*	512
351		H	3.43*	540
352		H	3.61*	528
353	NH*i*Pr	H	3.41*	514
354	$NH(CH_2)_2Ph$	H	3.74*	576
355	$NH(CH_2)_2Ome$	H	3.26*	530
356	$NH(CH_2)_2C(CH_3)_3$	H	3.70*	542
357	$NH(CH_2)_2OH$	H	3.06*	516

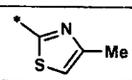
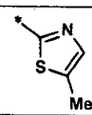
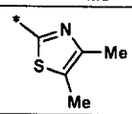
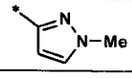
Ejemplo No.	NR_aR_b	X^3	Tr (min)	M/z $(MH)^+$
358	NH(*n*-Pr)	H	3.45*	514
359	$NH(CH_2)_3OH$	H	3.15*	530
360		H	3.36*	583
361	NHMe	OMe	3.30	516

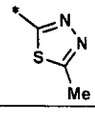
* HPLC analítica Método B

Ejemplos 362 hasta 368

Los siguientes compuestos 362 hasta 368 se prepararon del compuesto del título de la Preparación 57 de la misma forma como se describió para la preparación del compuesto del título de la Preparación 53a.

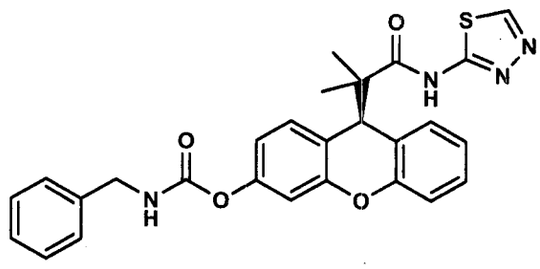


Ejemplo No.	Z	Tr (min)	M/z $(MH)^+$
362	*t*-Bu	2.47*	472
363		2.41*	513
364		2.45*	513
365		2.59*	527
366		1.98*	496

Ejemplo No.	Z	Tr (min)	M/z $(MH)^+$
367	CH_2CF_3	2.29*	498
378		2.07*	514

* HPLC analítica Método B

Ejemplo 369

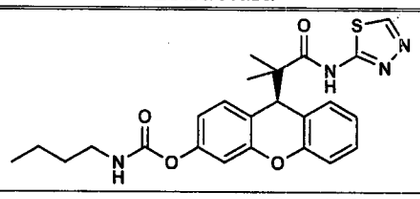
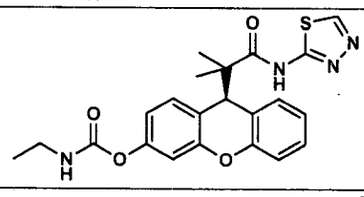
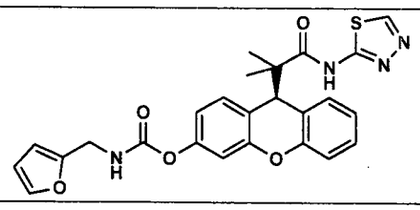


A una solución del producto del Ejemplo 90 (20 mg, 0.054 mmol) en dioxano (1 mL) se le agregó diisopropiletil amina (0.028 mL, 0.163 mmol) y (isocianatometil)benceno (6.8 mL, 0.054 mmol), respectivamente. La mezcla resultante se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se purificó por HPLC preparativa para producir bencilcarbamato de (S)-9-(1-(1,3,4-tiadiazol-2-ilamino)-2-metil-1-oxopropan-2-il)-9H-xanten-3-ilo puro (17 mg, 62% de rendimiento): EM (E+) m/z: 501 $(M+H)^+$; Tiempo de retención CL: 3.54 min.

Ejemplos 370 hasta 372

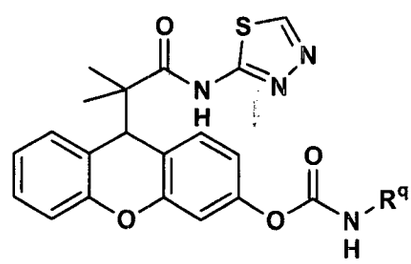
Los siguientes Ejemplos 370 hasta 372 se prepararon en la forma descrita anteriormente para la preparación del compuesto del título del Ejemplo 369.

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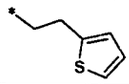
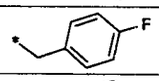
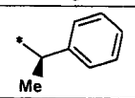
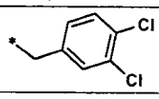
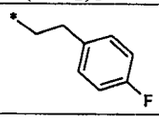
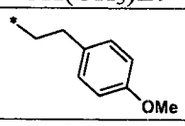
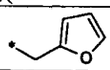
Ejemplo No.	Estructura	Tr (min)	m/z $(M+H)^+$
370		3.61	467
371		3.27	439
372		3.36	491

Ejemplos 373 hasta 393

Los siguientes compuestos 373 hasta 393 se prepararon del producto de la etapa 2 del Ejemplo 101 (101b) en la forma descrita anteriormente para la preparación de los compuestos del título de los Ejemplos 370 hasta 372, usando aminas comercialmente disponibles.

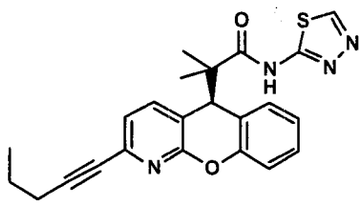


Ejemplo No.	R^q	Tr (min)	M/z $(MH)^+$
373	ciclohexilo	2.69*	493
374	*n*-octilo	3.31*	523
375	$(CH_2)_2Ph$	2.61*	515

Ejemplo No.	R^q	Tr (min)	M/z $(MH)^+$
376		2.59*	521
377		2.55*	519
378		2.63*	515
379		2.87*	569
380	$(CH_2)_3Ph$	2.74*	529
381		2.61*	533
382	*t*-Bu	2.57*	467
383	$CH(CH_3)Et$	2.51*	467
384		2.57*	545
385	Ciclohexilo	3.90	493
386	Me	3.23	425
387	Et	3.26	439
388	*n*-Bu	3.61	467
389	CH_2Ph	3.60	501
390	(*p*-OMe)Ph	3.56	517
391	(*p*-OMe)$PhCH_2$	2.54*	531
392	CH_2(ciclohexilo)	2.92*	507
393		2.36*	491

* HPLC analítica Método B

Ejemplo 394

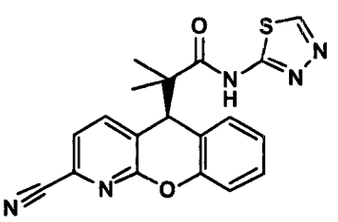


Una mezcla del compuesto del título de la Preparación 53a

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(42 mg, 0.11 mmol), cloruro de bis(trifenilfosfin)-paladio(II) (7.6 mg, 0.011 mmol) e yoduro de cobre (2.1 mg, 0.011 mmol) en diisopropil amina (0.39 mL) y DMF (0.49 mL) se purgó con una corriente de nitrógeno durante 30 min. El 1-pentino (0.012 mL, 0.12 mmol) se agregó luego gota a gota por medio de una jeringa. La mezcla se calentó con agitación bajo nitrógeno a 80°C durante 3 h 20 min, luego se purificó por HPLC preparativa, para dar un aceite el cual se liofilizó a partir del acetonitrilo/agua para dar un sólido blanco opaco (4.4 mg, 10% Y). EM (ES+) m/z: 420 (M+H); Tiempo de retención CL: 3.63 min.

Ejemplo 395

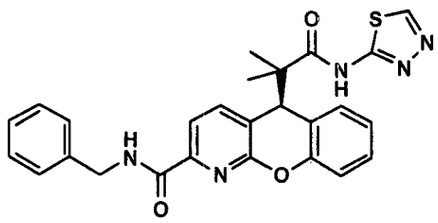


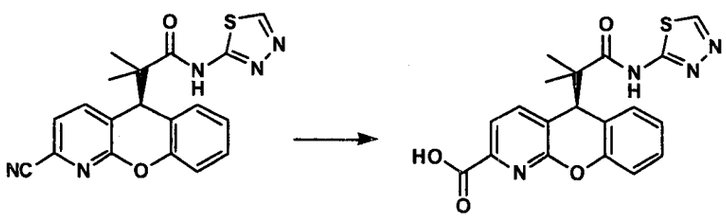
Una corriente de gas de nitrógeno se burbujeó a través de una mezcla del producto de la Preparación 53a (50 mg, 0.13 mmol), Zn $(CN)_2$ (31 mg, 0.26 mmol), y tetraquis(trifenilfosfina)paladio(0) (30 mg, 0.026 mmol) en DMF (1 mL) durante 10 min. La mezcla se calentó a 100°C durante 2.5 h, luego filtró a través de un filtro de punta de jeringa (0.45 micrones, PTFE) y se purificó por HPLC preparativa, dando material el cual contiene óxido de trifenilfosfina residual. El material semipurificado se

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purificó además por cromatografía de columna por desorción súbita (12 g sílice, 60% acetato de etilo en hexanos hasta 70% acetato de etilo en hexanos) para dar el compuesto del título (21 mg, Y = 43%) como un polvo blanco. EM (ES+) m/z: 378 (M+H); Tiempo de retención CL: 2.90 min. ^{1}H RMN (400 MHz, MeOD) δ ppm 1.12 (s, 3 H) 1.15 (s, 3 H) 4.66 (s, 1 H) 7.14 (t, J=7.38 Hz, 1 H) 7.21 - 7.28 (m, 2 H) 7.37 (t, J=8.65 Hz, 1 H) 7.62 (d, J=7.63 Hz, 1 H) 7.83 (d, J=7.63 Hz, 1 H) 9.09 (s, 1 H).

Ejemplo 396



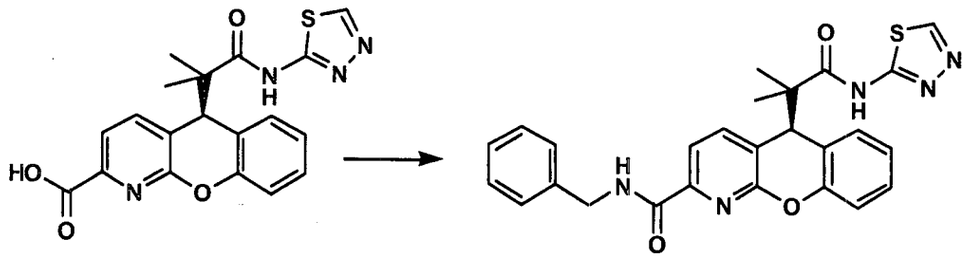


Etapa 1

Una suspensión del compuesto del título del Ejemplo 395 (8 mg, 0.021 mmol) en 1,4-dioxano (0.20 mL) y KOH acuoso (4N, 0.053 mL) se calentó a 80°C durante 4.5 h. La mezcla de reacción se dividió luego entre acetato de etilo y HCl acuoso 1N. La capa orgánica se secó sobre sulfato de sodio y se concentró para dar el producto (398a) como un sólido blanco (7

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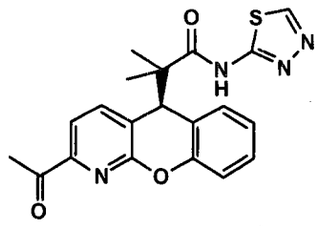
mg, Y = 84%). EM (ES+) m/z: 397 (M+H); Tiempo de retención CL: 2.75 min.



Etapa 2

A una solución del producto de la etapa 1 (396a) (10 mg, 0.025 mmol) en acetonitrilo (1 mL) se le agregó bencilamina (2.70 mg, 0.025 mmol), diisopropiletil amina (0.013 mL, 0.076 mmol) y clorohidrato de 1-(3-(dimetilamino)propil)-3-etil-carbodiimida (7.25 mg, 0.038 mmol) y 1-hidroxibenzotriazol (5.79 mg, 0.038 mmol). La mezcla resultante se calentó a 50°C durante 2h con agitación, luego se purificó por HPLC preparativa para dar el producto deseado, el cual se liofilizó del acetonitrilo/agua para proporcionar el compuesto del título (12.25 mg, Y = 86%) como un sólido blanco. EM (ES+) m/z: 486 (M+H); Tiempo de retención CL: 3.47 min. ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1.16 (d, J = 5.54 Hz, 6 H) 4.51 - 4.66 (m, 2 H) 4.68 (s, 1 H) 6.98 - 7.04 (m, 1 H) 7.11 - 7.34 (m, 8 H) 7.74 (d, J = 7.81 Hz, 1 H) 7.94 (d, J = 7.81 Hz, 1 H) 8.15 (t, J = 6.04 Hz, 1 H) 8.80 (s, 1 H).

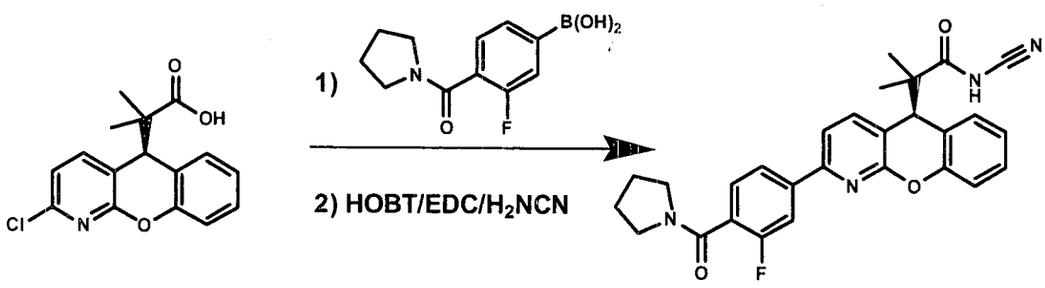
Ejemplo 397



Véase Jean-Yves Legros et al. Tetrahedron, 2001, 57, 2507. A una solución del producto de la primera etapa de la Preparación 53 (53a) (30 mg, 0.078 mmol) en tolueno (1 mL) se le agregó trifenilfosfina (2.03 mg, 0.008 mmol) y $Pd(dba)_2$ (7.10 mg, 0.008 mmol). La mezcla resultante se agitó a temperatura ambiente bajo argón (burbujeo) durante 15 min. El tributil(1-etoxivinil)estanano (28.0 mg, 0.078 mmol) se agregó y la mezcla resultante se agitó a 110°C durante 3 h, luego se enfrió a temperatura ambiente. Tres gotas de HCl 1M se agregaron, y la agitación se continuó durante 10 min a temperatura ambiente. El solvente se removió *in vacuo*, y el residuo se suspendió en metanol, luego se filtró a través de un filtro de punta de jeringa (0.45 micrones, PTFE) y se purificó por HPLC preparativa para proporcionar el producto el cual se liofilizó a partir de acetonitrilo/agua para proporcionar el compuesto del título como una sal de TFA. (22 mg, Y = 72%). EM (ES+) m/z: 395 (M+H); Tiempo de retención CL: 4.60 min. ^{1}H RMN (400 MHz, cloroformo-D) δ ppm 1.16 (s, 6 H) 2.67 (s, 3 H) 4.72 (s, 1 H) 6.97 - 7.03 (m, 1 H) 7.13 - 7.17 (m, 1 H) 7.23 - 7.28 (m, 2 H) 7.73 (s, 2 H) 8.82 (s, 1 H).

- 000682

Ejemplo 398



Etapa 1

Una mezcla del producto de la Preparación 30b (800 mg, 2.6 mmol), ácido 3-fluoro-4-(pirrolidina-1-carbonil)fenilborónico (1.7 g, 7.2 mmol), una solución acuosa 2 M de fosfato de potasio (9 mL, 18 mmol), y DMF (24 mL) se burbujeó con nitrógeno durante 5 min antes de agregar tetraquis(trifenilfosfina)paladio(0) (300 mg, 0.26 mmol). La mezcla se burbujeó con nitrógeno durante 5 minutos adicionales. La mezcla de reacción se agitó a 90°C bajo nitrógeno durante 3 hr antes de concentrarse *in vacuo*. El residuo se mezcló con agua (50 mL), se lavó con mezcla 1:1 acetato de etilo/heptano (30 mL). La mezcla orgánica se extrajo con agua (3 x 15 mL). Las soluciones acuosas combinadas se decoloraron con carbón vegetal activo, se neutralizaron a un pH = 6-7 con solución HCl acuosa 6N (4 mL) y luego solución de ácido cítrico acuoso al 10%. El acetato de etilo (15 mL) se agregó y la mezcla se agitó durante 1 hr. El sólido formado se filtró, se lavó con agua (3 x 2 mL) y acetato de etilo (2 x 1 mL), y se secó para dar el producto (1.1 g, Y = 88 %) como un sólido blanco. EM (E+) m/z: 461 (M+H); Tiempo de retención CL: 3.41 min.

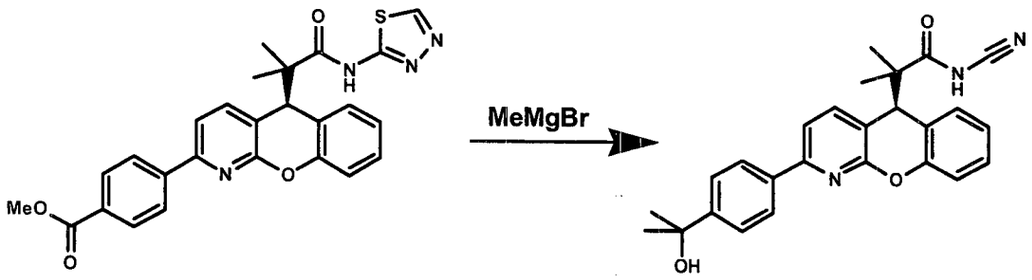
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Etapa 2

A una mezcla agitada del producto de la etapa 1 (398a) (33 mg, 0.072 mmol), hidrato HOBT (22 mg, 0.14 mmol), acetonitrilo anhidro (1 ml), y N,N-diisopropiletilamina (0.13 ml, 0.72 mmol) se le agregó EDC (41 mg, 0.22 mmol) a temperatura ambiente bajo nitrógeno. La mezcla se agitó a temperatura ambiente durante la noche antes de concentrarse. El residuo se dividió entre diclorometano (1 mL) y agua (2 mL). La capa acuosa se separó y se extrajo con cloruro de metileno (2 x 1 mL). Las soluciones orgánicas combinadas se secaron (Na_2SO_4). La cromatografía por desorción súbita en gel de sílice (20=>100% acetato de etilo en hexanos) dio el éster de HOBT, el cual se disolvió en THF (2 mL). La solución obtenida y NaOH acuoso 2 N (0.11 ml, 0.22 mmol) se agregaron gota a gota a una solución (20 mg, 0.48 mmol) de cianamida agitada vigorosamente en agua (2.5 ml) simultáneamente a 0°C. La mezcla de reacción se agitó luego a temperatura ambiente durante 1.5 h y se concentró *in vacuo* para remover el THF. El residuo acuoso se lavó con éter de dietilo (3 mL), se neutralizó con HCl acuoso 6N (0.036 mL), y se extrajo con acetato de etilo (3 x 1 mL). Los extractos de acetato de etilo combinados se secaron (Na_2SO_4) y se concentraron *in vacuo*. La purificación usando HPLC de fase inversa (YMC S5 20 x 100 mm, corrida de 10 min., solvente A: 10% MeOH: 90% H_2O: 0.1% TFA, solvente B: 90% MeOH, 10% H_2O, 0.1% TFA) dio el producto del título (20 mg, Y = 47 %) como una

sal de TFA. EM (E+) m/z: 485 (M+H); Tiempo de retención CL: 3.22 min. ^{1}H RMN (400 MHz, MeOD) δ ppm 7.91 - 8.01 (m, 2 H) 7.79 - 7.86 (m, 2 H) 7.54 (t, J=7.43 Hz, 1 H) 7.41 (td, J=7.70, 1.50 Hz, 1 H) 7.26 - 7.33 (m, 2 H) 7.23 (td, J=7.37, 1.13 Hz, 1 H) 4.46 (s, 1 H) 3.63 (t, J=6.92 Hz, 2 H) 3.39 (t, J=6.55 Hz, 2 H) 1.99 - 2.06 (m, 2 H) 1.91 - 1.98 (m, 2 H) 1.06 (s, 3 H) 1.04 (s, 3 H).

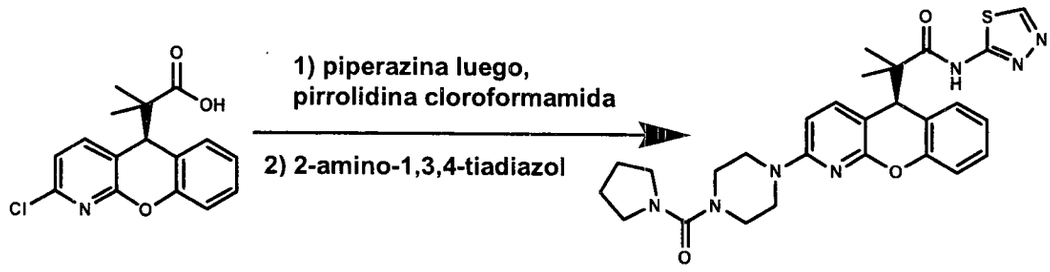
Ejemplo 399



A una solución transparente del compuesto del título del Ejemplo 192 (sal de TFA, 13 mg, 0.022 mmol) en THF anhidro (1 mL) se agregó una solución de bromuro de metilmagnesio (3 M en éter de dietilo, 0.25 mL, 0.75 mmol) gota a gota a -78°C bajo nitrógeno. La mezcla se agitó a la misma temperatura por 20 min antes de que el acetato de etilo (0.2 mL) se agregue para apagar la reacción a -78°C. Después de que la mezcla de reacción se agitó a temperatura ambiente durante 10 min, se agregó ácido acético (0.06 mL). La concentración *in vacuo* y purificación utilizando HPLC de fase inversa (YMC S5 20 x 100 mm, corrida de 10 min., solvente A: 10% MeOH: 90% H2O: 0.1% TFA, solvente B: 90% MeOH, 10% H2O, 0.1% TFA) dio el compuesto

del título (sal de TFA, 4.5 mg, Y = 32%) como un sólido blanco. EM (E+) m/z: 428 (M+H); Tiempo de retención CL: 3.18 min. 1H RMN (400 MHz, MeOD) δ ppm 8.00 (dt, J=8.60, 2.00 Hz, 2 H) 7.80 (d, J=8.00 Hz, 1 H) 7.73 (d, J=8.00 Hz, 1 H) 7.62 (dt, J=8.60, 2.00 Hz, 2 H) 7.38 - 7.43 (m, 1 H) 7.28 - 7.33 (m, 2 H) 7.22 (td, J=7.40, 1.20 Hz, 1 H) 4.44 (s, 1 H) 1.58 (s, 6 H) 1.06 (s, 3 H) 1.05 (s, 3 H).

Ejemplo 400



Etapa 1

Una mezcla del producto de la Preparación 30b (14 mg, 0.046 mmol) y piperazina (140 mg, 1.6 mmol) en un tubo sellado se calentó a 150°C bajo nitrógeno durante 30 min. La mayoría de la piperidina se removió luego a 160°C haciendo pasar una corriente de nitrógeno a través de la mezcla para obtener un sólido, el cual se disolvió en diclorometano anhidro (1 mL). El cloruro de 1-pirrolidincarbonilo (0.1 mL, 0.9 mmol) se agregó gota a gota, seguido por N,N-diisopropiletilamina (0.25 mL). La mezcla se agitó a temperatura ambiente durante 2 h, se apagó con solución de hidróxido de sodio acuoso (1 M, 1 mL), se concentró *in vacuo*, y purificó usando HPLC de fase inversa (YMC

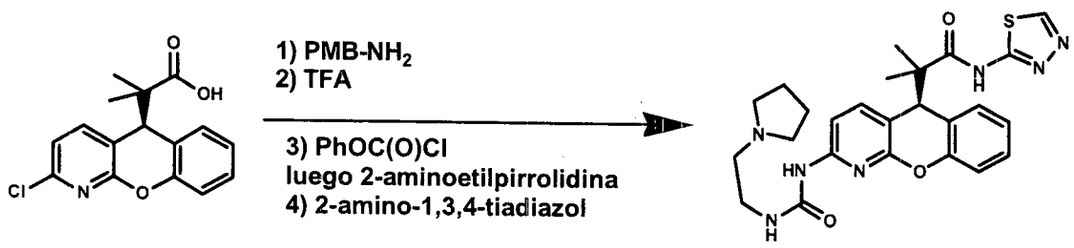
- 001636

S5 20 x 100 mm, corrida de 10 min., solvente A: 10% MeOH: 90% H_2O: 0.1% TFA, solvente B: 90% MeOH, 10% H_2O, 0.1% TFA) dio el producto (sal de TFA, 20 mg, Y = 77%) como un sólido blanco. EM (E+) m/z: 451 (M+H); Tiempo de retención CL: 3.32 min.

Etapa 2

Una mezcla del producto de la etapa 1 (400a) (20 mg, 0.052 mmol), 2-amino-1,3,4-tiadiazol (18 mg, 0.18 mmol), hidrato de HOBT (14 mg, 0.09 mmol), diisopropiletilamina (0.093 mL, 0.53 mmol), y EDC (27 mg, 0.14 mmol) en acetonitrilo anhidro (1.0 mL) se calentó durante 3 h a 80°C. Las purificación usando HPLC de fase inversa (YMC S5 20 x 100 mm, corrida de 10 min., solvente A: 10% MeOH: 90% H_2O: 0.1% TFA, solvente B: 90% MeOH, 10% H_2O, 0.1% TFA) dio el producto del título (sal de TFA, 12 mg, Y = 50%) como un sólido blanco. EM (E+) m/z: 534 (M+H); Tiempo de retención CL: 3.26 min. ^{1}H RMN (400 MHz, MeOD) δ ppm 9.09 (s, 1 H) 7.38 (d, J=8.56 Hz, 1 H) 7.27 - 7.33 (m, 1 H) 7.16 (dd, J=8.18, 1.13 Hz, 2 H) 7.04 (td, J=7.50, 1.30 Hz, 1 H) 6.52 (d, J=8.56 Hz, 1 H) 4.43 (s, 1 H) 3.54 - 3.59 (m, 4 H) 3.38 - 3.44 (m, 8 H) 1.85 - 1.90 (m, 4 H) 1.12 (s, 3 H) 1.10 (s, 3 H).

EJEMPLO 401



- 037637

Etapa 1

Una mezcla del producto de la Preparación 30b (50 mg, 0.17 mmol) y (4-metoxifenil)metanamina (0.4 mL) se agitó a 150°C bajo nitrógeno durante 26 hr. La mezcla se concentró *in vacuo*, y purificó por HPLC preparativa. El producto (60 mg, Y = 62%) se obtuvo como un sólido, sal de TFA. EM (E+) m/z: 405 (M+H); Tiempo de retención CL: 3.34 min.

Etapa 2

Una mezcla del producto de la etapa 1 (23 mg, 0.044 mmol), diclorometano (0.5 mL), y TFA (0.5 mL) se agitó a temperatura ambiente durante 3 hr antes de la concentración *in vacuo*. El residuo se mezcló con acetato de etilo (0.5 mL) y solución de bicarbonato de sodio acuoso saturado (0.5 mL). El carbonato de potasio sólido se agregó para hacer la mezcla básica. La solución acuosa se separó, se neutralizó con solución de ácido cítrico acuoso al 10%, y se extrajo con acetato de etilo (3 x 0.5 mL). Los extractos de acetato de etilo combinados se secaron (Na_2SO_4) y se concentraron para dar un aceite. EM (E+) m/z: 285 (M+H); Tiempo de retención CL: 2.21 min.

Etapa 3

El producto anterior de la Etapa 2 se mezcló con piridina (0.08 mL, 1 mmol) y diclorometano anhidro (0.5 mL). Se agregó cloroformoato de fenilo (0.03 mL, 0.24 mmol) a 0°C bajo nitrógeno. La mezcla se agitó a 0°C durante 40 min antes de agregar la 1-(2-aminoetil)pirrolidina (0.15 mL, 1.2 mmol). La mezcla de reacción se calentó hasta 100°C (el diclorometano se

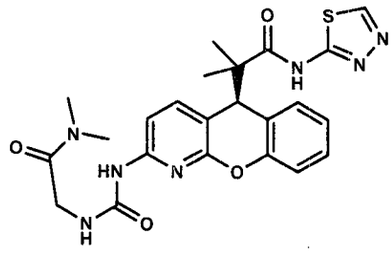
destiló completamente durante el calentamiento), se agitó a 100°C durante 40 min, y luego se concentró *in vacuo*. La purificación usando HPLC de fase inversa (YMC S5 20 x 100 mm, corrida de 10 min., solvente A: 10% MeOH: 90% H2O: 0.1% TFA, solvente B: 90% MeOH, 10% H2O, 0.1% TFA) dio un sólido (sal de 2TFA, 17 mg, Y = 59% para las etapas 2 + 3). EM (E+) m/z: 425 (M+H); Tiempo de retención CL: 2.29 min.

Etapa 4

Una mezcla del producto de la etapa 3 (16 mg, 0.025 mmol), 2-amino-1,3,4-tiadiazol (15 mg, 0.15 mmol), hidrato de HOBT (13 mg, 0.086 mmol), piridina (0.12 mL, 1.5 mmol), y EDC (24 mg, 0.12 mmol) en acetonitrilo (1.0 mL) se calentó durante 6 h a 80 °C. La concentración *in vacuo* y purificación usando HPLC de fase inversa (YMC S5 20 x 100 mm, corrida de 10 min., solvente A: 10% MeOH: 90% H_2O: 0.1% TFA, solvente B: 90% MeOH, 10% H_2O, 0.1% TFA) dio el producto del título, el cual se liofilizó para dar un sólido blanco (7 mg, Y = 37%) como una sal de 2 TFA. EM (E+) m/z: 508 (M+H); Tiempo de retención CL: 2.30 min. ^{1}H RMN (400 MHz, MeOD) δ ppm 9.09 (s, 1 H) 7.54 (d, J=8.31 Hz, 1 H) 7.32 - 7.37 (m, 1 H) 7.17 - 7.24 (m, 2 H) 7.11 (td, J=7.40, 1.40 Hz, 1 H) 6.83 (d, J=8.31 Hz, 1 H) 4.51 (s, 1 H) 3.77 - 3.86 (m, 2 H) 3.74 (t, J=5.54 Hz, 2 H) 3.44 (t, J=5.79 Hz, 2 H) 3.12 - 3.21 (m, 2 H) 2.18 (s amp., 2 H) 1.99 - 2.09 (m, 2 H) 1.15 (s, 3 H) 1.07 - 1.12 (m, 3 H).

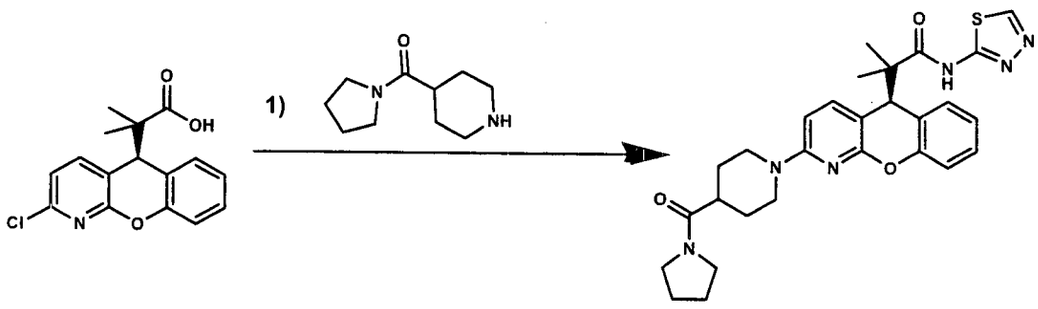
001663

Ejemplo 402



El compuesto del título se preparó de la misma forma como se describió para la preparación del compuesto del título del Ejemplo 401. EM (E+) m/z: 496 (M+H); Tiempo de retención CL: 2.76 min. ^{1}H RMN (400 MHz, MeOD) δ ppm 9.09 (s, 1 H) 7.49 (d, J=8.31 Hz, 1 H) 7.30 - 7.36 (m, 1 H) 7.17 - 7.26 (m, 2 H) 7.05 - 7.10 (m, 1 H) 6.88 (d, J=8.06 Hz, 1 H) 4.48 (s, 1 H) 4.24 (s, 2 H) 3.10 (s, 3 H) 3.01 (s, 3 H) 1.15 (s, 3 H) 1.12 (s, 3 H).

Ejemplo 403



Etapa 1

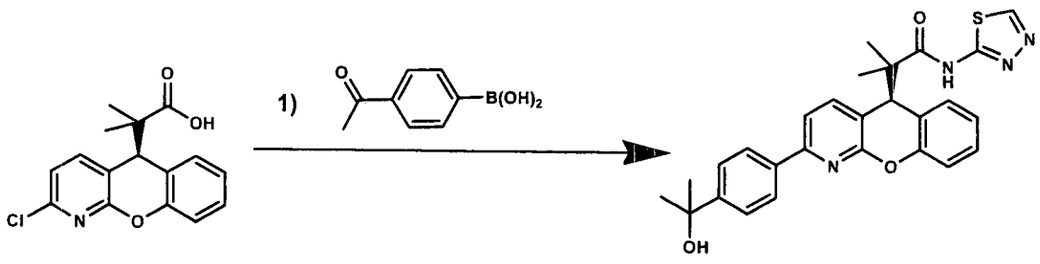
Una mezcla del producto de la Preparación 30b (14 mg, 0.046 mmol), piperidin-4-il(pirrolidin-1-il)metanona (95 mg, 0.521 mmol), y DMA anhidro (0.1 mL) se agitó a 150°C bajo nitrógeno durante 3 hr. La purificación usando la HPLC de fase

inversa (YMC S5 20 x 100 mm, corrida de 10 min., solvente A: 10% MeOH: 90% H_2O: 0.1% TFA, solvente B: 90% MeOH, 10% H_2O, 0.1% TFA) dio el producto (sal de TFA, 22 mg, Y = 85%) como un sólido. EM (E+) m/z: 450 (M+H); Tiempo de retención CL: 3.16 min.

Etapa 2

La etapa se completó de la misma forma como se describió en el Ejemplo 400, Etapa 2 para obtener el compuesto del título como un sólido blanco, una sal de TFA. EM (ES+) m/z: 533 (M+H); Tiempo de retención CL: 3.15 min. ^{1}H RMN (400 MHz, MeOD) δ ppm 9.09 (s, 1 H) 7.37 (d, J=8.31 Hz, 1 H) 7.27 - 7.32 (m, 1 H) 7.13 - 7.19 (m, 2 H) 7.03 (td, J=7.40, 1.20 Hz, 1 H) 6.53 (d, J=8.56 Hz, 1 H) 4.42 (s, 1 H) 4.35 (d, J=13.35 Hz, 2 H) 3.62 (t, J=6.80 Hz, 2 H) 3.41 (t, J=6.92 Hz, 2 H) 2.93 (t, J=12.72 Hz, 2 H) 2.75 - 2.84 (m, 1 H) 1.96 - 2.04 (m, 2 H) 1.85 - 1.94 (m, 2 H) 1.66 - 1.84 (m, 4 H) 1.12 (s amp., 3 H) 1.11 (s amp., 3 H).

Ejemplo 404



006691

Etapa 1

Una mezcla del producto de la Preparación 30b (45 mg, 0.15 mmol), ácido 4-acetilfenilborónico (73 mg, 0.44 mmol), solución 2 M acuoso de fosfato de potasio (0.52 mL, 1.0 mmol), y DMF (1 mL) se burbujeó con nitrógeno durante 5 min antes de agregar tetraquis(trifenilfosfina)paladio(0) (13 mg, 0.011 mmol). La mezcla se burbujeó con nitrógeno durante 5 min adicionales. Después que se agitó a 90°C bajo nitrógeno durante 1.5 h, la mezcla se dividió entre una solución de bicarbonato de sodio acuoso saturado (3 mL) y éter de dietilo (4 mL). La fase acuosa se separó, se acidificó a un pH = 6, y se extrajo con acetato de etilo (3 x 2 mL). Los extractos de acetato de etilo combinados se secaron (Na_2SO_4) y se concentraron *in vacuo* para dar la mezcla del producto como un líquido.

Etapa 2

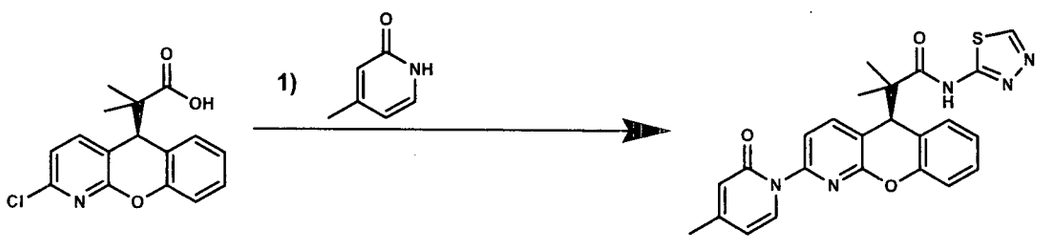
La mezcla del producto de la Etapa 1 se disolvió en THF anhidro (2 mL) y se trató con solución de bromuro de metil magnesio (3 M en éter de dietilo, 0.49 mL, 1.5 mmol) a -78°C bajo nitrógeno. Después que la mezcla se agitó a temperatura ambiente durante 30 min, 10% de solución de ácido cítrico se agregó para hacer pH = 6. La mezcla se extrajo con acetato de etilo (3 x 1 mL). Los extractos de acetato de etilo combinados se secaron (Na_2SO_4) y se concentraron *in vacuo*. La purificación usando HPLC de fase inversa (YMC S5 20 x 100 mm,

corrida 10 min., solvente A: 10% MeOH: 90% H_2O: 0.1% TFA, solvente B: 90% MeOH, 10% H_2O, 0.1% TFA) dio el producto (sal de TFA, 34 mg, Y = 44% por etapas 1 + 2) como un sólido blanco. EM (ES+) m/z: 404 (M+H); Tiempo de retención CL: 3.33 min.

Etapa 3

Una mezcla del producto de la etapa 2 (18 mg, 0.045 mmol), 2-amino-1,3,4-tiadiazol (23 mg, 0.22 mmol), hidrato HOBT (17 mg, 0.11 mmol), diisopropiletilamina (0.12 mL, 0.67 mmol), y EDC (34 mg, 0.18 mmol) en acetonitrilo anhidro (1.0 mL) se agitó a 80 °C durante 1 h y a temperatura ambiente durante la noche. La mezcla se concentró *in vacuo*. El residuo se mezcló con acetato de etilo (2 mL), se lavó con agua (1 mL) y solución de bicarbonato de sodio acuoso saturada (2 x 1 mL), se secó sobre sulfato de sodio, y se concentró *in vacuo*. La purificación usando TLC prep dio el producto (12 mg, Y = 47%) como un sólido. EM (ES+) m/z: 487 (M+H); Tiempo de retención CL: 3.34 min. ^{1}H RMN (400 MHz, CLOROFORMO-d) δ ppm 8.91 (s, 1 H) 8.01 (d, J=8.31 Hz, 2 H) 7.74 (d, J=7.81 Hz, 1 H) 7.58 (d, J=8.56 Hz, 2 H) 7.50 (d, J=7.81 Hz, 1 H) 7.27 - 7.36 (m, 2 H) 7.24 (d, J=7.30 Hz, 1 H) 7.01 - 7.08 (m, 1 H) 4.82 (s, 1 H) 1.62 (s, 6 H) 1.30 (s, 3 H) 1.26 (s, 3 H).

Ejemplo 405



Etapa 1

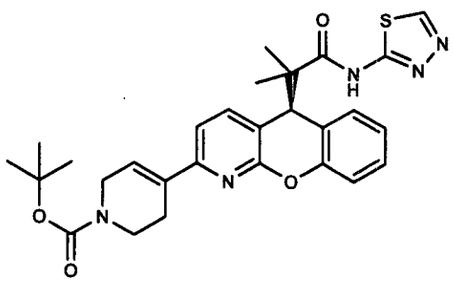
A una mezcla del producto de la Preparación 30b (15 mg, 0.049 mmol), 4-metilpiridin-2(1H)-ona (11 mg, 0.099 mmol), yoduro de cobre (I) (4.7 mg, 0.025 mmol), y carbonato de potasio (20 mg, 0.15 mmol) se agregó una solución de N,N'-dimetilciclohexano-1,2-diamina (11 mg, 0.077 mmol) en DMA anhidro (0.2 mL) bajo nitrógeno. La mezcla se agitó a 120°C durante 6 h y a 60°C durante la noche. La purificación usando HPLC de fase inversa (YMC S5 20 x 100 mm, corrida de 10 min., solvente A: 10% MeOH: 90% H_2O: 0.1% TFA, solvente B: 90% MeOH, 10% H_2O, 0.1% TFA) y neutralización dio el producto (7 mg, Y = 40%) como un sólido. EM (ES+) m/z: 377 (M+H); Tiempo de retención CL: 2.94 min.

Etapa 2

La etapa se completó de la misma forma como se describió en el Ejemplo 400, etapa 2 para obtener el producto como un sólido, una sal de TFA. EM (ES+) m/z: 460 (M+H); Tiempo de retención CL: 2.88 min. ^1H RMN

(400 MHz, MeOD) δ ppm 9.09 (s, 1 H) 7.85 (d, J=8.06 Hz, 1 H) 7.80 (d, J=7.05 Hz, 1 H) 7.52 (d, J=7.81 Hz, 1 H) 7.36 (t, J=7.68 Hz, 1 H) 7.24 (s amp., 1 H) 7.22 (s amp., 1 H) 7.11 (t, J=7.30 Hz, 1 H) 6.45 (s amp., 1 H) 6.40 (d, J=7.05 Hz, 1 H) 4.67 (s, 1 H) 2.30 (s, 3 H) 1.20 (s, 3 H) 1.17 (s, 3 H).

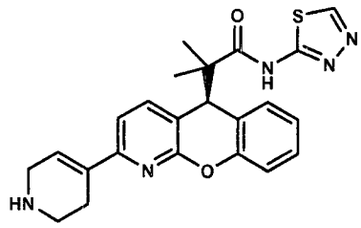
Ejemplo 406



El compuesto del título se preparó a partir del isómero S de la Preparación 30 (30b) en la forma descrita para la preparación del compuesto del título del Ejemplo 162, usando éster de pinacol del ácido (N-terc-butoxicarbonil)-1,2,3,6-tetrahidropiridina-4-borónico comercialmente disponible. EM (ES+) m/z: 534 (M+H); Tiempo de retención CL: 3.67 min. ^{1}H RMN (400 MHz, CLOROFORMO-d) δ ppm 12.14 (s amp., 1 H) 8.93 (s, 1 H) 7.71 (d, J=7.81 Hz, 1 H) 7.24 - 7.30 (m, 3 H) 7.12 (d, J=7.81 Hz, 1 H) 6.99 - 7.06 (m, 1 H) 6.72 (s amp., 1 H) 4.89 (s, 1 H) 4.14 (s amp., 2 H) 3.58 - 3.69 (m, 2 H) 2.63 (s amp., 2 H) 1.49 (s, 9 H) 1.28 (s, 3 H) 1.26 (s, 3 H).

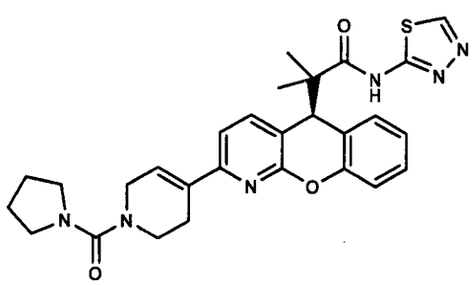
800695

Ejemplo 407



El compuesto del título del Ejemplo 406 (57 mg, 0.11 mmol) se mezcló con diclorometano (6 mL) y TFA (3 mL). La mezcla se agitó a temperatura ambiente durante 1 h antes que se concentre *in vacuo*. La purificación usando HPLC de fase inversa (YMC S5 20 x 100 mm, corrida de 10 min., solvente A: 10% MeOH: 90% H_2O: 0.1% TFA, solvente B: 90% MeOH, 10% H_2O, 0.1% TFA) dio el compuesto del título (sal de 2 TFA, 47 mg, Y = 67%) como un sólido blanco. EM (ES+) m/z: 434 (M+H); Tiempo de retención CL: 2.19 min. ^{1}H RMN (400 MHz, MeOD) δ ppm 9.10 (s, 1 H) 7.65 (d, J=7.81 Hz, 1 H) 7.35 (d, J=7.81 Hz, 2 H) 7.23 (td, J=7.93, 1.26 Hz, 2 H) 7.08 - 7.14 (m, 1 H) 6.69 - 6.74 (m, 1 H) 4.60 (s, 1 H) 3.88 - 3.94 (m, 2 H) 3.47 (t, J=6.17 Hz, 2 H) 2.84 - 2.94 (m, 2 H) 1.17 (s, 3 H) 1.10 (s, 3 H).

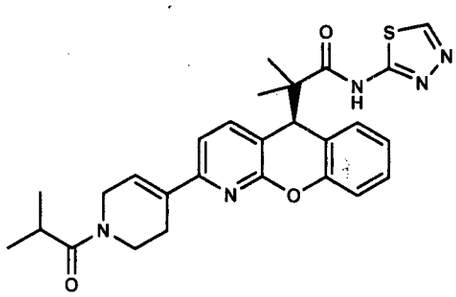
Ejemplo 408



MX 696

A una solución agitada del compuesto del título del Ejemplo 407 (14 mg, 0.021 mmol) y N,N-diisopropiletilamina (0.1 mL) en THF anhidro (1 mL) se agregó cloruro de 1-pirrolidinacarbonilo (0.01 mL, 0.09 mmol) bajo nitrógeno. La mezcla se agitó a temperatura ambiente durante 45 min antes de agregarse agua (0.1 mL) y metanol (1 mL) para apagar la reacción. La mezcla se concentró *in vacuo*. La purificación usando HPLC de fase inversa (YMC S5 20 x 100 mm, corrida de 10 min., solvente A: 10% MeOH: 90% H_2O: 0.1% TFA, solvente B: 90% MeOH, 10% H_2O, 0.1% TFA) dio el compuesto del título (sal de TFA, 10 mg, Y = 73%) como un sólido. EM (ES+) m/z: 531 (M+H); Tiempo de retención CL: 3.36 min. ^{1}H RMN (400 MHz, MeOD) δ ppm 9.09 (s, 1 H) 7.61 (d, J=7.81 Hz, 1 H) 7.31 - 7.37 (m, 1 H) 7.19 - 7.29 (m, 3 H) 7.06 - 7.11 (m, 1 H) 6.69 (s amp., 1 H) 4.57 (s, 1 H) 4.01 - 4.05 (m, 2 H) 3.53 (t, J=5.54 Hz, 2 H) 3.39 - 3.45 (m, 4 H) 2.66 (s amp., 2 H) 1.85 - 1.91 (m, 4 H) 1.15 (s, 3 H) 1.12 (s, 3 H).

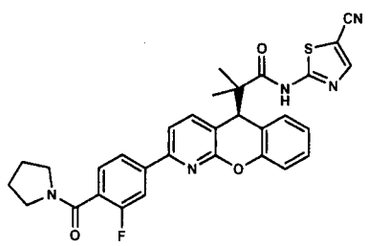
Ejemplo 409



A una solución agitada de hidrato de HOBT (20 mg, 0.13 mmol), y N,N-diisopropiletilamina (0.10 mL, 0.57 mmol) en acetonitrilo anhidro (1

mL) se agregó cloruro de isobutirilo (0.010 mL, 0.095 mmol) bajo nitrógeno. La mezcla se agitó a temperatura ambiente durante 10 min antes de agregar el compuesto del título del Ejemplo 10 (11 mg, 0.017 mmol). Después que la mezcla se agitó a temperatura ambiente durante 2 h, se agregó agua (0.1 mL) para apagar la reacción. La mezcla se concentró *in vacuo*. La purificación usando HPLC de fase inversa (YMC S5 20 x 100 mm, corrida de 10 min., solvente A: 10% MeOH: 90% H_2O: 0.1% TFA, solvente B: 90% MeOH, 10% H_2O, 0.1% TFA) dio el compuesto del título (sal de TFA, 7.6 mg, Y = 74%) como un sólido blanco. EM (ES+) m/z: 504 (M+H); Tiempo de retención CL: 3.32 min. ^{1}H RMN (400 MHz, MeOD) δ ppm 9.09 (s, 1 H) 7.61 (d, J=7.81 Hz, 1 H) 7.26 - 7.37 (m, 2 H) 7.22 (dt, J=7.81, 2.27 Hz, 2 H) 7.06 - 7.12 (m, 1 H) 6.69 (s amp., 1 H) 4.57 (s, 1 H) 4.34 (s amp., 1 H) 4.25 (s amp., 1 H) 3.81 (t, J=5.67 Hz, 2 H) 2.94 - 3.08 (m, 1 H) 2.72 (s amp., 1 H) 2.61 (s amp., 1 H) 1.11 - 1.16 (m, 12 H).

Ejemplo 410

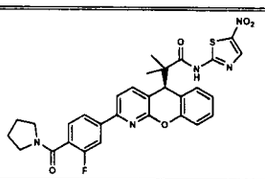
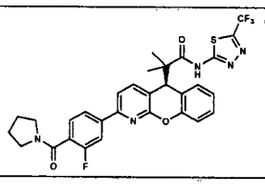
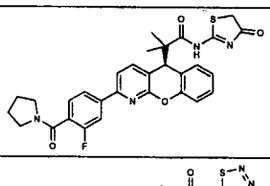
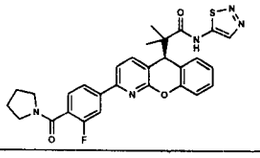


El producto de la etapa 1 del Ejemplo 398 (398a) (12 mg, 0.026 mmol) se mezcló con DMF (0.2 mL), N,N-diisopropiletilamina (0.050 mL, 0.29 mmol), HATU (30 mg, 0.078 mmol), y 2-amino-5-cianotiazol (16 mg, 0.13 mmol). La mezcla de reacción se agitó a 80°C durante 6 hr. La purificación usando HPLC de fase inversa

(YMC S5 20 x 100 mm, corrida de 10 min., solvente A: 10% MeOH: 90% H_2O: 0.1% TFA, solvente B: 90% MeOH, 10% H_2O, 0.1% TFA) dio el compuesto del título (sal de TFA, 5.7 mg, Y = 25%) como un sólido amarillo. EM (ES+) m/z: 568 (M+H); Tiempo de retención CL: 3.66 min. ^{1}H RMN (400 MHz, MeOD) δ ppm 8.15 (s, 1 H) 7.91 - 7.98 (m, 2 H) 7.73 (d, J=2.77 Hz, 2 H) 7.53 (t, J=7.43 Hz, 1 H) 7.35 - 7.41 (m, 1 H) 7.21 - 7.30 (m, 2 H) 7.10 - 7.16 (m, 1 H) 4.62 (s, 1 H) 3.63 (t, J=6.92 Hz, 2 H) 3.36 - 3.42 (m, 2 H) 1.91 - 2.06 (m, 4 H) 1.18 (s, 3 H) 1.15 (s, 3 H).

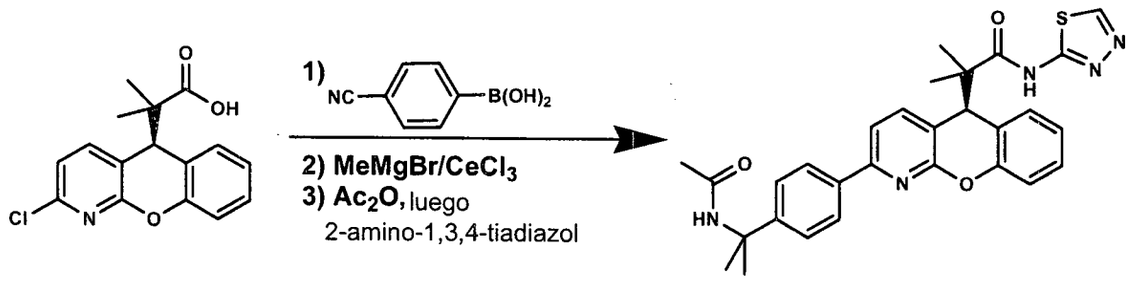
Ejemplos 411 hasta 414

Los siguientes Ejemplos 411 hasta 414 se prepararon de la misma forma como se describió para la preparación del compuesto del título del Ejemplo 410.

No de Ejemplo.	Estructura	Tr (min)	M/z $(MH)^+$
411		3.78	588
412		3.88	612
413		3.38	559
414		3.49	544

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Ejemplo 415



Etapa 1

Una mezcla del producto de la Preparación 30b (183 mg, 0.60 mmol), ácido 4-cianofenilborónico (240 mg, 1.6 mmol), solución 2 M de fosfato de potasio acuosa (2.1 mL, 4.2 mmol), y DMF (6 mL) se burbujeó con nitrógeno durante 5 min antes de agregar tetraquis(trifenilfosfina)paladio(0) (70 mg, 0.060 mmol). Después de burbujear con nitrógeno durante 5 min adicionales, la mezcla de reacción se agitó a 90°C bajo nitrógeno durante 4 h. La mezcla se concentró *in vacuo*, se mezcló con agua (5 mL), se neutralizó con solución HCl 6N acuosa, y se extrajo con acetato de etilo (3 x 2 mL). Los extractos de acetato de etilo combinados se secaron (Na_2SO_4) y se concentraron *in vacuo*. La purificación usando HPLC de fase inversa (YMC S5 20 x 100 mm, corrida de 10 min., solvente A: 10% MeOH: 90% H_2O: 0.1% TFA, solvente B: 90% MeOH, 10% H_2O, 0.1% TFA) dio el producto (195 mg, Y = 87%) como un sólido. EM (ES+) m/z: 371 (M+H); Tiempo de retención CL: 3.41 min.

Etapa 2

A un cloruro de cerio (III) agitado (340 mg, 1.4 mmol) en

un matraz seco se agregó THF anhidro (6 mL) bajo nitrógeno. La mezcla se agitó a temperatura ambiente durante 40 min antes de agregar metil-litio (0.85 mL, 1.4 mmol) gota a gota a -78°C bajo nitrógeno. Después que la mezcla se agitó a -78°C durante 40 min, se agregó el producto de la etapa 1 (93 mg, 0.25 mmol). La mezcla de reacción se agitó a -78°C durante 40 min y a temperatura ambiente durante 2 hr antes de agregar agua (3 mL). La capa acuosa se neutralizó con 10% ácido cítrico acuoso a un pH = 8, se extrajo con acetato de etilo (2 x 2 mL), y luego se neutralizó con 10% de ácido cítrico acuoso a un pH = 6, se extrajo con acetato de etilo (2 x 2 mL). Las soluciones orgánicas combinadas se secaron (Na_2SO_4) y se concentraron bajo presión reducida. El residuo se disolvió en metanol (1.8 mL) y ácido trifluoroacético (0.2 mL). La purificación usando HPLC de fase inversa (YMC S5 20 x 100 mm, corrida de 10 min., solvente A: 10% MeOH: 90% H_2O: 0.1% TFA, solvente B: 90% MeOH, 10% H_2O, 0.1% TFA) dio el producto (sal de TFA, 18 mg, Y = 14%) como un sólido amarillo. (ES+) m/z: 403 (M+H); Tiempo de retención CL: 2.46 min.

Etapa 3

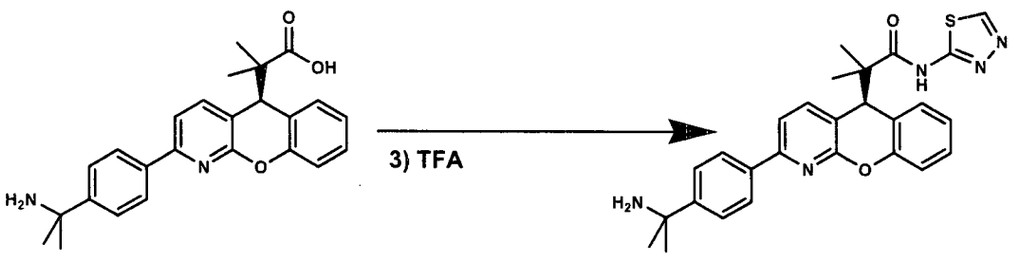
A una solución transparente del producto de la etapa 2 (8.0 mg, 0.015 mmol) y N,N-diisopropiletilamina (0.10 mL, 0.57 mmol) en diclorometano anhidro (1 mL) se agregó anhidruro acético (10 µL, 0.11 mmol) bajo nitrógeno. La mezcla de reacción se agitó a temperatura

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ambiente durante 1 hr y se concentró *in vacuo*. El residuo se mezcló con MeCN anhidro (1 mL), HOBT (40 mg, 0.26 mmol), 2-Amino-1,3,4-tiadiazol (60 mg, 0.59 mmol), EDC (100 mg, 0.52 mmol), y N,N-diisopropiletilamina (0.20 mL, 1.1 mmol). Después se agitó a 80°C bajo nitrógeno durante 2 hr, la mezcla se concentró, se mezcló con solución de bicarbonato de sodio acuoso saturado (5 mL), y se extrajo con diclorometano (3 x 1 mL). Los extractos de cloruro de metileno combinados se secaron (Na_2SO_4). La purificación por cromatografía por desorción súbita (0% hasta 100% acetato de etilo en hexanos luego 0=>10% MeOH en acetato de etilo) produjo un producto sin refinar, el cual se purificó usando HPLC de fase inversa (YMC S5 20 x 100 mm, corrida de 10 min., solvente A: 10% MeOH: 90% H_2O: 0.1% TFA, solvente B: 90% MeOH, 10% H_2O, 0.1% TFA) para dar el compuesto del título (sal de TFA, 3 mg, Y = 30%). EM (ES+) m/z: 528 (M+H); Tiempo de retención CL: 3.24 min. ^1H RMN (400 MHz, MeOD) δ ppm 9.10 (s, 1 H) 7.94 (d, J=8.31 Hz, 2 H) 7.70 (d, J=7.81 Hz, 1 H) 7.59 (d, J=7.81 Hz, 1 H) 7.48 (d, J=8.31 Hz, 2 H) 7.36 (t, J=7.68 Hz, 1 H) 7.20 - 7.29 (m, 2 H) 7.10 (t, J=7.43 Hz, 1 H) 4.61 (s, 1 H) 1.96 (s, 3 H) 1.66 (s, 6 H) 1.18 (s, 3 H) 1.16 (s, 3 H).

-616702

Ejemplo 416



Etapa 1

A una solución agitada del producto de la etapa 2 en el Ejemplo 415 (415b) (12 mg, 0.024 mmol), dioxano (0.5 mL), NaOH (0.097 mL, 0.048 mmol), y acetonitrilo (2 mL) se agregó Boc2O (8.4 µL, 0.036 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 4 h. Después que se agregó más Boc2O (30 mg), la mezcla se agitó a temperatura ambiente durante 2 hr y luego se concentró *in vacuo*. El residuo se mezcló con agua (0.5 mL), se acidificó con 10% de solución de ácido cítrico a un pH = 5, y se extrajo con acetato de etilo. Los extractos de acetato de etilo combinados se secaron (Na2SO4) y se concentró bajo presión reducida para dar un producto sin refinar como un líquido amarillo.

Etapa 2

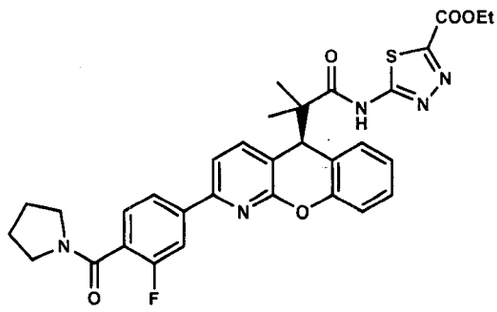
La etapa se completó de la misma forma como se describió en el Ejemplo 400, etapa 2, usando el producto de la etapa 1 (416a).

Etapa 3

El producto de la etapa 2 se disolvió en cloruro de

metileno (1 mL) y TFA (0.5 mL). La mezcla se agitó a temperatura ambiente durante 1 hr antes de concentrarse. La purificación usando HPLC de fase inversa (YMC S5 20 x 100 mm, corrida de 10 min., solvente A: 10% MeOH: 90% H_2O: 0.1% TFA, solvente B: 90% MeOH, 10% H_2O, 0.1% TFA) dio el compuesto del título (2TFA, 7 mg, Y = 40% por etapas 1 + 2 + 3) como un sólido blanco. EM (ES-) m/z: 484 (M-H); Tiempo de retención CL: 2.66 min. ^{1}H RMN (400 MHz, MeOD) δ ppm 9.11 (s, 1 H) 8.12 (d, J=8.56 Hz, 2 H) 7.73 (d, J=8.00 Hz, 1 H) 7.61 - 7.68 (m, 3 H) 7.35 - 7.40 (m, 1 H) 7.24 - 7.29 (m, 2 H) 7.13 (td, J=7.43, 1.26 Hz, 1 H) 4.64 (s, 1 H) 1.78 (s, 6 H) 1.20 (s, 3 H) 1.15 (s, 3 H).

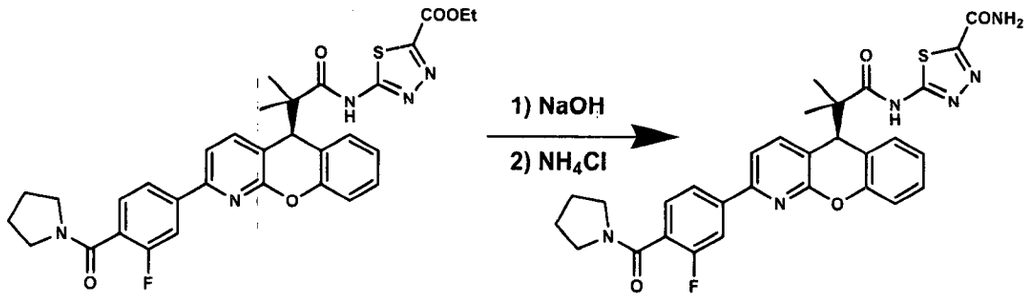
Ejemplo 417



A una mezcla agitada del producto de la etapa 1 en el Ejemplo 398 (400mg, 0.87 mmol), 5-amino-1,3,4-tiadiazol-2-carboxilato de etilo (400mg, 2.3 mmol), hidrato de HOBT (140mg, 0.91 mmol), y MeCN anhidro(10 mL) se agregó EDC (340mg, 1.8 mmol) a temperatura ambiente bajo nitrógeno, seguido por N,N-diisopropiletilamina (0.2 mL, 1.1 mmol). Después de agitar a 80°C durante 4.5 h, la mezcla de reacción

se concentró, mezclando con agua (15 mL) y acetato de etilo (15 mL). La capa acuosa se extrajo con acetato de etilo (3 x 10 mL). Las soluciones orgánicas combinadas se secaron (Na_2SO_4), se concentraron *in vacuo*, y la purificación por cromatografía por desorción súbita (20-100% acetato de etilo en hexanos) dio el producto del título (410 mg, Y = 77%) como un sólido amarillo. EM (ES+) m/z: 616 (M+H); Tiempo de retención CL: 3.70 min. ^{1}H RMN (400 MHz, CLOROFORMO-d) δ ppm 10.16 (s amp., 1 H) 8.04 (s amp., 1 H) 7.82 - 7.88 (m, 2 H) 7.53 (t, J=8.31 Hz, 2 H) 7.31 - 7.34 (m, 2 H) 7.22 (d, J=7.55 Hz, 1 H) 7.05 (ddd, J=7.87, 5.10, 3.15 Hz, 1 H) 4.86 (s, 1 H) 4.56 (q, J=7.13 Hz, 2 H) 3.68 (t, J=6.92 Hz, 2 H) 3.36 (t, J=6.55 Hz, 2 H) 1.87 - 2.06 (m, 4 H) 1.48 (t, J=7.18 Hz, 3 H) 1.35 (s, 3 H) 1.23 (s, 3 H).

Ejemplo 418



Etapa 1

A una solución agitada del compuesto del título del Ejemplo 417 (183 mg, 0.30 mmol) en MeOH (1.5 mL) se agregó solución de hidróxido de sodio acuoso 1M (1.0 ml, 1.0 mmol). La mezcla de reacción se agitó a temperatura ambiente durante

1.5 hr antes de concentrarse bajo presión reducida para remover el metanol y lifolizar para remover el agua para dar un sólido amarillo (207 mg).

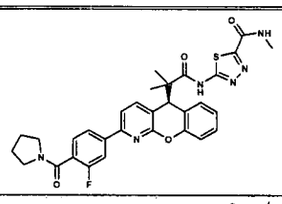
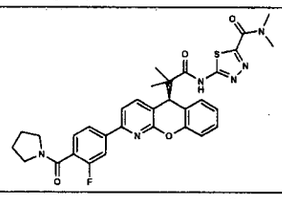
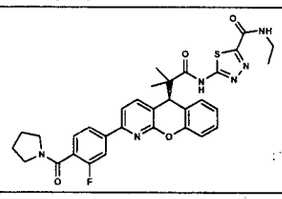
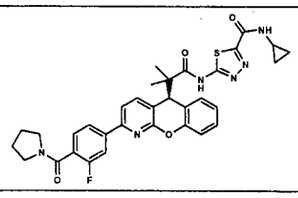
Etapa 2

A un matraz seco se agregaron el producto de la etapa 1 (21 mg, 0.029 mmol), cloruro de amonio (18 mg, 0.34 mmol), N,N-diisopropiletilamina (50 µL, 0.29 mmol), y DMF anhidro (0.3 mL) a temperatura ambiente bajo nitrógeno. La mezcla se agitó a temperatura ambiente durante 2 min antes de agregar PyBOP (20 mg, 0.038 mmol). La mezcla se deja en reposo a temperatura ambiente durante 1 h. La purificación usando HPLC de fase inversa (YMC S5 20 x 100 mm, corrida de 10 min., solvente A: 10% MeOH: 90% H_2O: 0.1% TFA, solvente B: 90% MeOH, 10% H_2O, 0.1% TFA) dio el producto del título (sal de TFA, 16 mg, Y = 79 %) como un sólido blanco. EM (ES+) m/z: 587 (M+H); Tiempo de retención CL: 3.34 min. ^1H RMN (400 MHz, MeOD) δ ppm 7.90 - 7.97 (m, 2 H) 7.69 - 7.76 (m, 2 H) 7.52 (t, J=7.43 Hz, 1 H) 7.35 - 7.40 (m, 1 H) 7.23 - 7.30 (m, 2 H) 7.13 (t, J=7.43 Hz, 1 H) 4.63 (s, 1 H) 3.63 (t, J=6.92 Hz, 2 H) 3.39 (t, J=6.55 Hz, 2 H) 1.91 - 2.06 (m, 4 H) 1.20 (s, 3 H) 1.16 (s, 3 H).

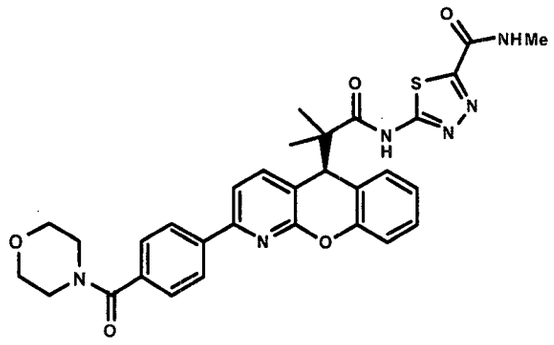
Ejemplo 419 hasta 422

Los siguientes Ejemplos 419 hasta 422 pueden ser preparados de la misma forma como se describió para la preparación del compuesto del título del Ejemplo 418 de la

amina correspondiente.

No de Ejemplo.	Estructura	Tr (min)	M/z $(MH)^+$
419		3.41	601
420		3.44	615
421		3.49	615
422		3.52	627

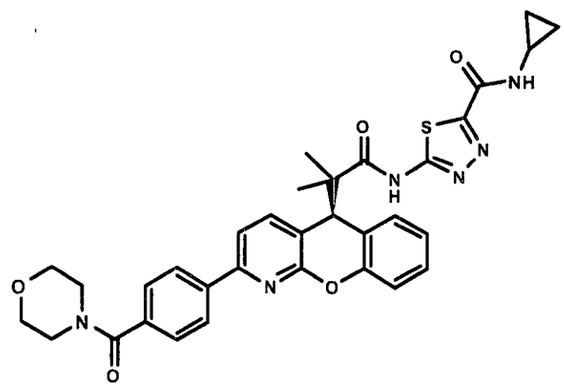
Ejemplo 422a



El compuesto del título se preparó de la misma forma descrita anteriormente para la preparación de los compuestos del título de los Ejemplos 419-422, substituyendo el ácido

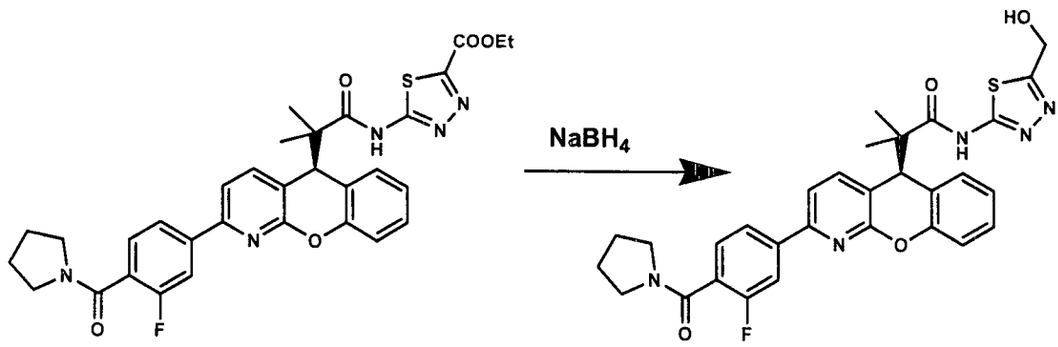
borónico comercialmente disponible (ácido 4-(morfolina-4-carbonil)fenilborónico) en lugar del ácido 3-fluoro-4-(pirrolidina-1-carbonil)fenilborónico en la primera etapa del Ejemplo 398. EM (ES+) m/z: 599 (M+H); Tiempo de retención CL: 3.15 min.

Ejemplo 422[b]



El compuesto del título se preparó de la misma forma descrita anteriormente para la preparación del compuesto del título de los Ejemplos 422[a]. EM (ES+) m/z: 625 (M+H); Tiempo de retención CL: 3.28 min.

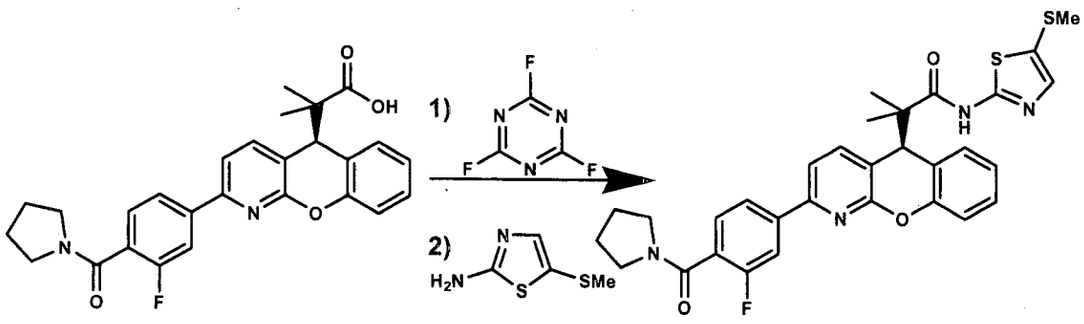
Ejemplo 423



A una solución agitada del compuesto del título del Ejemplo 417 (17 mg, 0.028 mmol) en THF (0.5 mL) y etanol (0.5

mL) se agregó NaBH4 (17mg, 0.45 mmol) en porciones. La mezcla se agitó a temperatura ambiente durante 1 hr antes de agregar acetona (1 mL) para apagar la reacción. La mezcla se concentró *in vacuo*. La purificación usando HPLC de fase inversa (YMC S5 20 x 100 mm, corrida de 10 min., solvente A: 10% MeOH: 90% H_2O: 0.1% TFA, solvente B: 90% MeOH, 10% H_2O, 0.1% TFA) dio el compuesto del título (sal de TFA, 12 mg, Y = 63%) como un sólido blanco. EM (ES+) m/z: 574 (M+H); Tiempo de retención CL: 3.28 min. ^{1}H RMN (400 MHz, MeOD) δ ppm 7.90 - 7.98 (m, 2 H) 7.69 - 7.77 (m, 2 H) 7.53 (t, J=7.43 Hz, 1 H) 7.35 - 7.40 (m, 1 H) 7.23 - 7.30 (m, 2 H) 7.13 (td, J=7.43, 1.26 Hz, 1 H) 4.92 (s, 2 H) 4.63 (s, 1 H) 3.63 (t, J=6.92 Hz, 2 H) 3.39 (t, J=6.55 Hz, 2 H) 1.91 - 2.06 (m, 4 H) 1.18 (s, 3 H) 1.15 (s, 3 H).

Ejemplo 424



Etapa 1

A una solución del producto de la etapa 1 en el Ejemplo 398 (170 mg, 0.37 mmol) y piridina (0.060 mL, 0.74 mmol) en diclorometano anhidro (2 mL) se agregó 2,4,6-trifluoro-1,3,5-

triazina (0.062 mL, 0.74 mmol) gota a gota a 0°C bajo nitrógeno. Después que se agitó a 0°C durante 30 min y a temperatura ambiente durante 1.5 hr, la mezcla se vació en agua (2 mL) a 0°C. La capa acuosa se separó y se extrajo con cloruro de metileno (3 x 1 mL). Las soluciones de cloruro de metileno combinadas se secaron (Na_2SO_4). La purificación por cromatografía por desorción súbita (20=>100% acetato de etilo en hexanos) produjo el producto (153 mg, Y = 90 %) como un sólido blanco. EM (ES+) m/z: 463 (M+H); Tiempo de retención CL: 3.56 min.

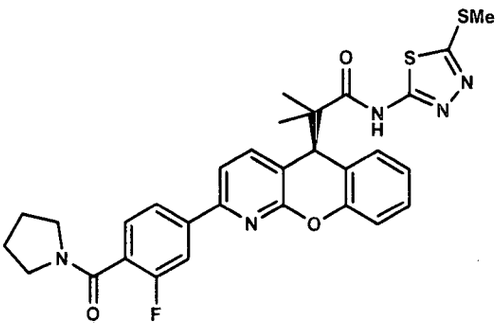
Etapa 2

Una mezcla del producto de la etapa 1 (30 mg, 0.065 mmol), 5-(metiltio)tiazol-2-amina (19 mg, 0.13 mmol), piridina (50 µL, 0.60 mmol), y acetonitrilo anhidro(1 mL) se agitó a temperatura ambiente bajo nitrógeno durante 60 h. Se agregó EDC (15 mg). La mezcla se agitó a 80°C 4 h y a 90°C durante 2 h. La purificación usando HPLC de fase inversa (YMC S5 20 x 100 mm, corrida de 10 min., solvente A: 10% MeOH: 90% H_2O: 0.1% TFA, solvente B: 90% MeOH, 10% H_2O, 0.1% TFA) dio el producto del título (32 mg, Y = 83 % de rendimiento) como un sólido amarillento. EM (ES+) m/z: 589 (M+H); Tiempo de retención CL: 3.82 min. ^1H RMN (400 MHz, MeOD) δ ppm 7.88 - 7.95 (m, 2 H) 7.73 (d, J=8.0 Hz, 1 H) 7.69 (d, J=8.0 Hz, 1 H) 7.51 (t, J=7.43 Hz, 1 H) 7.43 (s, 1 H) 7.36 (td, J=7.8, 1.2 Hz, 1 H) 7.26 (d, J=8.56 Hz, 2 H) 7.12 (td, J=7.5, 1.0 Hz, 1

- 000713

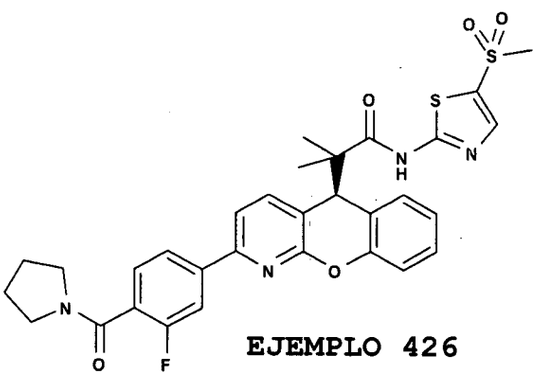
H) 4.61 (s, 1 H) 3.62 (t, J=6.80 Hz, 2 H) 3.38 (t, J=6.67 Hz, 2 H) 2.45 (s, 3 H) 1.91 - 2.06 (m, 4 H) 1.15 (s, 3 H) 1.10 (s, 3 H).

Ejemplo 425

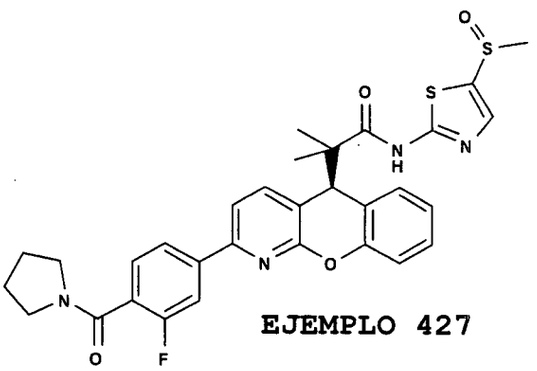


El compuesto del título se preparó de la misma forma como se describió para la preparación del compuesto del título del Ejemplo 424 de la 5-(metiltio)tiadiazol-2-amina. EM (ES+) m/z: 590 (M+H); Tiempo de retención CL: 3.71 min. ^{1}H RMN (400 MHz, MeOD) δ ppm 7.91 - 7.98 (m, 2 H) 7.75 (d, J=8.0 Hz, 1 H) 7.72 (d, J=8.0 Hz, 1 H) 7.53 (t, J=7.55 Hz, 1 H) 7.35 - 7.41 (m, 1 H) 7.23 - 7.30 (m, 2 H) 7.14 (t, J=7.43 Hz, 1 H) 4.61 (s, 1 H) 3.63 (t, J=6.92 Hz, 2 H) 3.39 (t, J=6.67 Hz, 2 H) 2.76 (s, 3 H) 1.92 - 2.05 (m, 4 H) 1.17 (s, 3 H) 1.13 (s, 3 H).

Ejemplos 426 Y 427



EJEMPLO 426



EJEMPLO 427

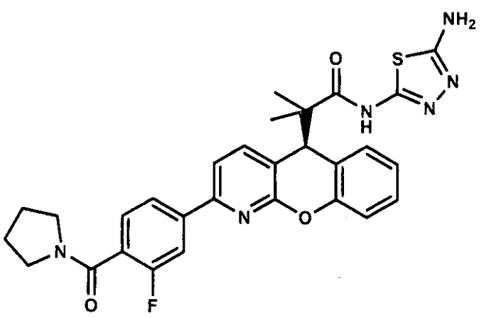
- 006711

A una solución transparente del compuesto del título del Ejemplo 424 (22 mg, 0.038 mmol) y TFA (15 µL, 0.20 mmol) en diclorometano (1 mL) se agregó mCPBA (57-86%, 14 mg) a 0°C. La mezcla de reacción se agitó a la misma temperatura durante 1.5 h y a temperatura ambiente durante 1 h antes de agregar la solución de bicarbonato de sodio acuoso saturada (1 mL). La solución acuosa se extrajo con diclorometano (2 x 1 mL). Las soluciones de diclorometano combinadas se secaron (Na_2SO_4). La purificación por cromatografía por desorción súbita (50=>100% acetato de etilo en heptanos; luego 0-20% metanol en acetato de etilo) produjo el sulfóxido (5 mg) y la sulfona (24 mg). Cada uno de estos se purificaron separadamente usando HPLC de fase inversa (YMC S5 20 x 100 mm, corrida de 10 min., solvente A: 10% MeOH: 90% H_2O: 0.1% TFA, solvente B: 90% MeOH, 10% H_2O, 0.1% TFA) para dar el compuesto del título del Ejemplo 427 (sal de TFA, 3 mg, Y = 11%) como un sólido blanco. (EM (ES+) m/z: 605 (M+H); Tiempo de retención CL: 3.27 min, ^{1}H RMN (400 MHz, MeOD) δ ppm 7.91 - 7.98 (m, 3 H) 7.70 - 7.78 (m, 2 H) 7.53 (t, J=7.43 Hz, 1 H) 7.35 - 7.40 (m, 1 H) 7.24 - 7.30 (m, 2 H) 7.13 (td, J=7.50, 1.20 Hz, 1 H) 4.64 (s, 1 H) 3.63 (t, J=6.92 Hz, 2 H) 3.39 (t, J=6.55 Hz, 2 H) 3.09 (s, 3 H) 1.91 - 2.06 (m, 4 H) 1.18 (d, J=3.53 Hz, 3 H) 1.14 (d, J=3.78 Hz, 3 H)) y el compuesto del título del Ejemplo 426 (sal de TFA, 19 mg, Y = 69%) como un sólido blanco. (EM (ES+) m/z: 621 (M+H); Tiempo de retención CL: 3.36 min, ^{1}H RMN (400 MHz, MeOD) δ ppm

- 000712

8.06 (s, 1 H) 7.89 - 7.96 (m, 2 H) 7.74 (d, J=8.0 Hz, 1 H) 7.71 (d, J=8.0 Hz, 1 H) 7.52 (t, J=7.43 Hz, 1 H) 7.37 (td, J=7.7, 1.3 Hz, 1 H) 7.23 - 7.29 (m, 2 H) 7.11 - 7.16 (m, 1 H) 4.62 (s, 1 H) 3.63 (t, J=6.92 Hz, 2 H) 3.39 (t, J=6.55 Hz, 2 H) 3.30 (s, 3 H) 1.92 - 2.05 (m, 4 H) 1.18 (s, 3 H) 1.14 (s, 3 H)).

Ejemplo 428

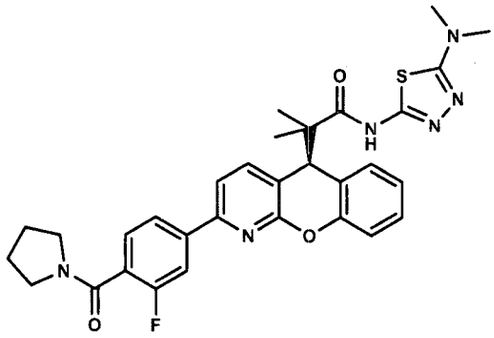


Una mezcla del producto de la etapa 1 del Ejemplo 398 (15 mg, 0.032 mmol), 1,3,4-tiadiazol-2,5-diamina (20 mg, 0.17 mmol), y DMF anhidro (0.2 mL) se sonicó y se agitó a temperatura ambiente durante la noche bajo nitrógeno. La purificación usando HPLC de fase inversa (YMC S5 20 x 100 mm, corrida de 10 min., solvente A: 10% MeOH: 90% H_2O: 0.1% TFA, solvente B: 90% MeOH, 10% H_2O, 0.1% TFA) dio el compuesto del título (sal de TFA, 20 mg, 90 % de rendimiento) como un sólido blanco. EM (E+) m/z: 559 (M+H); Tiempo de retención CL: 3.02 min. ^1H RMN (400 MHz, MeOD) δ ppm 7.97 (dd, J=8.0, 1.6 Hz, 1 H) 7.94 (dd, J=11.21, 1.38 Hz, 1 H) 7.79 (d, J=8.0 Hz, 1 H) 7.76 (d, J=8.0 Hz, 1 H) 7.54 (t, J=7.55 Hz, 1 H) 7.39 (td,

660713

J=7.8, 1.6 Hz, 1 H) 7.25 - 7.30 (m, 2 H) 7.17 (td, J=7.6, 1.2 Hz, 1 H) 4.54 (s, 1 H) 3.63 (t, J=6.92 Hz, 2 H) 3.39 (t, J=6.55 Hz, 2 H) 1.91 - 2.06 (m, 4 H) 1.15 (s, 3 H) 1.14 (s, 3 H).

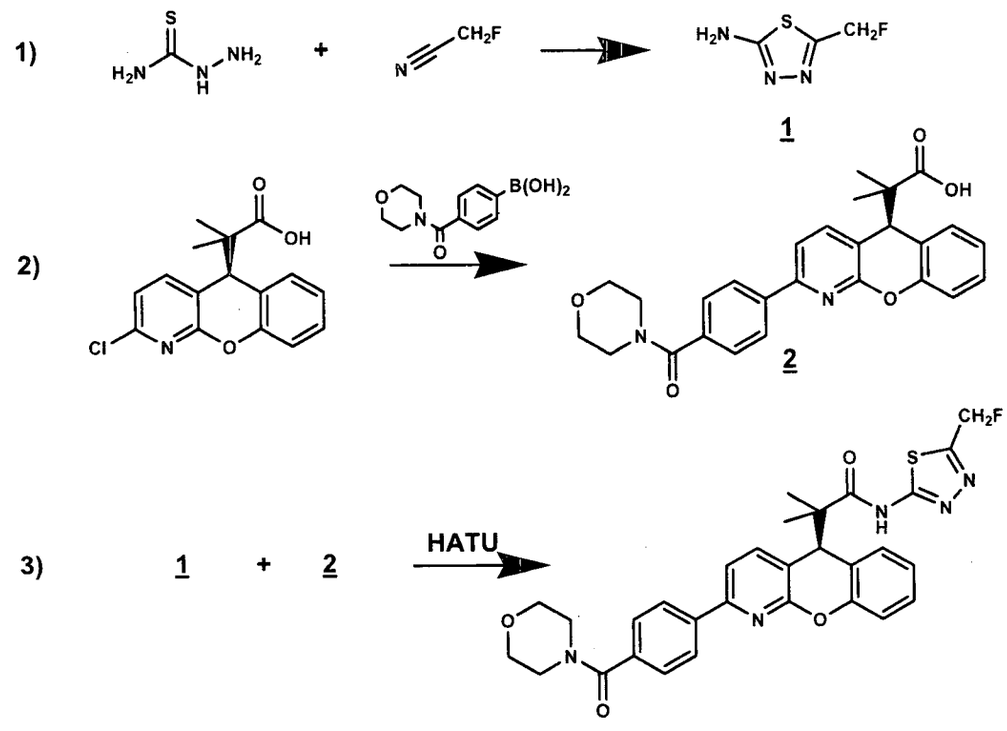
Ejemplo 429



Una mezcla de 5-bromo-1,3,4-tiadiazol-2-amina (90 mg, 0.50 mmol), clorhidrato de dimetilamina (410 mg, 5.0 mmol), 2-propanol (0.6 mL), y N,N-diisopropiletilamina (0.90 mL, 5.0 mmol) se agitó a 150°C durante 1 h bajo nitrógeno en un reactor de microondas CEM. La solución de bicarbonato de sodio acuoso saturado (6 mL) se agregó con precaución, y la mezcla se extrajo con acetato de etilo (4 x 2 mL). Los extractos de acetato de etilo combinados se secaron (Na_2SO_4) y se concentró bajo presión reducida para dar un producto sin refinar (16 mg, N2,N2-dimetil-1,3,4-tiadiazol-2,5-diamina), el cual se mezcló con acetonitrilo anhidro (1 mL), N,N-diisopropiletilamina (0.1 mL, 0.57 mmol), y el producto de la etapa 1 en el Ejemplo 426 (15 mg, 0.032 mmol). La mezcla se agitó a temperatura ambiente

bajo nitrógeno durante la noche. La purificación usando HPLC de fase inversa (YMC S5 20 x 100 mm, corrida de 10 min., solvente A: 10% MeOH: 90% H_2O: 0.1% TFA, solvente B: 90% MeOH, 10% H_2O, 0.1% TFA) dio el compuesto del título (sal de TFA, 4 mg, Y = 18 %) como un sólido blanco. EM (E+) m/z: 587 (M+H); Tiempo de retención CL: 3.32 min. ^{1}H RMN (400 MHz, MeOD) δ ppm 7.91 - 7.99 (m, 2 H) 7.79 (d, J=8.0 Hz, 1 H) 7.75 (d, J=8.0 Hz, 1 H) 7.54 (t, J=7.55 Hz, 1 H) 7.39 (td, J=7.7, 1.2 Hz, 1 H) 7.25 - 7.30 (m, 2 H) 7.16 (td, J=7.7, 1.2 Hz, 1 H) 4.56 (s, 1 H) 3.63 (t, J=6.92 Hz, 2 H) 3.39 (t, J=6.67 Hz, 2 H) 3.26 (s, 6 H) 1.91 - 2.07 (m, 4 H) 1.16 (s, 3 H) 1.14 (s, 3 H).

Ejemplo 430



001715

Etapa 1

Una mezcla de hidrazinacarbotioamida (550 mg, 6.0 mmol), 2-fluoroacetonitrilo (0.34 mL, 6.0 mmol), y TFA (3 mL) se agitó a 60°C durante 4 hr. La mezcla se concentró *in vacuo*. El residuo se disolvió en agua (15 mL), se basificó con solución de bicarbonato de sodio acuoso saturado (20 mL) y solución de fosfato de potasio saturado acuoso, y se mezcló con acetato de etilo (10 mL). El sólido se filtró, se lavó con agua y acetato de etilo, y se secó para dar un sólido blanco (100 mg). El filtrado se extrajo con acetato de etilo (3 x 10 mL). Todas las soluciones orgánicas se combinaron, se secaron (Na_2SO_4), y se concentraron bajo presión reducida. El residuo sólido obtenido se trituró con acetato de etilo para dar un sólido blanco (210 mg). Ambos de los sólidos son deseados 5-(fluorometil)-1,3,4-tiadiazol-2-amina (310 mg, 39% de rendimiento). EM (E+) m/z: 134 (M+H); Tiempo de retención CL: 0.28 min.

Etapa 2

La etapa se completó de la misma forma como se describió en el Ejemplo 398 Etapa 1 para obtener el producto como un sólido blanco. EM (ES+) m/z: 459 (M+H); Tiempo de retención CL: 3.10 min.

Etapa 3

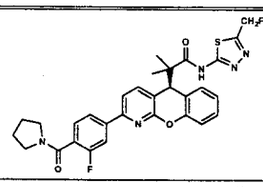
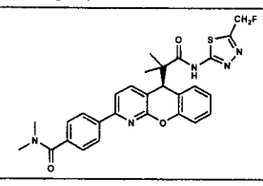
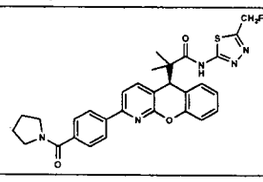
Una mezcla del producto de la etapa 2 (20 mg, 0.044 mmol), el producto de la etapa 1 (17 mg, 0.13 mmol), DMAP (11 mg, 0.087 mmol), HATU (33 mg, 0.087 mmol) y DMF (0.3 mL) se agitó a 80°C bajo nitrógeno durante 2 h. Después que se agregó más producto(10 mg) de la etapa 1, la mezcla se agitó a 80°C durante 1 h

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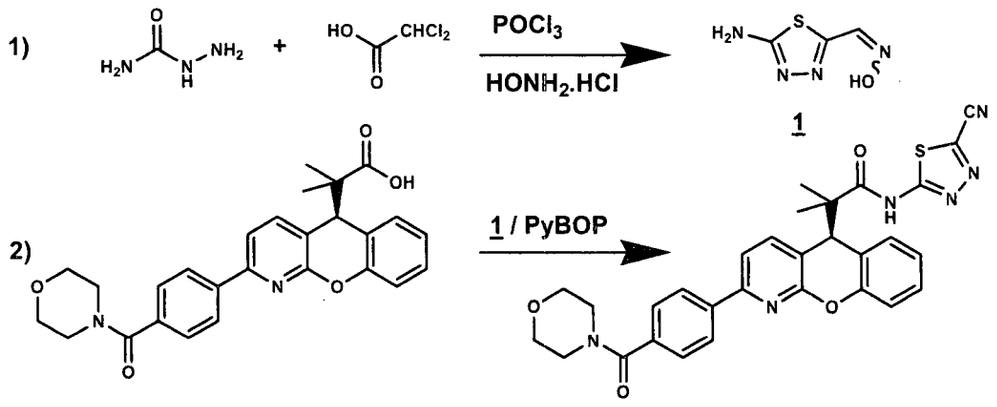
adicional. La purificación usando HPLC de fase inversa (YMC S5 20 x 100 mm, 10 min, corrida, solvente A: 10% MeOH: 90% H_2O: 0.1% TFA, solvente B: 90% MeOH, 10% H_2O, 0.1% TFA) dio el compuesto del título (sal de TFA, 20 mg, Y = 67%) como un sólido blanco. EM (E+) m/z: 574 (M+H); Tiempo de retención CL: 3.25 min. ^{1}H RMN (400 MHz, MeOD) δ ppm 8.13 (d, J=8.31 Hz, 2 H) 7.74 (d, J=8.0 Hz, 1 H) 7.68 (d, J=8.0 Hz, 1 H) 7.55 (d, J=8.56 Hz, 2 H) 7.37 (td, J=7.7, 1.4 Hz, 1 H) 7.23 - 7.30 (m, 2 H) 7.12 (td, J=7.5, 1.0 Hz, 1 H) 5.74 (d, J=47.0 Hz, 2 H) 4.63 (s, 1 H) 3.45 - 3.84 (m, 8 H) 1.19 (s, 3 H) 1.16 (s, 3 H).

Ejemplo 431 hasta 433

Los siguientes Ejemplos 431 hasta 433 se prepararon de la misma forma como se describió para la preparación del compuesto del título del Ejemplo 430 de los ácidos borónicos comercialmente disponible correspondientes.

No de Ejemplo.	Estructura	Tr (min)	M/z $(MH)^+$
431		3.52	576
432		3.32	532
433		3.46	558

Ejemplo 434



Etapa 1

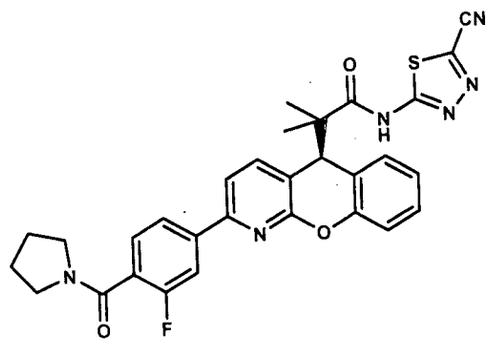
La etapa se completó siguiendo el procedimiento de la literatura (Remers, W.; et al EU 3790590). EM (E+) m/z: 145 (M+H); Tiempo de retención CL: 0.30 min.

Etapa 2

A una mezcla agitada del producto de la etapa 2 del Ejemplo 430 (20mg, 0.044 mmol), el producto de la etapa 1 (8.80 mg, 0.061 mmol), PyBOP (68 mg, 0.13 mmol), y MeCN anhidro (0.5 mL) se agregó diisopropiletilamina (0.053 mL, 0.31 mmol) a temperatura ambiente bajo nitrógeno. La mezcla se agitó a temperatura ambiente durante 1 h y a 80°C durante 2 h. Después que se agregó más del producto (5 mg) de la Etapa 1, la mezcla se agitó a 80°C durante 1 h adicional. La purificación usando HPLC de fase inversa (YMC S5 20 x 100 mm, corrida de 10 min., solvente A: 10% MeOH: 90% H_2O: 0.1% TFA, solvente B: 90% MeOH, 10% H_2O, 0.1% TFA) dio el producto del

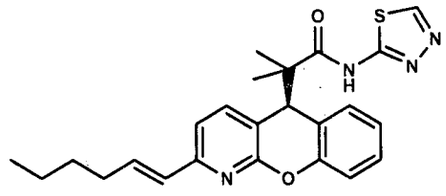
título (sal de TFA, 15 mg, 0.022 mmol, 51% de rendimiento) como un sólido amarillo. EM (E+) m/z: 567 (M+H); Tiempo de retención CL: 3.35 min. ^{1}H RMN (400 MHz, MeOD) δ ppm 8.13 (d, J=8.56 Hz, 2 H) 7.73 (d, J=8.0 Hz, 1 H) 7.69 (d, J=8.0 Hz, 1 H) 7.56 (d, J=8.31 Hz, 2 H) 7.38 (td, J=7.7, 1.4 Hz, 1 H) 7.28 (dd, J=8.06, 1.01 Hz, 1 H) 7.23 (dd, J=7.68, 1.38 Hz, 1 H) 7.13 (td, J=7.5, 1.2 Hz, 1 H) 4.61 (s, 1 H) 3.46 - 3.84 (m, 8 H) 1.20 (s, 3 H) 1.18 (s, 3 H).

Ejemplo 435



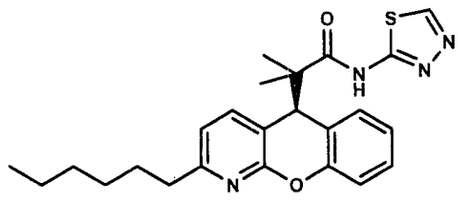
El compuesto del título se preparó de la misma forma como se describió para la preparación del compuesto del título del Ejemplo 434 del producto de la etapa 1 en el Ejemplo 398. EM (ES+) m/z: 569 (M+H); Tiempo de retención CL: 3.59 min. ^{1}H RMN (400 MHz, MeOD) δ ppm 7.89 - 7.99 (m, 2 H) 7.74 (d, J=8.0 Hz, 1 H) 7.72 (d, J=8.0 Hz, 1 H) 7.53 (t, J=7.43 Hz, 1 H) 7.35 - 7.41 (m, 1 H) 7.28 (d, J=8.06 Hz, 1 H) 7.22 (d, J=7.55 Hz, 1 H) 7.13 (t, J=6.92 Hz, 1 H) 4.62 (s, 1 H) 3.63 (t, J=6.80 Hz, 2 H) 3.39 (t, J=6.55 Hz, 2 H) 1.89 - 2.08 (m, 4 H) 1.20 (s, 3 H) 1.18 (s, 3 H).

Ejemplo 436



Una corriente de gas nitrógeno se burbujeó a través de una mezcla del producto de la Etapa 1 de la Preparación 53 (53a) (100 mg, 0.26 mmol), ácido trans-1-hexen-1-il borónico (66 mg, 0.52 mmol) y (trifenilfosfina)paladio(0) (10 mg, 0.009 mmol) en DMF (1.5 mL) y fosfato de potasio acuoso (2.0M, 0.3 mL) durante 10 min. La mezcla se calentó a 100°C durante 2.5 h, luego se purificó por HPLC preparativa para dar el compuesto del título como una sal de TFA amarilla clara (24 mg, Y = 17%). EM (ES+) m/z: 435 (M+H); Tiempo de retención CL: 3.95 min.

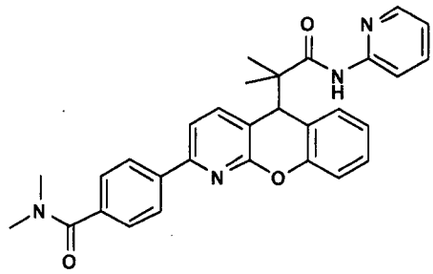
Ejemplo 437



A una solución del compuesto del título del Ejemplo 436 (10 mg, 0.023 mmol) en metanol (2 mL) se agregó paladio sobre carbono (10% p/p, 10 mg). La mezcla se evacuó, luego se puso bajo una atmósfera de hidrógeno, y se agitó durante la noche a temperatura ambiente. La mezcla se filtró luego (filtro PTFE

de punta de jeringa 0.45 micrones), y se purificó por HPLC preparativa de fase inversa para proporcionar el compuesto del título (6.1 mg, Y = 48%) como un polvo blanco, sal de TFA. EM (ES+) m/z: 437 (M+H); Tiempo de retención CL: 3.94 min.

Ejemplo 438



Etapa 1

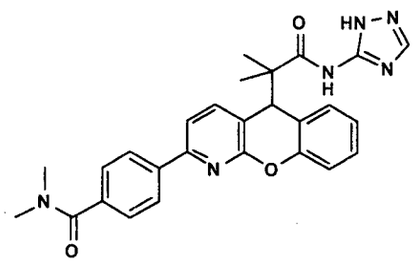
Una solución en CH_2Cl_2 1M de cloruro de oxalilo (0.7 mL, 3 eq.) se agregó a una suspensión del ácido de la Preparación 101 (200 mg, 0.24 mmol) y una cantidad de traza de DMF en CH_2Cl_2 (20 mL) a temperatura ambiente. Después de 20 min, la mezcla se concentró para dar el cloruro del ácido esperado como un sólido blanco opaco.

Etapa 2

A una solución de CH_2Cl_2 (1.4 mL) del cloruro del ácido de la última etapa (40 mg, 0.092 mmol) se agregó 2-aminopiridina (25 mg, 2.9 eq.) a temperatura ambiente. Después de 1 h, la mezcla se concentró y purificó por HPLC de fase inversa preparativa (usando cromatógrafos para líquidos Shimadzu 10A y columnas Waters Sunfire S10 30 x 250 mm) para dar el Ejemplo 501 como un sólido blanco (28.8 mg, 43%). ^1H

RMN (400 MHz, CDCl3) δ ppm 12.14 (s, 1 H), 8.75 (d, J = 8.81 Hz, 1 H), 8.18 - 8.37 (m, 2 H), 8.08 (d, J = 8.31 Hz, 2 H), 7.83 (d, J = 7.81 Hz, 1 H), 7.55 (dd, J = 13.22, 8.18 Hz, 3 H), 7.44 (t, J = 6.17 Hz, 1 H), 7.28 - 7.38 (m, 2 H), 7.22 (d, J = 7.30 Hz, 1 H), 7.03 - 7.14 (m, 1 H), 4.77 (s, 1 H), 3.18 (s, 3 H), 3.04 (s, 3 H), 1.22 (s, 3 H), 1.14 (s, 3 H); EM (ES+) m/z: 493 (M+H); Tiempo de retención CL: 3.69 min (HPLC analítica del Método D).

Ejemplo 439



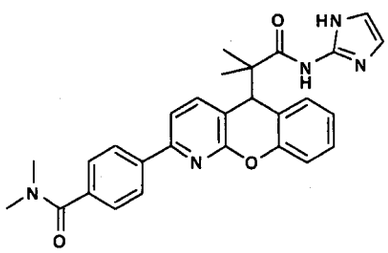
Etapa 1

A una solución en CH_2Cl_2 (2 mL) de sulfato de 2-metil-2-tioisourea (68.9 mg, 0.366 mmol) y NaOH 1 N(405 mL, 0.405 mmol) a 0 °C se agregó una solución del cloruro del ácido de la Etapa 1 del Ejemplo 501 (63.7 mg, 0.135 mmol) en CH_2Cl_2 (2 mL). Después de 1 h a 0 °C, la mezcla bifasica se separó y la capa acuosa se extrajo con CH_2Cl_2 (2 mL). La fase CH_2Cl_2 combinada se concentró para dar el producto esperado como un sólido café ligero. EM (ES+) m/z: 489 (M+H); Tiempo de retención CL: 3.34 min (HPLC analítica del Método D).

Etapa 2

Una solución de piridina (1.5 mL) del producto sin refinar de la última etapa, formohidrazida (14 mg, 0.233 mmol) y (S)-ácido alcanforsulfónico (56 mg, 0.241 mmol) se calentó a 100°C en un tubo sellado. Después de 3 h a 100 °C, la mezcla se purificó por HPLC de fase inversa preparativa (usando cromatógrafos para líquidos Shimadzu 10A y columnas Waters Sunfire S10 30 x 250 mm) para dar el compuesto del título como un sólido blanco (13 mg, 15% de rendimiento durante 2 etapas). ^{1}H RMN (400 MHz, DMSO-d6) δ ppm 8.16 (d, J = 8.56 Hz, 2 H), 7.87 (d, J = 7.81 Hz, 1 H), 7.74 (d, J = 8.06 Hz, 1 H), 7.52 (d, J = 8.31 Hz, 2 H), 7.33 - 7.42 (m, 2 H), 7.23 - 7.33 (m, 2 H), 7.12 - 7.21 (m, 1 H), 4.82 (s, 1 H), 3.01 (s, 3 H), 2.95 (s, 3 H), 1.02 (s, 3 H), 0.98 (s, 3 H); EM (ES+) m/z: 483 (M+H); Tiempo de retención CL: 3.55 min (HPLC analítica del Método D).

Ejemplo 440

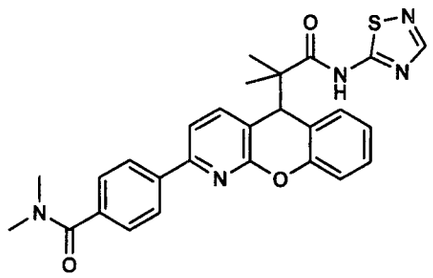
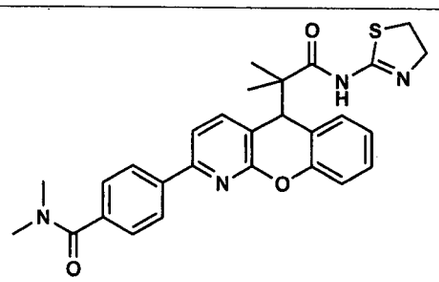
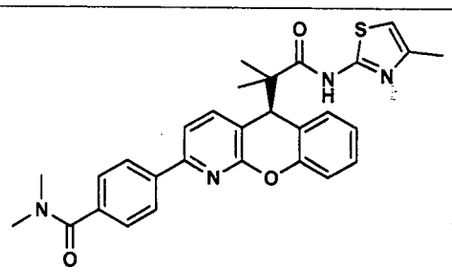
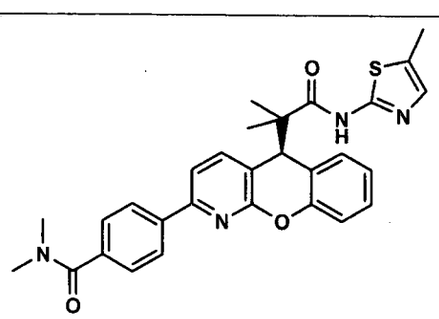


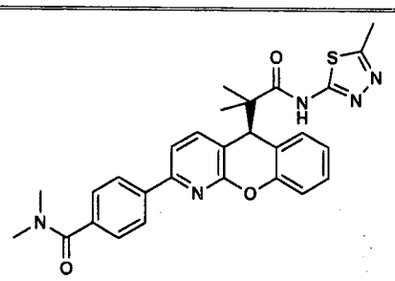
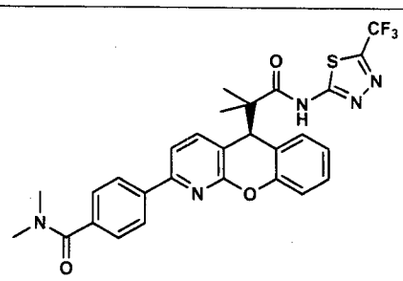
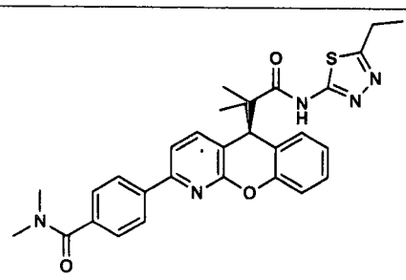
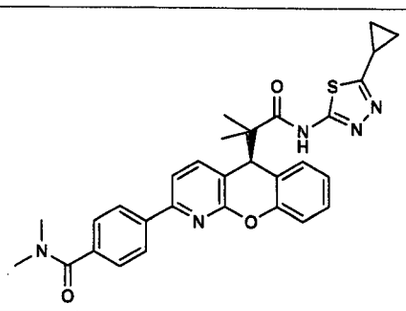
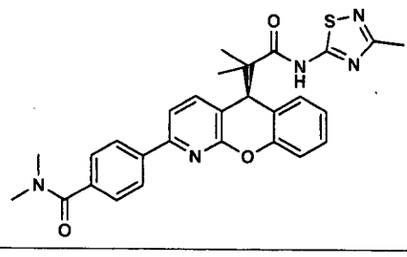
Una solución de acetonitrilo (2 mL) del producto de la Preparación 101 (35.8 mg, 0.086 mmol), 1-tritil-

2-aminoimidazol (66.2 mg, 2.4 eq., preparado siguiendo un procedimiento conocido J. Med. Chem. 2000, 43, 27-40), HOBt (30.5 mg, 2.6 eq.), EDC (52.5 mg, 3.2 eq.) y DIPEA (75 mL, 5 eq.) se calentó a 60°C durante 16 h. La mezcla sin refinar se vació en NH_4Cl saturado (20 mL) y se extrajo con acetato de etilo (10 mL). El acetato de etilo extraído se concentró, se disolvió en CH_2Cl_2 (0.5 mL), se trató con TFA (0.5 mL) durante 20 min y se concentró. La purificación por HPLC de fase inversa preparativa (usando cromatógrafos para líquidos Shimadzu 10A y columnas Waters Sunfire S10 30 x 250 mm) dio el Ejemplo 503 como un sólido blanco (15.5 mg, 37%). ^1H RMN (400 MHz, $CDCl_3$) δ ppm 14.11 (s, 1 H), 8.08 (d, J = 8.56 Hz, 2 H), 7.77 (d, J = 7.81 Hz, 1 H), 7.55 (dd, J = 16.37, 8.06 Hz, 3 H), 7.28 - 7.38 (m, 2 H), 7.15 - 7.22 (m, 1 H), 7.05 - 7.14 (m, 1 H), 6.99 (s, 2 H), 4.66 (s, 1 H), 3.16 (s, 3 H), 3.03 (s, 3 H), 1.21 (s, 3 H), 1.14 (s, 3 H); EM (E+) m/z: 482 (M+H); Tiempo de retención CL: 3.09 min (Método D de HPLC analítica).

Ejemplos 441 hasta 449

Siguiendo procedimientos análogos para la preparación del Ejemplo 440, los siguientes Ejemplos se prepararon por uniones entre aminas apropiadas (comercialmente disponibles) y el ácido de la Preparación 57 ó 65.

No. de Ejemplo	Estructura	Tr (min)*	M/z (M+H)
441		3.97	500
442		3.29	501
443		4.10	513
444		4.12	513

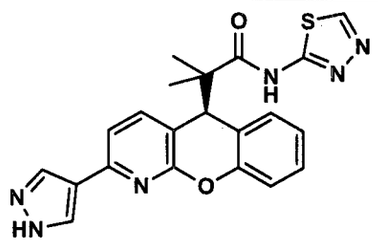
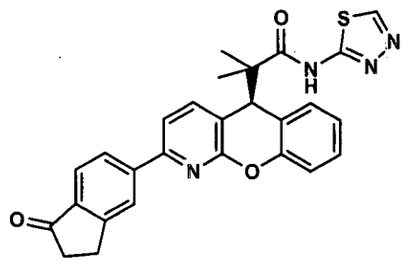
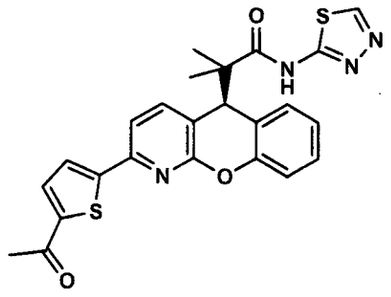
No. de Ejemplo	Estructura	Tr (min)*	M/z (M+H)
445		3.90	514
446		4.40	568
447		4.06	528
448		4.12	540
449		4.02	514

*HPLC Analítica del Método D

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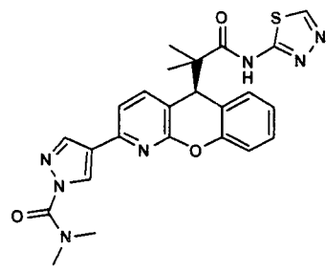
Ejemplos 450 hasta 452

Los siguientes Ejemplos 450 hasta 452 se prepararon de la misma forma descrita para la preparación de los compuestos del título de los Ejemplos 168 hasta 236, usando ácidos borónicos comercialmente disponibles y el producto de la Preparación 53a. Por Ejemplo 451, véase Bioorg. & Med. Chem. Lett. 2003, 13, 4143-4145.

No de Ejemplo.	Estructura	Tr (min)*	M/z (M+H)
450		3.52	419
451		4.01	483
452		3.96	477

* HPLC analítica del Método D.

Ejemplo 453

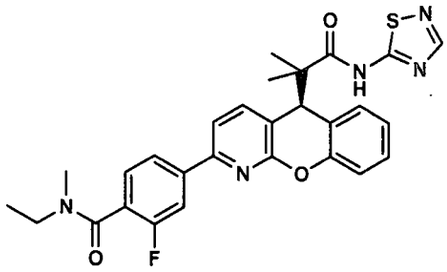
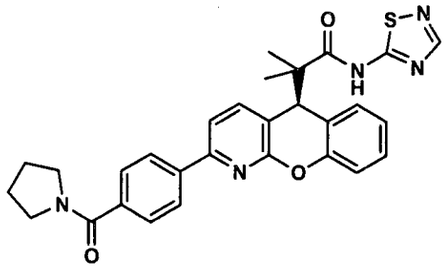
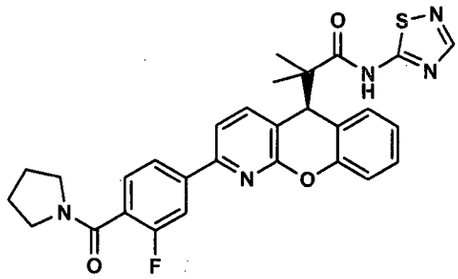
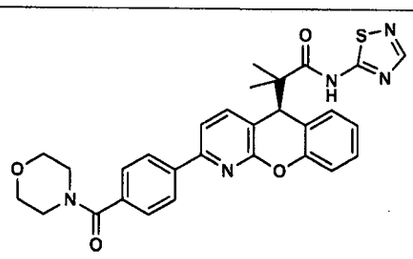
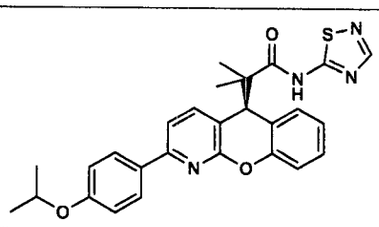


A una solución THF (1.5 mL) del Ejemplo 450 (8.1 mg, 0.019 mmol) y cloruro de dimetilcarbamilo (14 mg, 6.7 eq.) se agregó DBU (20.2 mL, 7 eq.). La mezcla resultante se calentó a 60°C durante 1h, se concentró y se purificó por cromatografía de columna por desorción súbita (ISCO, cartucho de 4 g gel de sílice, 20 hasta 100% acetato de etilo-hexanos) para dar el compuesto del título como un sólido blanco (2.5 mg, 26%). 1H RMN (400 MHz, CDCl3) δ ppm 8.89 (s, 1 H), 8.62 (s, 1 H), 8.19 (s, 1 H), 7.61 (d, J = 7.81 Hz, 1 H), 7.26 - 7.37 (m, 3 H), 7.15 - 7.21 (m, 1 H), 7.01 - 7.09 (m, 1 H), 4.63 (s, 1 H), 3.26 (s, 6 H), 1.24 (s, 3 H), 1.23 (s, 3 H); EM (E+) m/z: 490 (M+H); Tiempo de retención CL: 3.74 min (HPLC analítica del Método D).

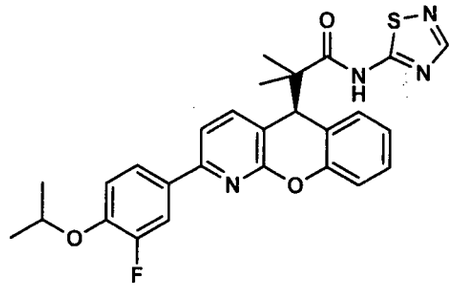
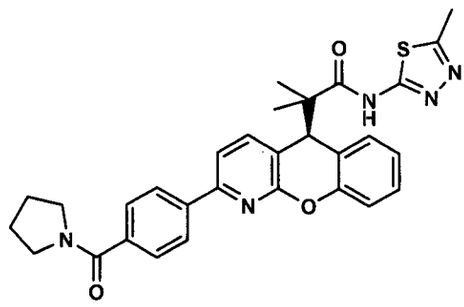
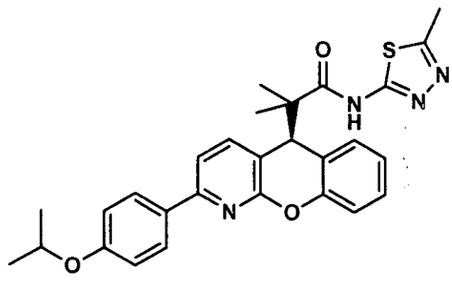
Ejemplos 454 hasta 461

Siguiendo procedimientos análogos para la preparación del Ejemplo 440, los siguientes Ejemplos se prepararon por unión entre 5-amino-1,2,4-tiadiazol o 2-amino-5-metil-1,3,4-tiadiazol y los ácidos de las Preparaciones 67 hasta 70 y 72 hasta 73.

000728

No de Ejemplo.	Estructura	Tr (min)*	M/z (M+H)
454		4.18	532
455		4.12	526
456		4.21	544
457		3.95	542
458		4.60	487

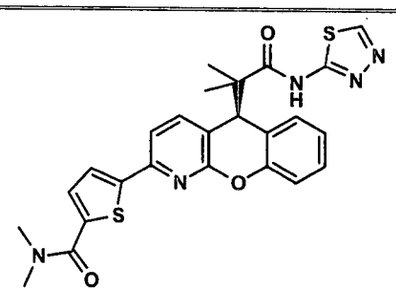
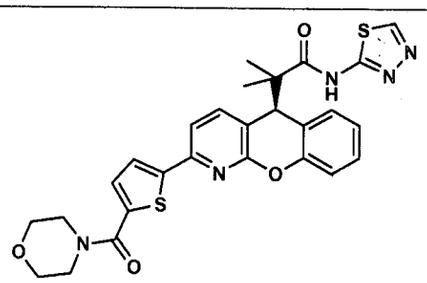
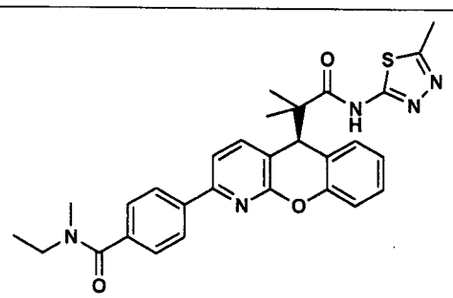
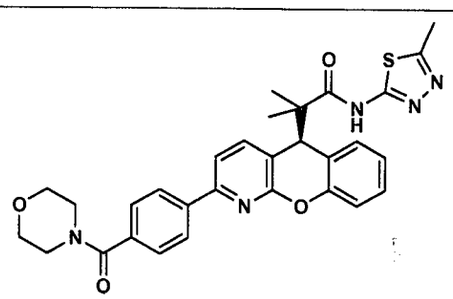
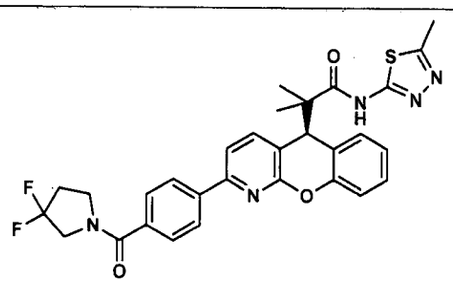
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No de Ejemplo.	Estructura	Tr (min)*	M/z (M+H)
459		4.60	505
460		4.07	540
461		4.52	501

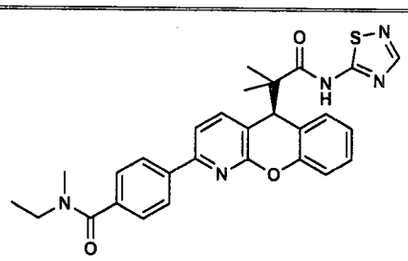
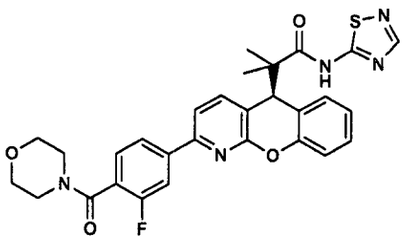
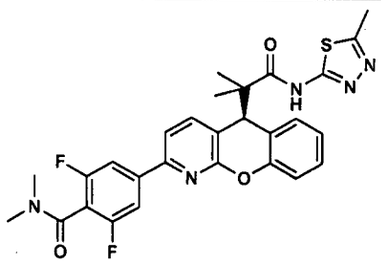
* HPLC analítica del Método D.

Ejemplos 462 hasta 469

Siguiendo procedimientos análogos para la preparación del Ejemplo 440, los siguientes Ejemplos se prepararon por unión entre amina comercialmente disponible y el ácido de la Preparaciones 78 hasta 82.

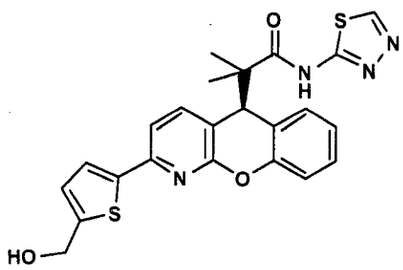
No de Ejemplo.	Estructura	Tr (min)*	M/z (M+H)
462		3.78	506
463		3.77	548
464		4.02	528
465		3.89	556
466		4.10	576

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No de Ejemplo.	Estructura	Tr (min)*	M/z (M+H)
467		4.09	514
468		4.07	560
469		4.00	550

* Método D de HPLC analítica.

Ejemplo 470

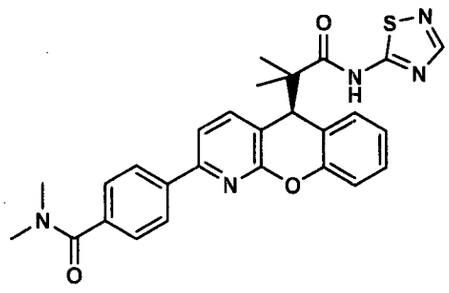
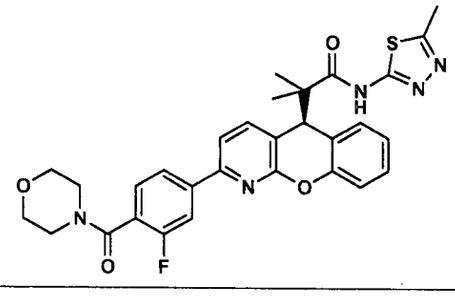


Usando procedimientos análogos para la preparación del Ejemplo 440, el compuesto del título se preparó por unión entre 2-amino-1,3,4-tiadiazol y el ácido de la Preparación 66. 1H RMN (400 MHz,

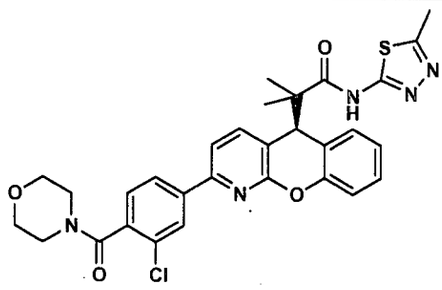
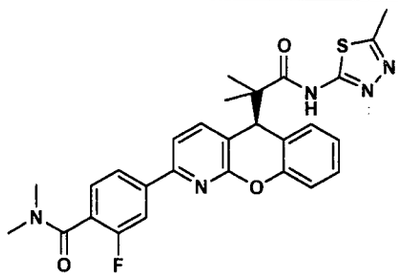
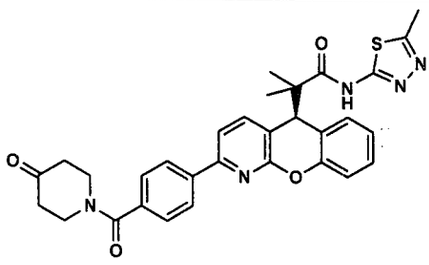
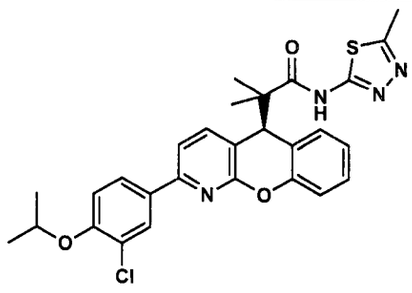
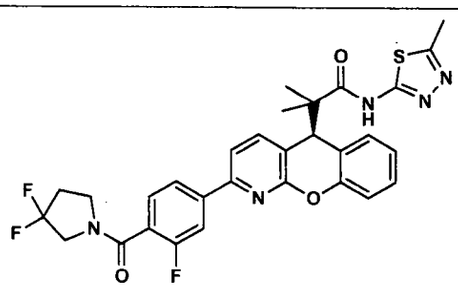
CDCl3) δ ppm 8.87 (s, 1 H), 7.49 - 7.60 (m, 2 H), 7.36 - 7.40 (m, 1 H), 7.28 - 7.33 (m, 2 H), 6.99 - 7.12 (m, 3 H), 4.86 (s, 2 H), 4.48 (s, 1 H), 1.26 (s, 3 H), 1.21 (s, 3 H); EM (E+) m/z: 465 (M+H); Tiempo de retención CL: 3.73 min (HPLC analítica del Método D).

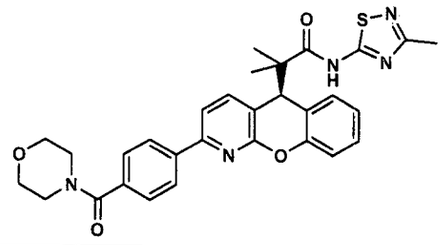
Ejemplos 471 hasta 478

Siguiendo procedimientos análogos para la Preparación 57, los siguientes Ejemplos se prepararon por unión de Suzuki entre ácidos borónico (comercialmente disponibles o preparados en Preparaciones 58, 61 y 64) e intermediarios de las Preparaciones 75 hasta 77.

No de Ejemplo.	Estructura	Tr (min)*	M/z (M+H)
471		3.97	500
472		4.00	574

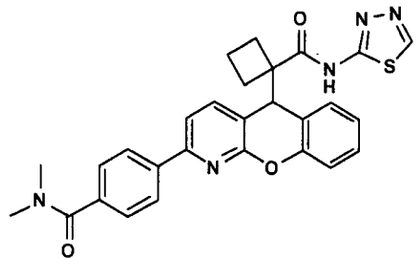
006733

No de Ejemplo.	Estructura	Tr (min)*	M/z (M+H)
473		4.07	590
474		3.98	532
475		3.85	568
476		4.68	535
477		4.16	594

No de Ejemplo.	Estructura	Tr (min)*	M/z (M+H)
478		3.99	556

* Método D de HPLC analítica.

Ejemplo 479



Etapa 1

A una solución en hexano 1.6 M de n-butil-litio (2.72 mL, 4.34 mmol) se agregó a una solución de diisopropilamina (440 mg, 4.34 mmol) en THF (6 mL) a -78 °C durante 5 minutos. La solución resultante se calentó hasta 0 °C durante 30 min y se enfrió hasta -78 °C. Una solución de ciclobutancarboxilato de etilo (464 mg, 3.62 mmol) en THF (1 mL) se agregó gota a gota. La mezcla se agitó a -78 °C durante 30 min. Se agregó clorotrimetilsilano (0.597 mL, 4.71 mmol). La mezcla se calentó a temperatura ambiente durante 1 h, se apagó con NaHCO3 saturado (5 mL), se diluyó con éter de dietilo (200 mL), se lavó con agua (20 mL), salmuera (20 mL), se secó

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(MgSO4) y se concentró para dar (ciclobutilideno(etoxi)metoxi)trimetilsilano, el cual se tomó para la siguiente etapa sin purificación adicional.

Etapa 2

Una solución en diclorometano 1.0 M de cloruro de titanio (IV) (0.254 mL, 0.254 mmol) se agregó a una solución del producto de la Preparación 83 (80 mg, 0.231 mmol) en diclorometano (10 mL) a 0 °C. Después de 10 min a 0 °C, se agregó el (ciclobutilideno(etoxi)metoxi)trimetilsilano sin refinar (350 mg, ~1.75 mmol). Después de 1 h a 0 °C, la mezcla se apagó con NaHCO3 saturado (5 mL), se diluyó con diclorometano (80 mL), se lavó con agua (10 mL), salmuera (10 mL), se secó (MgSO4) y se concentró. La purificación por cromatografía de columna por desorción súbita (gel de sílice, 50-100% acetato de etilo en hexanos) dio 1-(2-(4-(dimetilcarbomoil)fenil)-5H-cromeno[2,3-b]piridin-5-il)ciclobutanecarboxilato de etilo (80 mg, 76%). EM (ES+) m/z: 457 (M+H).

Etapa 3

El propan-2-tiolato de sodio (172 mg, 1.75 mmol) se agregó a una solución del producto de la Etapa 2 (80 mg, 0.175 mmol) en DMF (5 mL) a temperatura ambiente. Después de 15 h a 60 °C, la mezcla se enfrió a temperatura ambiente y se ajustó el pH2-3 con HCl 1 N acuoso. Después de la adición de acetato de etilo

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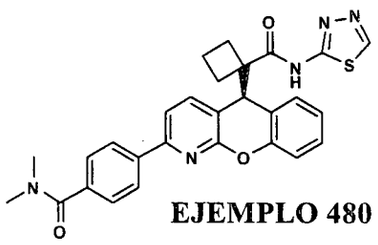
(100 mL), la mezcla se lavó con agua (10 mL), salmuera (10 mL), se secó (MgSO4) y se concentró. La purificación por HPLC preparativa dio el ácido 1-(2-(4-(dimetilcarbomoil)fenil)-5H-cromeno[2,3-b]piridin-5-il)ciclobutanecarboxílico deseado (45 mg, 60%). EM (ES+) m/z: 429 (M+H).

Etapa 4

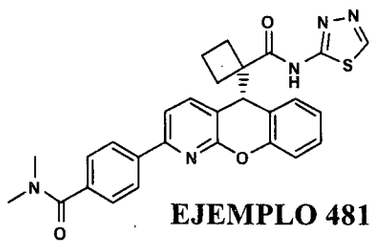
La mezcla del producto de la Etapa 3 (22 mg, 0.051 mmol), 1,3,4-tiadiazol-2-amina (10.4 mg, 0.103 mmol), EDC (19.7 mg, 0.103 mmol), HOBT (15.7 mg, 0.103 mmol) y DIEA (0.036 mL, 0.205 mmol) en acetonitrilo (2 mL) se calentó hasta 70 °C durante 15 h. Luego la mezcla se enfrió a temperatura ambiente, se apagó con NaHCO3 saturado (2 mL), se diluyó con acetato de etilo (60 mL), se lavó con agua (10 mL), salmuera (10 mL), se secó (MgSO4) y se concentró. El residuo se purificó por HPLC preparativa para dar el compuesto del título (12 mg, 46%). 1H-RMN (400 MHz, CDCl3) δ 11.93 (s, 1H), 8.93 (s, 1H), 8.06 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 7.6 Hz, 1H), 7.53 (m, 2H), 7.37 (d, J = 7.6 Hz, 1H), 7.28 (m, 3H), 7.07 (m, 1H), 4.69 (s, 1H), 3.14 (s, 3H), 3.01 (s, 3H), 2.45 (m, 4H), 1.67 (m, 1H), 1.31 (m, 1H); EM (ES+) m/z: 512 (M+H); HPLC tiempo de retención: 1.65 min (HPLC analítica del Método F).

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Ejemplos 480 Y 481



EJEMPLO 480



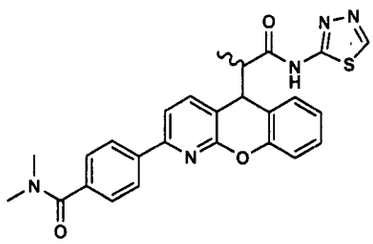
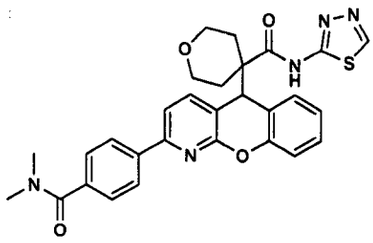
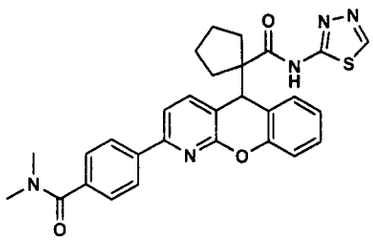
EJEMPLO 481

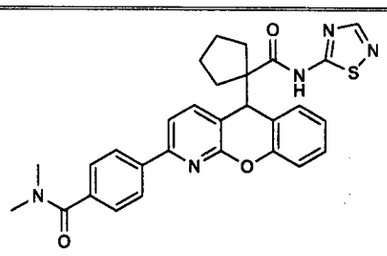
El compuesto del título del Ejemplo 480 (400 mg, 0.783 mmol) se purificó por SFC quiral (columna AD-H, CO_2/MeOH = 65/35) para proporcionar el Ejemplo 480 (enantiómero que eluye rápido, 113 mg, 28%) y el Ejemplo 481 (enantiómero que eluye lento, 120 mg, 30%). Datos para Ejemplo 480: ^{1}H-RMN (400 MHz, MeOH-d_4) δ 9.10 (s, 1H), 8.12 (d, J = 8.4 Hz, 2H), 7.75 (m, 2H), 7.56 (d, J = 8.4 Hz, 2H), 7.39 (m, 2H), 7.25 (m, 2H), 4.58 (s, 1H), 3.15 (s, 3H), 3.07 (s, 3H), 2.37 (m, 3H), 2.29 (m, 1H), 1.56 (m, 1H), 1.20 (m, 1H); EM (ES+) m/z: 512 (M+H); HPLC tiempo de retención: 1.65 min (HPLC analítica del Método F). Datos para Ejemplo 481: EM (ES+) m/z: 512 (M+H); HPLC tiempo de retención 1.65 min (HPLC analítica del Método F). Ambos enantiómeros son analizados usando HPLC quiral (columna quiralpak AD-H: 0.46x25 cm, 5 µm; temperatura: 40 °C; relación de flujo: 2.0 mL/min; fase móvil: CO_2/MeOH(65/35); Detector de longitud de onda: 252 nm). Tiempo de retenciones por Ejemplos 480 y 481 son 13.0 y 18.0 min, respectivamente.

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Ejemplos 482 hasta 485

Los Ejemplos 482 hasta 485 se prepararon en una secuencia similar al Ejemplo 479, substituyendo el propionato de metilo y ciclobutanocarboxilato de etilo por ciclobutanocarboxilato de etilo. Los Ejemplos 484 y 485 se prepararon siguiendo una secuencia similar para la Preparación 17, substituyendo el (ciclopentilideno(metoxi)-metoxi)trimetilsilano por metil trimetilsilil dimetilceteno acetal, Preparación 57 y unión con 2-amino-1,3,4-tiadiazol o 5-amino-1,2,4-tiadiazol.

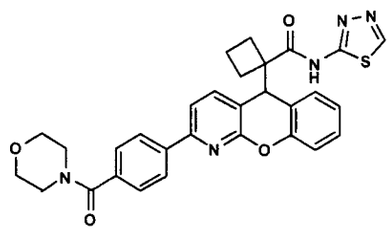
No de Ejemplo.	Estructura	Tr (min)*	M/z (M+H)
482		3.65*	486
483		1.89**	542
484		3.86*	526

No de Ejemplo.	Estructura	Tr (min)*	M/z (M+H)
485		4.04*	526

* HPLC analítica del Método D.

** HPLC analítica del Método F.

Ejemplos 486 Y 487



Etapa 1

Siguiendo procedimientos similares para la Etapa 2 del Ejemplo 479, el alcohol de la Preparación 84 (700 mg, 2.10 mmol) se hace reaccionar con (ciclobutilideno(etoxi)metoxi)trimetilsilano para dar 4-(5-(1-(etoxicarbonil)ciclobutil)-5H-cromeno[2,3-b]piridin-2-il)benzoato de metilo (250 mg, 27%). EM (ES+) m/z: 444 (M+H).

Etapa 2

Una solución 1 N acuosa de NaOH (5 mL, 5.00 mmol) se agregó a una solución del producto de la Etapa 1 (250 mg, 0.564 mmol) en MeOH (10 mL) a temperatura ambiente. Después de 24 h a 80 °C, la mezcla se enfrió a temperatura ambiente y se

ajustó el pH2-3 con HCl 1 N acuoso. MeOH se evaporó *in vacuo*. El precipitado café en el residuo acuoso se colectó por filtración y se secó bajo vacío para dar el ácido 4-(5-(1-carboxiciclobutil)-5H-cromeno[2,3-b]piridin-2-il)benzóico (210 mg, 93%). EM (ES+) m/z: 402 (M+H).

Etapa 3

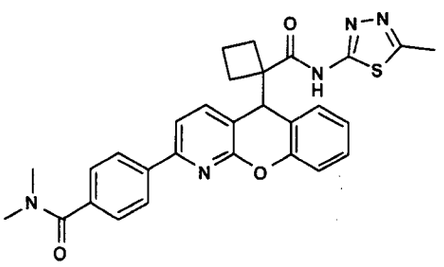
Una mezcla del producto de la Etapa 2 (50 mg, 0.125 mmol), EDC (71.6 mg, 0.374 mmol), HOBT (57.2 mg, 0.374 mmol) y DIEA (0.131 mL, 0.747 mmol) en acetonitrilo (2 mL) se agitó a temperatura ambiente durante 10 min y se enfrió hasta 0 °C. Una solución de morfolina (13.1 mg, 0.149 mmol) en acetonitrilo (1 mL) se agregó gota a gota. La mezcla resultante se agitó hasta 0 °C durante 1 h, se apagó con NH_4Cl saturado (2 mL). Después de la adición de acetato de etilo (60 mL), la mezcla se lavó con agua (5 mL), salmuera (5 mL), se secó (MgSO4) y se concentró para proporcionar 1-(2-(4-(morfolina-4-carbonil)fenil)-5H-cromeno[2,3-b]piridin-5-il)ciclobutanecarboxilato de 1H-benzo[d][1,2,3]triazol-1-ilo (75 mg), el cual se tomó para la siguiente etapa sin purificación adicional. EM (ES+) m/z: 588 (M+H).

Etapa 4

Siguiendo procedimientos similares como en la Etapa 4 del Ejemplo 479, el producto de la Etapa 3 (73.5 mg, 0.125 mmol) se convirtió al producto deseado (32 mg, 46%). La mezcla racemica se separó por SFC quiral (columna AD-H, CO_2/MeOH =

65/35) para proporcionar el Ejemplo 486 (enantiómero que eluye rápido, 10 mg) y el Ejemplo 487 (enantiómero que eluye lento, 10 mg). Datos para el Ejemplo 486: ^{1}H-RMN (400 MHz, MeOH-d_4) δ 8.99 (s, 1H), 8.02 (d, J = 8.4 Hz, 2H), 7.63 (m, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.27 (m, 2H), 7.13 (m, 2H), 4.45 (s, 1H), 3.40-3.80 (m, 8H), 2.25 (m, 3H), 2.15 (m, 1H), 1.40 (m, 1H), 1.15 (m, 1H); EM (ES+) m/z: 554 (M+H); HPLC tiempo de retención: 2.01 min (HPLC analítica del Método E). Datos para Ejemplo 487: EM (ES+) m/z: 554 (M+H); HPLC tiempo de retención: 2.02 min (HPLC analítica del Método E). Ambos enantiómeros se analizan usando HPLC quiral (columna quiralpak AD-H: 0.46x25 cm, 5 µm; temperatura: 40°C; relación de flujo: 3.0 mL/min; fase móvil: CO_2/MeOH(65/35); Detector de longitud de onda: 270 nm). Tiempos de retención para los Ejemplos 486 y 487 son 9.2 y 13.4 min, respectivamente.

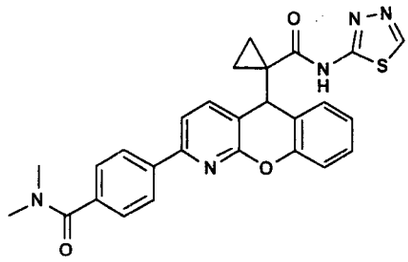
Ejemplo 488



Siguiendo procedimientos similares para las Etapas 3 y 4 de los Ejemplos 486 y 487, el producto de la Etapa 2 de los Ejemplos 486 y 487 (50 mg, 0.125 mmol) se convirtió al compuesto del título (5.8 mg, 7%). EM (ES+) m/z: 526 (M+H);

HPLC tiempo de retención: 2.03 min (HPLC analítica del Método E).

Ejemplo 489



Etapa 1

Siguiendo procedimientos similares para la Etapa 2 del Ejemplo 479, alcohol de la Preparación 83 (160 mg, 0.462 mmol) se convirtió al ácido metil 2-(2-(4-(dimetilcarbomoil)fenil)-5H-cromeno[2,3-b]piridin-5-il)acético (170 mg, 92%). EM (ES+) m/z: 403 (M+H); HPLC tiempo de retención: 1.65 min (HPLC analítica del Método F).

Etapa 2

Una solución de hexano 1.6 M de n-butil-litio (0.38 mL, 0.62 mmol) se agregó a una solución de diisopropilamina (0.089 mL, 0.62 mmol) en THF (5 mL) a -78 °C durante 5 min. La solución resultante se calentó hasta 0 °C durante 30 min y se enfrió hasta -78 °C. Una solución del producto de la Etapa 1 (100 mg, 0.248 mmol) en THF (1 mL) se agregó gota a gota. La mezcla se agitó a -78 °C durante 30 min y a -30 °C durante 30 min. El formaldehído (60 mg) se burbujeó en la mezcla por una corriente de N2 a -30 °C. La mezcla resultante se agitó a -30

°C durante 30 min, se apagó con MeOH (1 mL) y calentó a temperatura ambiente. Después de la adición de acetato de etilo (80 mL), la mezcla se lavó con NaHCO3 saturado (10 mL), agua (10 mL), salmuera (10 mL), se secó (MgSO4) y se concentró. El residuo se purificó por cromatografía de columna por desorción súbita (sílice, 50-100% acetato de etilo en hexanos) para proporcionar 2-(2-(4-(dimetilcarbomoil)fenil)-5H-cromeno[2,3-b]piridin-5-il)-3-hidroxipropanoato de metilo (80 mg, 74%). EM (ES+) m/z: 433 (M+H).

Etapa 3

El cloruro de metanosulfonilo (0.072 mL, 0.925 mmol) se agregó a una mezcla del producto de la Etapa 2 (80 mg, 0.185 mmol), TEA (0.258 mL, 1.85 mmol) y DMAP (24.9 mg, 0.203 mmol) en DCM (2 mL) a 0 °C. Después de 1 h a esta temperatura, la mezcla se concentró *in vacuo*. El residuo se suspendió en benzeno (4 mL), se trató con DBU (0.139 mL, 0.925 mmol) y se agitó a temperatura ambiente durante 1 h. Se agregan $NaHCO_3$ saturado (5 mL) y acetato de etilo (100 mL). La mezcla se lavó con agua (2x10 mL), salmuera (10 mL), se secó (MgSO4) y se concentró. El residuo se purificó por cromatografía de columna por desorción súbita (sílice, 50-100% acetato de etilo en hexanos) para proporcionar 2-(2-(4-(dimetilcarbomoil)fenil)-5H-cromeno[2,3-b]piridin-5-il)acrilato de metilo (45 mg, 59%). EM (ES+) m/z: 415 (M+H); HPLC tiempo de retención: 1.73 min (HPLC analítica del Método F).

Etapa 4

El hidruro de sodio (5.2 mg, 0.13 mmol, 60% en aceite mineral) se agregó a una solución de yoduro de trimetil sulfoxonio (28.7 mg, 0.13 mmol) en DMSO (1 mL) a temperatura ambiente. Después de 30 min a temperatura ambiente, la mezcla se agregó a una solución del producto de la Etapa 3 (45 mg, 0.109 mmol) en DMSO (1 mL). La mezcla resultante se agitó a temperatura ambiente durante 10 min y se apagó con $NaHCO_3$ saturado (1 mL). Después de la adición de acetato de etilo (80 mL), la mezcla se lavó con agua (2x10 mL), salmuera (10 mL), se secó (MgSO4) y se concentró. El residuo se purificó por cromatografía de columna por desorción súbita (sílice, 50-100% acetato de etilo en hexanos) para proporcionar 1-(2-(4-(dimetilcarbomoil)fenil)-5H-cromeno[2,3-b]piridin-5-il)ciclopropanocarboxilato de metilo (12 mg, 26%). EM (ES+) m/z: 429 (M+H).

Etapa 5

Una solución de NaOH 1 N acuoso (0.5 mL, 0.500 mmol) se agregó a una solución del producto de la Etapa 4 (11 mg, 0.026 mmol) en MeOH (1 mL) a temperatura ambiente. La mezcla se calentó hasta 60 °C durante 3 h, se enfrió a temperatura ambiente y se ajustó el pH2-3 con HCl 1 N acuoso. Seguido por adición de acetato de etilo (60 mL), la mezcla se lavó con salmuera (10 mL), se secó (MgSO4) y se concentró para dar ácido 1-(2-(4-(dimetilcarbomoil)fenil)-5H-cromeno[2,3-

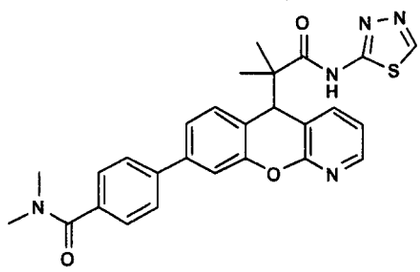
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b]piridin-5-il)ciclopropanocarboxílico como material sin refinar (11 mg), el cual se tomó para la siguiente etapa directamente. EM (ES+) m/z: 415 (M+H).

Etapa 6

Siguiendo procedimientos similares para la Etapa 4 del Ejemplo 479, el producto de la Etapa 5 (11 mg, 0.027 mmol) se convirtió al compuesto del título (5.0 mg, 40%). ^{1}H-RMN (400 MHz, MeOH-d_4) δ 8.90 (s, 1H), 8.42 (s, 1H), 8.00 (d, J = 8.4 Hz, 2H), 7.85 (m, 1H), 7.58 (m, 1H), 7.43 (d, J = 8.4 Hz, 2H), 7.24 (m, 2H), 7.10 (m, 2H), 4.65 (s, 1H), 3.02 (s, 3H), 2.94 (s, 3H), 1.13 (m, 4H); EM (ES+) m/z: 498 (M+H); HPLC tiempo de retención: 2.04 min (HPLC analítica del Método E).

Ejemplo 490



Etapa 1

Una solución en hexano 1.6 M de n-butil-litio (39.8 mL, 63.6 mmol) se agregó a una solución de diisopropilamina (9.45 mL, 66.3 mmol) en THF (100 mL) a -78 °C durante 10 min. La solución resultante se agitó a 0 °C durante 30 min y se enfrió hasta -78 °C. Se agregó acetonitrilo (3.32 mL, 63.6 mmol) gota a gota. La mezcla se agitó a -78 °C durante 30 min y luego se

agregó una solución de 4-cloro-2-fluorobenzoato (5.00 g, 26.5 mmol) en THF (5 mL) a -78 °C gota a gota. Después de agitar durante 1 h a -78 °C, la mezcla de reacción se apagó con salmuera (20 mL), se calentó a temperatura ambiente y se ajustó a pH1-2 con HCl acuoso 1N. Después de la adición de acetato de etilo (400 mL), la mezcla se lavó con agua (40 mL), salmuera (40 mL), se secó ($MgSO_4$) y se concentró para proporcionar 3-(4-cloro-2-fluorofenil)-3-oxopropanonitrilo como sólido color canela (5.10 g, 97%). EM (ES+) m/z: 198 (M+H).

Etapa 2

Una mezcla de (E)-3-(dimetilamino)acrilaldehído (3.26 g, 32.9 mmol), el producto de la Etapa 1 (5. 00 g, 25.3 mmol) y ácido acético (7.24 mL, 127 mmol) en DMF (40 mL) se calentó hasta 120 °C durante 48 h y se enfrió a temperatura ambiente. Se agregó acetato de etilo (400 mL) y la mezcla se lavó con $NaHCO_3$ saturado (40 mL), agua (40 mL), salmuera (40 mL), se secó (MgSO4) y se concentró. El residuo se purificó por cromatografía de columna por desorción súbita (sílice, 10-40% acetato de etilo en hexanos) para proporcionar 8-cloro-5H-cromeno[2,3-b]piridin-5-ona (600 mg, 10%). EM (ES+) m/z: 232 (M+H).

Etapa 3

El borohidruro de sodio (490 mg, 13.0 mmol) se agregó a una solución del producto de la Etapa 2 (600 mg, 2.59 mmol) en

MeOH (16 mL) y diclorometano (4 mL) a 0 °C. Después de 2 h a esta temperatura, la mezcla se apagó con $NaHCO_3$ saturada (5 mL). Los solventes orgánicos se evaporan *in vacuo*. El residuo se disolvió en diclorometano (100 mL), se lavó con agua (10 mL), salmuera (10 mL), se secó (MgSO4) y se concentró hasta 8-cloro-5H-cromeno[2,3-b]piridin-5-ol sin refinar (600 mg), el cual se tomó directamente para la siguiente etapa. EM (ES+) m/z: 234 (M+H).

Etapa 4

Siguiendo procedimientos similares como en la Etapa 2 del Ejemplo 479, el producto de la etapa 3 (600 mg, 2.59 mmol) se convirtió a 2-(8-cloro-5H-cromeno[2,3-b]piridin-5-il)-2-metilpropanoato de metilo (450 mg, 55%). EM (ES+) m/z: 318 (M+H).

Etapa 5

Un matraz de 25 mL que contiene Pd(dba)2 (25.3 mg, 0.044 mmol) se lavó con un flujo de N2. Se agregan dioxano (2 mL) y una solución THF 1.0 M de triciclohexilfosfina (0.106 mL, 0.106 mmol). La mezcla negra resultante se agitó a temperatura ambiente durante 30 min. Se agregan sucesivamente bis(pinacolato)diboro (123 mg, 0.485 mmol), fosfato de potasio (64.9 mg, 0.661 mmol) y el producto de la Etapa 4 (140 mg, 0.441 mmol). La mezcla se calentó hasta 80 °C durante 15 h y se enfrió a temperatura ambiente. Seguido por adición de agua (5 mL) y diclorometano (80mL), la mezcla se lavó con agua (10

mL), salmuera (10 mL), se secó (MgSO4) y se concentró. El residuo se purificó por cromatografía de columna por desorción súbita (sílice, 0-40% acetato de etilo en hexanos) para proporcionar el 2-metil-2-(8-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-5H-cromeno[2,3-b]piridin-5-il)propanoato de metilo (65 mg, 36%). EM (ES+) m/z: 410 (M+H).

Etapa 6

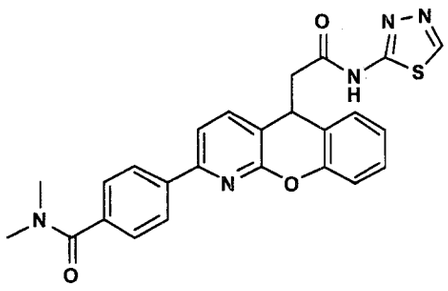
Una mezcla del producto de la Etapa 5 (65 mg, 0.159 mmol), 4-bromo-N,N-dimetilbenzamida (72.4 mg, 0.318 mmol), fosfato de potasio 2.0 M acuoso (0.397 mL, 0.794 mmol) y Pd(Ph3P)4 (27.5 mg, 0.024 mmol) en DMF (3 mL) se purgó con N2, se calentó hasta 100 °C durante 15 h, y se enfrió a temperatura ambiente. Después de la adición de acetato de etilo (80 mL), la mezcla se lavó con agua (10 mL), salmuera (10 mL), se secó (MgSO4) y se concentró. El residuo se purificó por cromatografía de columna por desorción súbita (sílice, 30-100% acetato de etilo en hexanos) para proporcionar el 2-(8-(4-(dimetilcarbomoil)fenil)-5H-cromeno[2,3-b]piridin-5-il)-2-metilpropanoato de metilo (50 mg, 73%). EM (ES+) m/z: 431 (M+H).

Etapa 7

Siguiendo procedimientos similares a la Etapa 4 hasta 5 del Ejemplo 479, el producto de la Etapa 6 (50 mg, 0.116 mmol) se convirtió al compuesto del título (3.0 mg, 5%). ^{1}H-RMN (400

MHz, CDCl3) δ 8.90 (s, 1H), 8.38 (s, 1H), 7.75 (m, 1H), 7.63 (m, 2H), 7.52 (m, 3H), 7.35 (m, 2H), 7.20 (m, 2H), 4.62 (s, 1H), 3.20 (s, 3H), 3.09 (s, 3H), 1.27 (s, 3H), 1.26 (s, 3H); EM (ES+) m/z: 500 (M+H); HPLC tiempo de retención: 2.01 min (Método E de la HPLC analítica).

Ejemplo 491



Etapa 1

El alilclorodimetilsilano (0.124 mL, 0.85 mmol) y cloruro de indio (18.8 mg, 0.085 mmol) se agregan a una solución amarilla del alcohol de la Preparación 83 (147 mg, 0.425 mmol) en diclorometano (25 mL). Después de 15 h a temperatura ambiente, se agregó otra porción de alilclorodimetilsilano (0.124 mL, 0.85 mmol). Después de la adición 6 h a temperatura ambiente, la mezcla se concentró y se purificó por cromatografía en gel de sílice (50% to 100% acetato de etilo en hexano) para dar 4-(5-alil-5H-cromeno[2,3-b]piridin-2-il)-N,N-dimetilbenzamida como un líquido amarillo (160 mg, ~90% pure). EM (ES+) m/z: 371 (M+H); HPLC tiempo de retención: 4.05 min (Método D de la HPLC analítica).

Etapa 2

El ozono se burbujeó a través de una solución del producto de la Etapa 1 (40 mg, 0.108mmol) en diclorometano (3 mL) y metanol (3 mL) a -78 °C hasta que la solución se torna azul. La solución se purgó con nitrógeno hasta que el color azul desaparece. Se agregó trifenilfosfina soportada en poliestireno (432 mg, 1 mmol/g). Después de 6 h de agitación a temperatura ambiente, la mezcla se filtró a través de un tapón de celite y el tapón se enjuagó con acetato de etilo. El filtrado se concentró hasta N,N-dimetil-4-(5-(2-oxoetil)-5H-cromeno[2,3-b]piridin-2-il)benzamida sin refinar, el cual se usó sin purificación. EM (ES+) m/z: 405 (M+MeOH+H).

Etapa 3

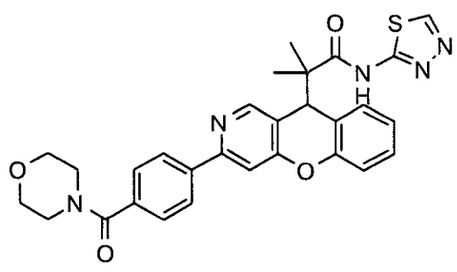
A una mezcla de aldehído de la Etapa 2, dihidrogenfosfato de potasio (0.047 ml, 0.810 mmol), y cloruro de sodio (0.098 g, 1.080 mmol) se agregan t-butanol (4 ml), una solución de THF 2 M de 2-metil-2-buteno (2 ml, 4.00 mmol) y agua (2 ml). Después de agitar a temperatura ambiente durante 2 h, el solvente orgánico se evaporó *in vacuo*. El residuo se recibió en acetato de etilo (50 mL), se lavó con salmuera (2x10 mL), se secó (MgSO4) y se concentró. La cromatografía en gel de sílice, usando 0 hasta 20% de metano en diclorometano dio ácido 2-(2-(4-(dimetilcarbomoil)fenil)-5H-cromeno[2,3-b]piridin-5-il)acético impuro, el cual se tomó para la siguiente etapa sin purificación adicional.

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Etapa 4

A una solución del ácido impuro de la Etapa 3 en acetonitrilo (5 mL) se agregó HOBT (24.81 mg, 0.162 mmol), EDC (31.1 mg, 0.162 mmol), 1,3,4-tiadiazol-2-amina (21.84 mg, 0.216 mmol) y Base de Hunig (0.094 ml, 0.540 mmol). La mezcla se agitó a temperatura ambiente durante 3 h y a 60°C durante 1 h. Los solventes orgánicos se evaporan *in vacuo*. El residuo se diluyó con NH4Cl saturado (10 mL) y se extrajo con diclorometano (3x10 mL). Los extractos combinados se concentraron y se purificaron por HPLC de fase inversa (YMC ODS S5 30x100 mm columna) para dar el compuesto del título como una sal de TFA (11.6 mg, 18% de rendimiento sobre tres etapas). ^{1}H-RMN (400 MHz, MeOH-d4) δ 8.93 (s, 1H), 7.98 -7.96 (m, 2H), 7.77 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.45 - 7.41 (m, 2H), 7.26 - 7.18 (m, 2H), 7.12 - 7.10 (m, 1H), 7.04 - 7.00 (m, 1H), 4.66 (t, J = 6.9 Hz, 1H), 3.02 (s, 3H), 2.93 (s, 3H), 2.88-2.85 (m, 2H); EM (ES+) m/z: 472 (M+H); HPLC tiempo de retención: 3.58 min (HPLC analítica del Método D).

Ejemplo 492



Etapa 1

Una solución de hexano 2.5 M de BuLi (16.46 mL, 41.1 mmol) se agregó gota a gota a una solución de diisopropilamina (6.11 mL, 42.9 mmol) en THF (150 mL) a -78 °C. La mezcla se agitó a 0 °C durante 15 min y se enfrió a -78 °C. La acetona (3.02 mL, 41.1 mmol) se agregó gota a gota. Después de 2 h a -78 °C, se agregó 2-cloruro de clorobenzoilo (3.00 g, 17.14 mmol) en THF (10 mL) gota a gota. El matraz se enjuagó con THF (2 mL) y se agregó. Después de 1 h a -78 °C, la mezcla se apagó con salmuera (200 mL) y se acidificó a pH ~1 con HCl 1 N. Los solventes orgánicos se evaporan *in vacuo*. El residuo acuoso se extrajo con EtOAc (3x100 mL). Los extractos combinados se secaron (MgSO4) y se concentró para dar 1-(2-clorofenil)butane-1,3-diona sin refinar como un líquido amarillo. El material sin refinar se tomó para la siguiente etapa con purificación. EM (ES+) m/z: 197 (M+H).

Etapa 2

Una mezcla de 1-(2-clorofenil)butano-1,3-diona sin refinar de la etapa anterior y 1,1-dimetoxi-N,N-dimetilmetanamina (2.042 g, 17.14 mmol) en tolueno (20 mL) se calentó a reflujo durante 2 h y se concentró. La cromatografía en gel de sílice, usando 70 hasta 100% acetato de etilo en gradientes de hexano, dio 1-(2-clorofenil)-2-((dimetilamino)metileno)butan-1,3-diona como un aceite rojo viscoso (2.20 g, 51% de rendimiento por 2 etapas). EM (ES+)

m/z: 252 (M+H); HPLC tiempo de retención: 2.51 min (Método D de la HPLC analítica).

Etapa 3

Una solución 1.0 M de LiHMDS (19.86 mL, 19.86 mmol) se agregó gota a gota a una solución de 1-(2-clorofenil)-2-((dimetilamino)metileno)butano-1,3-diona (2.00 g, 7.95 mmol) y 4-(clorocarbonil)benzoato de metilo (1.894 g, 9.53 mmol) en THF (100 mL) a -78 °C. Después de 1 h a -78 °C, el baño de enfriamiento se removió y se agregan ácido acético (5 mL) y acetato de amonio (1.225 g, 15.89 mmol). La mezcla se calentó hasta 70 °C durante 1 h, a reflujo durante 1.5 h, se concentró para secarse *in vacuo* y se tomó en N,N-dimetilacetamida (50 mL). Después de agregar el ácido acético (5 mL), la mezcla se calentó hasta 140°C durante 24 h, se enfrió a temperatura ambiente, se diluyó con MeOH (100 mL) y agua (10 mL), se enfrió hasta 0°C durante 30 min y se filtró. El sólido se lavó con MeOH tres veces para dar una mezcla 7:3 de 4-(10-oxo-10H-cromen[3,2-c]piridin-3-il)benzoato de metilo y ácido 4-(10-oxo-10H-cromeno[3,2-c]piridin-3-il)benzóico.

Etapa 4

Una mezcla de los productos de la Etapa 3, solución 1 N de NaOH (50 mL, 50.0 mmol), MeOH (50 mL) y THF (50 mL) se calentó hasta reflujo. Después de 1 h, se agregan MeOH (50 mL) y DMF (10 mL) adicionales para ayudar a disolver el material de partida. Después de un total de 6 h a reflujo, la mezcla se

enfrió a temperatura ambiente y se acidificó a pH~3 con HCl 1 N. El precipitado se colectó por filtración y se lavó con agua tres veces para dar ácido 4-(10-oxo-10H-cromeno[3,2-c]piridin-3-il)benzóico como un sólido color canela (906 mg, 36% por 2 etapas). EM (ES+) m/z: 318 (M+H).

Etapa 5

El HOBt (145 mg, 0.945 mmol), EDC (181 mg, 0.945 mmol) y la base de Hunig (0.550 mL, 3.15 mmol) se agregan a una suspensión de ácido 4-(10-oxo-10H-cromen[3,2-c]piridin-3-il)benzóico (200 mg, 0.630 mmol) en DMF (15 mL) y CH_2Cl_2 (10 mL) a temperatura ambiente. Después de 5 min, se agregó morfolina (0.110 mL, 1.261 mmol). Después de 13 h a temperatura ambiente, la mezcla se apagó con NH4Cl saturado (50 mL) y se extrajo con CH_2Cl_2 (3x50 mL). Los extractos combinados se secaron (MgSO4) y se concentraron para dar 3-(4-(morfolina-4-carbonil)fenil)-10H-cromeno[3,2-c]piridin-10-ona sin refinar, el cual se tomó para la siguiente reacción sin purificación. EM (ES+) m/z: 387 (M+H).

Etapa 6

El $NaBH_4$ (0.238 g, 6.30 mmol) se agregó a una suspensión de la 3-(4-(morfolina-4-carbonil)fenil)-10H-cromeno[3,2-c]piridin-10-ona sin refinar de la Etapa 5 en MeOH (50 mL) y CH_2Cl_2 (20 mL) a 0°C. Después de 1 h a 0 °C, la mezcla permaneció en suspensión, y HPLC y CLEM indican que no se forman productos. El baño de enfriamiento se removió. Adicionalmente se agregan MeOH (50 mL), CH_2Cl_2 (30 mL) y NaBH4 (0.5 g). Después de 2.5 h, otro baño de NaBH4 (0.5 g) se agregó. Después de 30 min, la mezcla se apagó con NH4Cl saturado (100 mL). El solvente orgánico se evaporó *in vacuo*. El residuo acuoso se extrajo con CH_2Cl_2

(3x100 mL). Los extractos combinados se secaron (MgSO4) y se concentró para dar la (4-(10-hidroxi-10H-cromeno[3,2-c]piridin-3-il)fenil)(morfolino)metanona sin refinar, la cual se tomó para la siguiente reacción con purificación.

Etapa 7

A una solución de la (4-(10-hidroxi-10H-cromeno[3,2-c]piridin-3-il)fenil)(morfolino)metanona sin refinar de la Etapa 6 en CH_2Cl_2 (50 mL) a 0°C se agregó a una solución en CH_2Cl_2 1 M de cloruro de titanio (IV) (1.890 mL, 1.89 mmol). La suspensión resultante color canela se agitó a 0 °C durante 5 min. Se agregó el metil trimetilsilil dimetilceteno acetal (0.512 mL, 2.52 mmol). La mezcla se agitó a 0 °C durante 1 h, se apagó con $NaHCO_3$ saturado (50 mL) y se filtró a través de un tapón de celite para remover la sal de titanio insoluble. El tapón del filtro se enjuaga con CH_2Cl_2. Las dos fases del filtrado se separan. La fase acuosa se extrajo con CH_2Cl_2 (2x50 mL). La fase de CH_2Cl_2 combinada (72170-085-01) se secó ($MgSO_4$) y se concentró. La cromatografía en gel de sílice, usando 60-100% acetato de etilo en gradiente de hexano, dio 2-metil-2-(3-(4-(morfolina-4-carbonil)fenil)-10H-cromeno[3,2-c]piridin-10-il)propanoato de metilo como un sólido blanco (179.2 mg, 60% de rendimiento durante 3 etapas).

Etapa 8

El 2-propanotiolato de sodio(58.5 mg, 0.596 mmol) se agregó a una solución de 2-metil-2-(3-(4-(morfolina-4-carbonil)fenil)-10H-cromeno[3,2-c]piridin-10-il)propanoato de metilo (140.9 mg, 0.298 mmol) en DMF (5 mL) y la mezcla se calentó hasta 50 °C. Después de 1 h a 50

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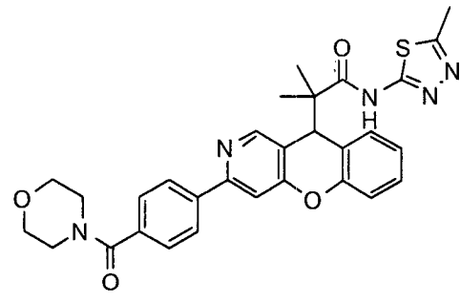
°C, se agregó 2-propanotiolato de sodio (58.5 mg) adicional. La mezcla se agitó a 50 °C durante la noche. Se agregó otra porción de 2-propanotiolato de sodio (200 mg). Después de otra hora a 50 °C, la mezcla se apagó con NH_4Cl saturado (20 mL) y se extrajo con EtOAc (4x20 mL). Los extractos combinados se lavaron con salmuera (5 mL), se secaron ($MgSO_4$) y se concentraron para dar el ácido 2-metil-2-(3-(4-(morfolina-4-carbonil)fenil)-10H-cromeno[3,2-c]piridin-10-il)propanóico como un sólido (145.5 mg). EM (ES+) m/z: 459 (M+H); HPLC tiempo de retención: 3.51 min (HPLC analítica del Método D).

Etapa 9

La base de Hunig (0.072 mL, 0.410 mmol) se agregó a una mezcla del ácido 2-metil-2-(3-(4-(morfolina-4-carbonil)fenil)-10H-cromeno[3,2-c]piridin-10-il)propanóico (31.3 mg, 0.068 mmol), HOBT (20.91 mg, 0.137 mmol), EDC (26.2 mg, 0.137 mmol) y 1,3,4-tiadiazol-2-amina (20.71 mg, 0.205 mmol) en DMF (2 mL). La mezcla se agitó a temperatura ambiente durante 5 min, a 60 °C durante 1 h, a 80 °C durante 4 h y se concentró. La purificación por HPLC de fase inversa preparativa (usando cromatógrafos para líquidos Shimadzu 10A y columnas Waters Sunfire S10 30 x 250 mm) dio el Ejemplo XX como un sólido blanco (25.5 mg, 57% de rendimiento), asumido como sal de TFA. 1H RMN (400 MHz, CD3OD) δ ppm 9.13 (s, 1 H), 8.63 (s, 1 H), 8.07 (s, 1 H), 8.05 (d, J = 8.26 Hz, 2 H), 7.70 (d, J = 8.22 Hz, 2 H), 7.45-7.49 (m, 1 H), 7.36-7.38 (m, 2 H), 7.28-7.30 (m, 1 H), 4.83 (s, 1 H), 3.81 (s amp., 4 H), 3.68 (s amp., 2 H), 3.50 (s amp.,

2 H), 1.27 (s, 3 H), 1.25 (s, 3H); EM (E+) m/z: 542 (M+H); Tiempo de retención CL: 3.52 min (HPLC analítica del Método D).

Ejemplo 493



Siguiendo procedimientos análogos para la Etapa 9 del Ejemplo 492, el compuesto del título se preparó a partir del ácido 2-metil-2-(3-(4-(morfolina-4-carbonil)fenil)-10H-cromeno[3,2-c]piridin-10-il)propanóico y 5-metil 1,3,4-tiadiazol-2-amina. EM (E+) m/z: 556 (M+H); Tiempo de retención CL: 3.68 min (HPLC analítica del Método D).

Datos de actividad biológica

La actividad AP-1 de los Ejemplos 1 hasta 491 se da donde el AP-1 EC_{50} es menor que 1 uM. también se dan los valores máximos acompañantes del inhibidor AP-1. Donde EC_{50} de AP-1 es mayor que 1 uM y/o la inhibición máxima es menor que 20%, se proporciona la afinidad del enlace del receptor glucocorticoide (GR) (Ki).

Los datos presentados anteriormente se obtienen usando los ensayos referidos en la tabla y descritos en la presente en la sección de ENSAYO *supra*.

No de Ejemplo.	GR (Ki, nM) (Ensayo de enlace GR(I)[a])	GR (Ki, nM) (Ensayo de enlace GR(II)[b])	EC_{50} AP-1, nM (Ensayo de Trans-represión Celular)	%inh.Max AP-1 (Ensayo de Trans-represión Celular)
1			156.90	69.29
2				42.73
3				47.84
4				56.46
5			58.20	65.97
6			460.60	67.91
7			302.70	64.91
8			546.20	69.02
9		154.20		
10			16.80	86.50
11			881.90	68.50
12			460.60	67.91
13			566.50	60.26
14		5455.00		
15			501.30	65.89
16			303.40	59.92
17			334.90	67.95
18			541.90	37.62
19				52.68
20			473.30	46.87
21				60.79
22		1637.00		
23		445.20		
24			15.72	78.77
25		41.10		
26				26.90
27				14.96
28				43.67
29			139.00	66.36
30			337.80	67.25
31			178.70	69.38
32			301.50	67.61
33			31.76	55.20
34			3.52	71.85
35			80.64	72.28
36		1040.00		
37		1.40		
38				70.38

030759

No de Ejemplo.	GR (Ki, nM) (Ensayo de enlace GR(I)[a])	GR (Ki, nM) (Ensayo de enlace GR(II)[b])	EC_{50} AP-1, nM (Ensayo de Trans-represión Celular)	%inh.Max AP-1 (Ensayo de Trans-represión Celular)
39		39.70		
40			461.00	47.76
41			5.82	73.76
42			3.70	73.41
43			13.41	71.92
44				69.30
45			102.40	71.48
46			90.23	67.62
47			534.10	66.66
48		60.90		
49			40.29	68.76
50			165.20	74.75
51			6.87	77.91
52			212.90	70.81
53			78.51	72.00
54			13.11	71.39
55			21.47	75.53
56		233.30		
57			11.54	74.78
58			3.71	70.02
59			11.76	58.39
60		35.70		
61		909.00		
62		58.00		
63				75.82
64			19.86	79.28
65			345.40	32.22
66		665.20		
67		107.00		
68		820.20		
69		515.40		
70		761.70		
71		517.20		
72	>1154			
73			735.40	60.62
74			318.60	71.16
75		29.00		
76		76.40		

No de Ejemplo.	GR (Ki, nM) (Ensayo de enlace GR(I)[a])	GR (Ki, nM) (Ensayo de enlace GR(II)[b])	EC_{50} AP-1, nM (Ensayo de Trans-represión Celular)	%inh.Max AP-1 (Ensayo de Trans-represión Celular)
77			91.63	73.89
78			163.80	65.08
79			9.42	62.34
80	56.09			
81		242.90		
82			125.80	72.61
83			15.03	69.64
84		103.70		
85				88.40
86		32.90		
87			91.11	45.95
88			127.70	49.23
89			18.08	68.32
90			6.43	59.47
91		2554.00		
92		1200.00		
93		1266.00		
94		403.50		
95			574.10	52.19
96		22.10		
97		296.00		
98		88.70		
99		18.30		
100			256.10	71.73
101	19.76			
102			57.97	45.01
103	6.06			
104	4.50			
105			12.19	30.54
106			24.12	48.41
107			833.30	22.82
108	13.60			
109			182.50	60.22
110			183.40	35.68
111			14.60	40.67
112		9.30		
113	62.63			
114	49.90			

No de Ejemplo.	GR (Ki, nM) (Ensayo de enlace GR(I)[a])	GR (Ki, nM) (Ensayo de enlace GR(II)[b])	EC_{50} AP-1, nM (Ensayo de Trans-represión Celular)	%inh.Max AP-1 (Ensayo de Trans-represión Celular)
115			3.90	31.34
116	346.10			
117	123.10			
118	76.60			
119			83.02	45.30
120			29.63	40.32
121			59.45	44.82
122	79.97			
123	17.82			
124	65.14			
125			94.33	33.24
126			49.73	30.84
127		29.70		
128			92.02	66.34
129			307.30	39.52
130			111.00	31.48
131			970.00	45.65
132			95.98	50.08
133			584.90	61.32
134		444.10		
135		537.30		
136		141.40		
137		221.50		
138		11.40		
139			95.54	26.80
140			93.65	64.12
141			92.10	44.23
142		156.20		
143		744.40		
144		5455.00		
145		1162.00		
146		37.00		
147		4026.00		
148		11.10		
149		11.00		
150		26.90		
151	7.58			
152		10.90		

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No de Ejemplo.	GR (Ki, nM) (Ensayo de enlace GR(I)[a])	GR (Ki, nM) (Ensayo de enlace GR(II)[b])	EC_{50} AP-1, nM (Ensayo de Trans-represión Celular)	%inh.Max AP-1 (Ensayo de Trans-represión Celular)
153			982.50	73.55
154			236.10	46.25
155		31.80		
156		80.90		
157		186.40		
158			200.00	62.52
159			478.80	30.33
160		5455.00		
161		36.60		
162		255.50		
163			16.78	49.60
163[a]			4.9	64.40
164[a]			8.5	57.97
165[a]			9.8	53.39
166[a]			14.5	56.11
164			5.58	57.26
165			25.63	56.92
166			43.40	54.18
167			36.57	57.94
168	485.60			
169			92.74	48.82
170			182.30	44.12
171	7.15	10.20		
172			13.21	59.04
173			82.49	44.82
174	10.16			
175	51.98	49.40		
176			118.50	43.54
177	>1154	459.70		
178	10.58	4.70		
179	64.62	37.90		
180	22.82	14.60		
181	>1154	182.70		
182			108.60	33.12
183	44.43	20.40		
184	6606.00	263.10		
185	>1154	697.40		

No de Ejemplo.	GR (Ki, nM) (Ensayo de enlace GR(I)[a])	GR (Ki, nM) (Ensayo de enlace GR(II)[b])	EC_{50} AP-1, nM (Ensayo de Trans-represión Celular)	%inh.Max AP-1 (Ensayo de Trans-represión Celular)
186	386.10	84.60		
187	33.10	34.40		
188	28.88	8.10		
189	19.63	11.70		
190	11.53	5.70		
191			22.64	37.51
192	12.33	13.10		
193	11.14	8.50		
194	4.63	7.10		
195	735.70	505.30		
196	6.26	15.90		
197	9.27	23.30		
198			22.17	34.38
199			27.60	48.94
200			133.80	53.76
201			36.34	65.46
202			218.60	38.37
203	4.61	13.10		
204			42.75	44.75
205			8.50	57.72
206			21.31	54.73
207			32.61	37.96
208			12.25	54.08
209			14.30	50.21
210			77.73	39.38
211			41.28	49.63
212			19.59	63.05
213	7.95			
214	1.37			
215	2.50			
216	4.14			
217			41.03	45.81
218	1.24			
219			180.30	35.87
220			105.20	52.23
221			28.92	62.97
222			100.20	61.88

000764

No de Ejemplo.	GR (Ki, nM) (Ensayo de enlace GR(I)[a])	GR (Ki, nM) (Ensayo de enlace GR(II)[b])	EC_{50} AP-1, nM (Ensayo de Trans-represión Celular)	%inh.Max AP-1 (Ensayo de Trans-represión Celular)
223			838.90	27.87
224	8.06			
225			919.70	45.65
226			18.14	49.05
227			37.94	42.50
228			51.53	28.32
229			42.01	39.34
230			550.10	52.33
231			733.40	38.36
232	4.57			
233	11.29			
234			405.40	27.08
235	4.85			
236	9.44			
237	6.04			
238			601.00	62.32
239			12.43	44.85
240			51.87	61.72
241			25.28	46.83
242	412.30			
243	>1154			
244	>1154			
245	1.01			
246			325.40	81.76
247			4.74	52.38
248			21.45	55.87
249			11.20	42.38
250			17.84	48.42
251			17.45	54.92
252			34.61	60.94
253	6.28			
254			23.62	41.80
255	16.11			
256	180.30			
257			12.44	63.96
258			533.50	40.99

No de Ejemplo.	GR (Ki, nM) (Ensayo de enlace GR(I)[a])	GR (Ki, nM) (Ensayo de enlace GR(II)[b])	EC_{50} AP-1, nM (Ensayo de Trans-represión Celular)	%inh.Max AP-1 (Ensayo de Trans-represión Celular)
259			72.21	23.33
260			23.14	67.28
261			4.74	52.38
262	18.19			
263			15.42	58.05
264			115.20	33.74
265	126.20			
266			11.20	42.38
267			568.70	40.78
268	9.45			
269	14.75			
270	20.94			27.98
271	218.00			
272	12.58			
273	19.91			20.96
274			234.10	62.19
275	2.60			26.02
276	4.05			27.21
277	81.32			24.52
278	30.53			
279	20.84			
280	10.75			33.52
281	33.50			
282	13.41			
283	9.21			24.64
284	17.37			
285	5.84			45.31
286	12.15			49.83
287	16.82			
288	13.80			35.54
289	19.98			24.29
290	20.36			28.80
291	43.96			26.99
292	10.84			
293	10.43			25.39
294	29.30			59.35
295	38.73			24.36

No de Ejemplo.	GR (Ki, nM) (Ensayo de enlace GR(I)[a])	GR (Ki, nM) (Ensayo de enlace GR(II)[b])	EC_{50} AP-1, nM (Ensayo de Trans-represión Celular)	%inh.Max AP-1 (Ensayo de Trans-represión Celular)
296	19.13			
297	>1154			
298	241.90			25.36
299	13.28			
300			14.83	61.77
301	20.25			28.57
302	126.30			
303	278.00			28.59
304	149.00			
305	24.71			38.32
306	9.85			43.48
307	67.51			37.14
308	313.00			
309			41.50	34.95
310			785.90	52.93
311	25.77			
312			266.70	73.06
313	4.65			
314			18.01	69.78
315			749.90	40.86
316			60.90	35.90
317	23.69			
318			63.08	27.55
319	110.30			
320	13.11			
321	30.56			
322	18.89			
323	3.69			
324			431.10	54.88
325			90.21	56.09
326	10.49			
327			8.93	59.45
328			18.63	66.06
329			582.70	40.81
330			21.94	60.62
331			33.71	36.28
332	9.56			

No de Ejemplo.	GR (Ki, nM) (Ensayo de enlace GR(I)[a])	GR (Ki, nM) (Ensayo de enlace GR(II)[b])	EC_{50} AP-1, nM (Ensayo de Trans-represión Celular)	%inh.Max AP-1 (Ensayo de Trans-represión Celular)
333			24.69	52.71
334			3.36	36.22
335			37.94	55.97
336			20.40	55.80
337			102.80	51.49
338	311.80			
339			184.70	38.40
340			54.77	67.61
341			14.82	50.27
342			51.68	41.54
343			18.44	29.68
344			39.64	44.55
345			124.30	54.25
346	3.04			
347	5.63			
348			300.30	34.37
349	5.88			31.72
350			519.90	45.06
351	146.70			
352	42.06			
353	13.03			
354	20.10			28.93
355	19.56			
356	581.90			
357	31.36			29.62
358	40.50			
359	30.08			
360	154.10			
361	14.62			
362	804.70			
363			247.10	47.74
364			244.20	58.90
365	18.25			
366	200.00			
367	692.30			
368			38.59	46.80
369			33.04	55.45

No de Ejemplo.	GR (Ki, nM) (Ensayo de enlace GR(I)[a])	GR (Ki, nM) (Ensayo de enlace GR(II)[b])	EC_{50} AP-1, nM (Ensayo de Trans-represión Celular)	%inh.Max AP-1 (Ensayo de Trans-represión Celular)
370			34.22	57.60
371			22.27	48.73
372			28.28	52.42
373			32.80	45.61
374			30.91	50.87
375			82.80	51.24
376			34.42	45.09
377			32.72	49.10
378			72.62	48.18
379			73.97	51.21
380			100.60	53.58
381			45.25	52.00
382			205.80	47.22
383			46.32	41.78
384			61.85	42.30
385			96.47	28.99
386			89.04	34.32
387			82.02	52.49
388			34.22	57.60
389			50.54	55.20
390			42.77	56.63
391			52.02	44.08
392			49.73	44.82
393			53.37	43.80
394	4.00			
395	1.19			
396	10.62			
397	40.89			
398			479.60	50.00
399			332.90	69.30
400	37.32			
401			778.30	35.10
402	698.60			
403	61.21			
404			22.49	70.62
405	423.70			
406	176.30			

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No de Ejemplo.	GR (Ki, nM) (Ensayo de enlace GR(I)[a])	GR (Ki, nM) (Ensayo de enlace GR(II)[b])	EC_{50} AP-1, nM (Ensayo de Trans-represión Celular)	%inh.Max AP-1 (Ensayo de Trans-represión Celular)
407	958.20			
408			363.90	24.10
409	78.16			
410			53.32	48.15
411			161.10	58.47
412	22.27			
413	37.74			
414	589.00			
415	64.10			
416	94.46			
417			67.32	54.11
418			82.09	29.07
419			71.86	46.63
420			41.94	42.14
421			49.78	42.56
422			84.14	41.58
422[a]			51.50	50.45
422[b]			46.72	63.52
423			81.98	30.36
424			150.30	59.58
425			84.43	49.89
426			117.10	31.80
427			187.80	25.13
428			30.29	26.89
429			67.27	41.78
430			34.69	47.22
431			69.04	41.78
432			52.66	40.25
433			40.97	46.21
434			197.10	38.45
435			291.80	27.88
436			95.67	44.01
437	11.06			
438	53.10			
439	65.80			
440	20.97			
441			63.91	52.35

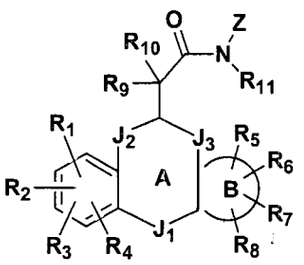
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No de Ejemplo.	GR (Ki, nM) (Ensayo de enlace GR(I)[a])	GR (Ki, nM) (Ensayo de enlace GR(II)[b])	EC_{50} AP-1, nM (Ensayo de Trans-represión Celular)	%inh.Max AP-1 (Ensayo de Trans-represión Celular)
442			126.60	50.14
443			134.40	51.70
444			44.20	57.54
445			38.48	45.74
446			412.60	27.69
447			95.37	53.02
448			178.40	56.59
449			126.40	48.87
450			59.16	26.30
451	5.57			
452			11.11	53.38
453	17.60			
454			25.34	49.46
455			24.61	58.63
456			41.48	45.84
457			16.56	51.89
458			53.25	35.19
459			101.70	35.43
460			30.33	56.91
461			53.38	50.80
462	3.78			
463			45.30	26.23
464			18.20	54.01
465			16.55	61.53
466			28.25	56.07
467			14.97	57.51
468			35.39	53.30
469	49.82			
470			24.60	43.03
471			63.91	52.35
472			26.92	47.04
473			40.19	52.52
474			85.40	37.88
475	18.31			
476	16.37			
477			39.75	44.78
478			16.02	41.78

No de Ejemplo.	GR (Ki, nM) (Ensayo de enlace GR(I)[a])	GR (Ki, nM) (Ensayo de enlace GR(II)[b])	EC_{50} AP-1, nM (Ensayo de Trans-represión Celular)	%inh.Max AP-1 (Ensayo de Trans-represión Celular)
479			47.00	44.36
480			27.01	43.97
481			579.30	33.76
482	44.97			
483	426.20			
484			19.32	29.79
485			42.36	38.86
486			15.78	50.34
487	>1154			
488			42.92	34.48
489	143.80			
490	14.82			
491	>1154			
492			182.00	28.40
493	108.90			

REIVINDICACIONES

1. Un compuesto de conformidad con la fórmula (I),



I

un enantiómero, diastereómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, caracterizado porque:

Z se selecciona de heterociclo, heteroarilo y ciano;

A se selecciona de un anillo carbocíclico de 5 hasta 8 elementos y un anillo heterocíclico de 5 hasta 8 elementos;

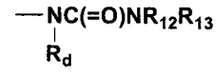
el anillo B se selecciona de un anillo cicloalquilo, cicloalquenilo, arilo, heterociclo, y anillo heteroarilo, en donde el anillo B se fusiona al anillo A, y el anillo B es opcionalmente substituido por uno hasta cuatro grupos los cuales son los mismos o diferentes y son independientemente seleccionados de R_5, R_6, R_7, y R_8;

J_1, J_2, y J_3 son los mismos o diferentes y cada que se presentan son independientemente $-A_1QA_2-$;

Q es independientemente cada que se presenta seleccionado de un enlace, O, S, S(O), y $S(O)_2$;

A_1 y A_2 son los mismos o diferentes y cada que se

presentan son independientemente seleccionados de un enlace, alquileno C_{1-3}, alquileno C_{1-3} substituido, alquenileno C_{2-4}, y alquenileno C_{2-4} substituido, con la condición de que A_1 y A_2 se eligen de manera que el anillo A es un anillo carbocíclico de 5 hasta 8 elementos o un anillo heterocíclico de 5 hasta 8 elementos;

R_1, R_2, R_3, R_4, R_5, R_6, R_7, y R_8 son los mismos o diferentes y cada que se presentan son independientemente seleccionados de (i) hidrógeno, halógeno, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, alcoxi, alcoxi substituido, nitro, ciano, OR_{12}, $-NR_{12}R_{13}$, $-C(=O)R_{12}$, $-CO_2R_{12}$, $-C(=O)NR_{12}R_{13}$, $-OC(=O)NR_{12},R_{13}$,  , $-OC(=O)R_{12}$, $-NR_{12}C(=O)R_{13}$, $-NR_{12}C(O)OR_{13}$, $-NR_{12}C(S)OR_{13}$, $S(O)_pR_{16}$, $NR_{12}SO_2R_{16}$, dialquilaminoalcoxi, alcoxialquiloxialquiloxi, $SO_2NR_{12}R_{13}$, cicloalquilo, cicloalquenilo, cicloalquinilo, heterociclo, arilo, y heteroarilo; y/o (ii) donde es posible, cada uno de R_1-R_8 se toma junto con cualquiera de R_1-R_8 localizado en un átomo adyacente para formar un anillo fusionado; y/o (iii) donde sea posible cualquiera de R_1-R_8 se toma junto con cualquiera de R_1-R_8 localizado en el mismo átomo para formar un grupo oxo, alquenilo, alquenilo substituido, cicloalquilo, cicloalquenilo, o heterociclo;

R_9 y R_{10} son los mismos o diferentes y cada que se

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presentan son independientemente seleccionados de (i) hidrógeno, halógeno, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, nitro, ciano, OR_{14}, $NR_{14}R_{15}$, $C(=O)R_{14}$, CO_2R_{14}, $C(=O)NR_{14}R_{15}$, $-O-C(=O)R_{14}$, $NR_{14}C(=O)R_{15}$, $NR_{14}C(=O)OR_{15}$, $NR_{14}C(=S)OR_{15}$, $S(O)_pR_{17}$, $NR_{14}SO_2R_{17}$, $SO_2NR_{14}R_{15}$, cicloalquilo, cicloalquenilo, heterociclo, arilo, y heteroarilo; o (ii) junto con el átomo al cual se enlazan, R_9 y R_{10} se toman juntos para formar un grupo carbonilo, alquenilo, alquenilo substituido, cicloalquilo, cicloalquenilo, o heterociclo;

R_{11} se selecciona de hidrógeno, alquilo, alquilo substituido, $C(=O)$alquilo, CO_2(alquilo), SO_2alquilo, alcoxi, amino, amino substituido, arilo, heteroarilo, heterociclo, y cicloalquilo;

R_{12}, R_{13}, R_{14}, y R_{15}, son los mismos o diferentes y cada que se presentan son independientemente seleccionados de (i) hidrógeno, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, cicloalquilo, cicloalquenilo, arilo, heteroarilo, y heterociclo; o (ii) donde sea posible R_{12} se toma junto con R_{13}, y/o donde es posible R_{14} se toma junto con R_{15} para formar un anillo heteroarilo o heterociclo;

R_{16} y R_{17}, son los mismos o diferentes y cada que se presentan son independientemente seleccionados de alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, cicloalquilo,

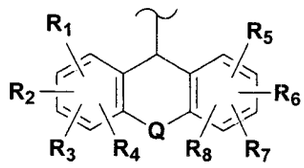
cicloalquenilo, arilo, heteroarilo, y heterociclo;

R_d es H, alquilo o arilo; y

p es 0, 1 ó 2,

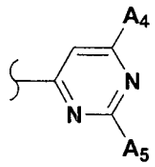
con la condición de que

(1) donde la porción tricíclica en la fórmula I el compuesto es



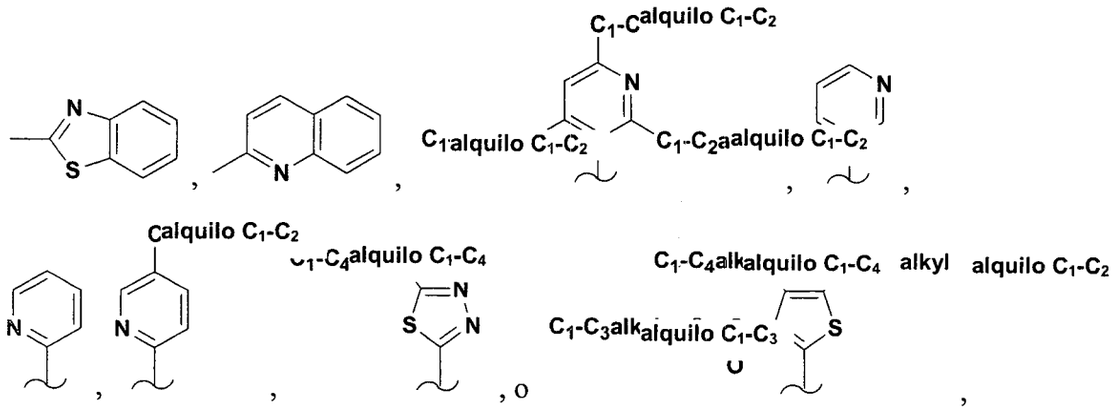
donde Q es O y R_1 hasta R_8 son cada uno H, entonces

(a) Z es diferente de



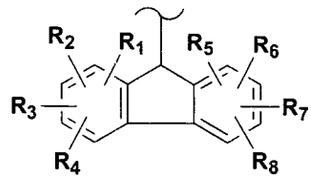
donde A_4 y A_5 son los mismos o diferentes y son independientemente H o alquilo C_1-C_2-; o

(b) Z es diferente de



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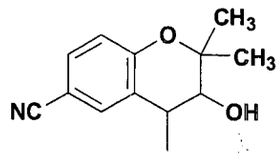
(2) donde la porción tricíclica es



donde R_1 hasta R_8 son cada uno H,

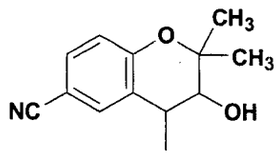
entonces

(a) Z es diferente de



, o

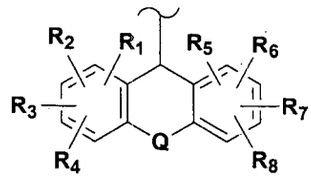
(b) donde Z es



,

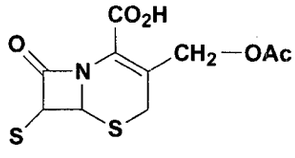
entonces R_{11} es diferente de un alquileno C_1-C_2 substituido;

(3) donde la porción tricíclica es



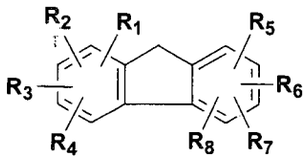
donde Q es S o SO_2, y R_1 hasta R_8 son cada uno H,

entonces Z es diferente de

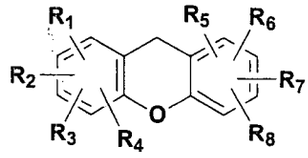


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(4) donde la porción tricíclica es

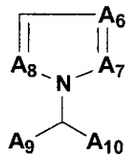


o



donde R_1 hasta R_8 son cada uno H,

entonces Z es diferente de



donde A_6, A_7 y A_8 son independientemente N o CH,

A_9 es $-(CH_2)_d-A_{11}$ donde d es 0 hasta 4;

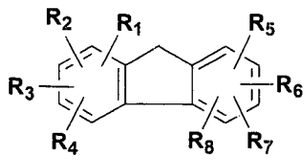
A_{11} es OH, CO_2H, 5-tetrazolilo, $-COO(\text{alquilo } C_1\text{-}C_4)_{n_a}$ o CN-

;

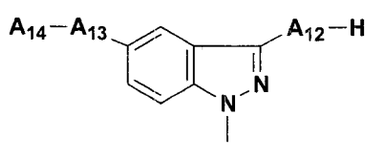
n_a es 0 hasta 4; y

A_{10} es alquilo de cadena recta C_4-C_7;

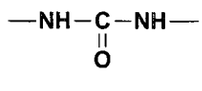
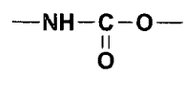
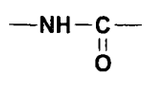
(5) donde la porción tricíclica es

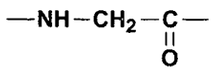


entonces Z es diferente de



donde A_{12} es O o S; y

A_{13} es O o un NH,  ,  ,  , o

 ,

en donde los 3 últimos grupos se unen al anillo aromático a través del átomo N;

A_{14} es H,

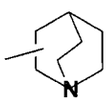
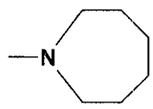
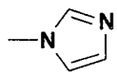
alquilo,

cicloalquilo C_3-C_7,

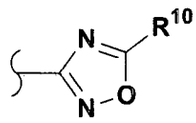
fenilo, naftilo, antranilo o fluorenilo opcionalmente substituido, o

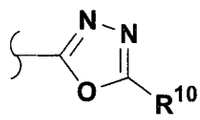
un quinolin-2-ilmetoxi o piridin-ilmetoxi; o

Z es diferente de

 ,  ,  , o  ; o

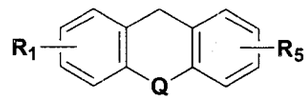
Z es diferente de





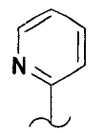
donde R^{10} es un sistema de anillo azacíclico no aromático o azabicíclico no aromático;

(6) donde la porción tricíclica es



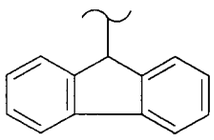
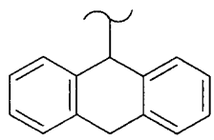
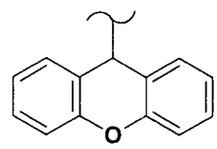
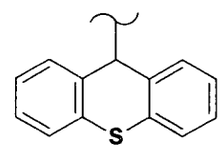
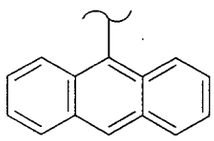
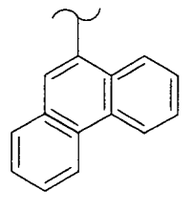
Q es -O-, -S-, $-C(R^3R^4)-$, $-CH_2CH_2-$, $-CH=CH-CH_2-$, $-CH_2-CH=CH-$, $-CH_2-(C=O)-$, $-(C=O)-CH_2-$, $CH_2CH_2CH_2-$, -CH=CH-, $-O-CH_2-$, $-CH_2-O-$, $-O-CH_2-O-$, $-CH_2-O-CH_2-$, $-S-CH_2-$, $-CH_2-S-$, $-CH(R^5)CH_2-$, $-CH_2CH(R^5)-$, -(C=O)-, o -(S=O)- donde R^3 y R^4 independientemente son hidrógeno o alquilo C_{1-7}; y en donde R^5 es alquilo C_{1-7} o fenilo;

entonces Z es diferente de

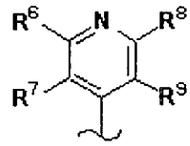


;

(7) donde la porción tricíclica es


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o

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entonces Z es diferente de



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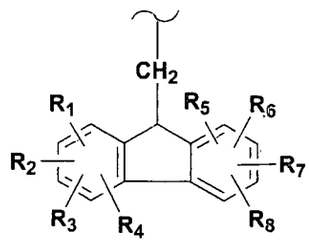
en donde:

R^6 y R^7 son cada uno independientemente seleccionados de alquilo C_1-C_6, halo-alquilo C_1-C_6 que contiene 1 hasta 5 átomos de halógeno, alcoxi C_1-C_2-alquilo C_1-C_6, nitro-alquilo C_1-C_6, ciano-alquilo C_1-C_6, alcanoilo C_1-C_2-alquilo C_1-C_6, alcoxicarbonilo C_1-C_2-alquilo C_1-C_6, alquiltio C_1-C_2-alquilo C_1-C_6, alcansulfinilo C_1-C_2-alquilo C_1-C_6, alcansulfonilo C_1-C_2-alquilo C_1-C_6, alquenilo C_2-C_6, halo-alquenilo C_2-C_6 que contiene 1-5 átomos de halógeno, alquinilo C_2-C_6, halo-alquinilo C_2-C_6 que contiene 1-5 átomos de halógeno, cicloalquilo C_3-C_7 y halógeno; o

R^6 y R^7, tomados juntos, forman un anillo carbocíclico o heterocíclico de 5 hasta 7 elementos saturado o no saturado el cual puede contener uno o dos heteroátomos seleccionados de O y S; y

R^8 y R^9 son cada uno independientemente seleccionados de hidrógeno, alquilo C_1-C_6 y halógeno;

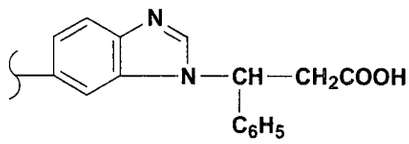
(8) donde la porción tricíclica es



entonces

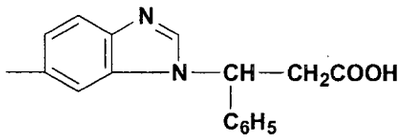
- 000781

a) Z es diferente de



o un homólogo del mismo,

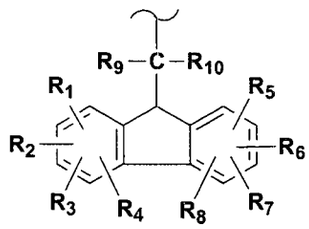
b) si Z es



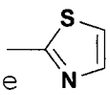
o un homólogo del mismo, entonces R_{11} es diferente de H;

o

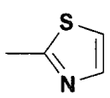
(9) donde la porción tricíclica es



entonces

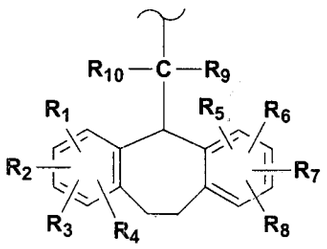
a) Z es diferente de  substituido o no substituido,

o

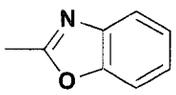
b) donde Z es  substituido o no substituido, entonces al menos uno o R_9 y R_{10} es diferente de H y/o R_{11} es diferente de H;

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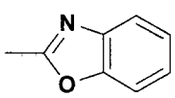
(10) donde la porción tricíclica es

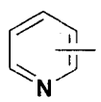


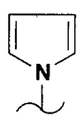
entonces

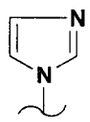
a) Z es diferente de 

,

b) donde Z es 

, 

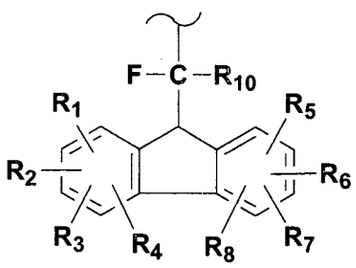
, 

, 

, o 

, entonces R_{11} es diferente de H y/o al menos uno de R_9 y R_{10} es diferente de H;

(11) donde la porción tricíclica es

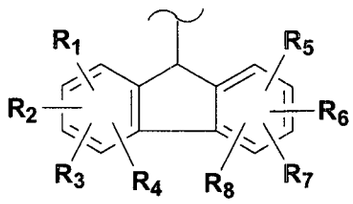


entonces

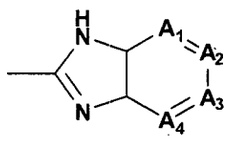
a) Z es diferente de heteroarilo, o

b) donde Z es heteroarilo, entonces R_{11} es diferente de H y/o R_{10} es diferente de H; o

(12) donde la porción tricíclica es

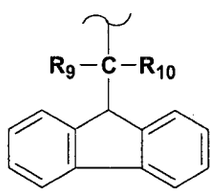


entonces R_1, R_2, R_3, R_4, R_5, R_6, R_7 y R_8 es diferente de

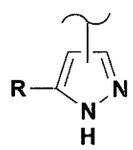


en donde A_1, A_2, A_3 y A_4 son seleccionados de CR_a o N, donde R_a es H o un substituyente; o

(13) donde la porción tricíclica es



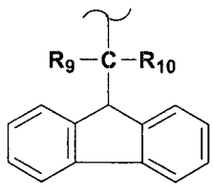
entonces Z es diferente de



donde R es cicloalquilo C_3-C_6 opcionalmente substituido por alquilo C_1-C_6 o arilalquilo o un homólogo del mismo;

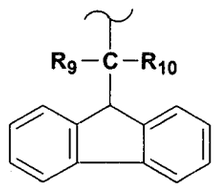
(14) donde la porción tricíclica es

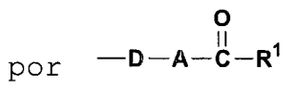
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y Z es heteroarilo que contiene o heterociclilo que contiene un átomo de N en el anillo, entonces el heteroarilo o heterociclilo Z no pueden substituirse con un grupo R'A donde R' es heterocíclico o fenilo opcionalmente substituido y A es $(CH_2)_{0-2}(O)_{0\ ó\ 1}$ o $(CR^3R^4)_{0\ ó\ 1}NR^5(CO)_{0\ ó\ 1}$ donde R^3, R^4 = H o R^3 + R^4-imino y R^5 = H o alquilo;

(15) donde la porción tricíclica es



y Z es diferente de un anillo heterocíclico de 5-7 elementos que contiene un anillo N, O y/o S cuyo anillo heterocíclico es substituido por  donde D es alquileno ^{1-4}C, O u S,

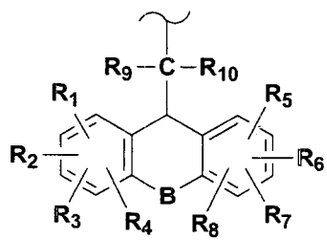
A es un anillo carbocíclico de 3 hasta 7 elementos o un anillo heterocíclico de 5 hasta 7 elementos que contiene N, O y/o S, y

R^1 es OH, alcoxi, o $NR^{10}R^{11}$ donde R^{10} y R^{11} pueden ser H o alquilo el cual Z y/o también puede ser

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opcionalmente substituido por 1-3 grupos los cuales pueden ser alquilo C_{1-4}, alcoxi C_{1-4}, halo, trihalometilo, CN, o NO_2; o

(16) donde la porción tricíclica es



donde B es O u S, entonces

a) Z es diferente de dihidrofurilo opcionalmente substituido o dihidrotienilo opcionalmente substituido,

b) o sí Z es dihidrofurilo opcionalmente substituido o dihidrotienilo opcionalmente sustituido, entonces

1) al menos uno de R_9 y/o R_{10} es diferente de H, o

2) R_{11} es diferente de H o alquilo inferior.

2. El compuesto de conformidad con la reivindicación 1, o un enantiómero, diastereómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, caracterizado porque:

B es un anillo fenilo, piridinilo o pirazinilo;

J_1 es O, S, SO, SO_2, un enlace, CH_2, o CH_2CH_2; y

J_2 y J_3 son cada uno un enlace.

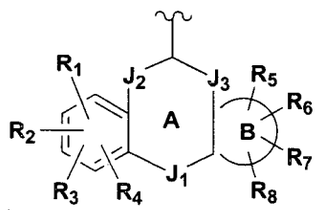
3. El compuesto de conformidad con las

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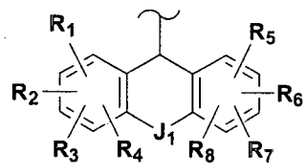
reivindicaciones 1-2, o un enantiómero, diastereómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, caracterizado porque J_1 es O, S, SO, SO_2, o un enlace.

4. El compuesto de conformidad con las reivindicaciones 1-3, o un enantiómero, diastereómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, caracterizado porque B es un anillo piridinilo substituido con arilo o arilo substituido.

5. El compuesto de conformidad con las reivindicaciones 1-3, o un enantiómero, diastereómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, caracterizado porque la porción tricíclica:



es



.

6. El compuesto de conformidad con las reivindicaciones 1-5, o un enantiómero, diastereómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, caracterizado porque

R_2, R_3, y R_4 son cada uno hidrógeno;

R_6, R_7, y R_8 son cada uno hidrógeno;

R_1 se selecciona de hidrógeno, CF_3, alcoxi, halógeno, hidroxilo, y dialquilaminoalcoxi; y

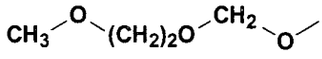
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R_5 se selecciona de hidrógeno, CF_3, alcoxi, halógeno, amino, dialquilamino, heterociclo, arilo, carboxiarilo, alcoxiarilo, alquilarilo, heterociclocarbonilarilo, alcoxi(halo)arilo, carboxi(halo)arilo, dialquilaminocarbonilarilo, alquilamino, hidroxilo, dialquilaminoalcoxi, arilalquilamino, alcoxiarilalquilamino, alquilheterociclo, arilalquilo, heterocicloalcoxi, arilheterociclo, arilalquil(alquil)amino, haloarilo, dialquilaminoarilo, haloarilo, alcoxialcoxialcoxilo, alquilcarbonilamino, heteroarilo, dialquilarilo, hidroxiarilo, alcoxicarbonilarilo, alquilcarbonilaminoarilo, alquilsulfonilaminoarilo, ariloxiarilo, alquiltioarilo, aminoarilo, alquilcarbonilarilo, arilalcoxiarilo, y cianoarilo.

7. El compuesto de conformidad con las reivindicaciones 1-5, o un enantiómero, diastereómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, caracterizado porque R_1, R_2 y R_3 son cada uno hidrógeno; y R_4 se selecciona de hidrógeno, CF_3, alcoxi, dialquilaminoalcoxi, hidroxilo y alcoxialquioxialcoxi, un enantiómero, diastereómero, o tautómero de los mismos, o un profármaco éster del mismo, o una sal farmacéuticamente aceptable de los mismos.

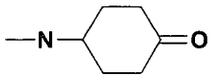
8. El compuesto de conformidad con las reivindicaciones 1-5, y 7, o un enantiómero, diastereómero, tautómero, o una

sal farmacéuticamente aceptable de los mismos, caracterizado porque R_1, R_2, y R_3 son cada uno hidrógeno, y R_4 se selecciona de hidrógeno, CF_3, CH_3O, $N(CH_3)_2CH_2CH_2O-$, OH, y



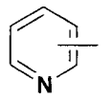
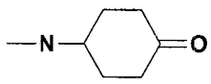
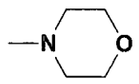
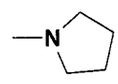
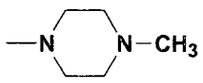
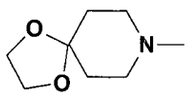
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9. El compuesto de conformidad con las reivindicaciones 1-8, o un enantiómero, diastereómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, caracterizado porque R_5, R_6, y R_7 son cada uno hidrógeno y R_8 se selecciona de hidrógeno, hidroxilo, CF_3, alcoxi, halógeno, dialquilaminoalcoxi, alcoxialquiloxialquiloxi, alquilamino, heterociclo, arilalquilamino, alcoxiarilalquilamino, dialquilamino,

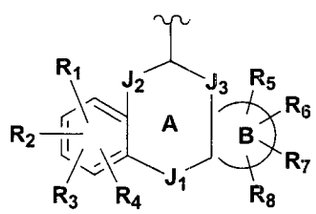


, alcoxiarilo, arilo, trifluorometoxilarilo, carboxiarilo, haloalquilo, dialquilaminoarilo, naftilo, alquilfenilo, CF_3arilo, alquilcarbonilaminoarilo, dialquilarilo, hidroxiarilo, alcoxicarbonilarilo, alquilcarbonilaminoarilo, alquilsulfonilaminoarilo, arilarilo, alquilsulfonilarilo, aminoarilo, arilalquiloxiarilcianoarilo, y alquilarilo.

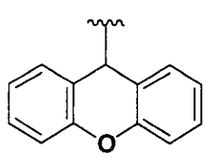
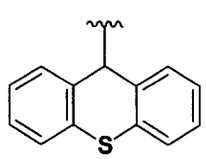
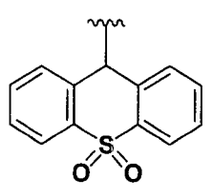
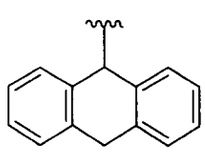
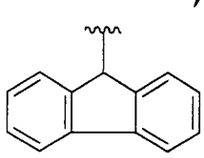
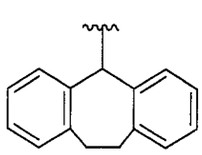
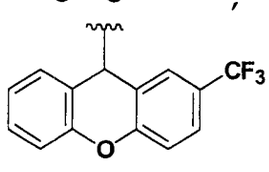
10. El compuesto de conformidad con las reivindicaciones 1-9, o un enantiómero, diastereómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, caracterizado porque R_5, R_6, y R_7 son cada uno hidrógeno y R_8 se selecciona de hidrógeno, Cl, $(CH_3)_2N(CH_2)_2O-$, $CH_3OCH_2CH_2OCH_2O-$, bencilamino, metoxibencilamino, $N(CH_3)_2CH_2CH_2O-$, OH, CF_3, CH_3O-, dimetilamino, metoxifenilo, fenilo, $CF_3OC_6H_4-$, $CO_2H-C_6H_4$, $CN-C_6H_4$, $s-C_4H_9-C_6H_4-C_2H_5O-C_6H_4$, $s-C_4H_9-C_6H_4$, $-C_3H_7-C_6H_4-$, $n-C_4H_9-O-C_6H_4-$, $C_2H_5-C_6H_4-$, t-

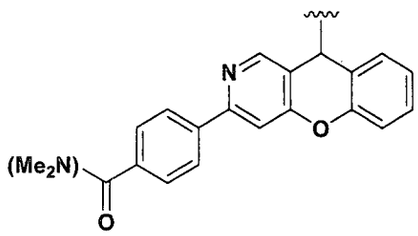
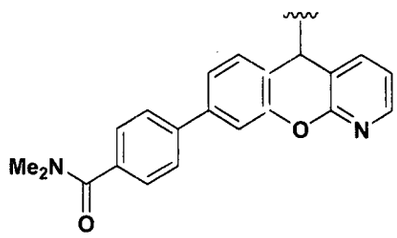
C_4H_9-C_6H_4-, $CH_3COC_6H_4$-, $C_6H_5CH_2OC_6H_4$-, C_6H_5-C_6H_4-, C_6H_5-O-C_6H_4-, $CH_3SC_6H_4$-, $NH_2C_6H_4$-, CH_3-SO_2-NHC_6H_4-, F-C_6H_4, C_6H_5-, ClC_6H_4, -diCH_3amino, naftilo, $CH_3C_6H_4$, $CF_3C_6H_4$-, $CH_3CONHC_6H_4$-, $CH_3OC_6H_4$,  , di-$CH_3C_6H_3$-, HOC_6H_4-, $CH_3OCOC_6H_4$-,  ,  ,  ,  y  .

11. El compuesto de conformidad con las reivindicaciones 1-2, o un enantiómero, diastereómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, caracterizado porque



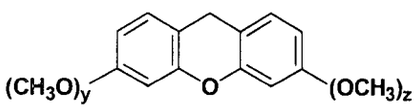
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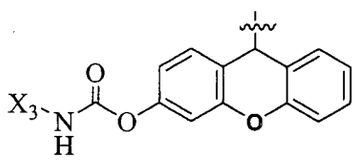



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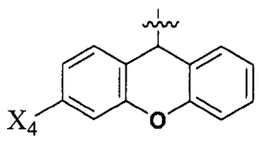
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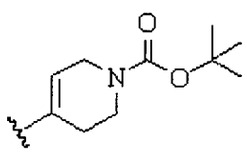
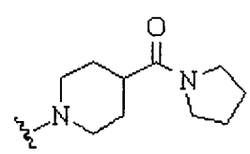
, donde z es 0 ó 1 e y es 0 ó 1;



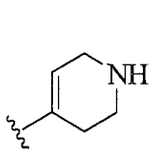
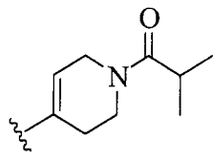
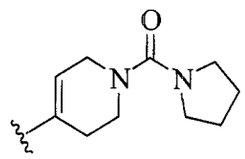
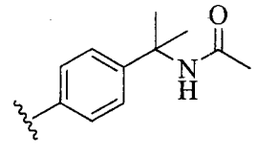
, donde X_3 es bencilo, $(CH_2)_3CH_3$, etilo, CH_2(2-furilo), ciclohexilo, $(CH_2)_7CH_3$, $(CH_2)_2$(fenilo), CH_2(2-tienilo), CH_2(4-fluorofenilo), terc-butilo, CH(CH_3)etilo, $(CH_2)_2$(4-metoxifenilo), 4-metoxifenilo, o CH_2(ciclohexilo);



, donde X_4 es NHC(O)O(ciclohexilo), NHC(O)O(metilo), -C≡C-$(CH_2)_2CH_3$, C(O)NHCH_2(fenilo), C(O)CH_3, -NHC(O)NH(CH_2)(O)N$(Me)_2$, -NHC(O)NH(CH_2)(N-pirrolidinilo),

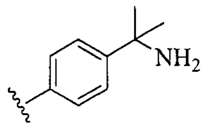
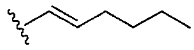
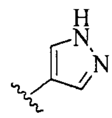
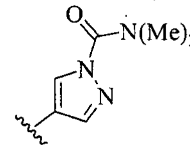
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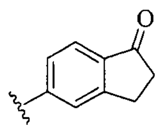
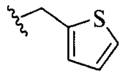
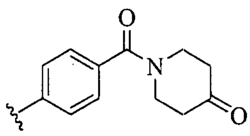





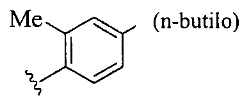
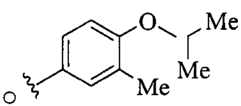
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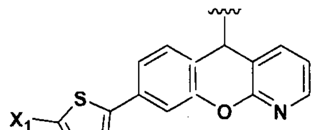
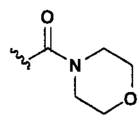
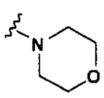
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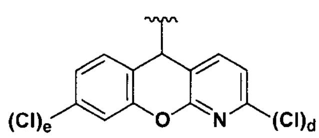
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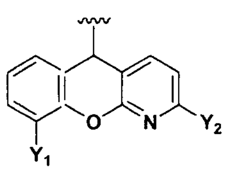
 ,  , -(CH2)$_5$CH$_3$,  ,  ,

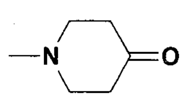
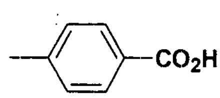
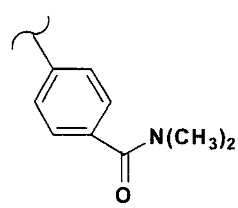
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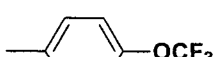
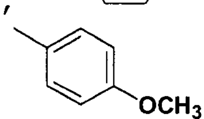
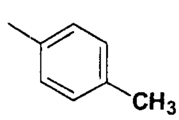
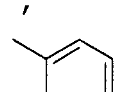
 , o  ;

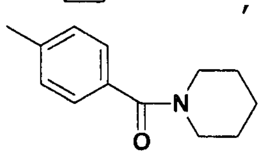
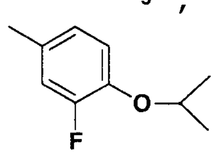
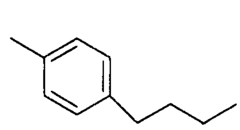
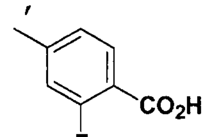
 , donde X_1 es CO_2H,  , N(Me)$_2$,  , o C(O)CH$_3$;

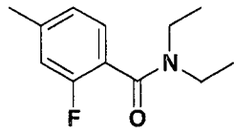
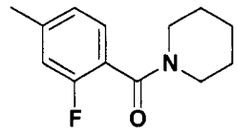
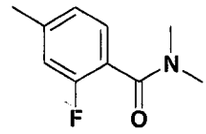
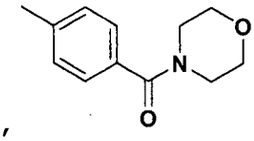
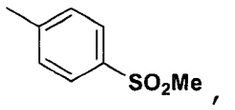
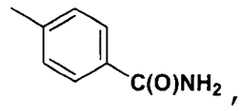
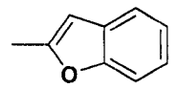
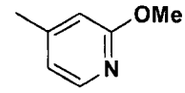
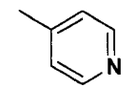
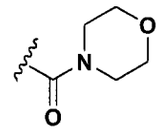
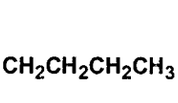
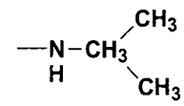
 , donde d es 0 ó 1 y e es 0 ó 1;

 , donde Y_1 es hidrógeno o halógeno; y Y_2 es

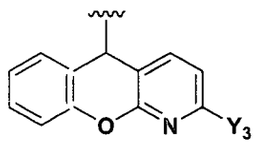
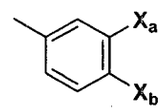
-OCH$_3$, -N(CH$_3$)$_2$,  ,  ,  ,

 ,  ,  ,  ,

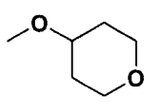
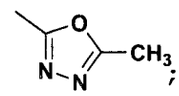
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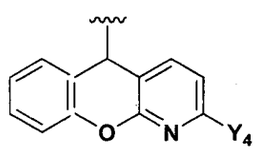
C(O)NMe$_2$, Cl, , o ;

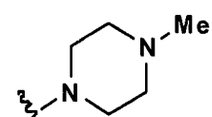



, donde Y_3 es , X_a es hidrógeno o fluoro, y X_b se selecciona de ciclohexilo, -O(isopropilo), hidróxilo, hidrógeno, -S(etilo), SO_2(etilo), SO_2(isopropilo), $C(O)CH_3$, -O(n-propilo), CH_2CO_2H, $SO_2N(CH_3)_2$, SO_2(N-morfolinilo), $C(OH)Me_2$, $SO_2NHCH_2CH_3$, SO_2NH(ciclopropilo), SO_2NH(isopropilo), CH2CO_2CH_3, $CH(OH)CH_3$, CH(OH)(Isopropilo), $S(O)CH_3$,

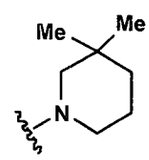



, O(ciclohexilo), O(ciclopentilo), y ;

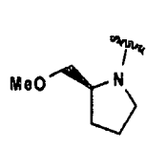
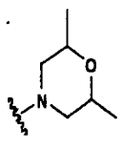
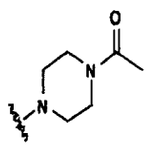
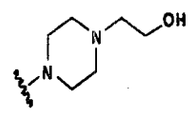


, donde Y_4 es NR_aR_b, NEt_2, piperidina, NMe_2, NMeEt, pirrolidina, NHMe, NMe(n-Pr), NMe(Bn),  , morfolina, NMe(i-Pr), NEt_2, NMe_2, piperidina, NEt_2, NEt_2, piperidina, piperidina, piperidina, $NMe(CH_2)_2CN$, 4-Me-,

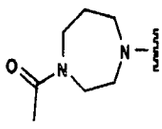
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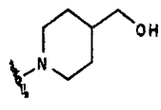
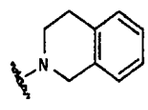
piperidina, 4-OH-piperidina, $NMe(CH_2)_2CH(CH_3)_2$,

, $N(Me)(CH_2)_2Ph$,

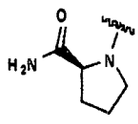
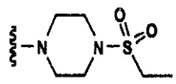
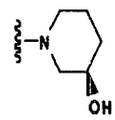
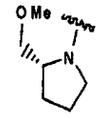


,4-Bn-piperidina,

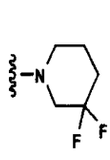
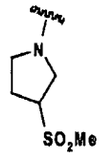
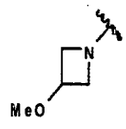



, 4-Ph-

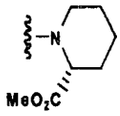
piperidina,

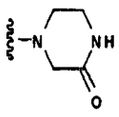
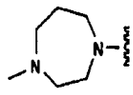
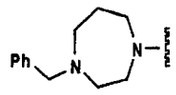
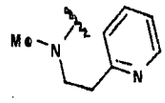
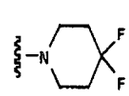
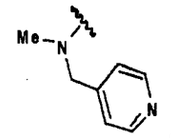
$NMe(CH_2)_2SO_2Me$,

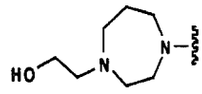
, 4-(CF_3)-piperidina,



, $NMe(n\text{-}Bu)$, $NMeCH_2CO_2Me$, $NMe(CH_2)_2OH$, $NMe(CH_2)_2OMe$,

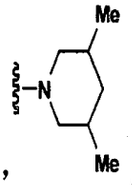
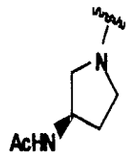
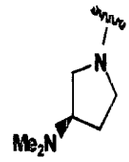
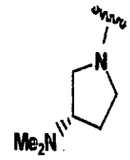







$NMe(CH_2)_2O(t\text{-}Bu)$,



,

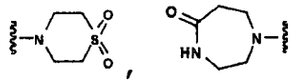
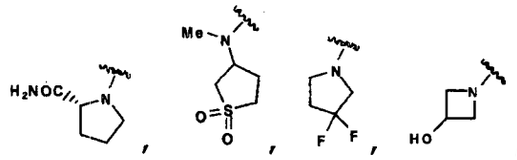
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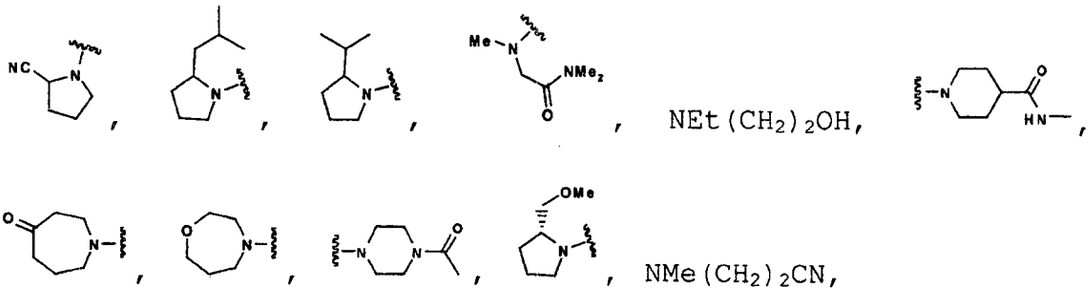





$N((CH_2)_2OH)_2$,

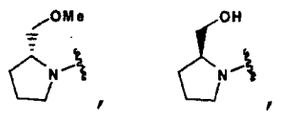
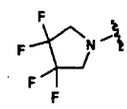
, 4-OMe,

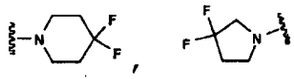
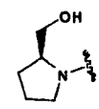
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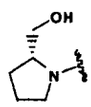
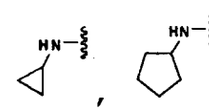
piperidina,  ,  ,

 , NEt$(CH_2)_2$OH, ,

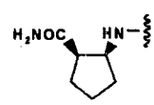
, NMe$(CH_2)_2$CN,

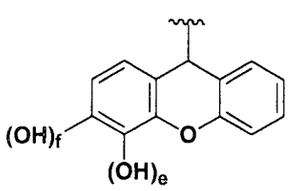
NMe(*i*-Pr),  , NEtMe,  ,

NMe$(CH_2)CO_2H$,  , pirrolidina,  , NMe(*n*-

Pr),  , NMeEt, NMe(*n*-Pr), NMe_2, NHMe, NHBn,  ,

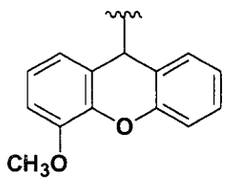
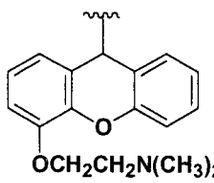
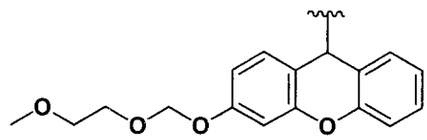
 , NHiPr, $NH(CH_2)_2Ph$, $NH(CH_2)_2Ome$, $NH(CH_2)_2C(CH_3)_3$,

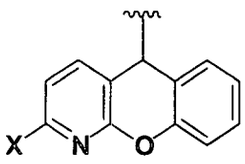
$NH(CH_2)_2OH$, NH(*n*-Pr), $NH(CH_2)_3OH$,  , o NHMe;

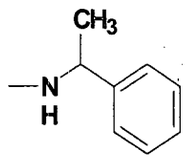
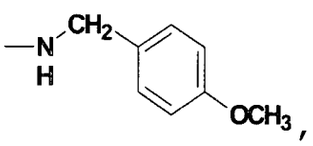
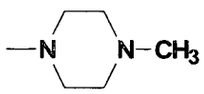
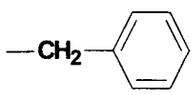
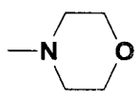
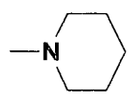
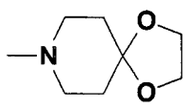
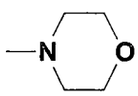
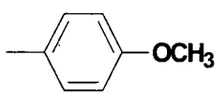
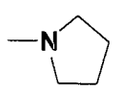
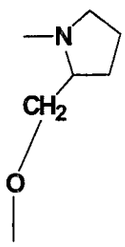
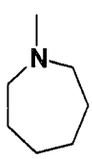
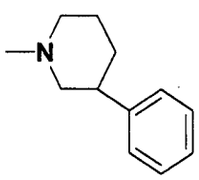
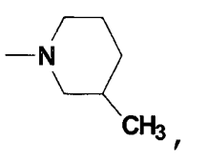
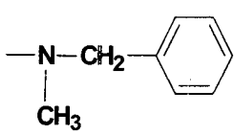
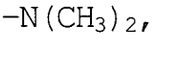
 , donde e es 0 ó 1 y f es 0 ó 1, con la

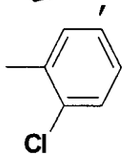
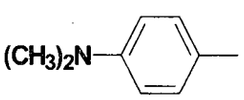
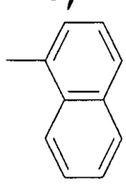
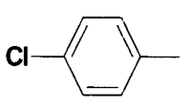
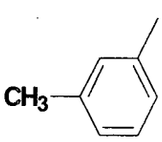
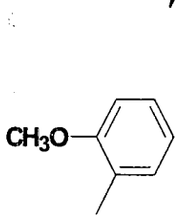
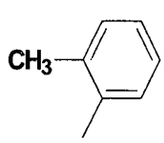
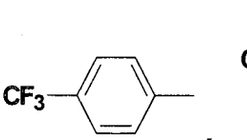
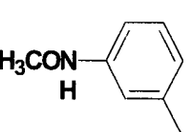
condición de que solo uno de e y f pueda ser 1;

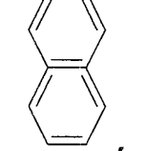
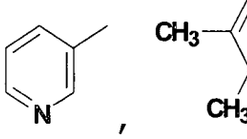
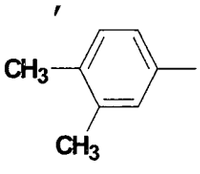
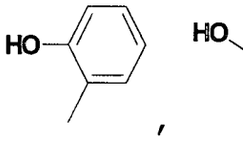
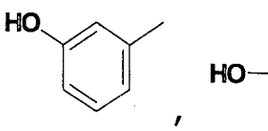
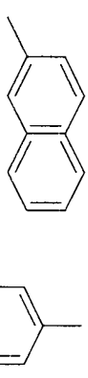
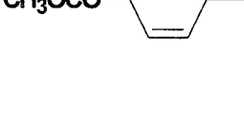
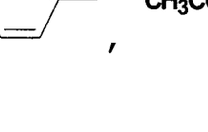
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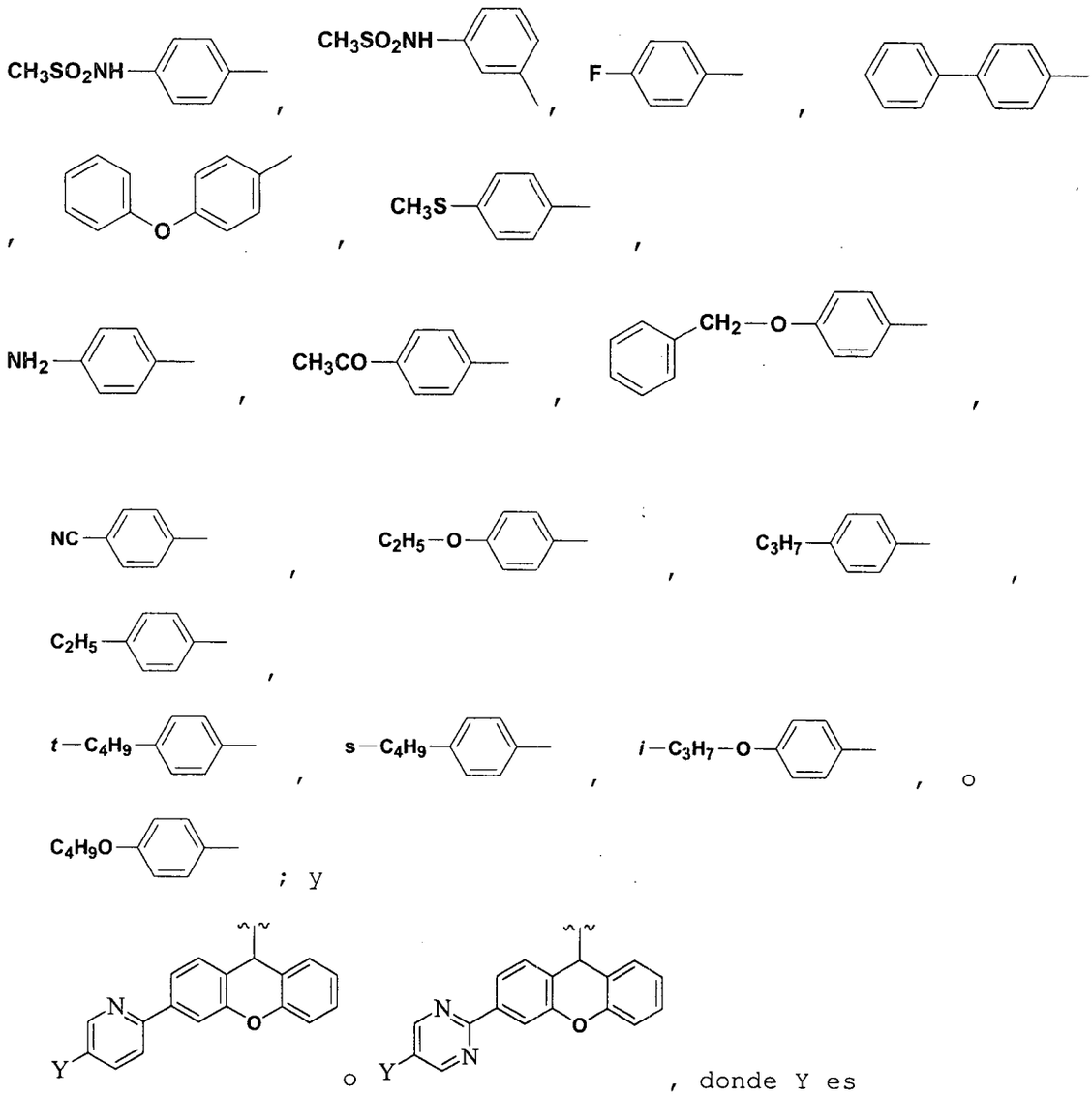

donde X es


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; y

, donde Y es alquilo C_{1-6}, $C(O)N(C_{1-6}alquilo)_2$, COOH, y O-alquilo C_{1-6}.

12. El compuesto de conformidad con las reivindicaciones 1-11, o un enantiómero, diastereómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, caracterizado porque:

R_9 y R_{10} son cada uno independientemente seleccionados de hidrógeno, alquilo, y alquilo substituido;

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o junto con el átomo al cual se enlazan, R_9 tomados juntos con R_{10} forman un cicloalquilo C_{3-6}; y

R_{11} es hidrógeno.

13. El compuesto de conformidad con las reivindicaciones 1-12, o un enantiómero, diastereómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, caracterizado porque R_9 y R_{10} son cada uno independientemente seleccionados de hidrógeno, metilo, ciclopropilo, ciclobutilo, y ciclopentilo.

14. El compuesto de conformidad con las reivindicaciones 1-13, o un enantiómero, diastereómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, caracterizado porque:

Z es un grupo heteroarilo o heterociclo de 5 hasta 6 elementos, cada grupo substituido con uno, dos o tres grupos los cuales son los mismos o diferentes y son independientemente seleccionados de hidrógeno, halógeno, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, nitro, ciano, OR^c, NR^aR^b, $C(=O)R^a$, CO_2R^a, $C(=O)NR^aR^b$, $-O-C(=O)R^a$, $NR^aC(=O)R^b$, $NR^aC(=O)OR^b$, $NR^aC(=S)OR^b$, $S(O)_pR^c$, $NR^aSO_2R^c$, $SO_2NR^aR^b$, cicloalquilo, cicloalquenilo, heterociclo, arilo, y heteroarilo;

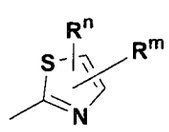
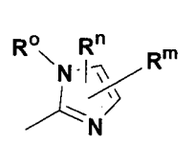
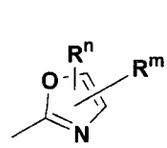
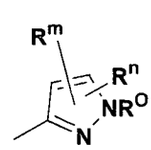
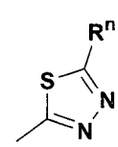
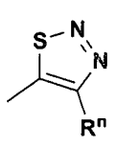
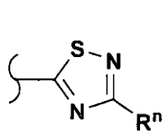
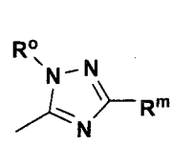
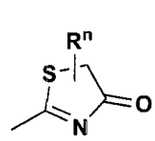
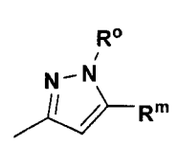
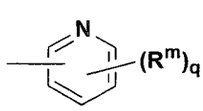
R^a y R^b son los mismos o diferentes y cada que se presentan son independientemente seleccionados de (i)

hidrógeno, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, cicloalquilo, cicloalquenilo, arilo, heteroarilo, y heterociclo; o (ii) donde sea posible junto con los átomos a los cuales se enlazan R^a se toma junto con R^b para formar un anillo heteroarilo o heterociclo; y

R^c cada que se presenta es independientemente seleccionado de alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, cicloalquilo, cicloalquenilo, arilo, heteroarilo, y heterociclo.

15. Un compuesto de conformidad con las reivindicaciones 1-14, o un enantiómero, diastereómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, caracterizado porque:

Z se selecciona de:











y

;

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R^m y R^n son los mismos o diferentes y cada que se presentan son independientemente seleccionados de hidrógeno, halógeno, alcoxi, $-COR_1^a$, $-CO_2R_1^a$, $-C(O)N(R_1^a)(R_1^b)$, alquilo C_{1-6}, CF_3, alquilo substituido, aril-NHC(O)-arilo, arilo, arilalquilo, CH_2OH, $-SR_1^a$, $S(O)_{1-2}R_1^c$, $N(R_1^a)(R_1^b)$, CH_2F, ciano, cicloalquilo C_{3-6}, y un heteroarilo de 5 hasta 7 elementos con un heteroátomo seleccionado de N, O o S;

R^o es hidrógeno o alquilo C_{1-6};

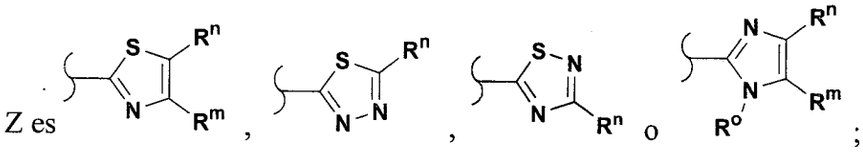
R_1^a y R_1^b son los mismos o diferentes y cada que se presentan son independientemente seleccionados de hidrógeno, alquilo, alquilo substituido, C(=O)alquilo, CO_2(alquilo), SO_2alquilo, alquenilo, alquenilo substituido, alcoxi, amino, amino substituido, arilo, heteroarilo, heterociclo, y cicloalquilo, proporcionando R_1^a y R_1^b ambos no son alcoxi, amino, o amino substituido;

o R_1^a y R_1^b, donde es posible pueden tomarse junto con el nitrógeno al cual se enlazan para formar un anillo heteroarilo o cicloheteroalquilo de 5, 6 ó 7 elementos el cual contiene 1, 2 ó 3 heteroátomos los cuales pueden ser N, O, o S;

R_1^c se selecciona de alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, alcoxi, amino, amino substituido, heteroarilo, heterociclo, cicloalquilo, y arilo; y

q es 1 ó 2.

16. El compuesto de conformidad con las reivindicaciones 1-15, o un enantiómero, diastereómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, caracterizado porque

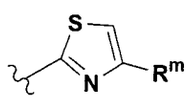
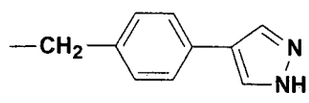
Z es  ;

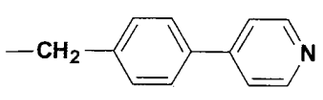
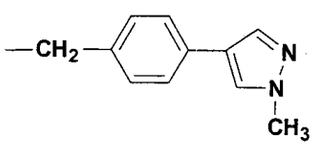
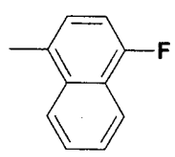
R^m y R^n son los mismos o diferentes y cada que se presentan son independientemente seleccionados de hidrógeno, -$C(O)N(R_1^a)(R_1^b)$, alquilo C_{1-6}, CF_3, CH_2OH, $-SR_1^a$, $N(R_1^a)(R_1^b)$, CH_2F, ciano, y cicloalquilo C_{3-6};

R^o es hidrógeno o alquilo C_{1-6}; y

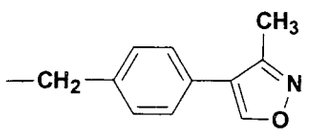
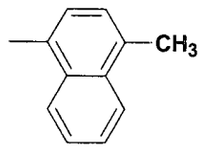
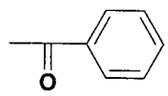
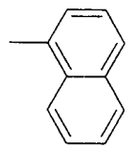
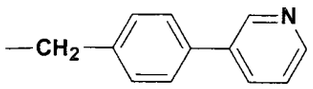
R_1^a y R_1^b son los mismos o diferentes y cada que se presentan son independientemente seleccionados de hidrógeno, alquilo C_{1-6}, y cicloalquilo C_{3-6}.

17. El compuesto de conformidad con las reivindicaciones 1-15, o un enantiómero, diastereómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, caracterizado porque:

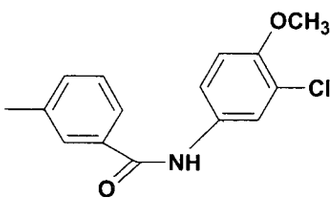
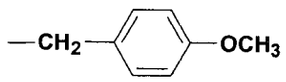
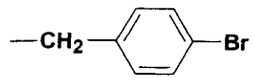
Z es  , donde R^m es  ,

 ,  ,  ,

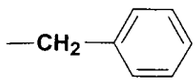
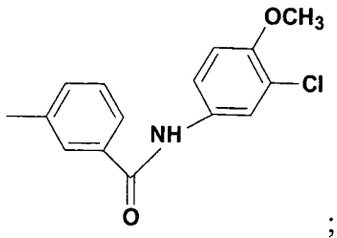
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, H, CH_3, $-CO_2C_2H_5$, $-CO_2CH_3$,

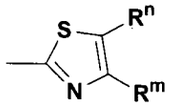




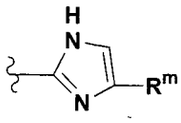
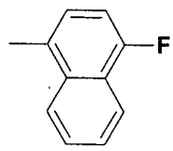
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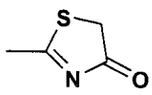



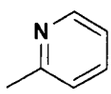
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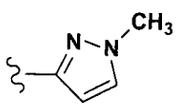
donde R^n es $S(CH_3)$, $S(O)(CH_3)$, $S(O)_2CH_3$, y CH_3;

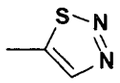
Z es  , donde R^n es CH_3, R^m es CH_3;

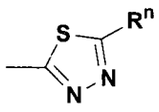
Z es  , donde R^m es  o H;

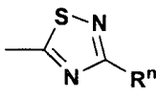
Z es  ;

Z es  ;

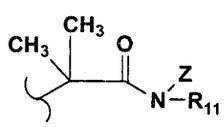
Z es  ;

Z es  ;

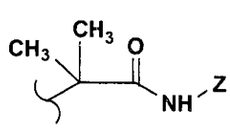
Z es  , donde R^n es CH_3, H, CF_3, C(O)OEt, $C(O)NH_2$, C(O)NH(ciclopropilo), $C(O)NHCH_3$, C(O)NHEt, CH_2OH, S(metilo), $N(metilo)_2$, CH_2F, ciano, etilo, o ciclopropilo; o

Z es  , donde R^n es CH_3 o H.

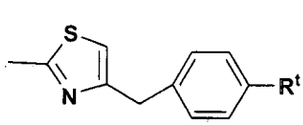
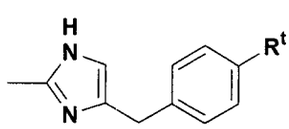
18. El compuesto de conformidad con las reivindicaciones 1-15, o un enantiómero, diastereómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, caracterizado porque



es



donde Z es

 o 

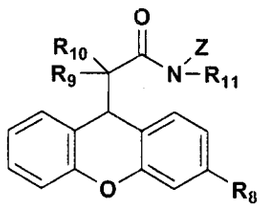
donde R^t es H o alquilo,

un enantiómero, diastereómero, o tautómero del mismo, o un profármaco éster del mismo, o una sal farmacéuticamente

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aceptable de los mismos.

19. El compuesto de conformidad con las reivindicaciones 1-3, 5-10, y 14-18 caracterizado porque tiene la estructura



o un enantiómero, diastereómero, tautómero o una sal farmacéuticamente aceptable del mismo, en donde:

R_8 es hidroxi, ciano, $-C(=O)NR_{14}R_{15}$, $-CO_2R_{14}$, $-C(NH_2)=NOH$, $-NR_{14}C(=O)OR_{15}$, $-OC(O)NR_{14}R_{15}$, $-NHC(O)NR_{14}R_{15}$, o $-NHC(O)R_{15}$;

R_9 y R_{10} son los mismos o diferentes y cada que se presentan son independientemente seleccionados de (i) hidrógeno, halógeno, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, nitro, ciano, $-OR_{14}$, $-NR_{14}R_{15}$, $-C(=O)R_{14}$, $-CO_2R_{14}$, $-C(=O)NR_{14}R_{15}$, $-O-C(=O)R_{14}$, $-NR_{14}C(=O)R_{15}$, $-NR_{14}C(=O)OR_{15}$, $-NR_{14}C(=S)OR_{15}$, $-S(O)_pR_{17}$, $-NR_{14}SO_2R_{17}$, $-SO_2NR_{14}R_{15}$, cicloalquilo, cicloalquenilo, heterociclo, arilo, y heteroarilo; o (ii) junto con el átomo al cual se enlazan, R_9 y R_{10} se toman juntos para formar un grupo carbonilo, alquenilo, alquenilo substituido, cicloalquilo, cicloalquenilo, o heterociclo;

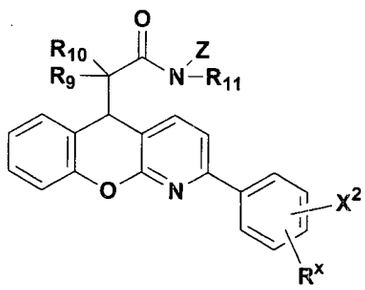
R_{11} se selecciona de hidrógeno, alquilo, alquilo substituido, C(=O)alquilo, CO_2(alquilo), SO_2alquilo, alcoxi, amino, amino substituido, arilo, heteroarilo, heterociclo, y

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cicloalquilo; y

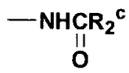
Z es un anillo heteroarilo el cual se enlaza por medio de un átomo de carbono al átomo N.

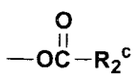
20. El compuesto de conformidad con las reivindicaciones 1-4, 6-10, y 14-19, caracterizado porque tiene la estructura



un enantiómero, diastereómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, en donde:

X^2 es halógeno, alcoxi, H, o alquilo;

R^x es H, $C(O)NR_2^aR_2^b$, OR_2^c, R_2^a, COOH, CF_3, 

, 

, $-NHSO_2R_2^c$, arilo, ariloxi, alquilthio, amino, acilo o ciano;

R_2^a y R_2^b son los mismos o diferentes y cada que se presentan son independientemente seleccionados de hidrógeno, alquilo, alquilo substituido, C(=O)alquilo, CO_2(alquilo), SO_2alquilo, hidrógeno, alquenilo, alquenilo substituido, alcoxi, amino, amino substituido, arilo, heteroarilo, heterociclo, y cicloalquilo;

o R_2^a y R_2^b, donde es posible pueden tomarse junto con el

805

nitrógeno al cual se enlazan para formar un anillo heteroarilo o cicloheteroalquilo de 5, 6 ó 7 elementos el cual contiene 1, 2 ó 3 heteroátomos los cuales pueden ser N, O, o S;

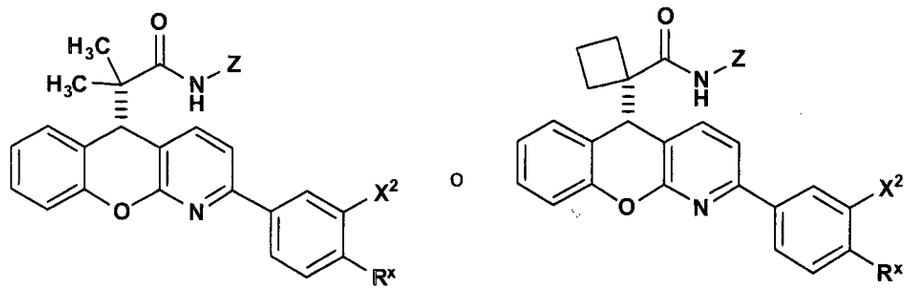
R_2^c se selecciona de hidrógeno, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, alcoxi, amino, amino substituido, heteroarilo, heterociclo, cicloalquilo, y arilo;

R_9 y R_{10} son los mismos o diferentes y cada que se presentan son independientemente seleccionados de (i) hidrógeno, halógeno, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, nitro, ciano, OR_{14}, $NR_{14}R_{15}$, $C(=O)R_{14}$, CO_2R_{14}, $C(=O)NR_{14}R_{15}$, $-O-C(=O)R_{14}$, $NR_{14}C(=O)R_{15}$, $NR_{14}C(=O)OR_{15}$, $NR_{14}C(=S)OR_{15}$, $S(O)_pR_{17}$, $NR_{14}SO_2R_{17}$, $SO_2NR_{14}R_{15}$, cicloalquilo, cicloalquenilo, heterociclo, arilo, y heteroarilo; o (ii) junto con el átomo al cual se enlazan, R_9 y R_{10} se toman juntos para formar un grupo carbonilo, alquenilo, alquenilo substituido, cicloalquilo, cicloalquenilo, o heterociclo; y

R_{11} se selecciona de hidrógeno, alquilo, alquilo substituido, C(=O)alquilo, CO_2(alquilo), SO_2alquilo, alcoxi, amino, amino substituido, arilo, heteroarilo, heterociclo, y cicloalquilo.

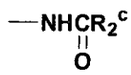
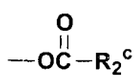
21. El compuesto de conformidad con las reivindicaciones 1-4, 6-10 y 14-20, o un enantiómero, diastereómero, tautómero, o una sal farmacéuticamente aceptable de los mismos,

caracterizado porque tiene la estructura:



en donde:

X^2 es H, halógeno, o alquilo;

R^x es H, $C(O)NR_2^aR_2^b$, OR_2^a, R_2^a, COOH, CF_3,  ,  , $-NHSO_2R_2^c$, arilo, ariloxi, alquiltio, amino, acilo o ciano;

R_2^a se selecciona de hidrógeno, alquilo, alquilo substituido, C(=O)alquilo, CO_2(alquilo), SO_2alquilo, hidrógeno, alquenilo, alquenilo substituido, alcoxi, amino, amino substituido, arilo, heteroarilo, heterociclo, y cicloalquilo;

R_2^b se selecciona de alquilo, alquilo substituido, C(=O)alquilo, CO_2(alquilo), SO_2alquilo, hidrógeno, alquenilo, alquenilo substituido, alcoxi, amino, amino substituido, arilo, heteroarilo, heterociclo, y cicloalquilo;

o R_2^a y R_2^b son tomados junto con el nitrógeno al cual se enlazan para formar un anillo heteroarilo o cicloheteroalquilo

de 5, 6 ó 7 elementos los cuales contienen 1, 2 ó 3 heteroátomos los cuales pueden ser N, O, o S; y

R_2^c se selecciona de alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, alcoxi, amino, amino substituido, heteroarilo, heterociclo, cicloalquilo, y arilo.

22. Un compuesto, caracterizado porque es seleccionado de:

N-{4-[4-(4-piridinil)bencil]-1,3-tiazol-2-il}-2-(9H-xanten-9-il)acetamida,

N-[4-(4-fluoro-1-naftil)-1,3-tiazol-2-il]-2-(9H-xanten-9-il)acetamida,

N-[4-(4-metil-1-naftil)-1,3-tiazol-2-il]-2-(9H-xanten-9-il)acetamida,

N-[4-(1-naftil)-1,3-tiazol-2-il]-2-(9H-xanten-9-il)acetamida,

2-metil-N-{4-[4-(4-piridinil)bencil]-1,3-tiazol-2-il}-2-(9H-tioxanten-9-il)propanamida,

2-metil-N-[4-(1-naftil)-1,3-tiazol-2-il]-2-(9H-tioxanten-9-il)propanamida,

2-metil-N-[4-(4-metil-1-naftil)-1,3-tiazol-2-il]-2-(9H-tioxanten-9-il)propanamida,

N-[4-(4-fluoro-1-naftil)-1,3-tiazol-2-il]-2-metil-2-(9H-tioxanten-9-il)propanamida,

2-metil-N-1,3-tiazol-2-il-2-(9H-tioxanten-9-

il)propanamida,

2-(10,10-dióxido-9H-tioxanten-9-il)-N-[4-(4-fluoro-1-naftil)-1,3-tiazol-2-il]-2-metilpropanamida,

2-(10,10-dióxido-9H-tioxanten-9-il)-2-metil-N-[4-(1-naftil)-1,3-tiazol-2-il]propanamida,

2-(10,10-dióxido-9H-tioxanten-9-il)-2-metil-N-[4-(4-metil-1-naftil)-1,3-tiazol-2-il]propanamida,

2-(10,10-dióxido-9H-tioxanten-9-il)-2-metil-N-1,3-tiazol-2-ilpropanamida,

2-(9,10-dihidro-9-antracenil)-2-metil-N-[4-(1-naftil)-1,3-tiazol-2-il]propanamida,

2-(9,10-dihidro-9-antracenil)-2-metil-N-[4-(4-metil-1-naftil)-1,3-tiazol-2-il]propanamida,

2-(9,10-dihidro-9-antracenil)-N-[4-(4-fluoro-1-naftil)-1,3-tiazol-2-il]-2-metilpropanamida,

2-(9H-fluoren-9-il)-2-metil-N-1,3-tiazol-2-ilpropanamida,

2-(9H-fluoren-9-il)-2-metil-N-[4-(1-naftil)-1,3-tiazol-2-il]propanamida,

2-(9H-fluoren-9-il)-2-metil-N-[4-(4-metil-1-naftil)-1,3-tiazol-2-il]propanamida,

2-(9H-fluoren-9-il)-N-[4-(4-fluoro-1-naftil)-1,3-tiazol-2-il]-2-metilpropanamida,

2-(2-hidroxi-9H-fluoren-9-il)-2-metil-N-1,3-tiazol-2-ilpropanamida,

2-{[2-(10,11-dihidro-5H-dibenzo[a,d][7]anulen-5-il)-2-

809

metilpropanoil]amino}-1,3-tiazol-4-carboxilato de etilo,

2-(10,11-dihidro-5H-dibenzo[a,d][7]anulen-5-il)-2-metil-N-{4-[4-(4-piridinil)bencil]-1,3-tiazol-2-il}propanamida,

2-(10,11-dihidro-5H-dibenzo[a,d][7]anulen-5-il)-2-metil-N-[4-(4-metil-1-naftil)-1,3-tiazol-2-il]propanamida,

2-(10,11-dihidro-5H-dibenzo[a,d][7]anulen-5-il)-2-metil-N-1,3-tiazol-2-ilpropanamida,

N-[4-(4-fluoro-1-naftil)-1,3-tiazol-2-il]-2-(9H-tioxanten-9-il)acetamida,

N-[4-(4-metil-1-naftil)-1,3-tiazol-2-il]-2-(9H-tioxanten-9-il)acetamida,

N-[4-(1-naftil)-1,3-tiazol-2-il]-2-(9H-tioxanten-9-il)acetamida,

N-(3-cloro-4-metoxifenil)-3-(2-{[2-metil-2-(9H-xanten-9il)propanoil]amino}-1,3-tiazol-4-il)benzamida,

2-metil-N-[4-(1-naftil)-1,3-tiazol-2-il]-2-(9H-xanten-9-il)propanamida,

2-metil-N-[4-(4-metil-1-naftil)-1,3-tiazol-2-il]-2-(9H-xanten-9-il)propanamida,

N-[4-(4-fluoro-1-naftil)-1,3-tiazol-2-il]-2-metil-2-(9H-xanten-9-il)propanamida,

N-[4-(4-metoxibencil)-1,3-tiazol-2-il]-2-metil-2-(9H-xanten-9-il)propanamida,

2-metil-N-{4-[4-(4-piridinil)bencil]-1,3-tiazol-2-il}-2-(9H-xanten-9-il)propanamida,

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N-[4-(4-bromobencil)-1,3-tiazol-2-il]-2-metil-2-(9H-xanten-9-il)propanamida,

N-(4-bencil-1,3-tiazol-2-il)-2-metil-2-(9H-xanten-9-il)propanamida,

N-(3-cloro-4-metoxifenil)-3-(2-{[2-metil-2-(9H-xanten-9-il)propanoil]amino}-1,3-tiazol-4-il)benzamida,

2-metil-N-1,3-tiazol-2-il-2-(9H-xanten-9-il)propanamida,

N-[4-(4-fluoro-1-naftil)-1H-imidazol-2-il]-2-metil-2-(9H-xanten-9-il)propanamida,

2-metil-N-1,3,4-tiadiazol-2-il-2-(9H-xanten-9-il)propanamida,

N-[4-(4-fluoro-1-naftil)-1,3-tiazol-2-il]-2-metil-2-[2-(trifluorometil)-9H-xanten-9-il]propanamida,

2-metil-N-{4-[4-(1H-pirazol-4-il)bencil]-1,3-tiazol-2-il}-2-(9H-xanten-9-il)propanamida,

2-metil-N-{4-[4-(1-metil-1H-pirazol-4-il)bencil]-1,3-tiazol-2-il}-2-(9H-xanten-9-il)propanamida,

N-{4-[4-(3,5-dimetil-4-isoxazolil)bencil]-1,3-tiazol-2-il}-2-metil-2-(9H-xanten-9-il)propanamida,

N-(4-benzoil-1,3-tiazol-2-il)-2-metil-2-(9H-xanten-9-il)propanamida,

N-[4-(4-fluoro-1-naftil)-1,3-tiazol-2-il]-2-(3-metoxi-9H-xanten-9-il)-2-metilpropanamida,

2-(3-metoxi-9H-xanten-9-il)-2-metil-N-[4-(4-metil-1-naftil)-1,3-tiazol-2-il]propanamida,

N-(4-bencil-1,3-tiazol-2-il)-2-(3-metoxi-9H-xanten-9-il)-2-metilpropanamida,

2-{[2-(3-metoxi-9H-xanten-9-il)-2-metilpropanoil]amino}-1,3-tiazol-4-carboxilato de etilo,

N-[4-(4-metoxibencil)-1,3-tiazol-2-il]-2-(3-metoxi-9H-xanten-9-il)-2-metilpropanamida,

N-[4-(4-bromobencil)-1,3-tiazol-2-il]-2-(3-metoxi-9H-xanten-9-il)-2-metilpropanamida,

2-(3-metoxi-9H-xanten-9-il)-2-metil-N-{4-[4-(4-piridinil)bencil]-1,3-tiazol-2-il}propanamida,

2-(3-metoxi-9H-xanten-9-il)-2-metil-N-[4-(1-naftil)-1,3-tiazol-2-il]propanamida,

2-(3-metoxi-9H-xanten-9-il)-2-metil-N-{4-[4-(3-piridinil)bencil]-1,3-tiazol-2-il}propanamida,

2-[(9R)-3-metoxi-9H-xanten-9-il]-2-metil-N-1,3-tiazol-2-ilpropanamida,

2-[(9S)-3-metoxi-9H-xanten-9-il]-2-metil-N-1,3-tiazol-2-ilpropanamida,

N-1H-imidazol-2-il-2-[(9S)-3-metoxi-9H-xanten-9-il]-2-metilpropanamida,

2-[(9S)-3-metoxi-9H-xanten-9-il]-2-metil-N-1,3,4-tiadiazol-2-ilpropanamida,

2-(5H-cromeno[2,3-b]piridin-5-il)-N-[4-(4-fluoro-1-naftil)-1,3-tiazol-2-il]-2-metilpropanamida,

2-(5H-cromeno[2,3-b]piridin-5-il)-2-metil-N-{4-[4-(4-

030812

piridinil)bencil]-1,3-tiazol-2-il}propanamida,

2-(5H-cromeno[2,3-b]piridin-5-il)-2-metil-N-1,3,4-tiadiazol-2-ilpropanamida,

2-(5H-cromeno[2,3-b]piridin-5-il)-2-metil-N-1,2,4-tiadiazol-5-ilpropanamida,

2-(5H-cromeno[2,3-b]piridin-5-il)-2-metil-N-1,3-tiazol-2-ilpropanamida,

2-{[2-(5H-cromeno[2,3-b]piridin-5-il)-2-metilpropanoil]amino}-1,3-tiazol-4-carboxilato de etilo,

2-(5H-cromeno[2,3-b]piridin-5-il)-2-metil-N-(5-metil-1,3-tiazol-2-il)propanamida,

2-(5H-cromeno[2,3-b]piridin-5-il)-2-metil-N-(4-metil-1,3-tiazol-2-il)propanamida,

2-(5H-cromeno[2,3-b]piridin-5-il)-2-metil-N-(5-metil-1,3,4-tiadiazol-2-il)propanamida,

2-(2-cloro-5H-cromeno[2,3-b]piridin-5-il)-N-[4-(4-fluoro-1-naftil)-1,3-tiazol-2-il]-2-metilpropanamida,

2-(2-cloro-5H-cromeno[2,3-b]piridin-5-il)-2-metil-N-[4-(1-naftil)-1,3-tiazol-2-il]propanamida,

2-(2-cloro-5H-cromeno[2,3-b]piridin-5-il)-2-metil-N-1,3-tiazol-2-ilpropanamida,

2-(2-cloro-5H-cromeno[2,3-b]piridin-5-il)-2-metil-N-1,3,4-tiadiazol-2-ilpropanamida,

N-[4-(4-metoxibencil)-1,3-tiazol-2-il]-2-(2-metoxi-5H-cromeno[2,3-b]piridin-5-il)-2-metilpropanamida,

N-[4-(4-fluoro-1-naftil)-1,3-tiazol-2-il]-2-(2-metoxi-5H-cromeno[2,3-b]piridin-5-il)-2-metilpropanamida,

2-(2-metoxi-5H-cromeno[2,3-b]piridin-5-il)-2-metil-N-{4-[4-(4-piridinil)bencil]-1,3-tiazol-2-il}propanamida,

2-(4-hidroxi-9H-xanten-9-il)-2-metil-N-1,3-tiazol-2-ilpropanamida,

N-[4-(4-fluoro-1-naftil)-1,3-tiazol-2-il]-2-(4-metoxi-9H-xanten-9-il)-2-metilpropanamida,

2-(4-metoxi-9H-xanten-9-il)-2-metil-N-{4-[4-(4-piridinil)bencil]-1,3-tiazol-2-il}propanamida,

2-(4-metoxi-9H-xanten-9-il)-2-metil-N-1,3-tiazol-2-ilpropanamida,

2-{4-[2-(dimetilamino)etoxi]-9H-xanten-9-il}-N-[4-(4-metoxibencil)-1,3-tiazol-2-il]-2-metilpropanamida,

N-(4,5-dimetil-1,3-tiazol-2-il)-2-[(9S)-3-hidroxi-9H-xanten-9-il]-2-metilpropanamida,

2-[(9S)-3-hidroxi-9H-xanten-9-il]-2-metil-N-(5-metil-1,3-tiazol-2-il)propanamida,

2-[(9S)-3-hidroxi-9H-xanten-9-il]-2-metil-N-(4-metil-1,3-tiazol-2-il)propanamida,

2-[(9S)-3-hidroxi-9H-xanten-9-il]-2-metil-N-1,3-tiazol-2-ilpropanamida,

2-[(9S)-3-hidroxi-9H-xanten-9-il]-2-metil-N-1,3,4-tiadiazol-2-ilpropanamida,

N-(4,5-dimetil-1,3-tiazol-2-il)-2-[(9R)-3-hidroxi-9H-

030814

xanten-9-il]-2-metilpropanamida,

2-[(9R)-3-hidroxi-9H-xanten-9-il]-2-metil-N-(5-metil-1,3-tiazol-2-il)propanamida,

9H-xanteno-9-acetamida, 3-hidroxi-alfa,alfa-dimetil-N-(4-metil-2-tiazolil)-, (9R)-,

9H-xanteno-9-acetamida, 3-hidroxi-alfa,alfa-dimetil-N-2-tiazolil-, (9R)-,

9H-xanteno-9-acetamida, 3-hidroxi-alfa,alfa-dimetil-N-1,3,4-tiadiazol-2-il-, (9R)-,

ácido 4-tiazolcarboxílico, 2-[[2-(3-hidroxi-9H-xanten-9-il)-2-metil-1-oxopropil]amino]-, éster de etilo,

ácido 4-tiazolcarboxílico, 2-[[2-[3-[(2-metoxietoxi)metoxi]-9H-xanten-9-il]-2-metil-1-oxopropil]amino]-, éster de etilo,

9H-xanteno-9-acetamida, 3-[(2-metoxietoxi)metoxi]-alfa,alfa-dimetil-N-2-tiazolilo,

ácido 4-tiazolcarboxílico, 2-[[2-(3-hidroxi-9H-xanten-9-il)-2-metil-1-oxopropil]amino]-, éster de metilo,

2-(3-hidroxi-9H-xanten-9-il)-2-metil-N-(5-metil-1,3,4-tiadiazol-2-il)propanamida,

2-metil-2-[2-(metilamino)-5H-cromeno[2,3-b]piridin-5-il]-N-1,3-tiazol-2-ilpropanamida,

2-{2-[(4-metoxibencil)amino]-5H-cromeno[2,3-b]piridin-5-il}-2-metil-N-1,3,4-tiadiazol-2-ilpropanamida,

2-metil-2-[2-(4-morfolinil)-5H-cromeno[2,3-b]piridin-5-

000815

il]-N-1,3,4-tiadiazol-2-ilpropanamida,

2-metil-2-[2-(1-pirrolidinil)-5H-cromeno[2,3-b]piridin-5-il]-N-1,3,4-tiadiazol-2-ilpropanamida,

2-metil-2-[2-(4-metil-1-piperazinil)-5H-cromeno[2,3-b]piridin-5-il]-N-1,3,4-tiadiazol-2-ilpropanamida,

2-metil-2-[2-(1-piperidinil)-5H-cromeno[2,3-b]piridin-5-il]-N-1,3,4-tiadiazol-2-ilpropanamida,

2-[2-(bencilamino)-5H-cromeno[2,3-b]piridin-5-il]-2-metil-N-1,3,4-tiadiazol-2-ilpropanamida,

2-metil-2-[(5R)-2-(1-piperidinil)-5H-cromeno[2,3-b]piridin-5-il]-N-1,3,4-tiadiazol-2-ilpropanamida,

2-[(5R)-2-(1,4-dioxa-8-azaspiro[4.5]dec-8-il)-5H-cromeno[2,3-b]piridin-5-il]-2-metil-N-1,3,4-tiadiazol-2-ilpropanamida,

2-{(5R)-2-[(4-metoxibencil)amino]-5H-cromeno[2,3-b]piridin-5-il}-2-metil-N-1,3,4-tiadiazol-2-ilpropanamida,

2-metil-2-[(5R)-2-(1-pirrolidinil)-5H-cromeno[2,3-b]piridin-5-il]-N-1,3,4-tiadiazol-2-ilpropanamida,

2-metil-2-[(5S)-2-(1-piperidinil)-5H-cromeno[2,3-b]piridin-5-il]-N-1,3,4-tiadiazol-2-ilpropanamida,

2-[(5S)-2-(1,4-dioxa-8-azaspiro[4.5]dec-8-il)-5H-cromeno[2,3-b]piridin-5-il]-2-metil-N-1,3,4-tiadiazol-2-ilpropanamida,

2-{(5S)-2-[(4-metoxibencil)amino]-5H-cromeno[2,3-b]piridin-5-il}-2-metil-N-1,3,4-tiadiazol-2-ilpropanamida,

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2-metil-2-[(5S)-2-(1-pirrolidinil)-5H-cromeno[2,3-b]piridin-5-il]-N-1,3,4-tiadiazol-2-ilpropanamida,

2-metil-2-[(5S)-2-{[(1S)-1-feniletil]amino}-5H-cromeno[2,3-b]piridin-5-il]-N-1,3,4-tiadiazol-2-ilpropanamida,

2-metil-2-[(5S)-2-{[(1R)-1-feniletil]amino}-5H-cromeno[2,3-b]piridin-5-il]-N-1,3,4-tiadiazol-2-ilpropanamida,

2-{(5S)-2-[(2S)-2-(metoximetil)-1-pirrolidinil]-5H-cromeno[2,3-b]piridin-5-il}-2-metil-N-1,3,4-tiadiazol-2-ilpropanamida,

2-{(5S)-2-[(2R)-2-(metoximetil)-1-pirrolidinil]-5H-cromeno[2,3-b]piridin-5-il}-2-metil-N-1,3,4-tiadiazol-2-ilpropanamida,

2-[(5S)-2-(1-azepanil)-5H-cromeno[2,3-b]piridin-5-il]-2-metil-N-1,3,4-tiadiazol-2-ilpropanamida,

2-metil-2-[(5S)-2-(3-fenil-1-piperidinil)-5H-cromeno[2,3-b]piridin-5-il]-N-1,3,4-tiadiazol-2-ilpropanamida,

2-metil-2-[(5S)-2-(1-piperidinil)-5H-cromeno[2,3-b]piridin-5-il]-N-1,3-tiazol-2-ilpropanamida,

2-[(5S)-2-(dimetilamino)-5H-cromeno[2,3-b]piridin-5-il]-2-metil-N-1,3,4-tiadiazol-2-ilpropanamida,

2-metil-2-[(5S)-2-(3-metil-1-piperidinil)-5H-cromeno[2,3-b]piridin-5-il]-N-1,3,4-tiadiazol-2-ilpropanamida,

2-{2-[(4-metoxibencil)amino]-5H-cromeno[2,3-b]piridin-5-il}-2-metil-N-1,3-tiazol-2-ilpropanamida,

2-metil-2-[2-(4-morfolinil)-5H-cromeno[2,3-b]piridin-5-

000817

il]-N-1,3-tiazol-2-ilpropanamida,

2-[2-(butilamino)-5H-cromeno[2,3-b]piridin-5-il]-2-metil-N-1,3-tiazol-2-ilpropanamida,

2-{2-[bencil(metil)amino]-5H-cromeno[2,3-b]piridin-5-il}-2-metil-N-1,3-tiazol-2-ilpropanamida,

2-[2-(isopropilamino)-5H-cromeno[2,3-b]piridin-5-il]-2-metil-N-1,3-tiazol-2-ilpropanamida,

2-(2-amino-5H-cromeno[2,3-b]piridin-5-il)-2-metil-N-1,3-tiazol-2-ilpropanamida,

2-(2-amino-5H-cromeno[2,3-b]piridin-5-il)-2-metil-N-1,3,4-tiadiazol-2-ilpropanamida,

2-[2-(dimetilamino)-5H-cromeno[2,3-b]piridin-5-il]-2-metil-N-1,3-tiazol-2-ilpropanamida,

2-metil-2-[(5R)-2-(4-oxo-1-piperidinil)-5H-cromeno[2,3-b]piridin-5-il]-N-1,3-tiazol-2-ilpropanamida,

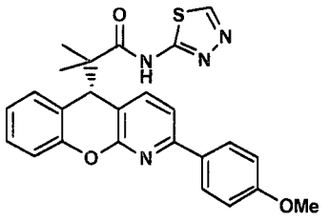
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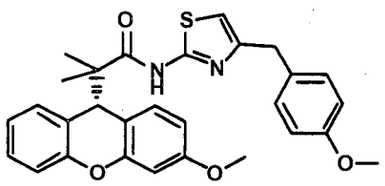
2-metil-2-[(5S)-2-(4-metilfenil)-5H-cromeno[2,3-b]piridin-5-il]-N-1,3,4-tiadiazol-2-ilpropanamida,

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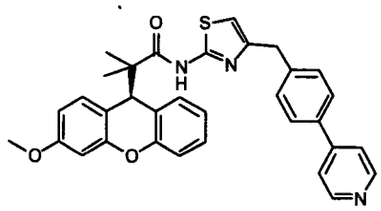
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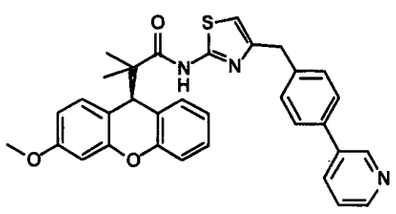
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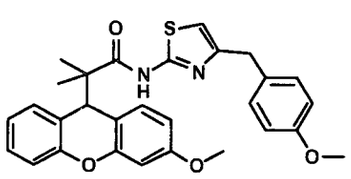
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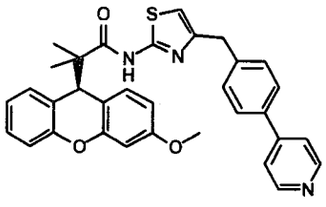
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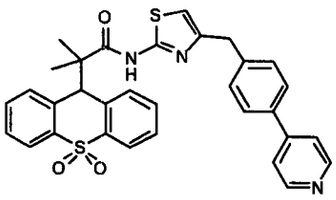
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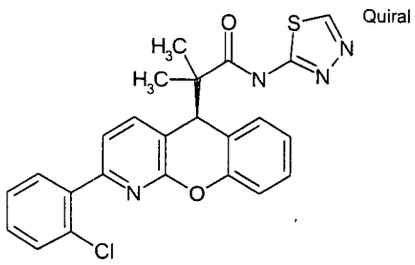


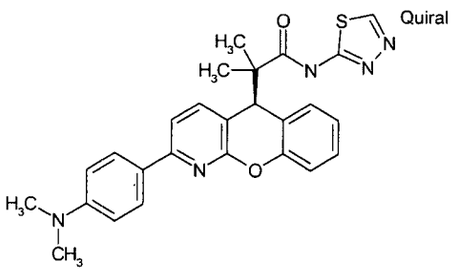
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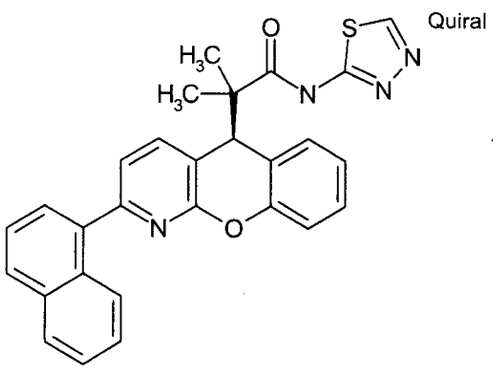


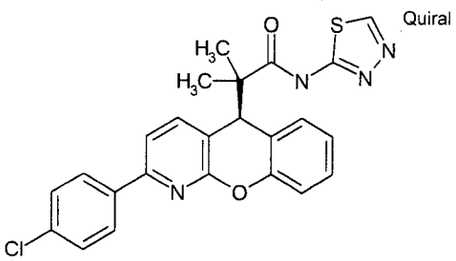
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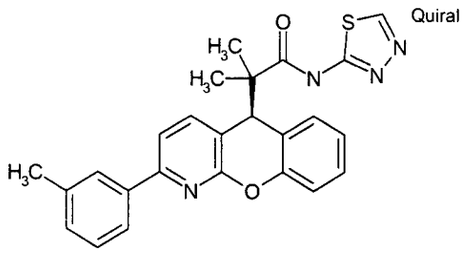

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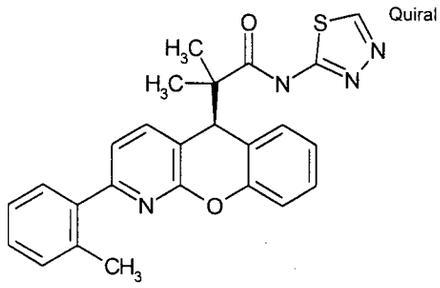

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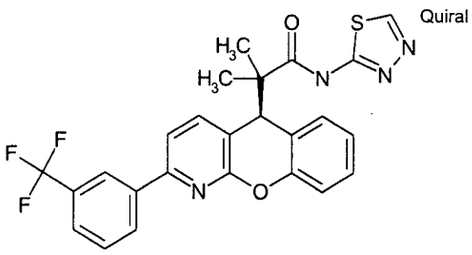

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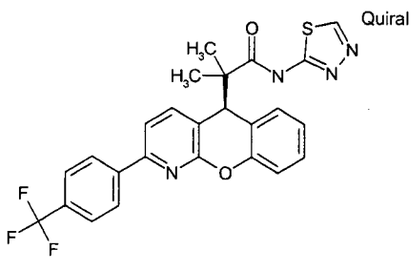

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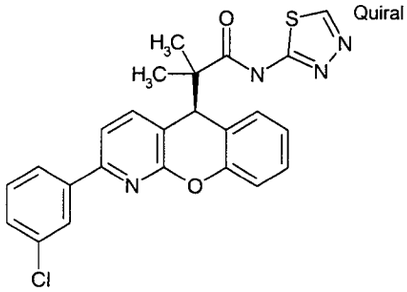
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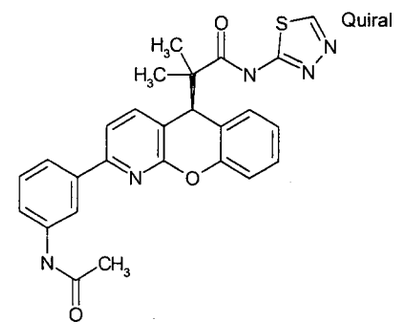

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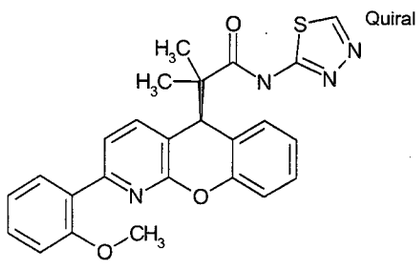

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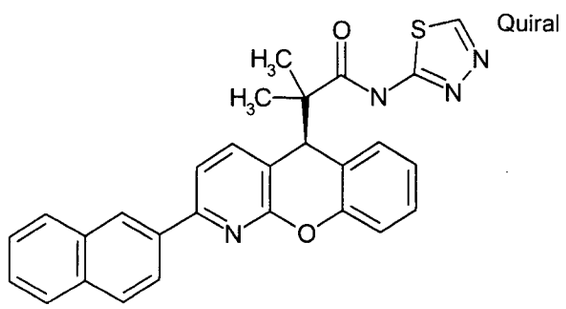

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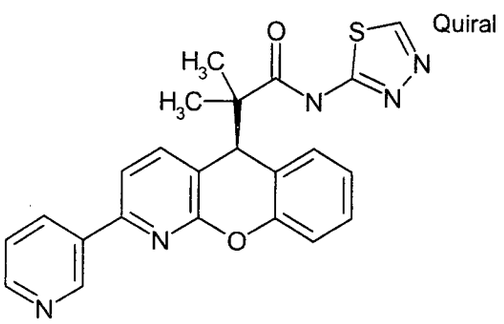

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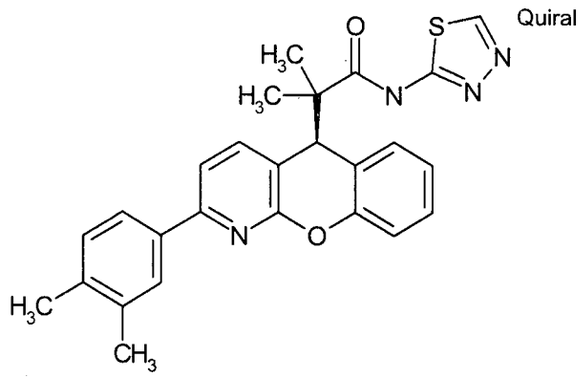
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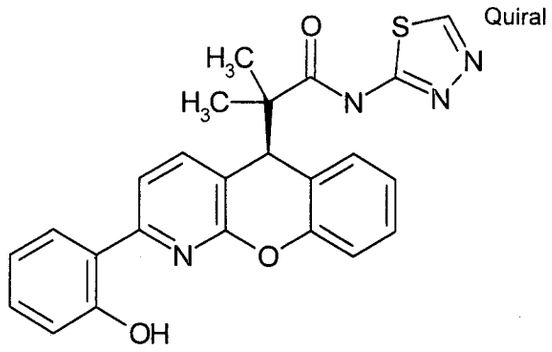

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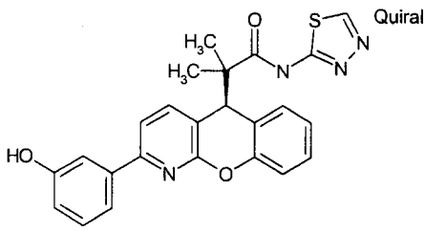

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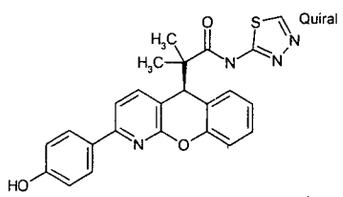

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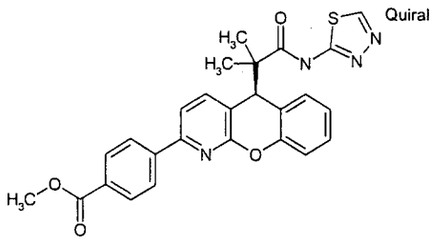

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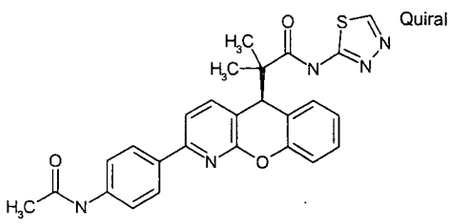

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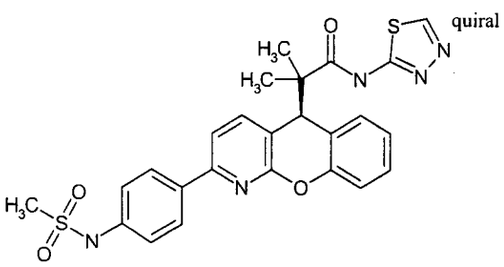

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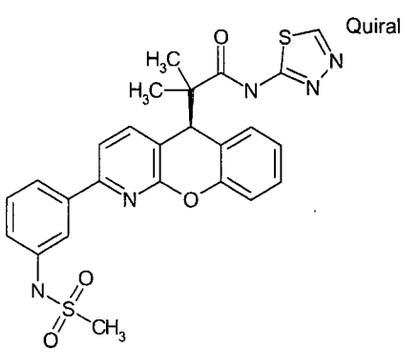

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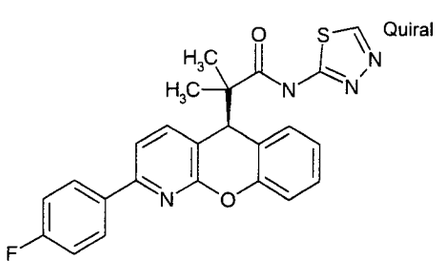
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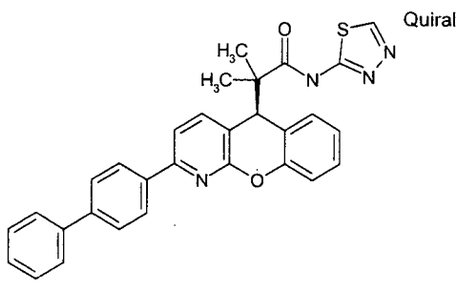


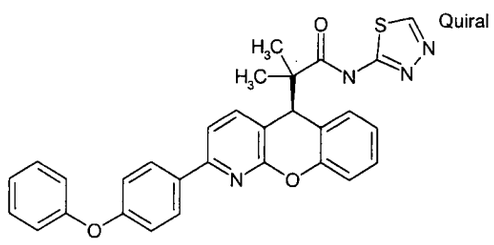


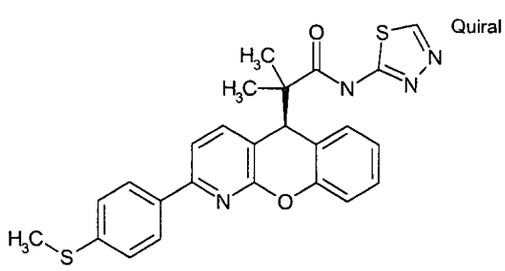


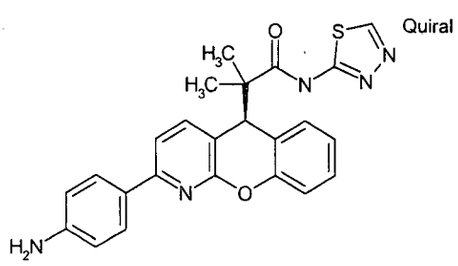


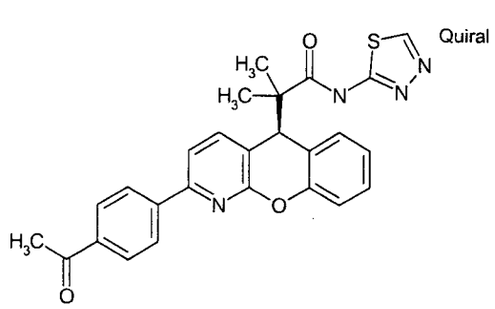
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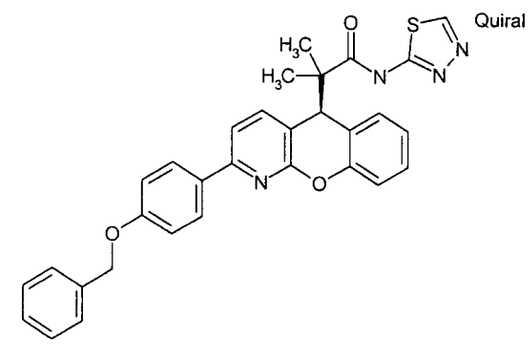

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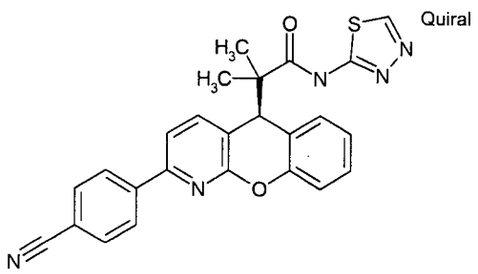

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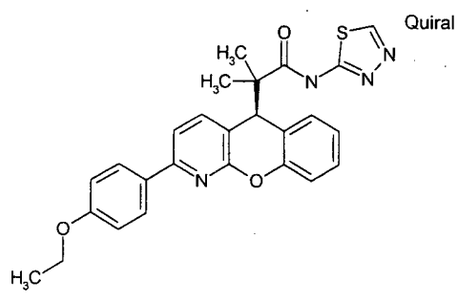

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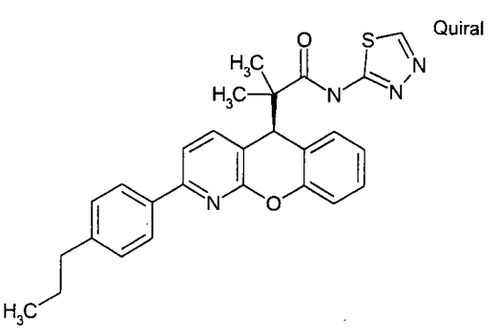

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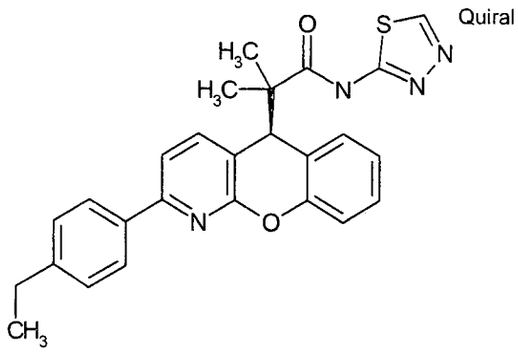


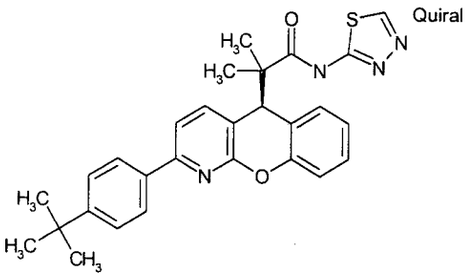


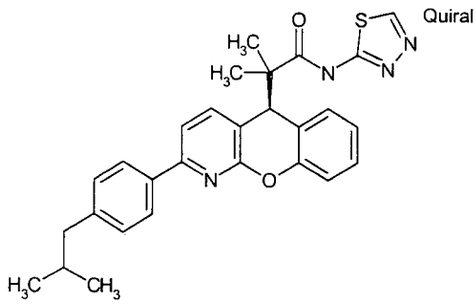


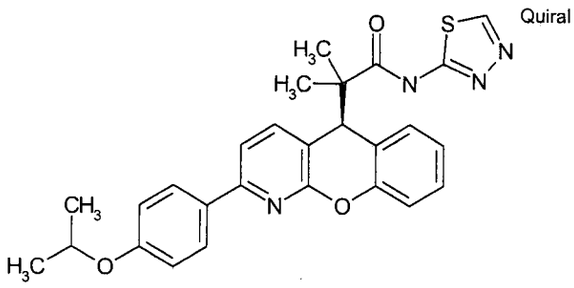


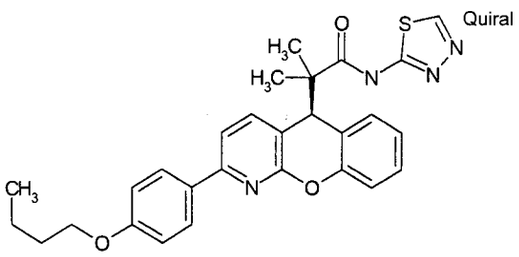
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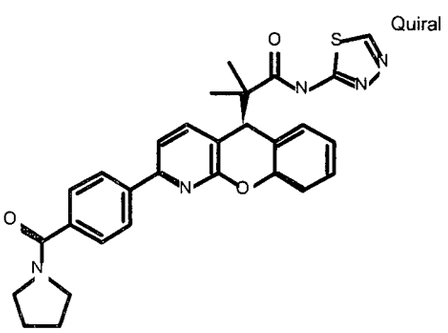

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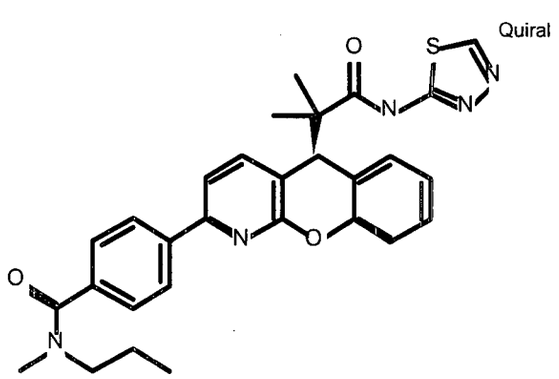

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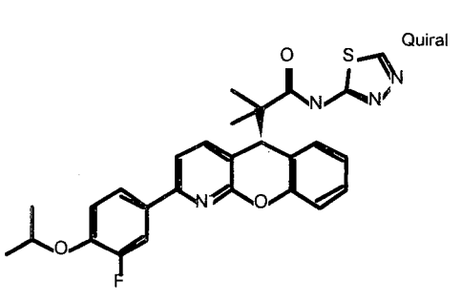

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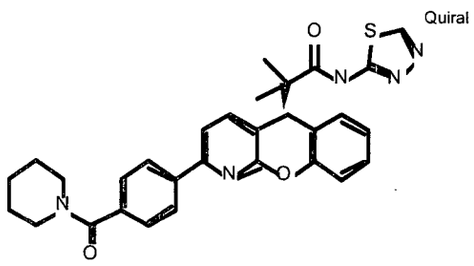

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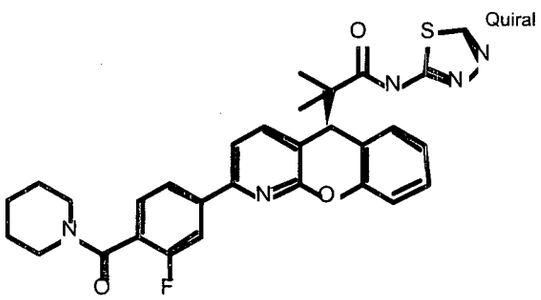

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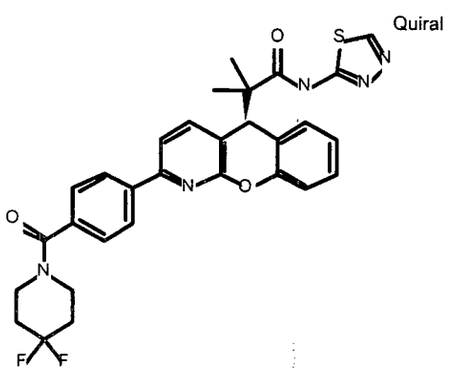

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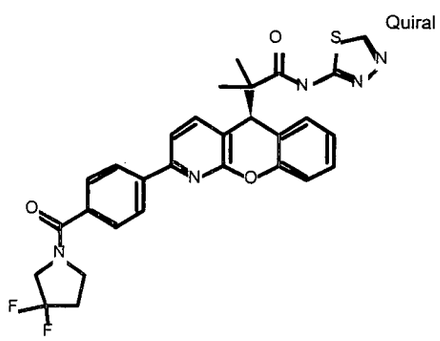

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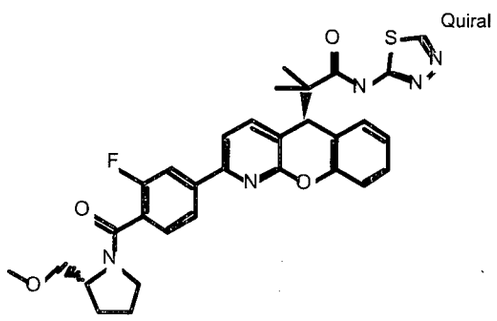

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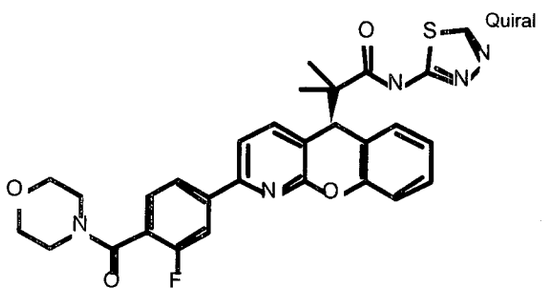

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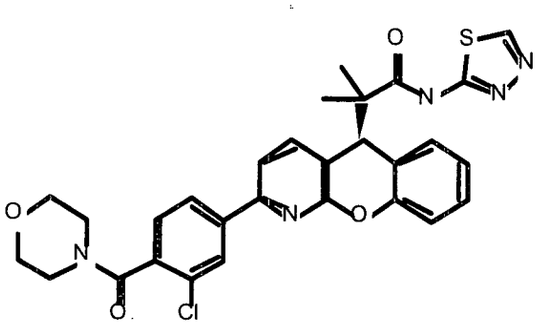

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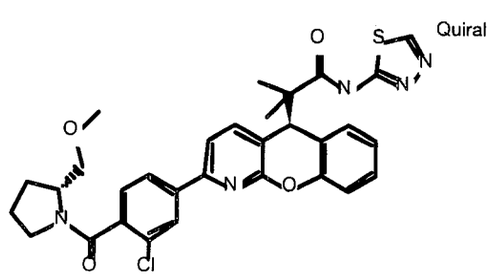

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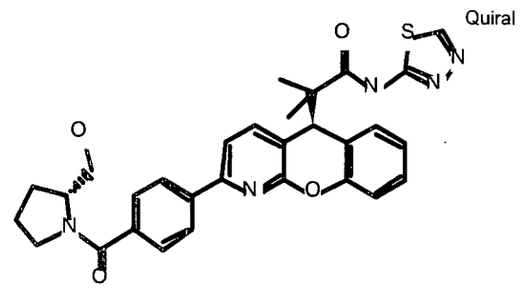

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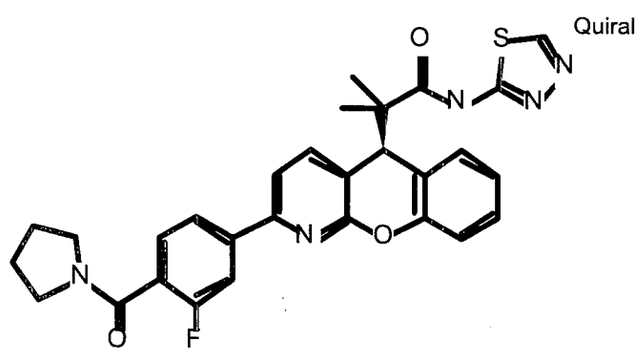

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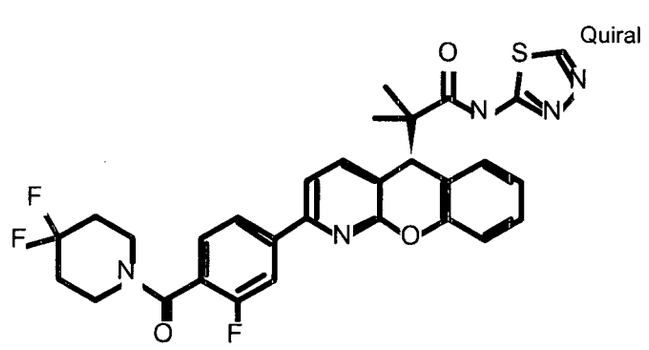

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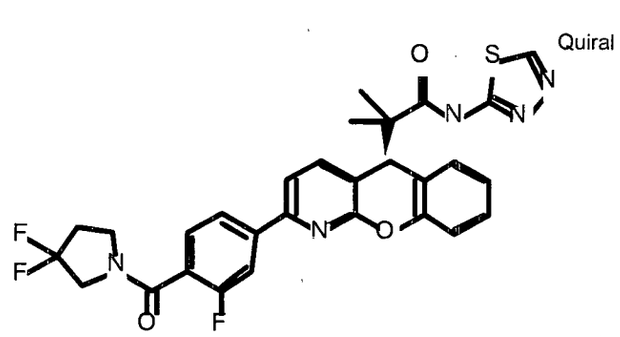

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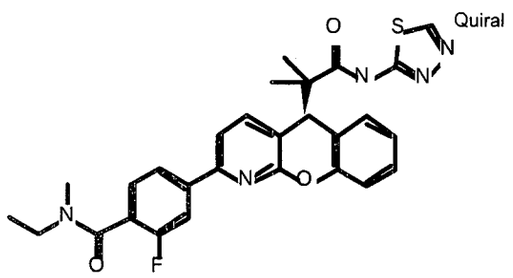

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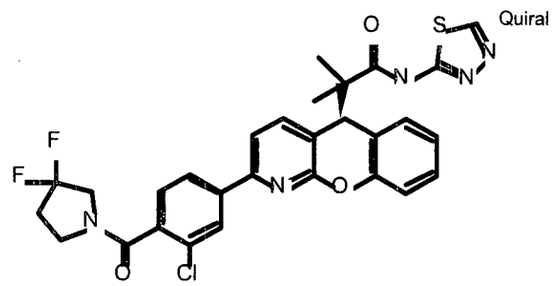

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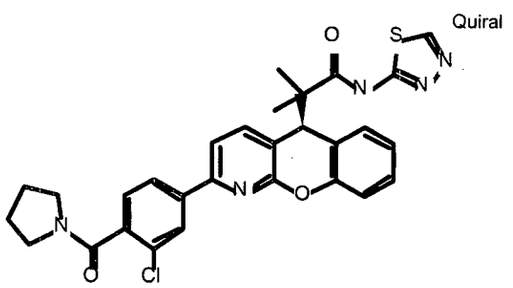

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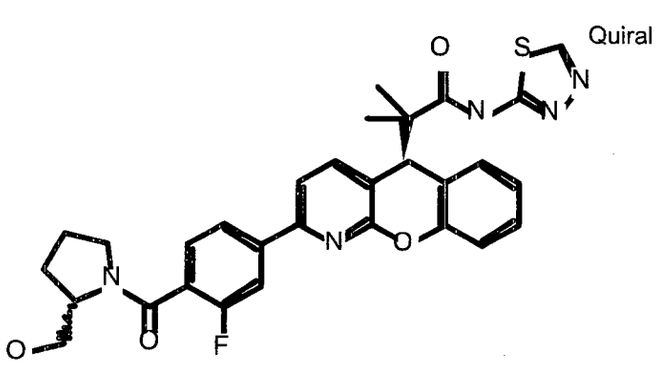

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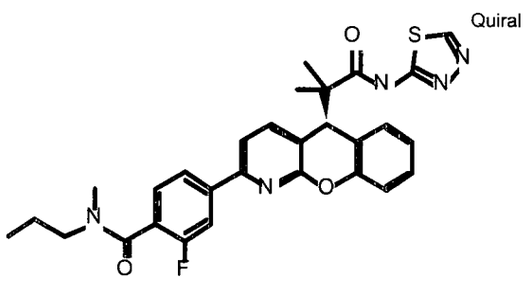

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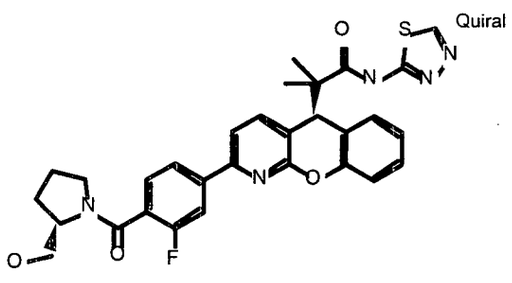

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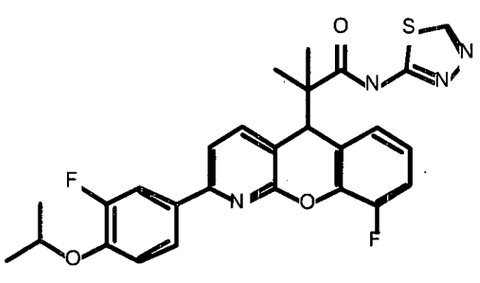

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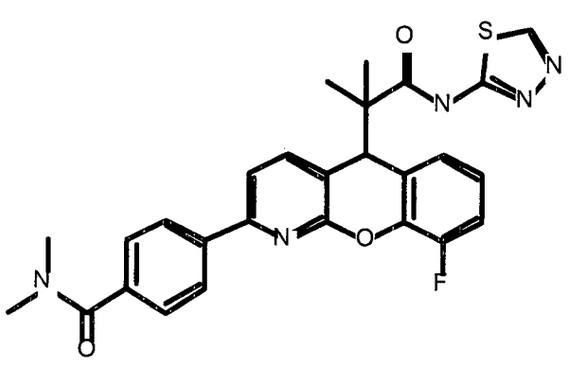

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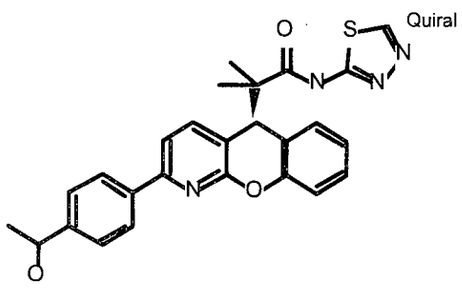


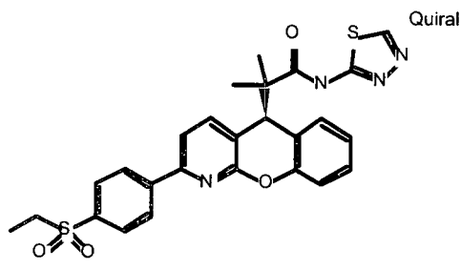


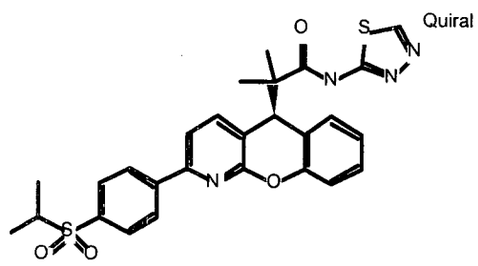


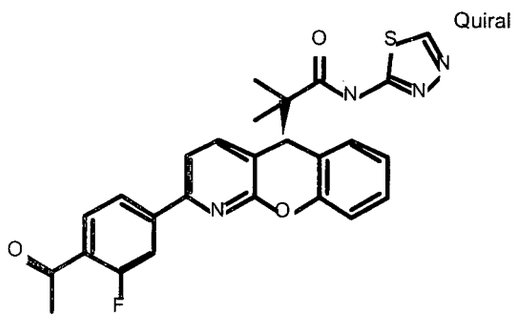


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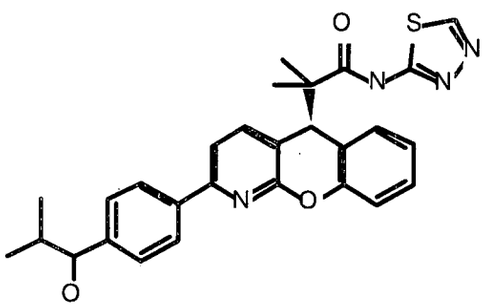

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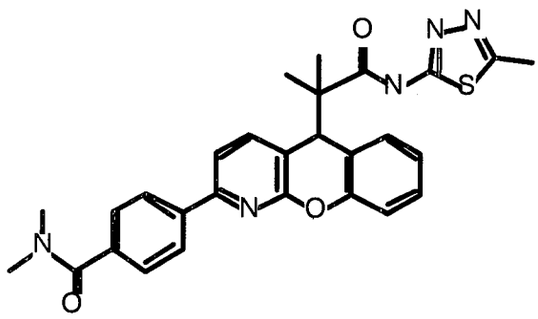

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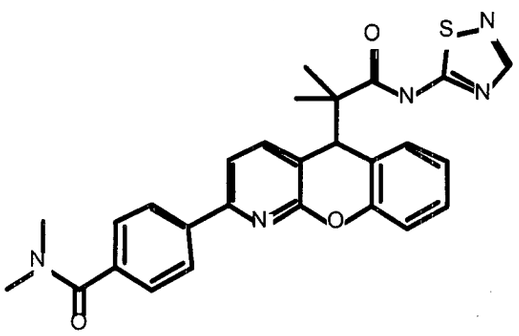

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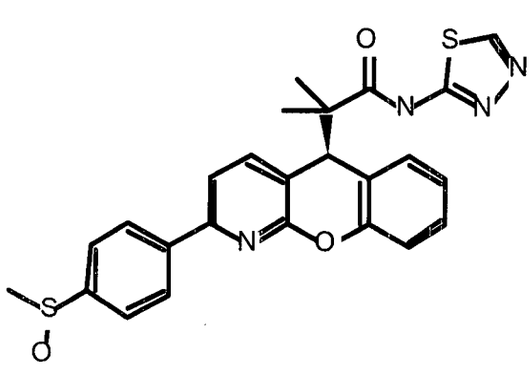

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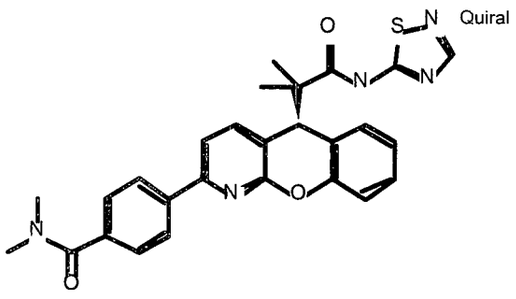


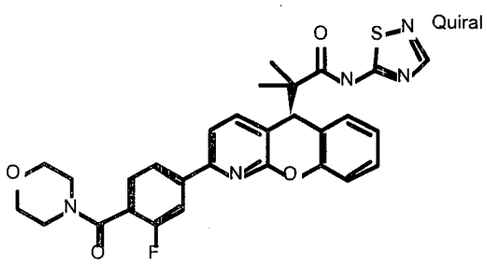


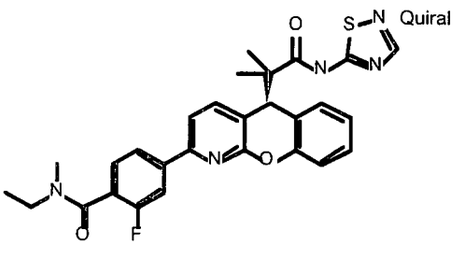


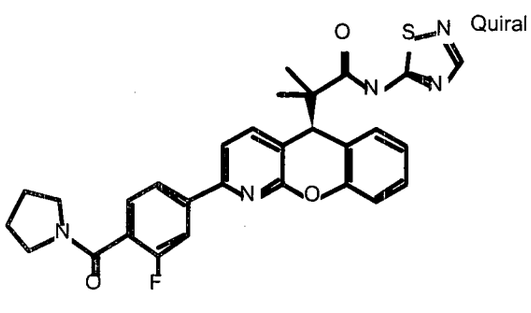


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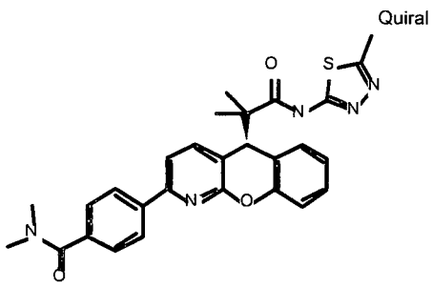


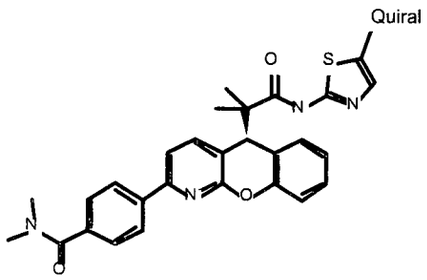


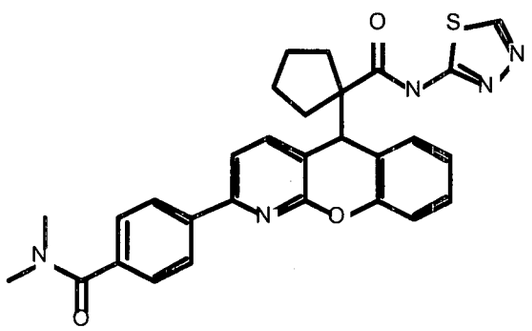


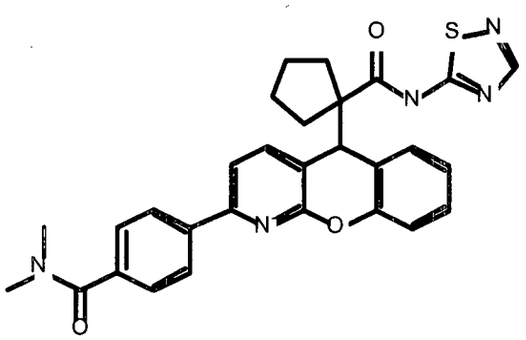


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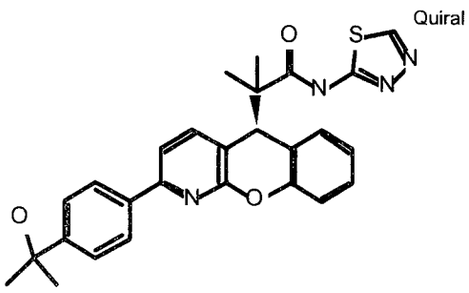


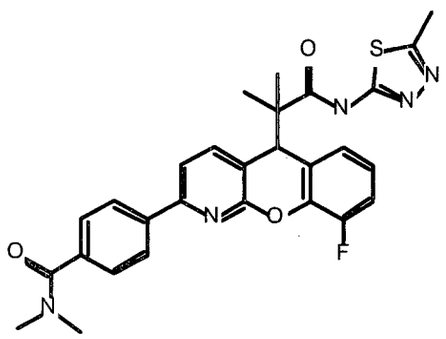


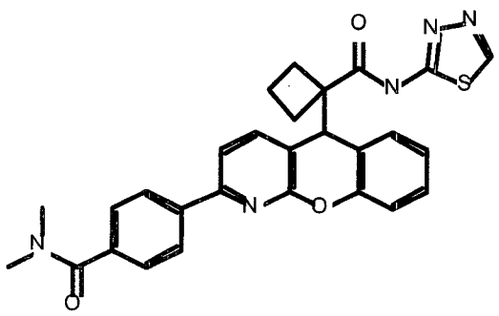


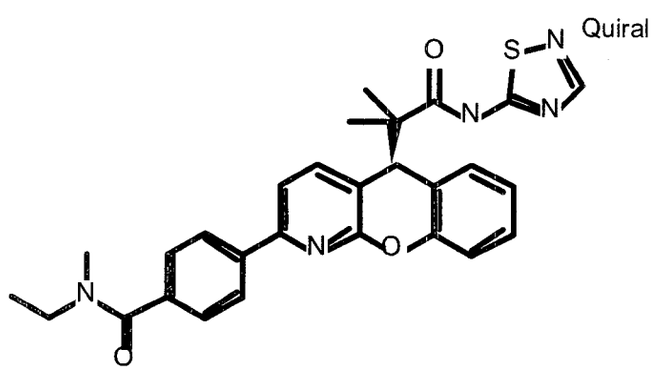


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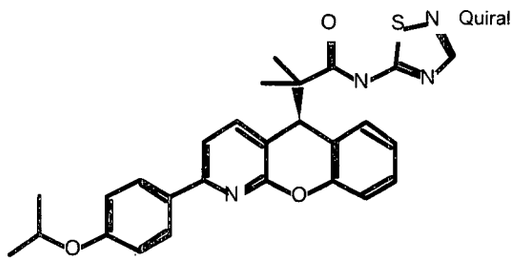


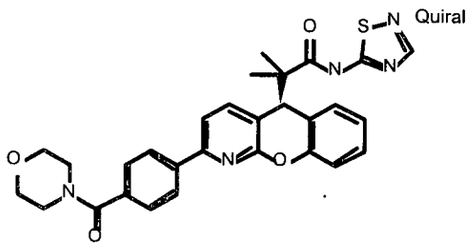


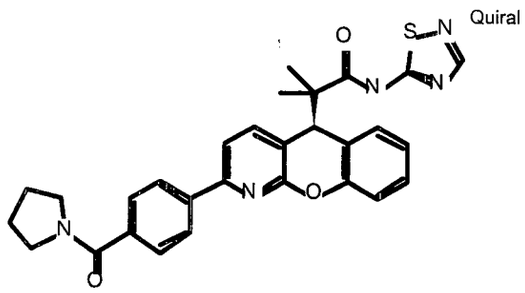


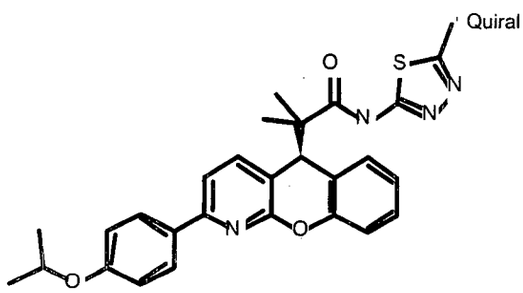


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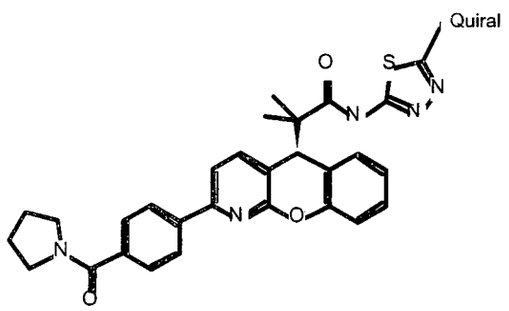

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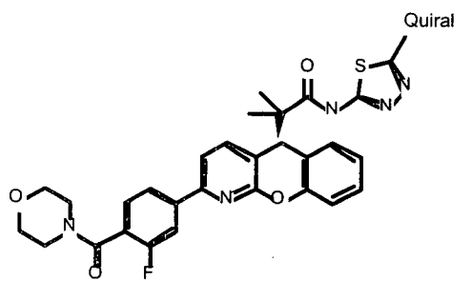

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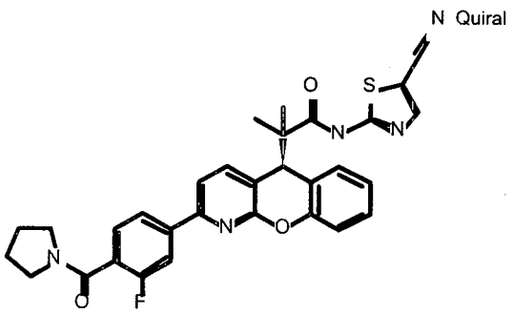

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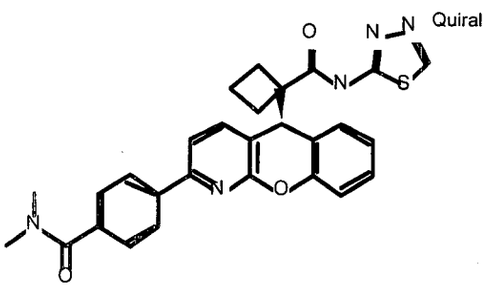

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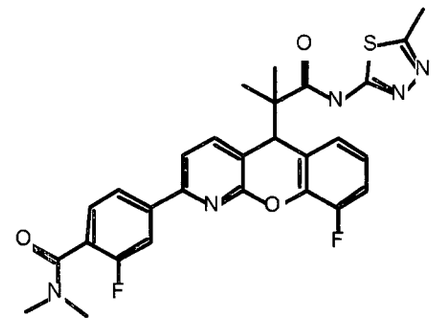

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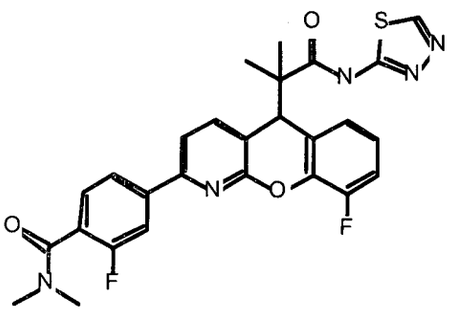

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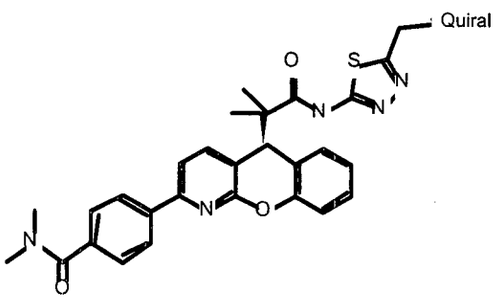

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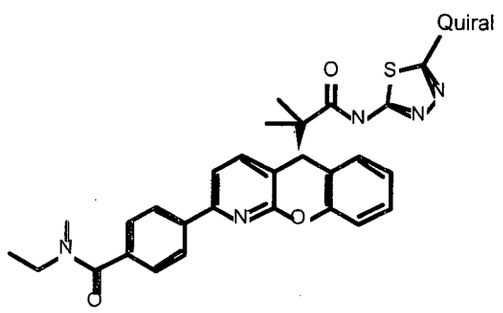

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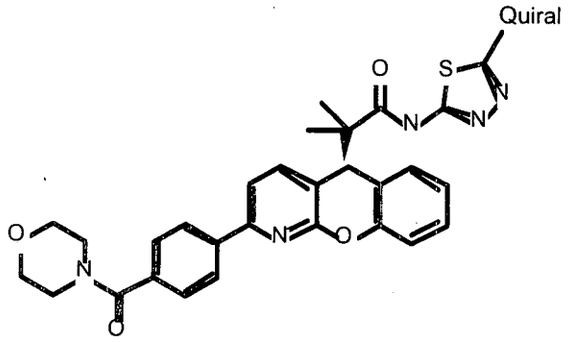


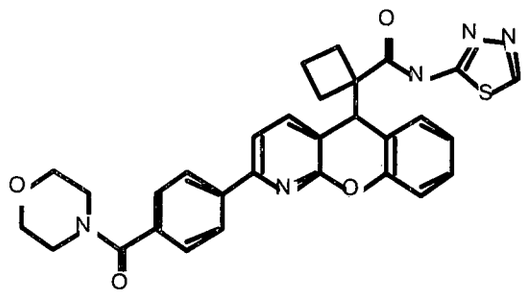


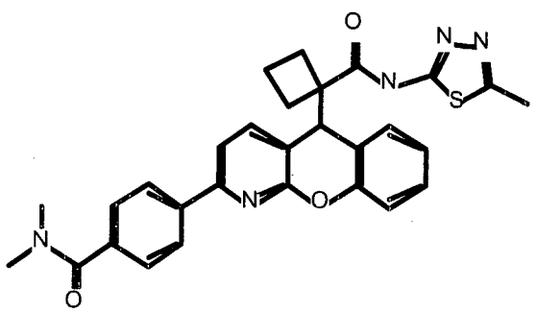


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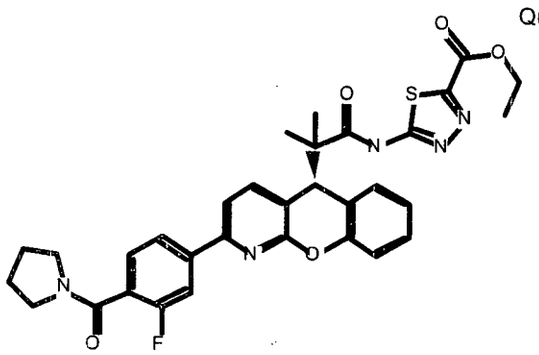
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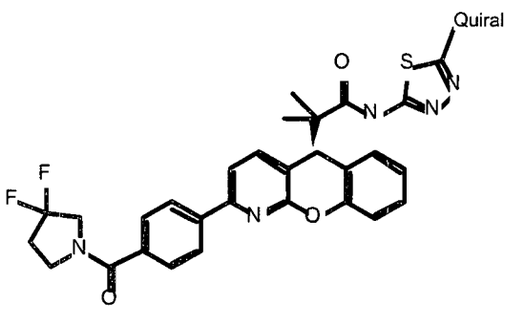


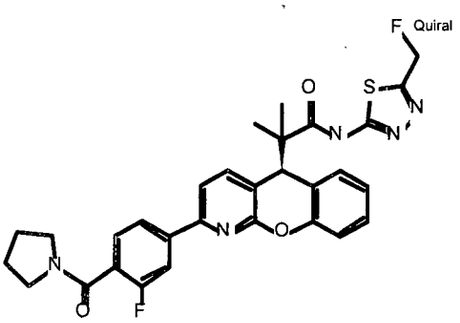


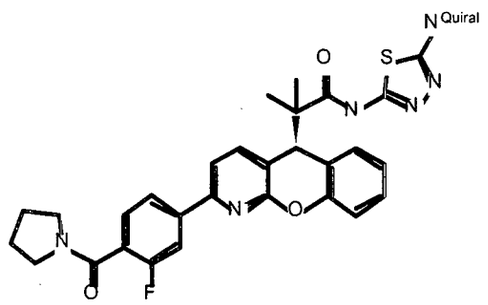
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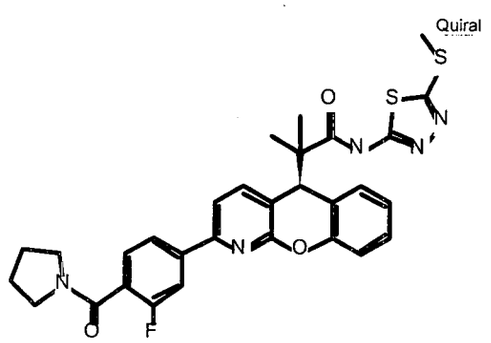


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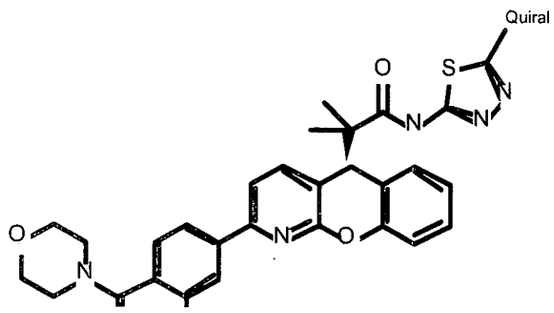

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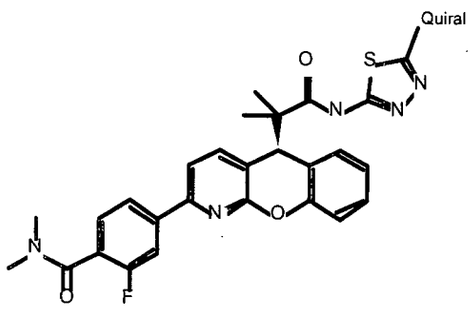

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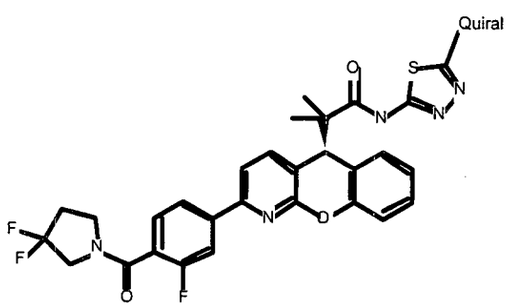

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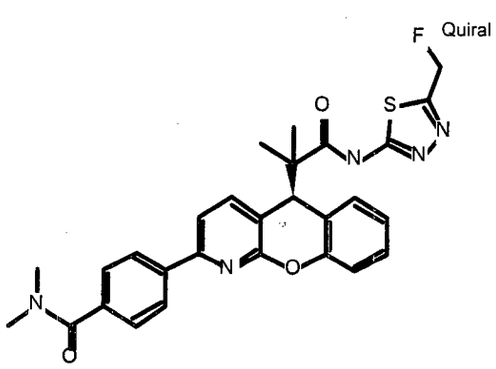

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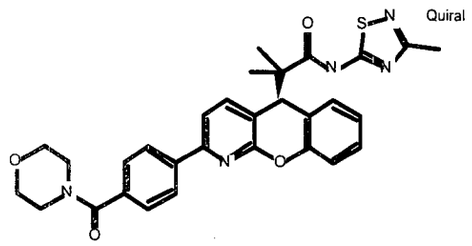
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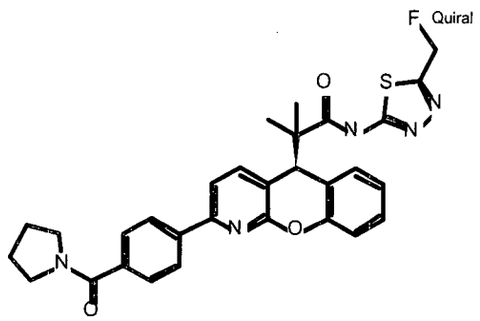

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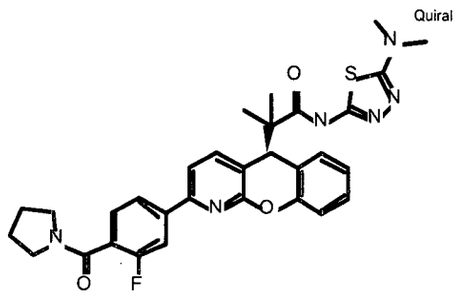

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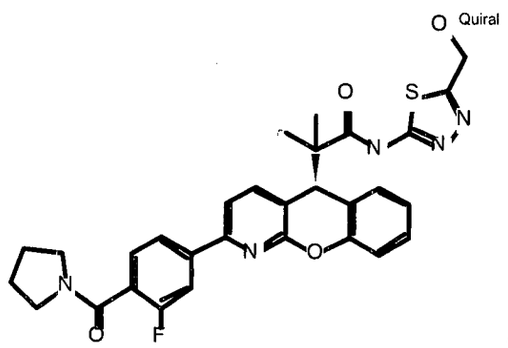

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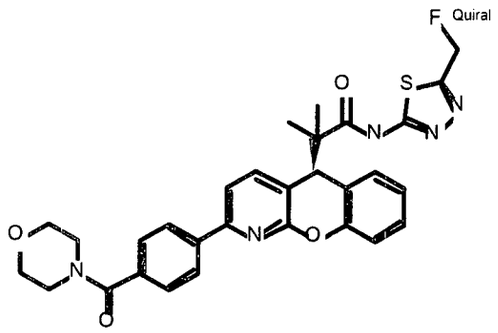

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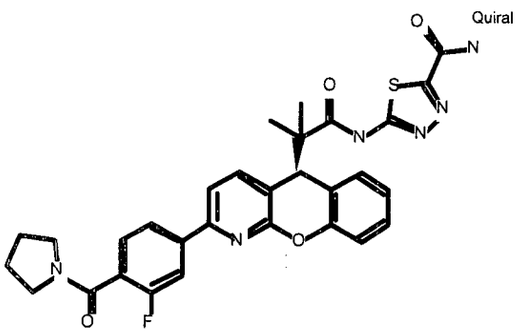

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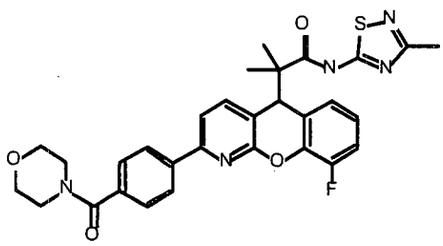

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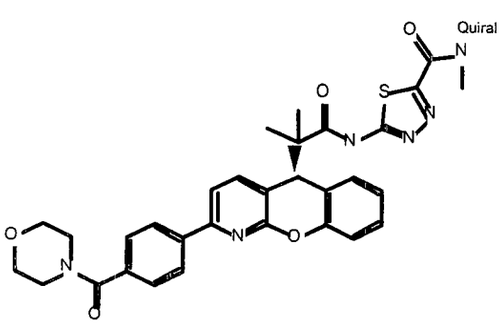

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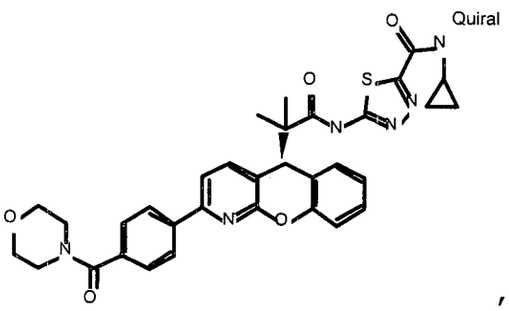

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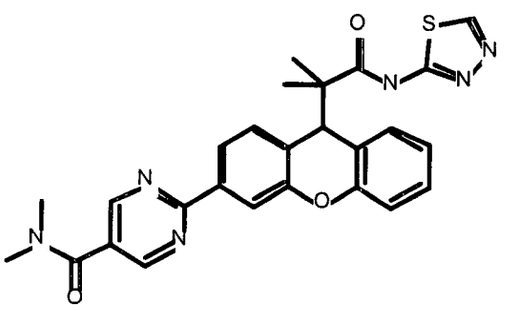

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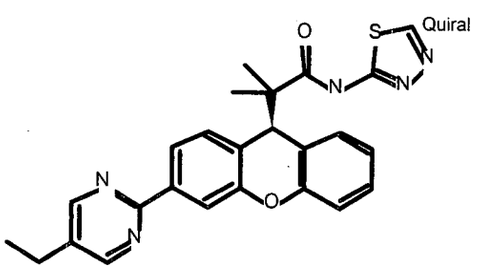

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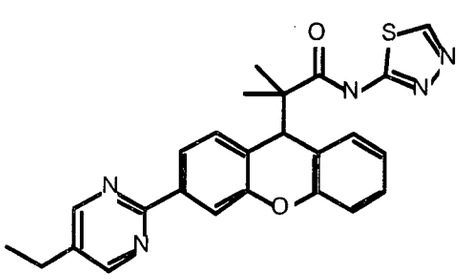

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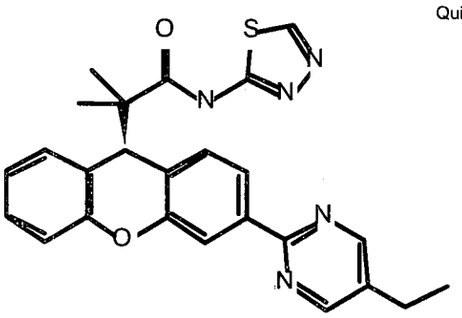




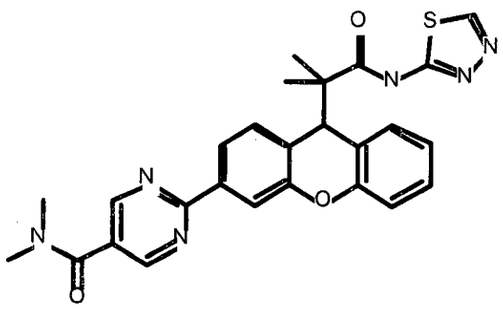


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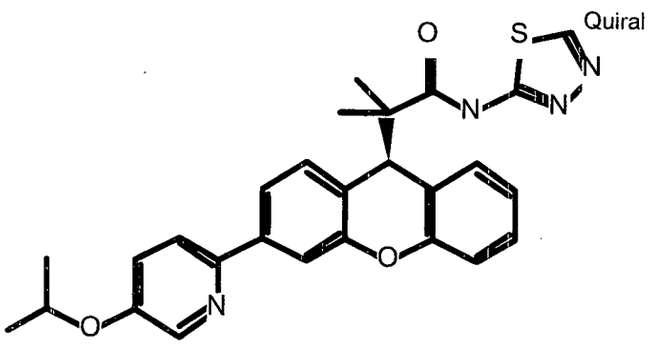


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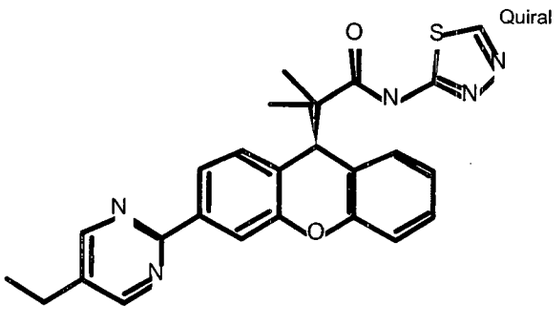
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23. El uso de un compuesto de conformidad con las reivindicaciones 1-22 para la manufactura de un medicamento para tratar una enfermedad o trastorno seleccionado de un trastorno endocrino, trastorno reumático, enfermedad de colágeno, enfermedad dermatológica, enfermedad alérgica, enfermedad oftálmica, enfermedad respiratoria, enfermedad hematológica, enfermedad gastrointestinal, enfermedad inflamatoria, enfermedad inmunitaria, enfermedad neoplásica y enfermedad metabólica.

24. El uso de conformidad con la reivindicación 23, en donde la enfermedad o trastorno es un enfermedad inflamatoria o autoinmunitaria seleccionada de rechazo de transplante de riñón, hígado, corazón, pulmón, páncreas, medula ósea, cornea, intestino delgado, aloinjertos de piel, homoinjertos de piel, xenoinjertos de válvula cardiaca, enfermedad del suero, y enfermedad injerto contra huésped, artritis reumatoide, artritis psoriática, esclerosis múltiple, asma, enfermedad inflamatoria del intestino, enfermedad de Crohn, colitis ulcerativa, pioderma gangrenosa, lupus eritematoso sistémico, miastenia grave, psoriasis, dermatitis, dermatomitosis; eccema, seborrea, inflamación pulmonar, uveítis ocular, hepatitis, enfermedad de Graves, tiroiditis de Hashimoto, tiroiditis autoinmunitaria, síndrome de Behcet o Sjogren, anemia perniciosa o inmunohemolítica, aterosclerosis, enfermedad de Addison, insuficiencia adrenal idiopática,

enfermedad poliglandular autoinmunitaria, glomerulonefritis, escleroderma, morfea, líquen plano, vitíligo, alopecia areata, alopecia autoinmunitaria, hipopituitarismo autoinmunitario, síndrome Guillain-Barre, y alveolitis; hipersensibilidad por contacto, hipersensibilidad de tipo retardado, dermatitis por contacto, urticaria, alergias de la piel, alergias respiratorias, rinitis polínica, rinitis alérgica y enteropatía sensible al gluten, osteoartritis, pancreatitis aguda, pancreatitis crónica, síndrome de tensión respiratoria aguda, síndrome de Sezary, restenosis, estenosis y aterosclerosis, hiperplasia congénita adrenal, tiroiditis no supurante, hipercalcemia asociada con cáncer, artritis reumatoide juvenil, espondilitis anquilosante, bursitis aguda y subaguda, tenosinovitis no específica aguda, artritis por gota, aguda, osteoartritis pos-traumática, sinovitis de osteoartritis, epicondilitis, carditis reumática aguda, pénfigo, dermatitis bulosa herpetiforme, eritema severo multiforme, dermatitis exfoliante, psoriasis, dermatitis seborreica, rinitis alérgica estacional o perenne, asma bronquial, dermatitis por contacto, dermatitis atópica, reacciones de hipersensibilidad a fármacos, conjuntivitis alérgica, queratitis, herpes zoster oftálmica, iritis e iridociclitis, corioretinitis, neuritis óptica, sarcoidosis sintomática, quimioterapia por tuberculosis pulmonar fulminante o diseminada, púrpura trombocitopénica idiopática

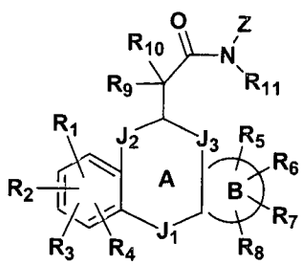
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en adultos, trombocitopenia secundaria en adultos, anemia hemolítica adquirida (autoinmunitaria), leucemias y linfomas en adultos, leucemia aguda de inicio en la infancia, colitis ulcerativa, enteritis regional, enfermedad de Crohn, síndrome de Sjogren, vasculitis autoinmunitaria, esclerosis múltiple, miastenia grave, sepsis, y enfermedad pulmonar obstructiva crónica.

25. El uso de conformidad con las reivindicaciones 23-24, en donde la enfermedad o trastorno se selecciona de rechazo de transplante, artritis reumatoide, artritis psoriática, esclerosis múltiple, asma, enfermedad inflamatoria del intestino, lupus sistémico, eritematosis, y psoriasis.

26. Una composición farmacéutica, caracterizada porque comprende un compuesto como se define de conformidad con las reivindicaciones 1-22 y un portador farmacéuticamente aceptable del mismo.

27. Un compuesto de conformidad con la fórmula (I),



I ,

un enantiómero, diastereómero, o tautómero del mismo, o un profármaco éster del mismo, o una sal farmacéuticamente

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aceptable de los mismos, caracterizado porque:

Z se selecciona de heterociclo y heteroarilo;

A se selecciona de un anillo carbocíclico de 5 hasta 8 elementos y un anillo heterocíclico de 5 hasta 8 elementos;

B se selecciona de un anillo cicloalquilo, cicloalquenilo, arilo, heterociclo, y anillo heteroarilo, en donde el anillo B se fusiona al anillo A, y el anillo B está opcionalmente substituido por uno hasta cuatro grupos los cuales son los mismos o diferentes y son independientemente seleccionados de R_5, R_6, R_7, y R_8;

J_1, J_2, y J_3 son los mismos o diferentes y cada que se presentan son independientemente $-A_1QA_2-$;

Q es independientemente cada que se presenta seleccionado de un enlace, O, S, S(O), y $S(O)_2$;

A_1 y A_2 son los mismos o diferentes y cada que se presentan son independientemente seleccionados de un enlace, alquileno C_{1-3}, alquileno C_{1-3} substituido, alquenileno C_{2-4}, y alquenileno C_{2-4} substituido, con la condición de que A_1 y A_2 se eligen de manera que el anillo A es un anillo carbocíclico de 5 hasta 8 elementos o un anillo heterocíclico de 5 hasta 8 elementos;

R_1, R_2, R_3, R_4, R_5, R_6, R_7, y R_8 son los mismos o diferentes y cada que se presentan son independientemente seleccionados de (i) hidrógeno, halógeno, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo

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substituido, alcoxi, alcoxi substituido, nitro, ciano, OR_{12}, $NR_{12}R_{13}$, $C(=O)R_{12}$, CO_2R_{12}, $C(=O)NR_{12}R_{13}$, $-O-C(=O)R_{12}$, $NR_{12}C(=O)R_{13}$, $NR_{12}C(O)OR_{13}$, $NR_{12}C(S)OR_{13}$, $S(O)_pR_{16}$, $NR_{12}SO_2R_{16}$, dialquilaminoalcoxi, alcoxialquiloxialquiloxi, $SO_2NR_{12}R_{13}$, cicloalquilo, cicloalquenilo, cicloalquinilo, heterociclo, arilo, y heteroarilo; y/o (ii) donde sea posible cada uno de R_1-R_8 se toma junto con cualquiera de R_1-R_8 localizado en un átomo adyacente para formar un anillo fusionado; y/o (iii) donde sea posible cualquiera de R_1-R_8 se toma junto con cualquiera de R_1-R_8 localizado en el mismo átomo para formar un grupo oxo, alquenilo, alquenilo substituido, cicloalquilo, cicloalquenilo, o heterociclo;

R_9 y R_{10} son los mismos o diferentes y cada que se presentan son independientemente seleccionados de (i) hidrógeno, halógeno, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, nitro, ciano, OR_{14}, $NR_{14}R_{15}$, $C(=O)R_{14}$, CO_2R_{14}, $C(=O)NR_{14}R_{15}$, $-O-C(=O)R_{14}$, $NR_{14}C(=O)R_{15}$, $NR_{14}C(=O)OR_{15}$, $NR_{14}C(=S)OR_{15}$, $S(O)_pR_{17}$, $NR_{14}SO_2R_{17}$, $SO_2NR_{14}R_{15}$, cicloalquilo, cicloalquenilo, heterociclo, arilo, y heteroarilo; o (ii) donde sea posible R_9 y R_{10} se toman juntos para formar un grupo oxo, alquilo, alquilo substituido, alquenilo, alquenilo substituido, cicloalquilo, cicloalquenilo, o heterociclo;

R_{11} se selecciona de hidrógeno, alquilo, alquilo substituido, $C(=O)$alquilo, CO_2(alquilo), SO_2alquilo, alcoxi,

amino, amino substituido, arilo, heteroarilo, heterociclo, y cicloalquilo;

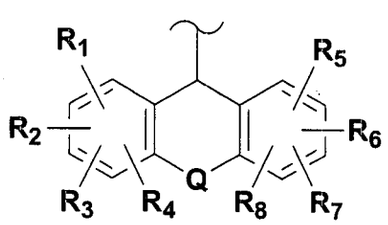
R_{12}, R_{13}, R_{14}, y R_{15}, son los mismos o diferentes y cada que se presentan son independientemente seleccionados de (i) hidrógeno, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, cicloalquilo, cicloalquenilo, arilo, heteroarilo, y heterociclo; o (ii) donde sea posible R_{12} se toma junto con R_{13}, y/o donde es posible R_{14} se toma junto con R_{15} para formar un anillo heteroarilo o heterociclo;

R_{16} y R_{17}, son los mismos o diferentes y cada que se presentan son independientemente seleccionados de alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, cicloalquilo, cicloalquenilo, arilo, heteroarilo, y heterociclo; y

p es 0, 1 ó 2,

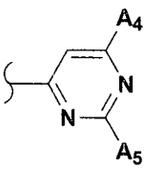
con la condición de que

(1) donde la porción tricíclica en la fórmula I del compuesto es



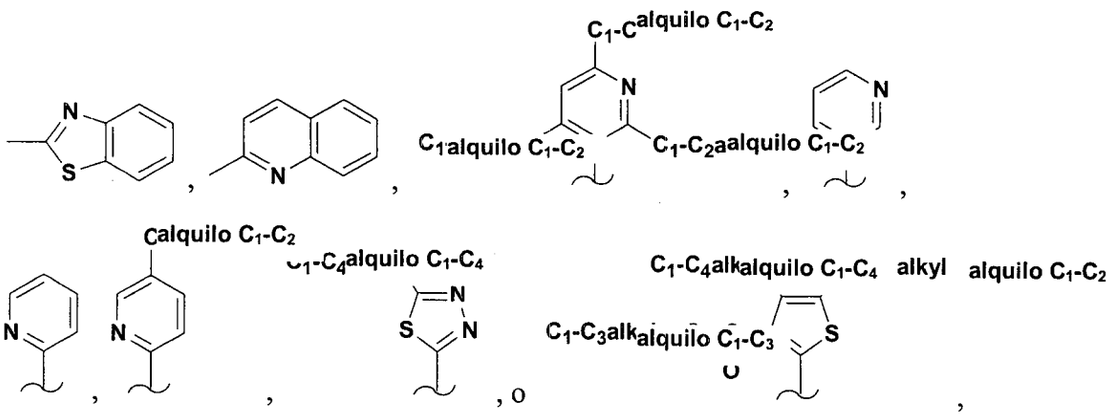
donde Q es O y R_1 hasta R_8 son cada H, entonces

(a) Z es diferente de

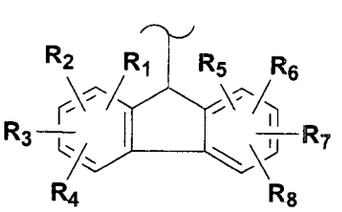


dnde A_4 y A_5 son los mismos o diferentes y son independientemente H o alquilo C_1-C_2-; o

(b) Z es diferente de



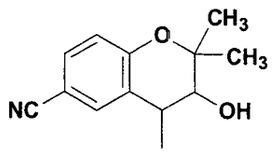
(2) donde la porción tricíclica es



donde R_1 hasta R_8 son cada uno H,

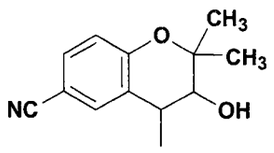
entonces Z es diferente de

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,

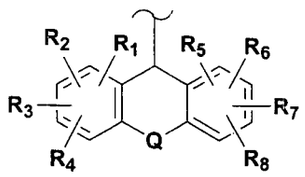
o donde Z es



,

R_{11} es diferente de un alquileno C_1-C_2 substituido;

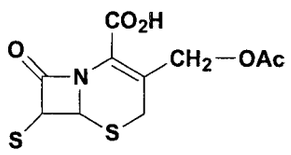
(3) donde la porción tricíclica es



;

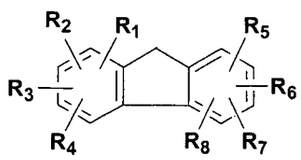
donde Q es S o SO_2, y R_1 hasta R_8 son cada uno H,

entonces Z es diferente de

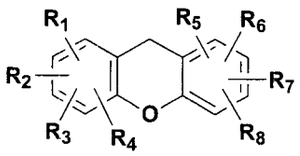


;

(4) donde la porción tricíclica es



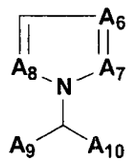
o



donde R_1 hasta R_8 son cada uno H,

entonces Z es diferente de

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donde A_6, A_7 y A_8 son independientemente N o CH,

A_9 es $-(CH_2)_d-A_{11}$ donde d es 0 hasta 4;

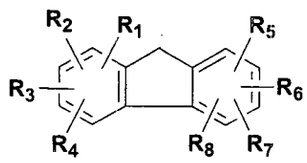
A_{11} es OH, CO_2H, 5-tetrazolilo, $-COO(\text{alquilo } C_1\text{-}C_4)_{n_a}$ o CN-

;

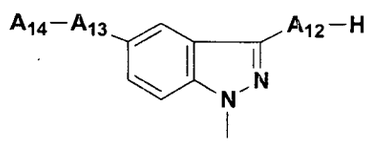
n_a es 0 hasta 4; y

A_{10} es alquilo de cadena recta C_4-C_7;

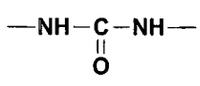
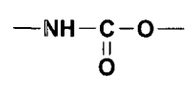
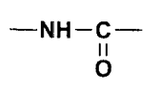
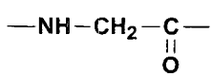
(5) donde la porción tricíclica es



entonces Z es diferente de



donde A_{12} es O o S; y

A_{13} es O o un NH,  ,  ,  , o  ,

en donde los 3 últimos grupos se unen al anillo aromático a través del átomo N;

A_{14} es H,

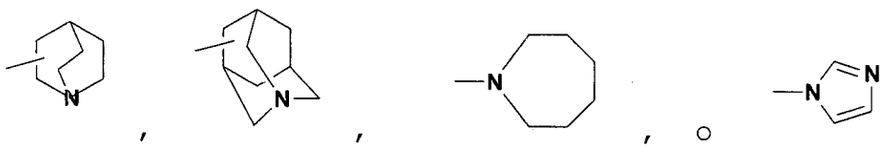
alquilo,

cicloalquilo C_3-C_7,

fenilo, naftilo, antranilo o fluorenilo opcionalmente sustituido, o

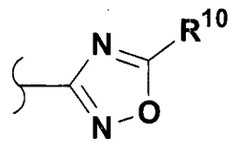
un quinolin-2-ilmetoxi o piridin-ilmetoxi; o

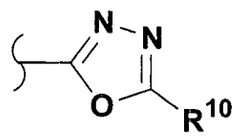
Z es diferente de



; o

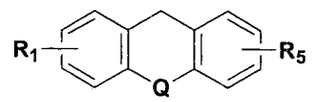
Z es diferente de





donde R^{10} es un sistema de anillo azacíclico no aromático o azabicíclico no aromático ;

(6) donde la porción tricíclica es

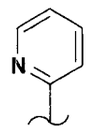


Q es -O-, -S-, $-C(R^3R^4)-$, $-CH_2CH_2-$, -CH=CH-CH_2-, $-CH_2$-CH=CH-, -CH_2-(C=O)-, -(C=O)-CH_2-, $CH_2CH_2CH_2$-, -CH=CH-, -O-CH_2-, $-CH_2$-O-, -O-

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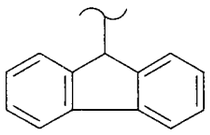
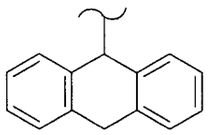
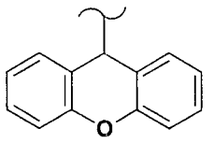
CH_2-O-, -CH_2-O-CH_2-, -S-CH_2-, -CH_2-S-, -CH(R^5)CH_2-, -CH_2CH(R^5)-, -(C=O)-, o -(S=O)- en donde R^3 y R^4 independientemente son hidrógeno o alquilo C_{1-7}; y en donde R^5 es alquilo C_{1-7} o fenilo;

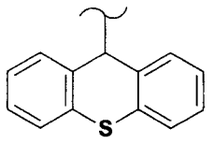
entonces Z es diferente de



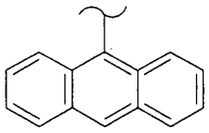
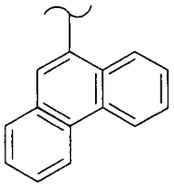
; o

(7) donde la porción tricíclica es


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o 
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entonces Z es diferente de



en donde:

R^6 y R^7 son cada uno independientemente seleccionados de alquilo C_1-C_6, halo-alquilo C_1-C_6 que contiene 1 hasta 5 átomos de halógeno, alcoxi C_1-C_2-alquilo C_1-C_6, nitro-alquilo C_1-C_6, ciano-alquilo C_1-C_6, alcanoilo C_1-C_2-alquilo C_1-C_6, alcoxicarbonilo C_1-C_2-alquilo C_1-C_6, alquiltio C_1-C_2-alquilo C_1-

AR085?

C_6, alcansulfinilo C_1-C_2-alquilo C_1-C_6, alcansulfonilo C_1-C_2-alquilo C_1-C_6, alquenilo C_2-C_6, halo-alquenilo C_2-C_6 que contiene 1-5 átomos de halógeno, alquinilo C_2-C_6, halo-alquinilo C_2-C_6 que contiene 1-5 átomos de halógeno, cicloalquilo C_3-C_7 y halógeno; o

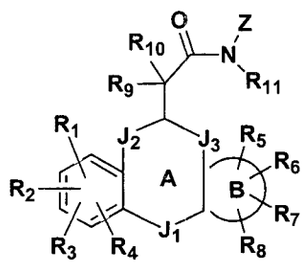
R^6 y R^7, tomados juntos, forman un anillo carbocíclico o heterocíclico de 5 hasta 7 elementos saturado o no saturado el cual puede contener uno o dos heteroátomos seleccionados de O y S; y

R^8 y R^9 son cada uno independientemente seleccionados de hidrógeno, alquilo C_1-C_6 y halógeno.

860

RESUMEN DE LA INVENCIÓN

La presente invención proporciona compuestos no esteroidales los cuales son útiles en el tratamiento de enfermedades asociadas con la modulación del receptor de glucocorticoide, AP-1, y/o de la actividad de NF-κB, incluyendo enfermedades inflamatorias e inmunológicas, que tiene la estructura de la fórmula (I), un enantiómero, diastereómero, o tautómero del mismo, o un éster de profármaco del mismo, o una sal farmacéuticamente aceptable de los mismos, en el cual: Z es heterociclo o heteroarilo; A es un anillo carbocíclico de 5 hasta 8 elementos o un anillo heterocíclico de 5 hasta 8 elementos; B es un anillo cicloalquilo, cicloalquenilo, arilo, heterociclo, o heteroarilo, en donde cada anillo se fusiona al anillo A en átomos adyacentes y opcionalmente substituido por uno hasta cuatro grupos los cuales son los mismos o diferentes y son independientemente seleccionados de R.



(I)

862

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO PROPIETARIOS

PATENTE DE INVENCION ___ PCT X MODELO DE UTILIDAD ___ DISEÑO INDUSTRIAL ___

(21) N° de solicitud: (22) Fecha de solicitud:

(51) Clasificación Internacional : C07D 277/46; C07D 405/12; C07D 417/12; C07D 417/14 ; C07D 491/04

(71)Solicitante(s) BRISTOL-MYERS SQUIBB COMPANY

(72) Inventor(es) WEINSTEIN, David; GONG, Hua Y OTROS

(74) Apoderado: ALVARO CORREA ORDOÑEZ

(30) Prioridad	(31) *No. Prioridad*	32) *Fecha*	(33) *País*
	60/836,496	09.08.2006	US
	11/835,438	08.08.2007	US

(85) Fecha inicio fase nacional: 09/03/2009

(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 09.08.2007
No. de solicitud : PCT/US2007/075543

(87) Publicación internacional
Fecha: 21.02.2008
N° publicación: WO/2008/021926

(54) Titulo: MODULADORES DEL RECEPTOR GLUCOCORTICOIDE, Y/O DE AP-1, Y/O DE LA ACTIVIDAD DE NF-κB Y SU USO

863

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO TEMATICO

SUPERINTENDENCIA PATENTE DE INVENCION ___ PCT X MODELO DE UTILIDAD ___ DISEÑO INDUSTRIAL ___

(21) N° de solicitud: (22) Fecha de solicitud:

(51) Clasificación Internacional : C07D 277/46; C07D 405/12; C07D 417/12; C07D 417/14 ; C07D 491/04

(71)Solicitante(s) BRISTOL-MYERS SQUIBB COMPANY

(72) Inventor(es) WEINSTEIN, David; GONG, Hua Y OTROS

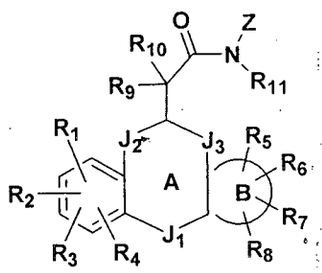
(74) Apoderado: ALVARO CORREA ORDOÑEZ

(30) Prioridad	(31) *No. Prioridad*	32) *Fecha*	(33) *País*
	60/836,496	09.08.2006	US
	11/835,438	08.08.2007	US

(8[illegible]echa límite inicio fase nacional: 09/03/2009

(86) Datos relativos a la presentación de la solic. PCT
[illegible]echa de presentación de la solicitud: 09.08.2007
No. de solicitud PCT/US2007/075543

(87) Publicación internacional:
Fecha: 21.02.2008
No. Publicación : WO/2008/021926



I

(54) Titulo: MODULADORES DEL RECEPTOR GLUCOCORTICOIDE, Y/O DE AP-1, Y/O DE LA ACTIVIDAD DE NF-κB Y SU USO

(57) Resumen: La presente invención proporciona compuestos no esteroidales los cuales son útiles en el tratamiento de enfermedades asociadas con la modulación del receptor de glucocorticoide, AP-1, y/o de la actividad de NF-κB, incluyendo enfermedades inflamatorias e inmunológicas, que tiene la estructura de la fórmula (I), un enantiómero, diastereómero, o tautómero del mismo, o un éster de profármaco del mismo, o una sal farmacéuticamente aceptable de los mismos, en el cual: Z es heterociclo o heteroarilo; A es un anillo carbocíclico de 5 hasta 8 elementos o un anillo heterocíclico de 5 hasta 8 elementos; B es un anillo cicloalquilo, cicloalquenilo, arilo, heterociclo, o heteroarilo, en donde cada anillo se fusiona al anillo A en átomos adyacentes y opcionalmente substituido por uno hasta cuatro grupos los cuales son los mismos o diferentes y son independientemente seleccionados de R.

864

2009/002

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 5,903
FECHA : ENERO 26 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-020345- -00000-0000
Fecha: 2009-02-27 16:43:35 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 869

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	VR. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	21549006	23/01/2009	54,828,500.00

***** 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	540,000.00
		TOTAL : $	540,000.00

SON: QUINIENTOS CUARENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

865

2009/002

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 5,850
FECHA : ENERO 26 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-020345- -00000-0000
Fecha: 2009-02-27 16:43:35 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONAL!
Act. 411 PRESENTACION Folios: 869

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	21549006	23/01/2009	54,828,500.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-06 REGISTRO DE CESION, CAMBIO NOM	13	NOMBRES Y ENSENAS COMERCIALES,MAR	273,000.00
			TOTAL : $	273,000.00

SON: DOSCIENTOS SETENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

866

2008/023

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 8001

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-020345- -00000-0000
Fecha: 2009-02-27 16:43:35 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 869

CERTIFICACION DE EXCEDENTE : 08 - 100,489
FECHA : DICIEMBRE 26 DE 2008

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	120646805	24/12/2008	46,377,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVCIOS ADMINISTRATIVOS	10,000.00
		TOTAL : $	10,000.00

SON: DIEZ MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

867

2008/023

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 08 - 100,490
FECHA : DICIEMBRE 26 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-020345- -00000-0000
Fecha: 2009-02-27 16:43:35 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 869

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	120646805	24/12/2008	46,377,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVCIOS ADMINISTRATIVOS	10,000.00
		TOTAL : $	10,000.00

SON: DIEZ MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

868

2008/023

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-020345- -00000-0000
Fecha: 2009-02-27 16:43:35
Tra. 11 PATENTEIYII Dep. 2020 NUECREACIONI
Act. 411 PRESENTACION Eve: 378 FASENACIONALI
Folios: 869

CERTIFICACION DE EXCEDENTE : 08 - 100,240
FECHA : DICIEMBRE 26 DE 2008

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	120646805	24/12/2008	46,377,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99	OTROS SERVCIOS ADMINISTRATIVOS	2,000.00
			TOTAL : $	2,000.00

SON: DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

869

2008/023

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 08 - 100,332
FECHA : DICIEMBRE 26 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-020345- -00000-0000

Fecha: 2009-02-27 16:43:35 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 869

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	120646805	24/12/2008	46,377,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99	OTROS SERVCIOS ADMINISTRATIVOS	5,000.00
			TOTAL : $	5,000.00

SON: CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

870

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-020345- -00000-0000

Fecha: 2009-02-27 16:43:35 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 869

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION [✓] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [✓]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [✓]
- Descripción de la invención [✓]
- Dibujos de ser estos pertinentes [✓]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Sandra Rodríguez
Firma Responsable

Fecha Febrero 27-09

Carrera 13 No. 27-00 Piso 5, 7 y 10
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