Industria y Comercio

SUPERINTENDENCIA

INVENTARIO
CBA221089
Organizacion y Digitalizacion CSA Ltda.

Delegatura de Propiedad Industrial

División de Nuevas Creciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 08-138163

54. **TÍTULO** INHIBIDORES DE SULFONAMIDA TRICICLICA FUSIONADA DE GAMASECRETASA

51. **CLASIFICACIÓN INTERNACIONAL**

71. **SOLICITANTE** ELAN PHARMACEUTICALS, INC.

DOMICILIO SOUTH SAN FRANCISCO. ESTADOS UNIDOS DE AMERICA

74. **APODERADO** EMILIO FERRERO
C.C. 438.019 de Usaquén

22. **BOGOTÁ, D. C.,**

(FORMA P-10)

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-138163- -00000-0000
Fecha: 2008-12-30 17:08:07 Dep: 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eva: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 659

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

(1) SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.
☒ Capítulo I. ☐ Capítulo II.

(2) SOLICITANTE (71)

Nombre: **ELAN PHARMACEUTICALS, INC.**
sociedad constituida y existente bajo las leyes del Estado de Delaware, Estados Unidos de América.

Dirección: 800 Gateway Boulevard,
South San Francisco,
California 94080,
Estados Unidos de América

Domicilio: South San Francisco,
California,
Estados Unidos de América

IDENTIFICACIÓN

C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número ____

(3) REPRESENTANTE O APODERADO

Nombre: EMILIO FERRERO
Dirección: Carrera 4ª. No. 72-35
Teléfono: 347 36 11
Fax: 211 86 50
E-mail: clientes@cavelier.com
Domicilio: Bogotá, Colombia.

IDENTIFICACIÓN

C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número 438.019 T.P 31.929

(4) INVENTOR (ES) (72)

1. **Andrei W. KONRADI**
30 Victoria Road,
Burlingame,
California 94010,
Estados Unidos de América

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Estados Unidos de América

3. **Danielle L. AUBELE**
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Burlingame,
California 94010,
Estados Unidos de América

4. **Albert W. GAROFALO**
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California 94080,
Estados Unidos de América

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6. **Martin L. NEITZEL**
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California 94536,
Estados Unidos de América

8. **Anh P. TRUONG**
1106 Laguna Avenue, Apt. 4,
Burlingame,
California 94010,
Estados Unidos de América

(5) PCT (86)

Solicitud Internacional No. PCT/US2007/070176 Fecha: 1 de junio de 2007
Publicación Internacional No. WO 2007/143523 A3 Fecha: 13 de diciembre de 2007

(6) Título (54)

INHIBIDORES DE SULFONAMIDA TRICÍCLICA FUSIONADA DE GAMASECRETASA

7 **Clasificación Internacional (51)** C07D 471/004

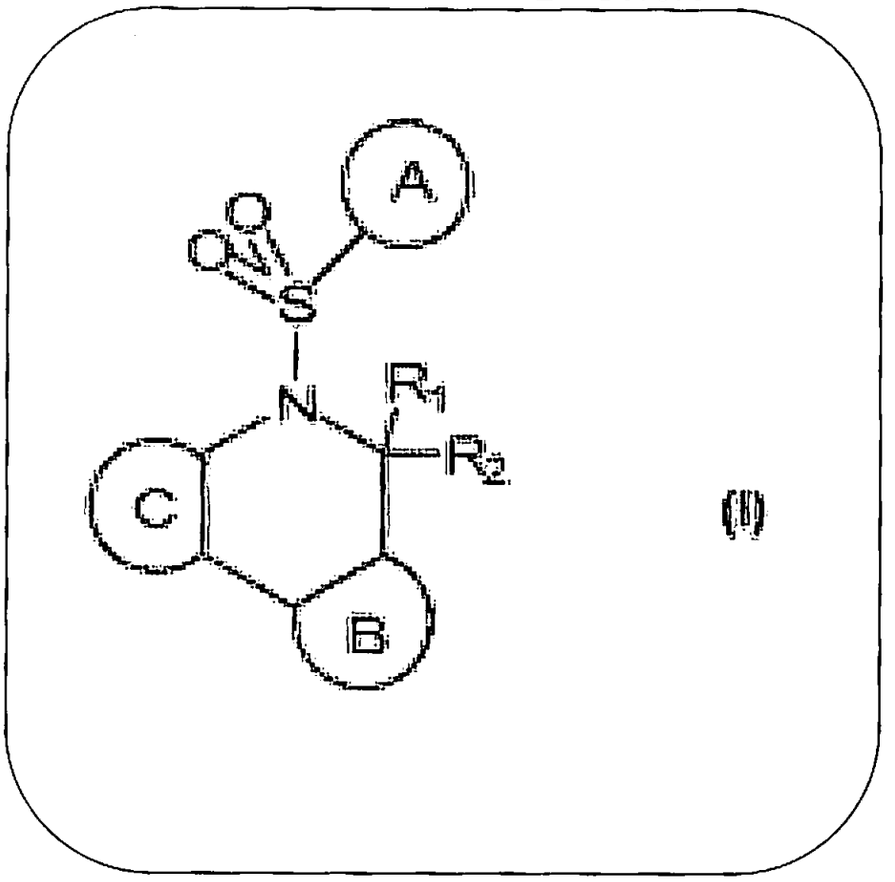
8 **Prioridad** SI☒ NO☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	US	2 de junio de 2006	60/810,431
	US	22 de diciembre de 2006	60/876,932
	US	10 de abril de 2007	60/922,771

9 **Comprobante de pago No.:** 08-97,011 **Fecha:** 15 de diciembre de 2008

10 **Anexos:**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 501.000.oo.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☒ Arte final 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros: VER HOJA DE DOCUMENTOS ANEXOS

11 **FIGURA CARACTERÍSTICA**



(I)

12 Solicito la concesión de la patente,

NOMBRE: EMILIO FERRERO

FIRMA : _____

C.C. 438.019 de Usaquén T.P. 31.929

SCT

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2007/143523 A3

   Descripción:

   Páginas 226 en el idioma original

   Páginas 372 en español

   Reivindicaciones: Número (s) 25

   Figuras: Número (s)

2. ☒ **Forma PCT/ISA/210.** Informe de Búsqueda Internacional.

3. ☒ Extracto de publicación.

NO SE REALIZARON MODIFICACIONES EN LA FASE INTERNACIONAL

COLO 13170-841-008-2 4676 5

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a Nº 72-35
BOGOTA, 8 – COLOMBIA

193 **Representación, Ratificación y Poder con autenticación notarial y Apostille para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, nombres de dominio, lemas comerciales, licencias.**

Representation, Ratification and Power-of-Attorney with notarial authentication and Apostille for patents, utility models, industrial designs, trademarks, commercial names, trade emblems, domain names, slogans, licenses.

REPRESENTACIÓN Y PODER

REPRESENTATION AND POWER OF ATTORNEY

13170
6654

Yo (nosotros), abajo firmado (s)/I (we), the undersigned

ELAN PHARMACEUTICALS, INC.

domiciliado (s) en/of 800 Gateway Boulevard, South San Francisco, California 94080, United States of America.

por el presente nombramos a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y GERMAN CAVELIER, tpa. 832, domiciliados en la Carrera 4a Nº 72-35, Bogotá, Colombia, en obedecimiento a lo dispuesto en el parágrafo 1o del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (umos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso- administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, nombres de dominio, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del

In due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and GERMAN CAVELIER, tpa. 832, domiciled at Carrera 4a Nº 72 -35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on case, and the mere fact or its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time. In addition, we grant a Power of Attorney in favor of the above-named attorneys-at law so that they may obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, domain names, vegetal varieties and denominations of origin; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) Actions of unfair competition, protection to the consumer,

© CAVELIER ABOGADOS

COMO NOTARIA SEXTA (6) DEL CIRCUITO DE BOGOTÁ, D.C., HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE TUVE A LA VISTA
BOGOTA D.C., REPUBLICA DE COLOMBIA
29 DIC 2006
MARÍA FERNANDA CASAS ROLL
NOTARIA ENCARGADA

consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso-administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

oppositions or observations, administrative or Court cancellation, nullity, infringement, granting of licenses, the action for writ mandamus, the protection of trade secrets, and in general the civil, penal, and administrative suits relating to those rights; actions and suits instituted by me (us) or against me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

Dado y firmado hoy/Given and signed this September 2, 2005

en/In South San Francisco, CA 94080, USA

Firma/Signature

Carl W. Battle, Senior Vice President
Chief Intellectual Property Counsel

© CAVELIER ABOGADOS
WPPODE01-181 (MINUTA N°12.1.1.2.6 USA)

COMO NOTARIA SEXTA (E) DEL CÍRCULO DE BOGOTÁ D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTÁ D.C. REPÚBLICA DE COLOMBIA
29 DIC 2005
MARÍA FERNANDA CASAS COLL
NOTARIA ENCARGADA

SEE ATTACHED NOTARY CERTIFICATE

CERTIFICACIÓN NOTARIAL (SOCIEDAD)

A los _____ días del mes de _____ de 200 __ compareció(eron) ante mí, Carl W. Battle, Senior Vice President, Chief Intellectual Property Counsel

Quien(es) conozco personalmente y que firma(n) este documento en representación de la Sociedad/compañía denominada **ELAN PHARMACEUTICALS, INC.**

Certifico:

1. Que he visto los siguientes documentos:*

2. Que dichos documentos prueban lo siguiente:

2.1. Que **ELAN PHARMACEUTICALS, INC.** es una Sociedad/Compañía legalmente constituida y existente de acuerdo con las leyes del Estado de Delaware, Estados Unidos de América

2.2. Que el domicilio de dicha Sociedad/Compañía es 800 Gateway Boulevard, South San Francisco, California 94080, Estados Unidos de América.

2.3. Que el objeto u objetos para los cuales se otorga el presente poder están comprendidos dentro del objeto social de la mencionada Sociedad/Compañía.

2.4. Que el(los) Sr.(Sres.) Carl W. Battle, Senior Vice President, Chief Intellectual Property Counsel está(n) autorizado(s) para otorgar el presente Poder.

Ciudad _____

Estado _____

Hoy _____ de 200 __

NOTARIAL CERTIFICATION (CORPORATION)

On this _____ day of _____ 200 __ appeared before me Carl W. Battle, Senior Vice President, Chief Intellectual Property Counsel

who(m) I know personally and who(m) signed this document as representative(s) of the Corporation/Company named **ELAN PHARMACEUTICALS, INC.**

I certify:

1. That I have seen the following documents:*

- Articles of Incorporation

2. That the above documents duly prove the following:

2.1. That **ELAN PHARMACEUTICALS, INC.** is a Corporation/Company legally constituted and in existence in accordance with the laws of The State of Delaware, United States of America.

2.2. That the domicile of said Corporation/Company is 800 Gateway Boulevard, South San Francisco, California 94080, United States of America.

2.3. That the purpose or purposes for which the present Power of Attorney is granted are comprised within the corporation purposes set forth in the charter of the mentioned Corporation/Company.

2.4. That Mr.(Messrs.) Carl W. Battle, Senior Vice President, Chief Intellectual Property Counsel is(are) authorized to grant the present Power of Attorney

City South San Francisco

State California

This _____ day of _____ 200 __

_____ NOTARIO PÚBLICO O FUNCIONARIO AUTORIZADO — NOTARY PUBLIC OR ATTESTING OFICIAL _____

* Los documentos que certifican la existencia de la compañía deben identificarse con fecha y origen

* The documents that certify the existence of the company must be identified with date and origin

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: _____
   This public document
2. has been signed by: _____
3. acting in the capacity of: _____
4. bears the seal/stamp of: _____

Certified

5. at: _____ 6. the _____
7. by _____
8. No. _____
9. Seal/stamp 10. Signature

© CAVELIER ABOGADOS
WPPODE01-181 (MINUTA N°12.1.12.6 USA)

COMO NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C. DOY FE QUE LA FOTOCOPIA QUE ANTECEDE COINCIDE CON EL ORIGINAL QUE TUVE A LA VISTA
BOGOTA D.C. COLOMBIA
29 DIC 2008
MARIA FERNANDA CASAS COLL
NOTARIA ENCARGADA

8

State of California

SECRETARY OF STATE

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

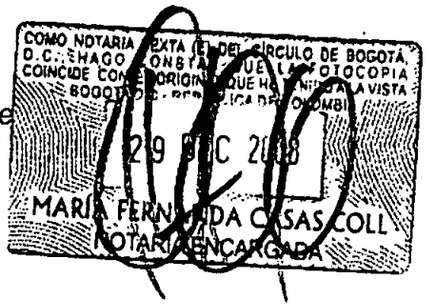
1. *Country: United States of America*
   This public document
2. *has been signed by PETER SURLA*
3. *acting in the capacity of Notary Public, State of California*
4. *bears the seal/stamp of PETER SURLA, Notary Public, State of California*

CERTIFIED

5. *At Sacramento, California*
6. *the 3rd day of October 2005*
7. *by Deputy Secretary of State, State of California*
8. *No. 257972*
9. *Seal/Stamp:*



10. *Signature*





Bruce McPherson

Secretary of State

BY

NP-24 A (REV. 4-05)

OSP 05 90772

CALIFORNIA ALL-PURPOSE ACKNOWLEDGMENT

State of California

County of SAN MATEO } ss.

On SEPTEMBER 2, 2005 (Date) before me, PETER SURLA, NOTARY PUBLIC (Name and Title of Officer (e.g., "Jane Doe, Notary Public"))

personally appeared CARL W. BATTLE (Name(s) of Signer(s))

☒ personally known to me
☐ proved to me on the basis of satisfactory evidence

PETER SURLA
Commission # 1538923
Notary Public - California
San Mateo County
My Comm. Expires Dec 26, 2008

to be the person(s) whose name(s) is/are subscribed to the within instrument and acknowledged to me that he/she/they executed the same in his/her/their authorized capacity(ies), and that by his/her/their signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

WITNESS my hand and official seal.

Signature of Notary Public

OPTIONAL

Though the information below is not required by law, it may prove valuable to persons relying on the document and could prevent fraudulent removal and reattachment of this form to another document.

Description of Attached Document

Title or Type of Document: REPRESENTATION AND POWER OF ATTORNEY

Document Date: N/A Number of Pages: 3

Signer(s) Other Than Named Above: N/A

Capacity(ies) Claimed by Signer

Signer's Name: CARL W. BATTLE
SENIOR VICE PRESIDENT,

☐ Individual
☒ Corporate Officer — Title(s): CHIEF INTELLECTUAL PROPERTY COUNSEL
☐ Partner — ☐ Limited ☐ General
☐ Attorney-in-Fact
☐ Trustee
☐ Guardian or Conservator
☐ Other:

Signer Is Representing: ELAN PHARMACEUTICALS, INC.

RIGHT THUMBPRINT OF SIGNER
Top of thumb here

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COMO NOTARIO SEXTA DEL CIRCULO DE BOGOTA, D.C. - COLOMBIA
CONCUERDA CON EL ORIGINAL QUE SE TUVO A LA VISTA
BOGOTA D.C. - REPUBLICA DE COLOMBIA
19 OCT 2008
MARIA FERNANDA CASAS COLL
NOTARIA ENCARGADA

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country : United States Of America
2. This public document has been signed by **LORRAINE F STRUNK**
3. acting in the capacity of NOTARY PUBLIC
4. bears the seal/stamp LORRAINE F STRUNK, NOTARY PUBLIC, MONTGOMERY COUNTY, COMMONWEALTH OF PENNSYLVANIA

Certified

5. at Harrisburg, Pennsylvania
6. The 3rd day of October, 2005
7. by Pedro A. Cortés, Secretary of the Commonwealth of Pennsylvania
8. No : 200536342
9. Seal/Stamp
10. Signature

Pedro A. Cortés

Pedro A. Cortés

COMO NOTARIA SEXTA (E) DEL CIRCULO DE BOGOTÁ D.C. HAGO CONSTAR QUE LA PRESENTE FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTÁ D.C., REPÚBLICA DE COLOMBIA
29 DIC 2005
MARIA FERNANDA CASAS COLL
NOTARIA ENCARGADA

CERTIFICATION OF AUTHORITY

1. I, Richard Collier (name), Executive Vice President, General Counsel & Secretary (title) of **ELAN PHARMACEUTICALS, INC.** do hereby certify that:

1.1. Carl W. Battle is the Senior Vice President, Chief Intellectual Property Counsel of **ELAN PHARMACEUTICALS, INC.** and that he/she is the authorized by **ELAN PHARMACEUTICALS, INC.** to execute this Power of Attorney on its behalf.

1.2. That **ELAN PHARMACEUTICALS, INC.** is a corporation/company legally constituted and in existence in accordance with the laws of the State of Delaware, United States of America.

1.3. That the domicile of said corporation/company is 800 Gateway Boulevard, South San Francisco, California 94080, United States of America.

1.4. That the purpose or purposes for which the present Power of Attorney is granted are comprised within the corporation purposes set forth in the charter of the mentioned corporation/company.

2. For issuing this certification that I have seen the following documents:

2.1. The Articles of Incorporation of **ELAN PHARMACEUTICALS, INC.**, dated March 19, 2004

2.2. The Resolution of the Board of Directors and/or the By-Laws of **ELAN PHARMACEUTICALS, INC.**, dated _____

Signed this 6th of SEPTEMBER Of the year 2005.

Richard F. Collier
(name)
(Title)

Richard Collier
Executive Vice President, General Counsel & Secretary
Elan Pharmaceuticals, Inc.

COMMONWEALTH OF PENNSYLVANIA
Notarial Seal
Lorraine F. Strunk, Notary Public
Upper Merion Twp., Montgomery County
My Commission Expires Apr. 4, 2009
Member, Pennsylvania Association of Notaries

Lorraine F. Strunk 9-6-05

COMO NOTARIA SEXTA (E) DEL CIRCULO DE BOGOTÁ, D.C., HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. - PUBLICO DE CONFIANZA
29 DIC 2008
MARIA FERNANDA CASAS GOLL
NOTARIA ENCARGADA

TRADUCCIÓN OFICIAL 243/2005 DE UN DOCUMENTO ESCRITO EN INGLÉS Y EN ESPAÑOL, REALIZADA POR EDUARDO CALADO NOGUERA, TRADUCTOR OFICIAL APROBADO POR RESOLUCIÓN 541 DEL 27 DE FEBRERO DE 1976 POR EL MINISTERIO DE JUSTICIA Y DEBIDAMENTE REGISTRADO ANTE EL MINISTERIO DE RELACIONES EXTERIORES DE LA REPÚBLICA DE COLOMBIA Y MEDIANTE EL CUAL **ELAN PHARMACEUTICALS, INC.**, EMPRESA DOMICILIADA EN 800 GATEWAY BOULEVARD, SOUTH SAN FRANCISCO, CALIFORNIA 94080, ESTADOS UNIDOS DE AMÉRICA, OTORGA PODER A EMILIO FERRERO, TPA 31929, GONZALO PERDOMO, TPA 831; LUZ CLEMENCIA DE PAEZ TPA 23555 Y A GERMÁN CAVELIER, TPA 832. EXPEDIDO Y FIRMADO HOY 2 DE SEPTIEMBRE DE 2005 EN SOUTH SAN FRANCISCO CA 94080, ESTADOS UNIDOS DE AMÉRICA. FIRMADO: CARL W. BATTLE, VICEPRESIDENTE PRINCIPAL, JEFE DE ASUNTOS JURÍDICOS DE PROPIEDAD INTELECTUAL.

CERTIFICADO NOTARIAL EN INGLES Y EN ESPAÑOL POR EL CUAL SE CERTIFICA LA COMPARECENCIA DE CARL W. BATTLE, VICEPRESIDENTE PRINCIPAL, JEFE DE ASUNTOS JURÍDICOS DE PROPIEDAD INTELECTUAL PARA FIRMAR EL PODER ARRIBA CITADO A NOMBRE DE ELAN PHARMACEUTICALS INC. Y PARA CERTIFICAR LA EXISTENCIA LEGAL, EL DOMICILIO DE DICHA EMPRESA Y LA CAPACIDAD DE CARL W. BATTLE PARA COMPROMETER A DICHA FIRMA.

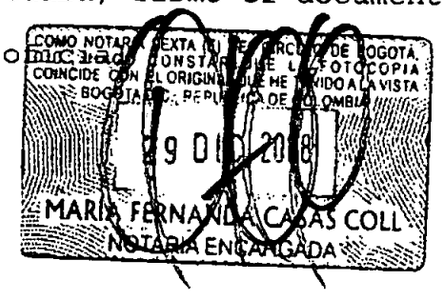
RECONOCIMIENTO MULTIPROPÓSITO DE CALIFORNIA

ESTADO DE CALIFORNIA, CONDADO DE SAN MATEO

El 2 de septiembre de 2005, ante mi, PETER SURLA, notario público, compareció personalmente CARL W. BATTLE, conocido personalmente por mi como la persona cuyo nombre está escrito en el documento adjunto y reconoció ante mi que ella firmó el mismo en su calidad autorizada y que mediante su firma en el documento la persona o entidad a cuyo nombre actuaba, firmó el documento.

Atestiguo mediante mi firma y sello oficiales.

Peter Surla



Sello: PETER SURLA, Cargo 1538923, notario público, California. Condado de San Mateo. Mi cargo vence el 26 de diciembre de 2008.

Descripción del documento adjunto: Poder y representación.

Calidad reclamada por el firmante

Nombre del firmante: Carl W. Battle, vice-presidente principal, Jefe de asuntos jurídicos de propiedad intelectual

El firmante representa a ELAN PHARMACEUTICALS, INC.

CERTIFICACIÓN DE AUTORIZACIÓN

1. Yo, Richard Collier, vicepresidente ejecutivo, abogado general y secretario de ELAN PHARMACEUTICALS INC., por la presente certifico que:

1.1. Carl W. Battle es el vicepresidente principal, abogado principal de propiedad intelectual, de ELAN PHARMACEUTICALS INC, y que se encuentra autorizado por ELAN PHARMACEUTICALS, INC para firmar este poder a su nombre.

1.2. Que ELAN PHARMACEUTICALS INC, es una sociedad/compañía legalmente constituida y existente de conformidad con las leyes del estado de Delaware, Estados Unidos de América.

1.3. Que el domicilio de dicha sociedad/compañía es 800 Gateway Boulevard, South San Francisco, California 940080, Estados Unidos de América.

1.4. Que el objeto u objetos del presente poder están comprendidos dentro de los objetos sociales de la sociedad, de acuerdo con lo que se expone en el documento de constitución de dicha sociedad/entidad.

2. Con el fin de emitir esta certificación he visto los siguientes documentos:

2.1. El documento de constitución de ELAN PHARMACEUTICALS INC, de fecha 19 de marzo de 2004.

2.2. La Resolución de la Junta directiva y o los estatutos de ELAN PHARMACEUTICALS, INC de fecha (dato en blanco).

Firmado hoy 6 de septiembre de 2005.

COMO NOTARIA SEXTA (E) DEL CIRCULO DE BOGOTA D.C. COINCIDE CON EL ORIGINAL QUE A LA VISTA BOGOTA D.C. 29 DIC 2008 MARÍA FERNANDA CARVAJAL NOTARIA SEXTA (E)

Firmado: Richard Collier

Vicepresidente ejecutivo, abogado y secretario de Elan Pharmaceuticals Inc.

SELLO: ESTADO DE PENSILVANIA

SELLO NOTARIAL, Lorraine F. Strunk, notario público

Upper Merion Twp. Condado de Montgomery

Mi cargo vence el 4 de abril de 2009

Miembro de la asociación de notarios de Pensilvania.

FIRMADO: LORRAINE F. STRUNK, 9-6-05

ESTADO DE CALIFORNIA

APOSTILLA:

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

1. Estados Unidos de América

Este documento público

2. ha sido firmado por PETER SURLA

3. quien actúa en su calidad de NOTARIO PÚBLICO, ESTADO DE CALIFORNIA

4. lleva el sello de PETER SURLA NOTARIO PÚBLICO, ESTADO DE CALIFORNIA

CERTIFICADO

5. en SACRAMENTO, CALIFORNIA

6. el 3 de octubre de 2005

7. por el Secretario de estado suplente, estado de California

8. Número 257972

9. Sello:

GRAN SELLO DEL ESTADO DE CALIFORNIA

10. Firma: (ILEGIBLE) secretario de estado

Eduardo Calado M.
Eduardo Calado Noguera
TRADUCTOR OFICIAL
INGLES - ESPAÑOL ESPAÑOL
Febrero de 19..

COMO NOTARIA SEXTA (E) DEL CIRCULO DE BOGOTA D.C. HAGO CONSTAR QUE LA PRESENTE FOTOCOPIA COINCIDE CON EL ORIGINAL QUE SE ME PRESENTO A LA VISTA
29 DIC 2005
MARIA FERNANDA CASAS COLL
NOTARIA ENCARGADA

APOSTILLA:

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

1. Estados Unidos de América

MINISTERIO DE RELACIONES EXTERIORES

NO SE ASUME RESPONSABILIDAD DEL TEXTO

2005 OCT 20 P 1:50

17111

Eduardo Galado

CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

COMO NOTARIA SEXTA (E) DEL CIRCULO DE BOGOTA, D.C., HAGO CONSTAR QUE LA FOTOCOPIA CONCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

BOGOTA D.C., REPUBLICA DE COLOMBIA

10 OCT 2005

MARIA FERNANDA CABAS TOLL
NOTARIA SEXTA (E) ENCARGADA

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE LA(S) PRESENTE(S) FIRMA(S) CONCUERDA(N) CON LA FIRMA REGISTRADA POR EL (LOS) SEÑOR(ES) EN ESTA NOTARIA

SANTAFE DE BOGOTA

20 OCT 2005

NOTARIA SEXTA
PABLO PEREZ BARRAGAN
Oficial Encargado

Este documento público

2. ha sido firmado por LORRAINE F STRUNK

3. quien actúa en su calidad de NOTARIO PÚBLICO

4. lleva el sello de LORRAINE F STRUNK NOTARIO PÚBLICO, CONDADO DE MONTGOMERY, ESTADO DE PENSILVANIA

CERTIFICADO

5. en Harrisburg, Pensilvania

6. El 3 de octubre de 2005

7. por Pedro A. Cortés, secretario de estado de Pensilvania

8. Número 200536342

9. Sello: SECRETARIO DEL ESTADO DE PENSILVANIA

10. Firma: PEDRO A. CORTÉS.

COLO-13562-841-001-5

WPCL002G ID 7193

Bogotá, 20 de octubre de 2005.

Eduardo Calado M.

Eduardo Calado Noguera
TRADUCTOR OFICIAL
INGLES - ESPAÑOL INGLES
Res. 541. Febrero de 19**

COMO NOTARIA SESENTA (E) DEL CIRCULO DE BOGOTÁ, D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTÁ, D.C., REPÚBLICA DE COLOMBIA
28 DIC 2005
MARÍA FERNANDA CASAS COLL
NOTARIA ENCARGADA

MINISTERIO DE RELACIONES EXTERIORES

171118

Eduardo Galado

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JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

COMO NOTARIA SEXTA (E) DEL CIRCULO DE BOGOTA, D.C. HAGO CONSTAR: QUE LA FOTOCOPIA CONCUERDA CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C., REPUBLICA DE COLOMBIA

20 OCT 2005

MARIA FERNANDA OSSIO COLL
NOTARIA ENCARGADA

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE(S) FIRMA(S) QUE APARECE(N) EN EL PRESENTE DOCUMENTO CONCUERDA CON LA FIRMA REGISTRADA POR EL INTERESADO EN ESTA NOTARIA
SANTAFE DE BOGOTA, - 20 OCT 2005

NOTARIA SEXTA
PABLO MENDEZ BARRAS

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(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.

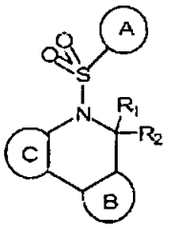
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(54) Title: FUSED, TRICYCLIC SULFONAMIDE INHIBITORS OF GAMMA SECRETASE



(I)

(57) Abstract: The invention provides compounds of formula (I): or pharmaceutically salts thereof, where R_1, R_2 and the A, B, and C-rings are as defined herein. Compounds of formula (I) are useful in treating or preventing cognitive disorders, such as Alzheimer's disease. The invention also encompasses pharmaceutical compositions comprising compounds or salts of formula (I), methods of preparing the desired compunds, and methods of treating cognitive disorders, such as Alzheimer's disease, using the compounds or salts of Formula (I).

WO 2007/143523 A3

Fused, Tricyclic Sulfonamide Inhibitors of Gamma Secretase

This application claims priority from U.S. Provisional Application No. 60/810,431, filed June 2, 2006; U.S. Provisional Application No. 60/876,932, filed December 22, 2006; and U.S. Provisional Application No. 60/922,771, filed April 10, 2007. Each reference is incorporated by reference in its entirety.

Background of the Invention

Field of the Invention

The invention relates to fused, tricyclic sulfonamido compounds, which inhibit gamma secretase, ß-amyloid peptide release and/or its synthesis. Therefore, the fused, tricyclic sulfonamido compounds are useful in the prevention of cognitive disorders, such as Alzheimer's disease, in patients susceptible to cognitive disorders and/or in the treatment of patients with cognitive disorders in order to inhibit further deterioration in their condition. The compounds of the invention are also useful for initiating or increasing angiogenesis.

State of the Art

Alzheimer's Disease (AD) is a degenerative brain disorder characterized clinically by progressive loss of memory, cognition, reasoning, judgment and emotional stability that gradually leads to profound mental deterioration and ultimately death. AD is a very common cause of progressive mental failure (dementia) in aged humans and is believed to represent the fourth most common medical cause of death in the United States. AD has been observed in races and ethnic groups worldwide and presents a major present and future public health problem. The disease is currently estimated to affect about two to three million individuals in the United States alone. AD is at present incurable. No treatment that effectively prevents AD or reverses its symptoms and course is currently known.

The brains of individuals with AD exhibit characteristic lesions termed senile (or amyloid) plaques, amyloid angiopathy (amyloid deposits in blood vessels) and neurofibrillary tangles. Large numbers of these lesions, particularly amyloid plaques and neurofibrillary tangles, are generally found in several areas of the human brain important for memory and cognitive function in patients with AD. Smaller numbers of these lesions in a more restrictive anatomical distribution are also found in the brains of most aged humans who do not have clinical AD. Amyloid plaques and amyloid angiopathy also characterize the brains of individuals with Trisomy 21 (Down's Syndrome) and Hereditary Cerebral Hemorrhage

with Amyloidosis of the Dutch Type (HCHWA-D). At present, a definitive diagnosis of AD usually requires observing the aforementioned lesions in the brain tissue of patients who have died with the disease or, rarely, in small biopsied samples of brain tissue taken during an invasive neurosurgical procedure.

The principal chemical constituent of the amyloid plaques and vascular amyloid deposits (amyloid angiopathy) characteristic of AD and the other disorders mentioned above is an approximately 4.2 kilodalton (kD) protein of about 39-43 amino acids designated the ß-amyloid peptide (ßAP) or sometimes Aß, AßP or ß/A4. ß-Amyloid peptide was first purified and a partial amino acid sequence was provided by Glenner et al., Biochem. Biophys. Res. Commun., 120:885-890 (1984) The isolation procedure and the sequence data for the first 28 amino acids are described in U.S. Patent No. 4,666,829.

Molecular biological and protein chemical analyses have shown that the ß-amyloid peptide is a small fragment of a much larger precursor protein termed the amyloid precursor protein (APP), that is normally produced by cells in many tissues of various animals, including humans. Knowledge of the structure of the gene encoding APP has demonstrated that ß-amyloid peptide arises as a peptide fragment that is cleaved from APP by protease enzyme(s). Sequential processing of the precursor protein by the enzymes referred to generically as beta- and gamma-secretases, give rise to the ß-amyloid peptide fragment. Both enzymes have now been molecularly cloned, and characterized to differing levels.

Several lines of evidence indicate that progressive cerebral deposition of ß-amyloid peptide plays a seminal role in the pathogenesis of AD and can precede cognitive symptoms by years or decades. See, for example, Selkoe, Neuron, 6:487-498 (1991). The most important line of evidence is the discovery that missense DNA mutations at amino acid 717 of the 770-amino acid isoform of APP can be found in affected members but not unaffected members of several families with a genetically determined (familial) form of AD (A. Goate, et al. Nature, 349:704-706 (1991); M-C. Chartier-Harlin, Nature, 353:844-846, (1991); and Murrell et al., Science, 254:97-99 (1991.) Another such mutation, known as the Swedish variant, is comprised of a double mutation changing lysine^{595}-methionine^{596} to asparagine^{595}-leucine^{596} (with reference to the 695 isoform was found in a Swedish family) was reported in 1992 (Mullan et al., Nature Genet., 1:345-347 (1992). Genetic linkage analyses have demonstrated that these mutations, as well as certain other mutations in the APP gene, are the specific molecular cause of AD in the affected members of such families. In addition, a mutation at amino acid 693 of the 770-amino acid isoform of APP has been

identified as the cause of the ß-amyloid peptide deposition disease, HCHWA-D, and a change from alanine to glycine at amino acid 692 appears to cause a phenotype that resembles AD is some patients but HCHWA-D in others. The discovery of these and other mutations in APP in genetically based cases of AD prove that alteration of APP metabolism, and subsequent deposition of its ß-amyloid peptide fragment, can cause AD.

Despite the progress which has been made in understanding the underlying mechanisms of AD and other ß-amyloid peptide related diseases, there remains a need to develop methods and compositions for treatment of the disease(s). Ideally, the treatment methods would advantageously be based on drugs, which are capable of inhibiting ß-amyloid peptide release and/or its synthesis *in vivo*.

One approach toward inhibiting amyloid peptide synthesis *in vivo* is by inhibiting gamma secretase, the enzyme responsible for the carboxy-terminal cleavage resulting in production of ß-amyloid peptide fragments of 40 or 42 residues in length. The immediate substrates for gamma secretase are β-cleaved, as well as α-cleaved carboxy-terminal fragments (CTF) of APP. The gamma-secretase cleavage site on β- and α-CTF fragments occurs in the predicted transmembrane domain of APP. Inhibitors of gamma-secretase have been demonstrated to effect amyloid pathology in transgenic mouse models (Dovey, H. F., V. John, J. P. Anderson, L. Z. Chen, P. de Saint Andrieu, L. Y. Fang, S. B. Freedman, B. Folmer, E. Goldbach, E. J. Holsztynska et al. (2001). "Functional gamma-secretase inhibitors reduce beta-amyloid peptide levels in brain." J Neurochem 76(1): 173-81.)

Gamma secretase is recognized to be a multi-subunit complex comprised of the presenilins (PS1 or PS2), Nicastrin, Aph-1, and Pen 2 (De Strooper, B. (2003). "Aph-1, Pen-2, and Nicastrin with Presenilin generate an active gamma-Secretase complex." Neuron 38(1): 9-12; Edbauer, D., E. Winkler, J. T. Regula, B. Pesold, H. Steiner and C. Haass (2003). "Reconstitution of gamma-secretase activity." Nat Cell Biol 5(5): 486-8; Kimberly, W. T., M. J. LaVoie, B. L. Ostaszewski, W. Ye, M. S. Wolfe and D. J. Selkoe (2003). "Gamma-secretase is a membrane protein complex comprised of presenilin, nicastrin, Aph-1, and Pen-2." Proc Natl Acad Sci U S A 100(11): 6382-7). Much evidence indicates that PS comprises the catalytic moiety of the complex, while the other identified subunits are necessary for proper maturation and sub-cellular localization of the active enzyme complex (reviewed in De Strooper, B. (2003). "Aph-1, Pen-2, and Nicastrin with Presenilin generate an active gamma-Secretase complex." Neuron 38(1): 9-12.) Consistent with this hypothesis: PS knock-out mice exhibit significant reductions in β-amyloid production (De Strooper, B.,

P. Saftig, K. Craessaerts, H. Vanderstichele, G. Guhde, W. Annaert, K. Von Figura and F. Van Leuven (1998). "Deficiency of presenilin-1 inhibits the normal cleavage of amyloid precursor protein." Nature 391(6665): 387-90; Haass, C. and D. J. Selkoe (1998). "Alzheimer's disease. A technical KO of amyloid-beta peptide." Nature 391(6665): 339-40; Herreman, A., L. Serneels, W. Annaert, D. Collen, L. Schoonjans and B. De Strooper (2000). "Total inactivation of gamma-secretase activity in presenilin-deficient embryonic stem cells." Nat Cell Biol 2(7): 461-2); point mutations of putative active site aspartate residues in PS trans-membrane domains inhibit β-amyloid production in cells in a dominant negative fashion (Wolfe, M. S., W. Xia, B. L. Ostaszewski, T. S. Diehl, W. T. Kimberly and D. J. Selkoe (1999). "Two transmembrane aspartates in presenilin-1 required for presenilin endoproteolysis and gamma-secretase activity." Nature 398(6727): 513-7; Kimberly, W. T., W. Xia, T. Rahmati, M. S. Wolfe and D. J. Selkoe (2000). "The transmembrane aspartates in presenilin 1 and 2 are obligatory for gamma-secretase activity and amyloid beta-protein generation." J Biol Chem 275(5): 3173-8); active site directed substrate-based transition state isosteres designed to inhibit gamma secretase directly conjugate to PS (Esler, W. P., W. T. Kimberly, B. L. Ostaszewski, T. S. Diehl, C. L. Moore, J. Y. Tsai, T. Rahmati, W. Xia, D. J. Selkoe and M. S. Wolfe (2000). "Transition-state analogue inhibitors of gamma-secretase bind directly to presenilin-1." Nat Cell Biol 2(7): 428-34; Li, Y. M., M. Xu, M. T. Lai, Q. Huang, J. L. Castro, J. DiMuzio-Mower, T. Harrison, C. Lellis, A. Nadin, J. G. Neduvelil et al. (2000). "Photoactivated gamma-secretase inhibitors directed to the active site covalently label presenilin 1." Nature 405(6787): 689-94); finally, allosteric gamma secretase inhibitors have likewise been demonstrated to bind directly to PS (Seiffert, D., J. D. Bradley, C. M. Rominger, D. H. Rominger, F. Yang, J. E. Meredith, Jr., Q. Wang, A. H. Roach, L. A. Thompson, S. M. Spitz et al. (2000). "Presenilin-1 and -2 are molecular targets for gamma-secretase inhibitors." J Biol Chem 275(44): 34086-91.)

Current evidence indicates that in addition to APP processing leading to β-amyloid synthesis, gamma-secretase also mediates the intra-membrane cleavage of other type I transmembrane proteins (reviewed in Fortini, M. E. (2002). "Gamma-secretase-mediated proteolysis in cell-surface-receptor signaling." Nat Rev Mol Cell Biol 3(9): 673-84, see also Struhl, G. and A. Adachi (2000). "Requirements for presenilin-dependent cleavage of notch and other transmembrane proteins." Mol Cell 6(3): 625-36.) Noteworthy among the known substrates of gamma-secretase is mammalian Notch 1. The Notch 1 protein is important for cell fate determination during development, and tissue homeostasis in the adult. Upon ligand

engagement via the Notch ecto-domain, Notch undergoes sequential extra-cellular and intra-membrane processing analogous to APP. The intra-membrane processing of Notch mediated by gamma secretase leads to release of the Notch intracellular domain (NICD). The NICD fragment mediates Notch signaling via translocation to the nucleus, where it regulates expression of genes mediating cellular differentiation in many tissues during development, as well as in the adult.

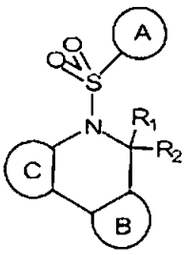
Disruption of Notch signaling via genetic knock-out (KO) results in embryonic lethal phenotype in mice (Swiatek, P. J., C. E. Lindsell, F. F. del Amo, G. Weinmaster and T. Gridley (1994). "Notch1 is essential for postimplantation development in mice." Genes Dev 8(6): 707-19; Conlon, R. A., A. G. Reaume and J. Rossant (1995). "Notch1 is required for the coordinate segmentation of somites." Development 121(5): 1533-45.) The Notch KO phenotype is very similar to the phenotype observed PS1 KO mice, and precisely reproduced by PS1/PS2 double KO mice (De Strooper et al. (1998). "Deficiency of presenilin-1 inhibits the normal cleavage of amyloid precursor protein." Nature 391(6665): 387-90; Donoviel, D. B., A. K. Hadjantonakis, M. Ikeda, H. Zheng, P. S. Hyslop and A. Bernstein (1999). "Mice lacking both presenilin genes exhibit early embryonic patterning defects." Genes Dev 13(21): 2801-10; Herreman, A., L. Serneels, W. Annaert, D. Collen, L. Schoonjans and B. De Strooper (2000). "Total inactivation of gamma-secretase activity in presenilin-deficient embryonic stem cells." Nat Cell Biol 2(7): 461-2.) This convergence of phenotypes observed in knock-out mice of either the substrate (Notch) or the enzyme (PS) suggests that inhibitors of gamma secretase that also inhibit Notch function may be limited as therapeutic agents owing to the importance of Notch function in adult tissues (Fortini, M. E. (2002). "Gamma-secretase-mediated proteolysis in cell-surface-receptor signaling." Nat Rev Mol Cell Biol 3(9): 673-84.) As APP knock-out mice develop normally and without an overt phenotype Zheng, H., M. Jiang, M. E. Trumbauer, R. Hopkins, D. J. Sirinathsinghji, K. A. Stevens, M. W. Conner, H. H. Slunt, S. S. Sisodia, H. Y. Chen et al. (1996). "Mice deficient for the amyloid precursor protein gene." Ann N Y Acad Sci 777: 421-6; Zheng, H., M. Jiang, M. E. Trumbauer, D. J. Sirinathsinghji, R. Hopkins, D. W. Smith, R. P. Heavens, G. R. Dawson, S. Boyce, M. W. Conner et al. (1995). "beta-Amyloid precursor protein-deficient mice show reactive gliosis and decreased locomotor activity." Cell 81(4): 525-31, the cumulative evidence, therefore, suggests that preferred gamma secretase inhibitors would have selectivity for inhibiting gamma secretase processing of APP over gamma secretase processing of Notch.

Acute inhibition of gamma secretase by DAPT in-vivo was demonstrated to lead to reduction of Aβ in the brain of PDAPP mice. Dovey, H. F., John, V., et al. (2001). "Functional gamma-secretase inhibitors reduce beta-amyloid peptide levels in brain." J Neurochem 76(1): 173-81.

Gamma-secretase inhibitors have also been shown to increase angiogenesis. See US 2006/0264380. As such, the gamma secretase inhibitors of the invention are useful in promoting angiogenesis.

Summary of the Invention

In a broad aspect, the invention provides compounds of Formula I:



stereoisomers, tautomers, hydrates, mixtures of stereoisomers and/or tautomers, or pharmaceutically acceptable salts thereof, wherein

the C-ring is cycloalkyl, aryl, heterocycloalkyl, or heteroaryl, each of which is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, aryloxy, aryl-(C_1-C_6alkoxy), C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), -NR'R", -(C_1-C_6 alkyl)-NR'R", -NR'C(O)OR', -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, oxo, aryl-(C_1-C_6 alkyl), aryl, heteroaryl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -$S(O)_z$ aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl), or -$S(O)_z$ (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2 or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R"; or

where two adjacent substituents form –O-$(CH_2)_{1-3}$-O-;

the A-ring is aryl, cycloalkyl, heteroaryl or heterocycloalkyl, where each ring is optionally substituted at a substitutable position with halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, hydroxyl, hydroxy-(C_1-C_6 alkyl), CN, NO_2, aryloxy, aryl-(C_1-C_6 alkoxy)-, -SO_2-(C_1-C_6 alkyl), -NR'R", C_1-C_6 alkanoyl, -C(O)OR', -(C_1-C_6 alkyl)-C(O)OR', heteroaryl, aryl, aryl-(C_1-C_6 alkyl)-, -SO_2-NR'R", -C(O)NR'R", -OC(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", or -NR'C(O)OR';

the B-ring is a heteroaryl or heterocycloalkyl ring, each of which is optionally substituted at a substitutable position with a group that is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, -NR'R", -SO_2-NR'R", -C(O)NR'R", -NR'SO_2R", -NR'SO_2NR'R", -NR'SO_2-(C_1-C_6 alkyl), -NR'SO_2-phenyl, -NR'C(O)R", -NR'C(O)NR'R", -NR'C(O)OR', -(C_1-C_6 alkyl)-NR'R", -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", NO_2, CN, -C(O)OR', hydroxyl, hydroxy-(C_1-C_6 alkyl), -S(O)z (C_1-C_6 alkyl), -S(O)z aryl, halogen, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, phenyl, C_1-C_6 alkanoyl, aryl-(C_1-C_6 alkanoyl) (where the aryl group is preferably naphthyl or phenyl, more preferably phenyl), aryl-(C_1-C_6 alkyl) (preferably phenethyl or benzyl, more preferably, benzyl), arylcarbonyl, heteroarylcarbonyl, or heteroaryl-(C_1-C_6 alkanoyl), where the heteroaryl group is preferably pyridyl, pyrimidyl, thienyl or furanyl; where the aryl or heteroaryl groups are optionally substituted with 1 to 5 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, CN or NO_2; and

where each z is independently 0, 1, or 2;

R_1 is hydrogen or C_1-C_6 alkyl;

R_2 is hydrogen, C_1-C_6 alkyl, C_1-C_4 haloalkyl, hydroxyl, hydroxy-(C_1-C_4 alkyl), -NO_2, -CN, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, -C(O)OR', -NR'R", -X(CO)Y, -$(C(R_{30})_2)_{1-4}$X(CO)Y, unsubstituted C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl substituted with one or more (e.g., 1-4) R_{50} groups, unsubstituted aryl, aryl substituted with one or more (e.g., 1-4) R_{50} groups, unsubstituted heteroaryl; or heteroaryl substituted with one or more (e.g., 1-4) R_{50} groups, unsubstituted heterocycloalkyl; or heterocycloalkyl substituted with one or more (e.g., 1-4) R_{50} groups; where

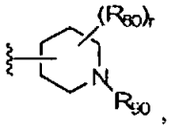
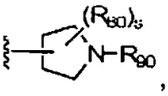
each R_{30} is independently hydrogen or C_1-C_6 alkyl;

each R_{50} is independently selected from: halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -OH, -O-(C_1-C_6 alkyl), -OCF_3, -CN, -$NR_{60}R_{70}$, -C(O)O-(C_1-C_6 alkyl), -$CONR_{60}R_{70}$,

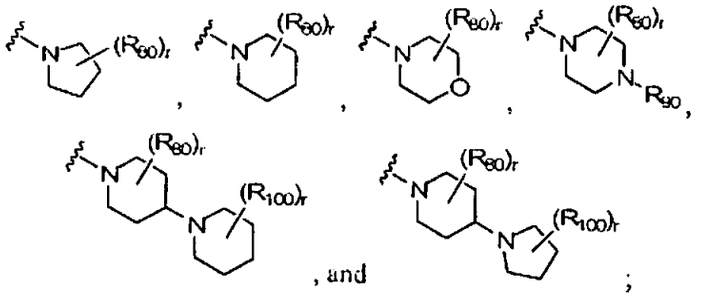
-(C_1-C_6) alkyl-$NR_{60}R_{70}$, -NR_{60}COalkyl, -NR_{60}COaryl, -NR_{60}COheteroaryl, -$NR_{60}CONR_{60}R_{70}$,

X is: -O-, -NH-, or -N(alkyl)-;

Y is selected from –O-(C_1-C_6 alkyl), –O-phenyl, -$NR_{60}R_{70}$, or -$N(R_{30})(CH_2)_{2-6}NR_{60}R_{70}$;

R_{60} and R_{70} are independently selected from: hydrogen, C_1-C_6 alkyl, cycloalkyl, arylalkyl; heteroarylalkyl;  , and  , or

R_{60} and R_{70} taken together with the nitrogen atom to which they are bound form a heterocycloalkyl group selected from:



, and ;

where

each R_{30} is independently unsubstituted C_1-C_6 alkyl or C_1-C_6 alkyl substituted with hydroxyl or halogen;

each R_{90} is independently H; unsubstituted C_1-C_6 alkyl; C_1-C_6 alkyl substituted with hydroxyl or halogen, unsubstituted cycloalkyl; cycloalkyl substituted with one or more (e.g., 1-4) R_{50} groups; aryl-(C_1-C_6alkyl); heteroarylalkyl; -C(O)O-(C_1-C_6alkyl), -C(O)O-aryl; -SO_2-(C_1-C_6alkyl); -SO_2-aryl; unsubstituted aryl; aryl substituted with one or more (e.g., 1-4) R_{50} groups; heteroaryl; or heteroaryl substituted with one or more (e.g., 1-4) R_{50} groups;

each R_{100} is independently hydrogen or C_1-C_6 alkyl;

each r is 0 to 4;

each s is 0 to 3; or

R_1 and R_2 combined are oxo or =N-OR where R is hydrogen, C_1-C_6 alkyl, aryl or arylalkyl; or R_1 and R_2 together with the carbon to which they are attached form a C_3-C_6 cycloalkyl group wherein one of the carbons might be replaced with a heteroatom selected from N, O

or S and wherein said C_3-C_6 cycloalkyl ring may be optionally substituted with C_1-C_6 alkyl or halogen; and

R' and R" are independently hydrogen, C_1-C_6 alkyl, or phenyl, where the phenyl is optionally substituted with 1 to 5 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, CN or NO_2, or

R' and R" taken together with the nitrogen atom to which they are bound form a 3 to 7 membered heterocycloalkyl group that may have an additional heteroatom selected from N, O or S and that may be optionally substituted with 1 to 3 R_{80} or R_{90} groups;

provided that 5-tosyl-4,5-dihydro-2H-pyrazolo[4,3-c]quinoline, 2-phenyl-5-tosyl-4,5-dihydro-2H-pyrazolo[4,3-c]quinoline, 7-methoxy-2-phenyl-5-tosyl-4,5-dihydro-2H-pyrazolo[4,3-c]quinoline, 8-methoxy-5-tosyl-4,5-dihydro-2H-pyrazolo[4,3-c]quinoline, 8-methoxy-2-phenyl-5-tosyl-4,5-dihydro-2H-pyrazolo[4,3-c]quinoline, 3-(methylthio)-5-tosyl-4,5-dihydro-2H-pyrazolo[4,3-c]quinoline, 7-methoxy-5-tosyl-4,5-dihydro-2H-pyrazolo[4,3-c]quinoline, 5-tosyl-4,5-dihydro-2H-pyrazolo[4,3-c]quinoline, ethyl 1-(4-sulfamoylphenyl)-5-tosyl-4,5-dihydro-1H-pyrazolo[4,3-c]quinoline-3-carboxylate, 1-(4-sulfamoylphenyl)-5-tosyl-4,5-dihydro-1H-pyrazolo[4,3-c]quinoline-3-carboxamide;and ethyl 1-methyl-5-tosyl-4,5-dihydro-1H-pyrazolo[4,3-c]quinoline-3-carboxylate, are not encompassed by formula I.

The compounds of Formula I inhibit β-amyloid peptide release and/or its synthesis and, therefore, are useful in the prevention of Alzheimer's Disease (AD) in patients susceptible to AD and/or in the treatment of patients with AD in order to inhibit further deterioration in their condition. The invention also, encompasses pharmaceutical compositions containing the compounds of Formula I, and methods employing such compounds or compositions in the treatment of cognitive diseases, including Alzheimer's disease.

The invention also provides a method of treating a patient who has, or in preventing a patient from getting, a disease or condition selected from the group consisting of Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's disease, for treating patients with mild cognitive impairment (MCI) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i.e. single and recurrent lobar hemorrhages, for treating other degenerative dementias, including

dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, age related macular degeneration or diffuse Lewy body type of Alzheimer's disease and who is in need of such treatment which comprises administration of a therapeutically effective amount of a compound of formula I.

The invention further provides a method of influencing a disease state in a cell, a group of cells, or an organism, comprising: administering at least one gamma-secretase inhibitor or a gamma-secretase pathway inhibitor of formula I, or a pharmaceutically acceptable salt thereof, to the cell, group of cells, or organism, wherein the disease is selected from the group consisting of atherosclerosis, hemangioma, hemangioendothelioma, vascular malformations, warts, pyogenic granulomas, hair growth, Kaposi's sarcoma, scar keloids, allergic edema, neoplasms, psoriasis, decubitus or stasis ulcers, gastrointestinal ulcers, dysfunctional uterine bleeding, follicular cysts, ovarian hyperstimulation, endometriosis, neoplasms, preeclampsia, placental insufficiency, respiratory distress, ascites, peritoneal sclerosis, adhesion formation, metastatic spreading, coronary artery disease, ischemic heart disease, ischemic limb disease, obesity, rheumatoid arthritis, synovitis, bone destruction, cartilage destruction, osteomyelitis, pannus growth, osterphyte formation, cancer, aseptic necrosis, impaired fracture healing, hepatitis, pneumonia, glomerulonephritis, asthma, nasal polyps, liver regeneration, pulmonary hypertension, systemic hypertension, diabetes, retinopathy of prematurity, diabetic retinopathy, choroidal disorders, intraocular disorders (e.g. age related macular degeneration), leukomafacia, stroke, vascular dementia, disease, thyroiditis, thyroid enlargement, thyroid pseudocyst, tumor metastasis, lymphoproliferative disorders, lympgoedema, AIDS, and hematologic malignancies.

Still further, the invention provides a method of increasing the angiogenic process in a cell, a group of cells, or an organism, comprising administering a pharmaceutical composition comprising a pharmaceutically effective amount of at least one gamma-secretase inhibitor or gamma-secretase pathway inhibitor of formula I, or a pharmaceutically acceptable salt thereof, to the cell, group of cells, or organism.

Further still, the invention provides a method of increasing the angiogenic process in a cell, a group of cells, or an organism, comprising administering a pharmaceutical composition comprising a pharmaceutically effective amount of at least one gamma-secretase inhibitor or gamma-secretase pathway inhibitor of formula I, or a pharmaceutically acceptable salt thereof, to the cell, group of cells, or organism, wherein the pharmaceutical

composition is administered to prevent, treat, or cure a condition selected from the group consisting of atherosclerosis, hemangioma, hemangioendothelioma, vascular malformations, warts, pyogenic granulomas, hair growth, Kaposi's sarcoma, scar keloids, allergic edema, neoplasms, psoriasis, decubitus or stasis ulcers, gastrointestinal ulcers, dysfunctional uterine bleeding, follicular cysts, ovarian hyperstimulation, endometriosis, neoplasms, preeclampsia, placental insufficiency, respiratory distress, ascites, peritoneal sclerosis, adhesion formation, metastatic spreading, coronary artery disease, ischemic heart disease, eschemic limb disease, obesity, rheumatoid arthritis, synovitis, bone destruction, cartilage destruction, osteomyelitis, pannus growth, osterphyte formation, cancer, aseptic necrosis, impaired fracture healing, hepatitis, pneumonia, glomerulonephritis, asthma, nasal polyps, liver regeneration, pulmonary hypertension, systemic hypertension, diabetes, retinopathy of prematurity, diabetic retinopathy, choroidal disorders, intraocular disorders (e.g. age related macular degeneration), leukomafacia, stroke, vascular dementia, disease, thyroiditis, thyroid enlargement, thyroid pseudocyst, tumor metastasis, lymphoproliferative disorders, lympgoedema, AIDS, and hematologic malignancies.

The invention also provides a method for screening for a substance which initiates or increases angiogenesis, comprising: measuring an activity of a gamma-secretase pathway in the presence of a candidate compound in a suitable model; measuring an activity of a gamma-secretase pathway in the absence of a candidate compound; and comparing said activity in the presence of a candidate compound with said activity in the absence of the candidate compound, wherein a change in activity indicates that said candidate initiates or increases angiogenesis.

In another aspect, the invention provides methods of preparing the compounds of interest, as well as intermediates useful in preparing the compounds of interest.

The invention further provides a method of treating an A beta-related disease comprising administering a therapeutically effective amount of a compound or salt of Formula I to a patient in need of such treatment.

Detailed Description of the Invention

As described above, the invention provides for compounds according to Formula I.

In another aspect, the invention provides compounds of formula 2, i.e., compounds of formula I wherein the A-ring is phenyl or naphthyl, each which is optionally substituted at a substitutable position with halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy,

C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, hydroxyl, hydroxy-(C_1-C_4 alkyl), CN, aryloxy, aryl-(C_1-C_4 alkoxy), -SO_2-(C_1-C_6 alkyl), -NR'R", C_1-C_6 alkanoyl, -C(O)OR', -(C_1-C_4alkyl)-C(O)OR', pyridyl, phenyl, phenyl-(C_1-C_4 alkyl), -SO_2-NR'R", -C(O)NR'R", -OC(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", or -NR'C(O)OR', where each R' and R" is independently hydrogen, C_1-C_6 alkyl or phenyl.

In still another aspect, the invention provides compounds of formula 3, i.e., compounds of formula I wherein the B-ring is pyrazolyl, imidazolyl, pyrrolyl, triazolyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, pyridyl, pyrimidyl, or isoxazolyl, each of which is optionally substituted at a substitutable position with a group that is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, -NR'R", -C(O)OR', -SO_2NR'R", -C(O)NR'R", -NR'SO_2R", -NR'SO_2NR'R", -NR'SO_2-(C_1-C_6 alkyl), -NR'SO_2-phenyl, -NR'C(O)R", -NR'C(O)NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -(C_1-C_4 alkyl)-NR'R", -(C_1-C_4 alkyl)-C(O)OR', -(C_1-C_4 alkyl)-C(O)NR'R", NO_2, CN, hydroxyl, hydroxy-(C_1-C_6 alkyl), -$S(O)_z$ (C_1-C_6 alkyl), -$S(O)_z$ phenyl, halogen, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, phenyl, C_1-C_6 alkanoyl, phenyl-(C_1-C_4 alkanoyl), phenethyl, benzyl, phenylcarbonyl, heteroarylcarbonyl, or heteroaryl-(C_1-C_4 alkanoyl), where the heteroaryl group is pyridyl, pyrimidyl, thienyl or furanyl; where the phenyl or heteroaryl groups are optionally substituted with 1 to 5 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, CN or NO_2.

In yet another aspect, the invention provides compounds of formula 4, i.e., compounds of formula I wherein the A-ring is phenyl or naphthyl, each of which is optionally substituted at a substitutable position with halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, hydroxyl, hydroxy-(C_1-C_4 alkyl), CN, phenyloxy, benzyloxy, -SO_2-(C_1-C_6 alkyl), -NR'R", C_1-C_6 alkanoyl, -C(O)OR', -(C_1-C_4alkyl)-C(O)OR', pyridyl, phenyl, phenyl-(C_1-C_4 alkyl), -SO_2-NR'R", -C(O)NR'R", -OC(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", or -NR'C(O)OR', where each R' and R" is independently H, C_1-C_6 alkyl or phenyl; and the B-ring is pyrazolyl, imidazolyl, pyrrolyl, triazolyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, pyridyl, pyrimidyl, or isoxazolyl, each of which is optionally substituted at a substitutable position with a group that is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, -NR'R", -SO_2-NR'R", -C(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, NO_2, CN, -C(O)OR',

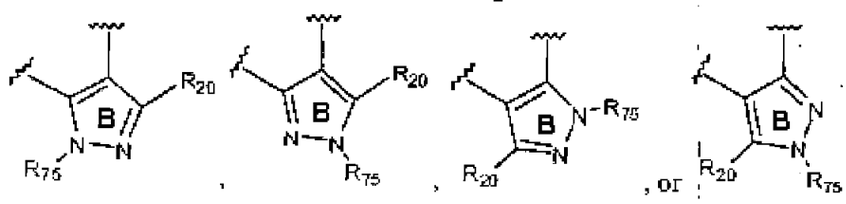
hydroxyl, hydroxy-(C_1-C_6 alkyl), halogen, -$S(O)_2$ (C_1-C_6 alkyl), -$S(O)_2$ aryl, halogen, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, benzyl, or phenyl.

In yet another aspect, the invention provides compounds of formula 4-1, i.e., compounds of formula I wherein the C-ring is cyclohexyl, cyclopentyl, phenyl, naphthyl, thienyl, imidazolyl, pyrimidyl, pyrazinyl, furanyl, thiazolyl, or pyridyl, each of which is optionally substituted at each substitutable position with groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, aryloxy, aryl-(C_1-C_4alkoxy), C_1-C_6 haloalkyl, (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), -NR'R", -(C_1-C_4 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R", -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, oxo, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -$S(O)_2$ (C_1-C_6 alkyl), or -$S(O)_2$ aryl, where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2 or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R"; or

where two adjacent substituents of the C-ring C –O-$(CH_2)_{1-3}$-O-.

In still another aspect, the invention provides compounds of formula 4-2, i.e., compounds of formula I, 4, or 4-1, wherein the B-ring is pyrazolyl, imidazolyl, pyrrolyl, triazolyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, pyridyl, pyrimidyl, or isoxazolyl, each of which is optionally substituted at a substitutable position with a group that is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, -NR'R", -SO_2-NR'R", -C(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, NO_2, CN, -C(O)OR', hydroxyl, hydroxy-(C_1-C_6 alkyl), halogen, -$S(O)_2$ (C_1-C_6 alkyl), -$S(O)_2$ aryl, halogen, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, benzyl, or phenyl.

In still another aspect, the invention provides compounds of formula 4-3, i.e., compounds of formula I, 4, or 4-1, wherein the B-ring has the formula:

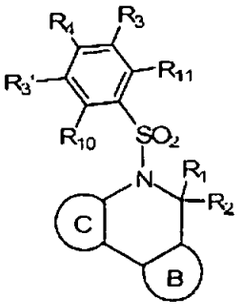


wherein

R_{20} is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, -NR'R", -(C_1-C_4 alkyl)-NR'R", -S(O)$_Z$ (C_1-C_6 alkyl), hydroxyl, halogen, CN, NO_2, CH_2F, CHF_2, CF_3, -C(O)OR', -C(O)NR'R", -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", or phenyl, and

R_{75} is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl-(C_1-C_6 alkanoyl)-, -C(O)NR'R", -S(O)$_Z$ (C_1-C_6 alkyl), -S(O)$_Z$-aryl, -SO_2NR'R", phenyl, phenyl-(C_1-C_6alkyl) (preferably phenethyl or benzyl, more preferably, benzyl), phenylcarbonyl, benzylcarbonyl, or heteroarylcarbonyl, where the heteroaryl group is pyridyl, pyrimidyl, thienyl or furanyl; where z is 0, 1, or 2.

In still another aspect, the invention provides compounds of formula 5, i.e., compounds of according to any one of formulas I, 4, 4-1, or 4-2, having the formula:



Formula 5

stereoisomers, tautomers, mixtures of stereoisomers and/or tautomers or pharmaceutically acceptable salts thereof, wherein

the C-ring is an optionally substituted cyclohexyl, phenyl, thienyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrrolyl, pyrazolyl, pyrimidyl, pyrazinyl, thiazolyl, or pyridyl;

R_3, R_3', R_4, R_{10} or R_{11} are independently hydrogen, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, hydroxyl, hydroxy-(C_1-C_4 alkyl), CN, NO_2, aryloxy (such as phenyloxy), aryl-(C_1-C_4alkoxy) such as benzyloxy, -SO_2-(C_1-C_6 alkyl), -NR'R", C_1-C_6 alkanoyl, -C(O)OR', -(C_1-C_4 alkyl)-C(O)OR', pyridyl, phenyl, phenyl-(C_1-C_4 alkyl)-, -SO_2-NR'R", -C(O)NR'R", -OC(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", or -NR'C(O)O-R', where each R' and R" is independently hydrogen, C_1-C_6 alkyl, or phenyl, where the phenyl is optionally substituted with 1 to 5 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, CN or NO_2; or

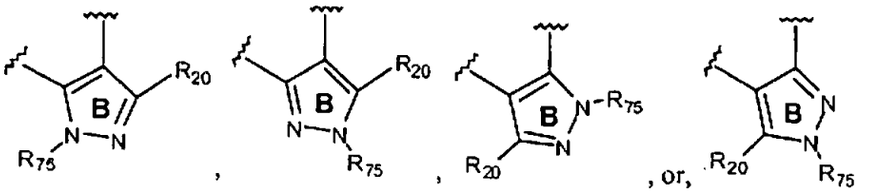
R_4 and $R_{3'}$, or R_{10} and $R_{3'}$ and the carbons to which they are attached form a benzo ring.

In another aspect, the invention provides compounds of formula 6, i.e., compounds of formula 5, wherein the C-ring is cyclohexyl, phenyl, thienyl, imidazolyl, pyrimidyl, pyrazinyl, thiazolyl, or pyridyl, each of which is optionally substituted at each substitutable position with groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, aryloxy, aryl-(C_1-C_4alkoxy), C_1-C_6 haloalkyl, (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), -NR'R", -(C_1-C_4 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", - OC(O)NR'R", -NR'C(O)NR'R", -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, oxo, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -S(O)z (C_1-C_6 alkyl), or -S(O)z aryl, where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2 or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R"; or

where two adjacent substituents of the C-ring C –O-$(CH_2)_{1-3}$-O-.

In still another aspect, the invention provides compounds of formula 6-1, i.e., compounds of formula 6 wherein the B-ring is pyrazolyl, imidazolyl, pyrrolyl, triazolyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, or isoxazolyl, each of which is unsubstituted.

In still another aspect, the invention provides compounds of formula 6-2, i.e., compounds of formula 6 wherein the B-ring has the formula:



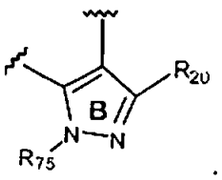
wherein

R_{20} is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, -NR'R", -(C_1-C_4 alkyl)-NR'R", -S(O)z (C_1-C_6 alkyl), hydroxyl, halogen, CN, NO_2, CH_2F, CHF_2, CF_3, -C(O)OR', -C(O)NR'R", -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", or phenyl, and

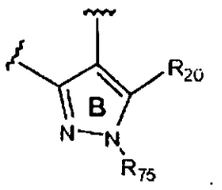
R_{75} is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl-(C_1-C_6 alkanoyl)-, -C(O)NR'R", -S(O)z (C_1-C_6 alkyl), -S(O)z -aryl, -SO_2NR'R", phenyl, phenyl-(C_1-C_6alkyl) (preferably phenethyl or benzyl, more preferably, benzyl), phenylcarbonyl, benzylcarbonyl, or

heteroarylcarbonyl, where the heteroaryl group is pyridyl, pyrimidyl, thienyl or furanyl.

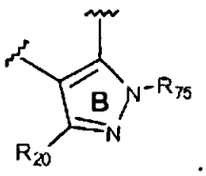
In yet another aspect, the invention provides compounds of formula 6-3, i.e., compounds of formula 6-2 wherein the B-ring has the formula:



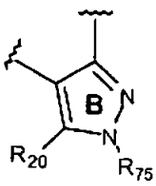
In yet another aspect, the invention provides compounds of formula 6-4, i.e., compounds of formula 6-2 wherein the B-ring has the formula:



In yet another aspect, the invention provides compounds of formula 6-5, i.e., compounds of formula 6-2 wherein the B-ring has the formula:



In yet another aspect, the invention provides compounds of formula 6-6, i.e., compounds of formula 6-2 wherein the B-ring has the formula:



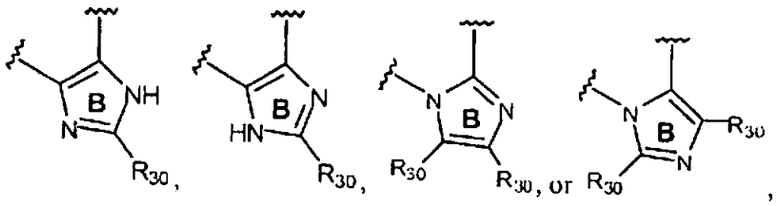
In a further aspect, the invention provides compounds of formula 6-6a, i.e., compounds according to any one of formulas 6-2, 6-3, 6-4, 6-5, or 6-6, wherein R_{20} is hydrogen, C_1-C_4 alkyl, CH_2F, CHF_2, CF_3, -C(O)OR', -S(O)z (C_1-C_4 alkyl), or hydroxyl; and R_{75} is hydrogen, C_1-C_4 alkyl, or -S(O)z –phenyl.

In another aspect, the invention provides compounds of formula 6-6b, i.e., compounds of formula 6-6a, wherein R_{20} is hydrogen or methyl, and R_{75} is hydrogen or methyl.

In yet another aspect, the invention provides compounds of formula 6-6c, i.e., compounds of formula 6-6a, wherein R_{20} is hydrogen or methyl, and R_{75} is hydrogen.

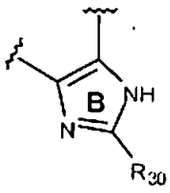
In still yet another aspect, the invention provides compounds of formula 6-6d, i.e., compounds of formula 6-6a, wherein R_{20} is hydrogen and R_{75} is hydrogen.

In yet another aspect, the invention provides compounds of formula 6-7, i.e., compounds of formula 6 wherein the B-ring has the formula:

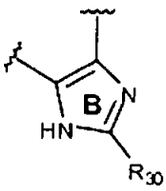


wherein each R_{30} is independently hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -NR'R", C_1-C_4 alkythio, hydroxyl, halogen, CH_2F, CHF_2, CF_3, or phenyl.

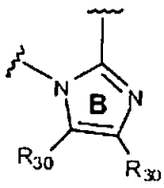
In still yet another aspect, the invention provides compounds of formula 6-8, i.e., compounds of formula 6-7 wherein the B-ring has the formula:



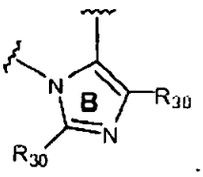
In yet another aspect, the invention provides compounds of formula 6-9, i.e., compounds of formula 6-7 wherein the B-ring has the formula:



In yet another aspect, the invention provides compounds of formula 6-10, i.e., compounds of formula 6-7 wherein the B-ring has the formula:



In yet another aspect, the invention provides compounds of formula 6-11, i.e., compounds of formula 6-7 wherein the B-ring has the formula:

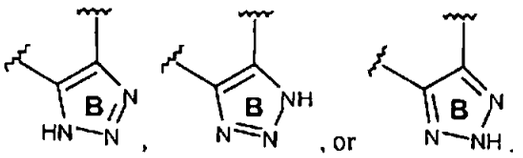


In a further aspect, the invention provides compounds of formula 6-11a, i.e., compounds according to any one of formulas 6-8, 6-9, 6-10, or 6-11, wherein each R_{30} is independently hydrogen, C_1-C_4 alkyl, CH_2F, CHF_2, or CF_3.

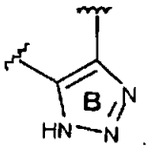
In another aspect, the invention provides compounds of formula 6-11b, i.e., compounds of formula 6-11a, wherein each R_{30} is independently hydrogen or methyl.

In still another aspect, the invention provides compounds of formula 6-11c, i.e., compounds of formula 6-11a, wherein each R_{30} is hydrogen.

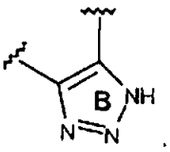
In yet still another aspect, the invention provides compounds of formula 6-12, i.e., compounds of formula 6 wherein the B-ring has the formula:



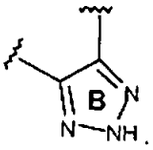
In yet another aspect, the invention provides compounds of formula 6-13, i.e., compounds of formula 6-12 wherein the B-ring has the formula:



In yet another aspect, the invention provides compounds of formula 6-14, i.e., compounds of formula 6-12 wherein the B-ring has the formula:



In yet another aspect, the invention provides compounds of formula 6-15, i.e., compounds of formula 6-12 wherein the B-ring has the formula:



In still another aspect, the invention provides compounds of formula 7, i.e., compounds of formulas 4, 4-1, 4-2, 4-3, 5, or any one of formulas 6, 6-1, 6-2, 6-3, 6-4, 6-5, 6-6, 6-6a, 6-6b, 6-6c, 6-6d, 6-7, 6-8, 6-9, 6-10, 6-11, 6-11a, 6-11b, 6-11c, 6-12, 6-13, 6-14, or 6-15 wherein the C-ring is phenyl or cyclohexyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryloxy, aryl-(C_1-C_4 alkoxy), C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", -(C_1-C_4 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, oxo, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -S(O)z phenyl, or -S(O)z (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2 or 3 groups that are independently halogen, hydroxy, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R" or

where two adjacent substituents from the C-ring form $-O-(CH_2)_{1-3}-O-$. In one embodiment, the C-ring is an optionally substituted phenyl.

In another aspect, the invention provides compounds of formula 7-1, i.e., compounds of formula 7 wherein the C-ring is unsubstituted phenyl.

In another aspect, the invention provides compounds of formula 7-1a, i.e., compounds of formula 7 wherein the C-ring is unsubstituted cyclohexyl.

In another aspect, the invention provides compounds of formula 7-2, i.e., compounds of formula 7, wherein the C-ring is phenyl substituted with 1 or 2 groups that are independently Cl, F, methyl, ethyl, isopropyl, methoxy, ethoxy, CF_3, OCF_3, OH, CH_2OH, NH_2, $NH(CH_3)$, $N(CH_3)_2$, or $-OC(O)N(CH_3)_2$. In one embodiment, the C-ring is bis-substituted with at least one halogen. In another embodiment, the halogen is F. In still another embodiment, the halogen is Cl. In another embodiment, the C-ring is bis-substituted with two halogens, which are the same or different. In still another embodiment, the C-ring is substituted at least at position 7. In another embodiment, the C-ring is substituted at positions 7 and 8. In another embodiment, the C-ring is monosubstituted with a halogen. In another embodiment, the halogen is F. In still another embodiment, the halogen is Cl. In still another embodiment, the C-ring is substituted at position 7. In yet another embodiment, the C-ring is substituted at position 8.

In another aspect, the invention provides compounds of formula 7-2a, i.e., compounds of formula 7, wherein the C-ring is cyclohexyl substituted with 1 or 2 groups that are independently Cl, F, methyl, ethyl, isopropyl, methoxy, ethoxy, CF_3, OCF_3, OH, CH_2OH, NH_2, $NH(CH_3)$, $N(CH_3)_2$, or $-OC(O)N(CH_3)_2$.

In yet another aspect, the invention provides compounds of formula 7-3, i.e., compounds of formula 7, wherein the C-ring is phenyl substituted with 1 or 2 groups that are Cl, F, methyl, ethyl, isopropyl, methoxy, CF_3, OCF_3, OH, $-OC(O)N(CH_3)_2$ or with two adjacent substituents forming $-O-(CH_2)_{1-3}-O-$. In one embodiment, the C-ring is monosubstituted with a halogen. In another embodiment, the halogen is Cl. In still another embodiment, the halogen is F. In another embodiment, the C-ring is substituted at the 7-position. In yet another embodiment, the C-ring is substituted at the 8-position. In another embodiment, the C-ring is bis-substituted at the 7- and 8-positions. In still another embodiment, the C-ring is substituted at the 7- and 8-positions, with a group that is halogen, methyl, or methoxy. In yet another embodiment, the two groups are the same. In a further embodiment, the two groups are the same, and are a halogen (such as F or Cl).

In yet another aspect, the invention provides compounds of formula 7-3a, i.e., compounds of formula 7, wherein the C-ring is cyclohexyl substituted with 1 or 2 groups that are Cl, F, methyl, ethyl, isopropyl, methoxy, CF_3, OCF_3, OH, or $-OC(O)N(CH_3)_2$.

In still yet another aspect, the invention provides compounds of formula 7-3b, i.e., compounds of formula 7, wherein the C-ring is phenyl substituted with 1 or 2 groups that are independently -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -C(O)OR', -C(O)NR'R", -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R"; NO_2, CN, phenyl, -S(O)z phenyl, or -S(O)z (C_1-C_6 alkyl), where the phenyl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl) or -NR'R". In one embodiment, the C-ring is substituted at least at the 7-position. In another embodiment, the C-ring is substituted at least at the 8-position.

In still yet another aspect, the invention provides compounds of formula 7-3c, i.e., compounds of formula 7, wherein the C-ring is cyclohexyl substituted with 1 or 2 groups that are independently -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -C(O)OR', -C(O)NR'R", -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_4 alkyl)-C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R"; NO_2, CN, phenyl, -S(O)z phenyl, or -S(O)z (C_1-C_6 alkyl), where the phenyl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are

independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

In still another aspect, the invention provides compounds of formula 7-3d, i.e., compounds of formula 7, wherein the C-ring is phenyl substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1 or 2 groups that are independently halogen, hydroxy, -NR'R" or C_1-C_4 alkoxy. In one embodiment, the C-ring is substituted at least at the 7-position. In another embodiment, the C-ring is substituted at least at the 8-position.

In still another aspect, the invention provides compounds of formula 7-3e, i.e., compounds of formula 7, wherein the C-ring is cyclohexyl substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1 or 2 groups that are independently halogen, hydroxy, -NR'R" or C_1-C_4 alkoxy.

In still another aspect, the invention provides compounds of formula 7-3f, i.e., compounds of formula 7, wherein the C-ring is phenyl substituted with 1 or 2 groups that are independently -C(O)OH, -C(O)O-(C_1-C_6 alkyl), NO_2, CN, or phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In one embodiment, the C-ring is substituted at least at the 7-position. In another embodiment, the C-ring is substituted at least at the 8-position.

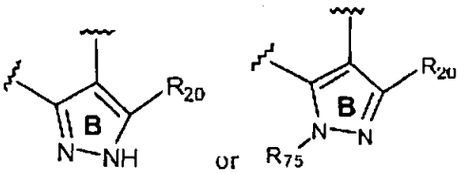
In still another aspect, the invention provides compounds of formula 7-3g, i.e., compounds of formula 7, wherein the C-ring is cyclohexyl substituted with 1 or 2 groups that are independently -C(O)OH, -C(O)O-(C_1-C_6 alkyl), NO_2, CN, or phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

In yet another aspect, the invention provides compounds of formula 7-3h, i.e., compounds of formula 7, wherein the C-ring is phenyl substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R", -NR'C(O)O-(C_1-C_6 alkyl), or -NR'C(O)O-phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as

OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In one embodiment, the C-ring is substituted at least at the 7-position. In another embodiment, the C-ring is substituted at least at the 8-position.

In yet another aspect, the invention provides compounds of formula 7-3i, i.e., compounds of formula 7, wherein the C-ring is cyclohexyl substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R", -NR'C(O)O-(C_1-C_6 alkyl) or -NR'C(O)O-phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

In another aspect, the invention provides compounds of formula 7-4, i.e., compounds of any one of formulas 7, 7-1, 7-1a, 7-2, 7-2a, 7-3, 7-3a, 7-3b, 7-3c, 7-3d, 7-3e, 7-3f, 7-3g, 7-3h, 7-3i, wherein the B-ring has the formula:



wherein R_{20} is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, -NR'R", -(C_1-C_4 alkyl)-NR'R", -$S(O)_Z$ (C_1-C_6 alkyl), hydroxyl, halogen, CN, NO_2, CH_2F, CHF_2, CF_3, -C(O)OR', -C(O)NR'R", -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", or phenyl; and R_{75} is H or C_1-C_4 alkyl (such as methyl or ethyl). In one embodiment, R_{20} is hydrogen or methyl. In another embodiment, R_{20} is hydrogen. In still another embodiment, R_{20} and R_{75} are both H.

In yet still another aspect, the invention provides compounds of formula 7-4a, i.e., compounds of formula 7-4, wherein R_4 is halogen, C_1-C_6 haloalkyl, or C_1-C_6 haloalkoxy; R_3, $R_{3'}$, R_{10} and R_{11} are independently halogen, methyl or hydrogen; and R_2 is hydrogen, C_1-C_3 alkyl, or C_3-C_6 cycloalkyl. In one embodiment, R_4 is Cl, while R_3, $R_{3'}$, R_{10} and R_{11} are H.

In yet still another aspect, the invention provides compounds of formula 7-4aa, i.e., compounds of formula 7-4a, wherein R_4 is Cl, F, CH_2F, CHF_2, CF_3, OCH_2F, $OCHF_2$, or OCF_3; R_3, $R_{3'}$, R_{10} and R_{11} are independently Cl, F, methyl or hydrogen; and R_2 is independently hydrogen, methyl, ethyl, propyl, isopropyl, or cyclopropyl. In one embodiment, R_1 is hydrogen or methyl. In another embodiment, R_1 is hydrogen.

In yet still another aspect, the invention provides compounds of formula 7-4a1, i.e., compounds of formula 7-4, wherein R_4 is halogen (in one aspect, chloro or fluoro) C_1-C_6

haloalkyl or C_1-C_6 haloalkoxy; R_3, $R_{3'}$, R_{10} and R_{11} are independently halogen, methyl or hydrogen; and R_2 is NO_2 or CN.

In yet still another aspect, the invention provides compounds of formula 7-4a2, i.e., compounds of formula 7-4, wherein R_4 is halogen (in one aspect, chloro or fluoro) C_1-C_6 haloalkyl or C_1-C_6 haloalkoxy; R_3, $R_{3'}$, R_{10} and R_{11} are independently halogen, methyl or hydrogen; and R_2 is C_2-C_6 alkenyl or C_2-C_6 alkynyl.

In yet still another aspect, the invention provides compounds of formula 7-4a3, i.e., compounds of formula 7-4, wherein R_4 is halogen (in one aspect, chloro or fluoro) C_1-C_6 haloalkyl or C_1-C_6 haloalkoxy; R_3, $R_{3'}$, R_{10} and R_{11} are independently halogen, methyl or hydrogen; and R_2 is C_1-C_4 haloalkyl. In one embodiment, R_4 is Cl, while R_3, $R_{3'}$, R_{10} and R_{11} are H.

In still another aspect, the invention provides compounds of formula 7-4a4, i.e., compounds of formula 7-4, 7-4a, 7-4a1, 7-4a2, or 7-4a3 wherein R_1 is hydrogen.

In still yet another aspect, the invention provides compounds of formula 7-4a5, i.e., compounds of formula 7-4, wherein R_1 and R_2 combined are oxo.

In still yet another aspect, the invention provides compounds of formula 7-4a6, i.e., compounds of formula 7-4, wherein R_1 and R_2 combined are =N-OR where R is hydrogen, C_1-C_6 alkyl, aryl (such as phenyl) or arylalkyl (such as benzyl or phenethyl).

In yet another aspect, the invention provides compounds of formula 7-4a7, i.e., compounds of formula 7-4, wherein R_1 and R_2 together with the carbon to which they are attached form a C_3-C_6 cycloalkyl group.

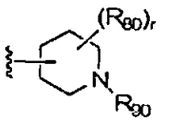
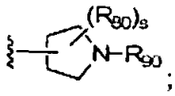
In yet another aspect, the invention provides compounds of formula 7-4a8, i.e., compounds of formula 7-4, wherein R_1 and R_2 together with the carbon to which they are attached form a cyclopropyl group.

In yet another aspect, the invention provides compounds of formula 7-4a9, i.e., compounds of formula 7-4 or 7-4a, wherein R_1 is hydrogen and R_2 is cyclopropyl. In one embodiment, the compound is racemic. In another embodiment, the compound is enantiomerically enriched.

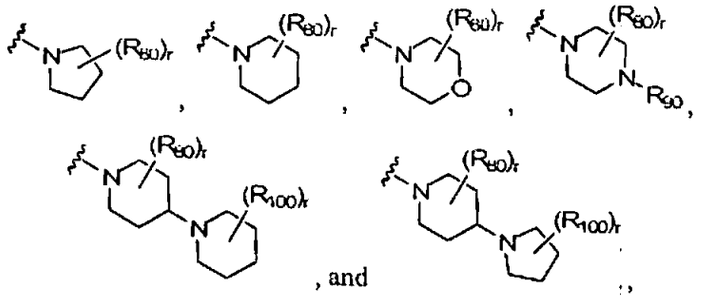
In yet another aspect, the invention provides compounds of formula 7-4a10, i.e., compounds of formula 7-4 or 7-4a, wherein R_4 is CF_3; R_1 is H; R_2 is H, or C_3-C_6 cycloalkyl; R_{20} is H or methyl; R_{75} is H or methyl; and the C-ring is phenyl substituted with two halogens.

In yet still another aspect, the invention provides compounds of formula 7-4b, i.e., compounds according to any one of formulas 7, 7-1, 7-1a, 7-2, 7-2a, 7-3, 7-3a, 7-3b, 7-3c, 7-3d, 7-3e, 7-3f, 7-3g, 7-3h, 7-3i, 7-4, wherein R_2 is -X(CO)Y or -$(C(R_3)_2)_{1-4}$X(CO)Y.

In yet still another aspect, the invention provides compounds of formula 7-4c, i.e., compounds of formula 7-4b, wherein X is O; and Y is -$NR_{60}R_{70}$ or -$N(R_{30})(CH_2)_{2-6}NR_{60}R_{70}$; where

R_{60} and R_{70} are independently selected from: hydrogen, methyl, ethyl, (C_3 –C_8)cycloalkyl, aryl-(C_1-C_6 alkyl) (such as benzyl or phenethyl), 4-pyridylmethyl,  or  ; or

R_{60} and R_{70} taken together with the nitrogen atom to which they are bound form a heterocycloalkyl group selected from:



where

each R_{80} is independently unsubstituted C_1-C_4 alkyl or C_1-C_4 alkyl substituted with hydroxyl or halogen;

each R_{90} is independently hydrogen, unsubstituted C_1-C_4 alkyl, C_1-C_4 alkyl substituted with hydroxyl or halogen, unsubstituted C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl substituted with one or more (e.g., 1-4) R_{50}groups, phenyl-(C_1-C_4 alkyl)-, pyridyl-(C_1-C_4 alkyl)-, thienyl-(C_1-C_4 alkyl), -C(O)O-(C_1-C_4 alkyl), -C(O)O-phenyl, -SO_2-(C_1-C_6 alkyl), -SO_2-phenyl, unsubstituted phenyl, phenyl substituted with one or more (e.g., 1-4) R_{50} groups, pyridyl, thienyl, pyridyl substituted with one or more (e.g., 1-4) R_{50} groups, thienyl substituted with one or more (e.g., 1-4) R_{50} groups, where

each R_{50} is independently selected from: halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -OH, -O-(C_1-C_4 alkyl), OCF_3, -CN, -$NR_{60}R_{70}$, -C(O)O-(C_1-C_4 alkyl), -$CONR_{60}R_{70}$,

-(C_1-C_6 alkyl)-$NR_{60}R_{70}$, -$NR_{60}CO$-(C_1-C_4 alkyl), -$NR_{60}CO$-phenyl, -$NR_{60}CO$-pyridyl, -$NR_{60}CO$-thienyl, and -$NR_{60}CONR_{60}R_{70}$;

each R_{100} is independently hydrogen or C_1-C_4 alkyl;

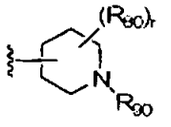
each r is 0 to 4; and

each s is 0 to 3.

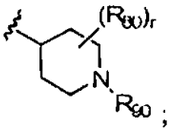
In yet still another aspect, the invention provides compounds of formula 7-4c1, i.e., compounds of formula 7-4b, wherein Y is –O-(C_1-C_6 alkyl). In one embodiment, Y is –O-(C_1-C_4 alkyl).

In yet still another aspect, the invention provides compounds of formula 7-4c2, i.e., compounds of formula 7-4b, wherein Y is –O-phenyl.

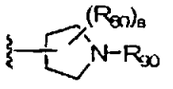
In yet still another aspect, the invention provides compounds of formula 7-4d, i.e., compounds of formula 7-4c, wherein said group



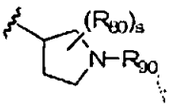
is a group of the formula:



and said group

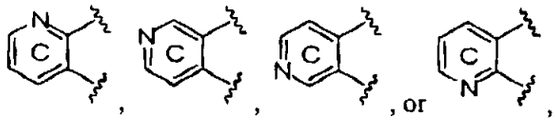


is a group of the formula:



In a further aspect, the invention provides compounds of formula 7-4d1, i.e., compounds according to any one of formulas, 7-4b, 7-4c, 7-4c1, 7-4c2, or 7-4d, wherein R_1 is H or C_1-C_4 alkyl. In one embodiment, R_1 is H or methyl. In another embodiment, R_1 is H.

In still another aspect, the invention provides compounds of formula 7-5, i.e., compounds of formulas 4, 4-1, 4-2, 4-3, 5, or any one of formulas 6, 6-1, 6-2, 6-3, 6-4, 6-5, 6-6, 6-6a, 6-6b, 6-6c, 6-6d, 6-7, 6-8, 6-9, 6-10, 6-11, 6-11a, 6-11b, 6-11c, 6-12, 6-13, 6-14, or 6-15 wherein the C-ring is

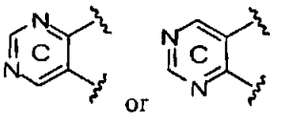


or N-oxide derivatives thereof,

each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryloxy, aryl-(C_1-C_4 alkoxy), C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", -(C_1-C_6 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -S(O)$_Z$ aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl), or -S(O)$_Z$ (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In one embodiment, the invention provides compounds of wherein the C-ring is pyridyl or pyridyl N-oxide substituted with 1 or 2 groups that are independently -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -C(O)OR', -C(O)NR'R", -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R"; NO_2, CN, phenyl, -S(O)$_Z$ aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl) or -S(O)$_Z$ (C_1-C_6 alkyl) where the aryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In an alternative embodiment, the C-ring is pyridyl or pyridyl N-oxide substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1 or 2 groups that are independently halogen, hydroxy, -NR'R" or C_1-C_4 alkoxy. In another alternative embodiment, the C-ring is pyridyl or pyridyl N-oxide substituted with 1 or 2 groups that are independently -C(O)OH, -C(O)O-(C_1-C_4 alkyl), NO_2, CN, or phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In still another

alternative embodiment, the C-ring is pyridyl or pyridyl N-oxide substituted with 1 or 2 groups that are independently C_1-C_3 alkyl, C_1-C_4 alkoxy, halogen, -C(O)NR'R", -NR'C(O)R", -OC(O)N-(C_1-C_6 alkyl)$_2$, -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF3), C_1-C_6 haloalkoxy (such as OCF3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

In still another aspect, the invention provides compounds of formula 7-5a, i.e., compounds of formulas 4, 4-1, 4-2, 4-3, 5, or any one of formulas 6, 6-1, 6-2, 6-3, 6-4, 6-5, 6-6, 6-6a, 6-6b, 6-6c, 6-6d, 6-7, 6-8, 6-9, 6-10, 6-11, 6-11a, 6-11b, 6-11c, 6-12, 6-13, 6-14, or 6-15 wherein the C-ring is

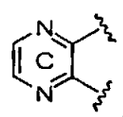


or

each of which is optionally substituted with 1 or 2, groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryloxy, aryl-(C_1-C_4 alkoxy), C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", -(C_1-C_4 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$ aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl), or -S(O)$_z$ (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2 or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In one embodiment, the invention provides compounds wherein the C-ring is pyrimidinyl substituted with 1 or 2 groups that are independently -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -C(O)OR', -C(O)NR'R", -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", NO_2, CN, phenyl, -S(O)$_z$ aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl) or -S(O)$_z$ (C_1-C_6 alkyl) where the aryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl),

or -NR'R". In an alternative, the C-ring is pyrimidinyl substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1 or 2 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_4 alkoxy. In a further alternative embodiment, the C-ring is pyrimidinyl substituted with 1 or 2 groups that are independently –COOH, -C(O)O-(C_1-C_4 alkyl), NO_2, CN, or phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In still another alternative embodiment, the C-ring is pyrimidinyl substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, -C(O)NR'R", -NR'C(O)R", -OC(O)N-(C_1-C_6 alkyl)$_2$, -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

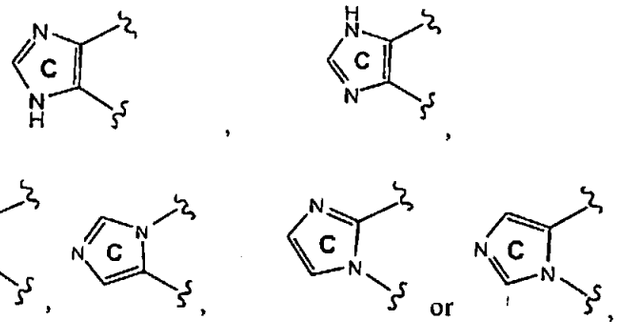
In still another aspect, the invention provides compounds of formula 7-5b, i.e., compounds of formulas 4, 4-1, 4-2, 4-3, 5, or any one of formulas 6, 6-1, 6-2, 6-3, 6-4, 6-5, 6-6, 6-6a, 6-6b, 6-6c, 6-6d, 6-7, 6-8, 6-9, 6-10, 6-11, 6-11a, 6-11b, 6-11c, 6-12, 6-13, 6-14, or 6-15, wherein the C-ring is



which is optionally substituted with 1 or 2, groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryloxy, aryl-(C_1-C_4alkoxy), C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", -(C_1-C_4 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)Ophenyl, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$ aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl), or -S(O)$_z$ (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl),

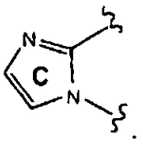
or -NR'R". In one embodiment, the invention provides compounds wherein the C-ring is pyrazine substituted with 1 or 2 groups that are independently -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -C(O)OR', -C(O)NR'R", -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", -OC(O)N(C_1-C_6 alkyl)$_2$, NO_2, CN, phenyl, -S(O)$_z$ aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl) or -S(O)$_z$ (C_1-C_6 alkyl) where the aryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In an alternative embodiment, the C-ring is pyrazine substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1 or 2 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_4 alkoxy. In another alternative aspect, the C-ring is pyrazine substituted with 1 or 2 groups that are independently -C(O)OH, -C(O)O-(C_1-C_4 alkyl), NO_2, CN, or phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In still another alternative embodiment, the C-ring is pyrazine substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, -C(O)NR'R", -NR'C(O)R", -OC(O)N(C_1-C_6 alkyl)$_2$, -NR'C(O)O-(C_1-C_6 alkyl) or -NR'C(O)O-phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

In still another aspect, the invention provides compounds of formula 7-5c, i.e., compounds of formulas 4, 4-1, 4-2, 4-3, 5, or any one of formulas 6, 6-1, 6-2, 6-3, 6-4, 6-5, 6-6, 6-6a, 6-6b, 6-6c, 6-6d, 6-7, 6-8, 6-9, 6-10, 6-11, 6-11a, 6-11b, 6-11c, 6-12, 6-13, 6-14, or 6-15 wherein the C-ring is:

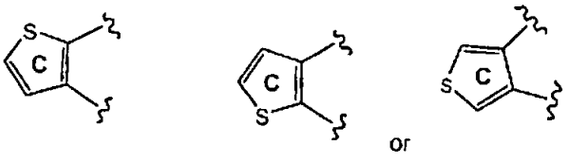


each of which is optionally substituted with 1 or 2 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryloxy, aryl-(C_1-C_4 alkoxy), C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", -(C_1-C_6 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -$S(O)_z$ aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl), or -$S(O)_z$ (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

In still another aspect, the invention provides compounds of formula 7-5c1, i.e., compounds of formula 7-5c wherein the C-ring is:



In still another aspect, the invention provides compounds of formula 7-5d, i.e., compounds of formula 4, 4-1, 4-2, 4-3, 5, or any one of formulas 6, 6-1, 6-2, 6-3, 6-4, 6-5, 6-6, 6-6a, 6-6b, 6-6c, 6-6d, 6-7, 6-8, 6-9, 6-10, 6-11, 6-11a, 6-11b, 6-11c, 6-12, 6-13, 6-14, or 6-15, wherein the C-ring is:

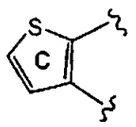


or

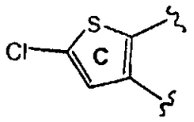
each of which is optionally substituted with 1 or 2 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryloxy, aryl-(C_1-C_4 alkoxy), C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", -(C_1-C_6 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl,

pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -$S(O)_Z$ aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl), or -$S(O)_Z$ (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

In still another aspect, the invention provides compounds of formula 7-5d1, i.e., compounds of formula 7-5d wherein the C-ring is:



In still another aspect, the invention provides compounds of formula 7-5d2, i.e., compounds of formula 7-5d wherein the C-ring is:

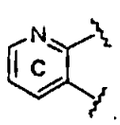


In another aspect, the invention provides compounds of formula 7-6, i.e., compounds of formula 7-5, 7-5a, 7-5b, 7-5c or 7-5d, wherein the C-ring is unsubstituted.

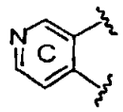
In another aspect, the invention provides compounds of formula 7-7, i.e., compounds of formula 7-5, 7-5a, 7-5b, 7-5c or 7-5d, wherein the C-ring is substituted with 1 or 2 groups that are independently Cl, F, methyl, ethyl, isopropyl, methoxy, ethoxy, CF_3, OCF_3, OH, or $C(O)CH_3$.

In yet another aspect, the invention provides compounds of formula 7-8, i.e., compounds of formula 7-5, 7-5a, 7-5b, 7-5c or 7-5d, wherein the C-ring is substituted with 1 or 2 groups that are Cl, F, or methyl.

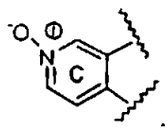
In still yet another aspect, the invention provides compounds of formula 7-9, i.e., compounds according to any one of formulas 7-5, 7-6, 7-7, or 7-8, where the C-ring has the following structure:



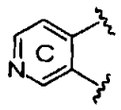
In still yet another aspect, the invention provides compounds of formula 7-10, i.e., compounds according to any one of formulas 7-5, 7-6, 7-7, or 7-8, where the C-ring has the following structure:



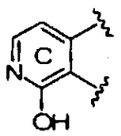
In still yet another aspect, the invention provides compounds of formula 7-10a, i.e., compounds according to any one of formulas 7-5, 7-6, 7-7, or 7-8, where the C-ring has the following structure:



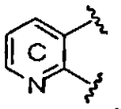
In still yet another aspect, the invention provides compounds of formula 7-11, i.e., compounds according to any one of formulas 7-5, 7-6, 7-7, or 7-8, where the C-ring has the following structure:



In still yet another aspect, the invention provides compounds of formula 7-11a, i.e., compounds according to formula 7-5, where the C-ring has the following structure:



In still yet another aspect, the invention provides compounds of formula 7-12, i.e., compounds according to any one of formulas 7-5, 7-6, 7-7, or 7-8, where the C-ring has the following structure:



In a further aspect, the invention provides compounds of formula 7-12a, i.e., compounds of formula 4, 4-1, 4-2, 4-3, 5, or any one of formulas 6, 6-1, 6-2, 6-3, 6-4, 6-5, 6-6, 6-6a, 6-6b, 6-6c, 6-6d, 6-7, 6-8, 6-9, 6-10, 6-11, 6-11a, 6-11b, 6-11c, 6-12, 6-13, 6-14, or 6-15, wherein the C-ring is thiazolyl, which is optionally substituted with 1 or 2 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryloxy, aryl-(C_1-C_4 alkoxy), C_1-C_4

haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", -(C_1-C_6 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R", -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$ aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl), or -S(O)$_z$ (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

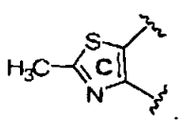
In another aspect, the invention provides compounds of formula 7-12b, i.e., compounds of formula 7-12a, wherein the thiazolyl ring is substituted with one group that is halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, or benzyl.

In still another aspect, the invention provides compounds of formula 7-12c, i.e., compounds of formula 7-12a, wherein the thiazolyl ring is substituted with C_1-C_4 alkyl.

In yet another aspect, the invention provides compounds of formula 7-12d, i.e., compounds of formula 7-12a, wherein the thiazolyl ring is substituted with C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", or -(C_1-C_6 alkyl)-NR'R".

In yet still another aspect, the invention provides compounds of formula 7-12e, i.e., compounds of formula 7-12a, wherein the thiazolyl ring is substituted with C_2-C_4 alkyl, -(C_1-C_4 alkyl)-C(O)OR', or -(C_1-C_4 alkyl)-C(O)NR'R".

In another aspect, the invention provides compounds of formula 7-12f, i.e., compounds of formula 7-12a, wherein the thiazolyl ring is:



In yet still another aspect, the invention provides compounds of formula 7-13, i.e., compounds according to any one of formulas 7-5, 7-5a, 7-5b, 7-5c, 7-5c1, 7-5d, 7-5d1, 7-5d2, 7-6, 7-7, 7-8, 7-9, 7-10, 7-10a, 7-11, 7-11a, 7-12, 7-12a, 7-12b, 7-12c, 7-12d, 7-12e, or 7-12f, wherein R_2 is -X(CO)Y or -($C(R_3)_2$)$_{1-4}$X(CO)Y.

In still another aspect, the invention provides compounds of formula 7-13a, i.e., compounds according to any one of formulas 7-5, 7-5a, 7-5b, 7-5c, 7-5c1, 7-5d, 7-5d1, 7-5d2, 7-6, 7-7, 7-8, 7-9, 7-10, 7-10a, 7-11, 7-11a, 7-12, 7-12a, 7-12b, 7-12c, 7-12d, 7-12e, or 7-12f, wherein R_2 is hydrogen, C_1-C_3 alkyl or C_3-C_6 cycloalkyl.

In still another aspect, the invention provides compounds of formula 7-13b, i.e., compounds according to any one of formulas 7-5, 7-5a, 7-5b, 7-5c, 7-5c1, 7-5d, 7-5d1, 7-5d2, 7-6, 7-7, 7-8, 7-9, 7-10, 7-10a, 7-11, 7-11a, 7-12, 7-12a, 7-12b, 7-12c, 7-12d, 7-12e, or 7-12f, wherein R_2 is NO_2 or CN.

In still another aspect, the invention provides compounds of formula 7-13c, i.e., compounds according to any one of formulas 7-5, 7-5a, 7-5b, 7-5c, 7-5c1, 7-5d, 7-5d1, 7-5d2, 7-6, 7-7, 7-8, 7-9, 7-10, 7-10a, 7-11, 7-11a, 7-12, 7-12a, 7-12b, 7-12c, 7-12d, 7-12e, or 7-12f, wherein R_2 is C_2-C_6 alkenyl or C_2-C_6 alkynyl.

In still another aspect, the invention provides compounds of formula 7-13d, i.e., compounds according to any one of formulas 7-5, 7-5a, 7-5b, 7-5c, 7-5c1, 7-5d, 7-5d1, 7-5d2, 7-6, 7-7, 7-8, 7-9, 7-10, 7-10a, 7-11, 7-11a, 7-12, 7-12a, 7-12b, 7-12c, 7-12d, 7-12e, or 7-12f, wherein R_2 is C_1-C_4 haloalkyl.

In still another aspect, the invention provides compounds of formula 7-13e, i.e., compounds according to any one of formulas 7-5, 7-5a, 7-5b, 7-5c, 7-5c1, 7-5d, 7-5d1, 7-5d2, 7-6, 7-7, 7-8, 7-9, 7-10, 7-10a, 7-11, 7-11a, 7-12, 7-12a, 7-12b, 7-12c, 7-12d, 7-12e, 7-12f, 7-13, 7-13a, 7-13b, 7-13c, or 7-13d, wherein R_1 is hydrogen.

In still yet another aspect, the invention provides compounds of formula 7-13f, i.e., compounds according to any one of formulas 7-5, 7-5a, 7-5b, 7-5c, 7-5c1, 7-5d, 7-5d1, 7-5d2, 7-6, 7-7, 7-8, 7-9, 7-10, 7-10a, 7-11, 7-11a, 7-12, 7-12a, 7-12b, 7-12c, 7-12d, 7-12e, or 7-12f, wherein R_1 and R_2 combined are oxo.

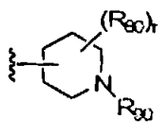
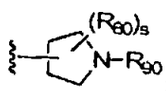
In still yet another aspect, the invention provides compounds of formula 7-13g, i.e., compounds according to any one of formulas 7-5, 7-5a, 7-5b, 7-5c, 7-5c1, 7-5d, 7-5d1, 7-5d2, 7-6, 7-7, 7-8, 7-9, 7-10, 7-10a, 7-11, 7-11a, 7-12, 7-12a, 7-12b, 7-12c, 7-12d, 7-12e, or 7-12f, wherein R_1 and R_2 combined are =N-OR, where R is hydrogen, C_1-C_6 alkyl, aryl (such as phenyl) or arylalkyl (such as benzyl or phenethyl).

In yet another aspect, the invention provides compounds of formula 7-13h, i.e., compounds according to any one of formulas 7-5, 7-5a, 7-5b, 7-5c, 7-5c1, 7-5d, 7-5d1, 7-5d2, 7-6, 7-7, 7-8, 7-9, 7-10, 7-10a, 7-11, 7-11a, 7-12, 7-12a, 7-12b, 7-12c, 7-12d, 7-12e, or 7-12f, wherein R_1 and R_2 together with the carbon to which they are attached form a C_3-C_6 cycloalkyl group.

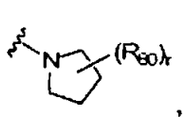
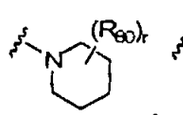
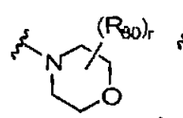
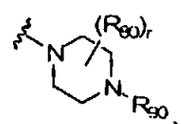
In yet another aspect, the invention provides compounds of formula 7-13i, i.e., compounds according to any one of formulas 7-5, 7-5a, 7-5b, 7-5c, 7-5c1, 7-5d, 7-5d1, 7-5d2, 7-6, 7-7, 7-8, 7-9, 7-10, 7-10a, 7-11, 7-11a, 7-12, 7-12a, 7-12b, 7-12c, 7-12d, 7-12e, or 7-12f, wherein R_1 and R_2 together with the carbon to which they are attached form a cyclopropyl group.

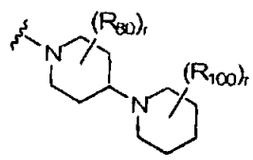
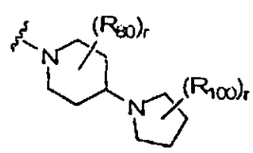
In yet another aspect, the invention provides compounds of formula 7-13j, i.e., compounds according to any one of formulas 7-5, 7-5a, 7-5b, 7-5c, 7-5c1, 7-5d, 7-5d1, 7-5d2, 7-6, 7-7, 7-8, 7-9, 7-10, 7-10a, 7-11, 7-11a, 7-12, 7-12a, 7-12b, 7-12c, 7-12d, 7-12e, or 7-12f, wherein R_1 is hydrogen and R_2 is cyclopropyl. In one embodiment, the compound is racemic. In another embodiment, the compound is enantiomerically enriched.

In yet still another aspect, the invention provides compounds of formula 7-14, i.e., compounds of formula 7-13, wherein,

X is O; and Y is $-NR_{60}R_{70}$ or $-N(R_{30})(CH_2)_{2\text{-}6}NR_{60}R_{70}$; where R_{60} and R_{70} are independently selected from: hydrogen, methyl, ethyl, -(C_3 –C_8)cycloalkyl, aryl-(C_1-C_6 alkyl) (such as benzyl or phenethyl), 4-pyridylmethyl,  or  ; or

R_{60} and R_{70} taken together with the nitrogen atom to which they are bound form a heterocycloalkyl group selected from

 ,  ,  ,  ,

 , and  ,

where

each R_{80} is independently unsubstituted C_1-C_4 alkyl or C_1-C_4 alkyl substituted with hydroxyl or halogen;

each R_{90} is independently hydrogen, unsubstituted C_1-C_4 alkyl, C_1-C_4 alkyl substituted with hydroxyl or halogen, unsubstituted C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl substituted with one or more (e.g., 1-4) R_{50} groups, phenyl-(C_1-C_4 alkyl), pyridyl-(C_1-C_4 alkyl), thienyl-(C_1-C_4 alkyl), -C(O)O-(C_1-C_4 alkyl), -C(O)O-phenyl, $-SO_2$-(C_1-C_6alkyl), $-SO_2$-phenyl, unsubstituted phenyl, phenyl

substituted with one or more (e.g., 1-4) R_{50} groups, pyridyl, thienyl, pyridyl substituted with one or more (e.g., 1-4) R_{50} groups, thienyl substituted with one or more (e.g., 1-4) R_{50} groups, where

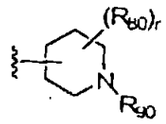
each R_{50} is independently selected from: halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -OH, -O (C_1-C_4 alkyl), OCF_3, -CN, -$NR_{60}R_{70}$, -C(O)O-(C_1-C_4 alkyl), -$CONR_{60}R_{70}$, -(C_1-C_6alkyl)-$NR_{60}R_{70}$, -$NR_{60}CO$-(C_1-C_4 alkyl), -$NR_{60}CO$-phenyl, -$NR_{60}CO$-pyridyl, -$NR_{60}CO$-thienyl, and -$NR_{60}CONR_{60}R_{70}$,

each R_{100} is independently hydrogen or C_1-C_4 alkyl;

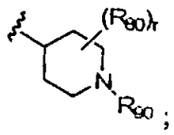
each r is 0 to 4; and

each s is 0 to 3.

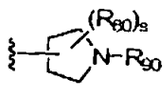
In yet still another aspect, the invention provides compounds of formula 7-15, i.e., compounds of formula 7-14, wherein said group



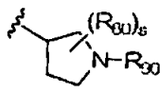
is a group of the formula:



and said group



is a group of the formula:



In yet still another aspect, the invention provides compounds of formula 7-16, i.e., compounds of formula 7-13, wherein Y is –O-(C_1-C_6 alkyl). In one embodiment, Y is –O-(C_1-C_4 alkyl).

In yet still another aspect, the invention provides compounds of formula 7-17, i.e., compounds of formula 7-13, wherein Y is –O-phenyl.

In a further aspect, the invention provides compounds of formula 7-18, i.e., compounds according to any one of formulas, 7-14, 7-15, 7-16, or 7-17, wherein R_1 is H or C_1-C_4 alkyl. In one embodiment, R_1 is H or methyl. In another embodiment, R_1 is H.

In still yet another aspect, the invention provides compounds of formula 8, i.e., compounds according to formula 6 or any one of formulas 7, 7-1, 7-1a, 7-2, 7-2a, 7-3, 7-3a, 7-3b, 7-3c, 7-3d, 7-3e, 7-3f, 7-3g, 7-3h, 7-3i, 7-4, 7-4a, 7-4aa, 7-4a1, 7-4a2, 7-4a3, 7-4a4, 7-4a5, 7-4a6, 7-4a7, 7-4a8, 7-4a9, 7-4a10, 7-4b, 7-4c, 7-4c1, 7-4c2, 7-4d, 7-4d1, 7-5, 7-5a, 7-5b, 7-5c, 7-5c1, 7-5d, 7-5d1, 7-5d2, 7-6, 7-7, 7-8, 7-9, 7-10, 7-10a, 7-11, 7-11a, 7-12, 7-12a, 7-12b, 7-12c, 7-12d, 7-12e, 7-12f, 7-13, 7-13a, 7-13b, 7-13c, 7-13d, 7-13e, 7-13f, 7-13g, 7-13h, 7-13i, 7-13j, 7-14, 7-15, 7-16, 7-17, or 7-18 wherein

R_3 and R_3' are hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, CF_3, CN;

R_4 is hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, CN, $-SO_2$-(C_1-C_6 alkyl), or -NR'R",

R_{10} and R_{11} are independently hydrogen, or methyl.

In still yet another aspect, the invention provides compounds of formula 8-1, i.e., compounds of formula 8, wherein R_3 and R_3' are independently hydrogen, halogen, or methyl.

In still yet another aspect, the invention provides compounds of formula 8-2, i.e., compounds of formula 8, wherein R_4 is hydrogen, F, Cl, C_1-C_6 alkoxy, CH_2F, CHF_2, CF_3, OCF_3, $OCHF_2$, OCH_2F, or CN.

In still yet another aspect, the invention provides compounds of formula 8-3, i.e., compounds of formula 8 wherein R_4 is, $-SO_2$-(C_1-C_6 alkyl), or -NR'R".

In still yet another aspect, the invention provides compounds of formula 8-4, i.e., compounds according to any one of formulas 8, 8-1, 8-2,or 8-3, wherein R_3, R_3' R_{10} and R_{11} are hydrogen.

In still yet another aspect, the invention provides compounds of formula 8-5, i.e., compounds of formula 8, 8-1, 8-2, or 8-4, wherein R_4 is CF_3.

In still yet another aspect, the invention provides compounds of formula 8-6, i.e., compounds of formula 8, 8-1, 8-2, or 8-4, wherein R_4 is chloro. In one embodiment, R_4 is Cl, while R_3, R_3', R_{10} and R_{11} are H.

In still yet another aspect, the invention provides compounds of formula 8-7, i.e., compounds of formula 8, 8-1, 8-2, or 8-4, wherein R_4 is fluoro.

In still yet another aspect, the invention provides compounds of formula 8-8, i.e., compounds of formula 8, 8-1, 8-2, or 8-4, wherein R_4 is OCF_3.

In still another aspect, the invention provides compounds of formula 8-9, i.e., compounds of formula 8-5. 8-6, 8-7 or 8-8, wherein the B-ring is a pyrazolyl ring, the C ring is a phenyl ring optionally substituted with halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, haloalkyl, haloalkoxy, OH or $OC(O)N(C_1$-C_6 alkyl$)_2$; R_1 is hydrogen or C_1-C_6 alkyl, and R_2 is hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or haloalkyl. In one embodiment, the C-ring is substituted at least at the 7-position. In another embodiment, the C-ring is substituted at least at the 8-position. In still another embodiment, the C-ring is substituted at the 7- and 8-positions.

In still another aspect, the invention provides compounds of formula 8-10, i.e. compounds of formula 8-5, 8-6, 8-7, or 8-8, wherein the B-ring is a pyrazolyl ring, the C ring is a phenyl ring optionally substituted with one or more groups that are independently halogen (such as F or Cl), C_1-C_6 alkyl, C_1-C_6 alkoxy, haloalkyl (such as CF_3), haloalkoxy (such as OCF_3), OH or $OC(O)N(C_1$-C_6 alkyl$)_2$; and R_1 and R_2 together form a cycloalkyl, oxo or C=N-OR group where R is hydrogen, alkyl or phenyl. In one embodiment, the C-ring is substituted at least at the 7-position. In another embodiment, the C-ring is substituted at least at the 8-position. In still another embodiment, the C-ring is substituted at both the 7- and 8-positions.

In still another aspect, the invention provides compounds of formula 8-11, i.e. compounds of formula 8-5. 8-6, 8-7 or 8-8, wherein the B-ring is a pyrazolyl ring, the C-ring is a pyridyl ring or an N-oxide-pyridyl ring optionally substituted with halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, haloalkyl, haloalkoxy, OH or $OC(O)N(C_1$-C_6 alkyl$)_2$; R_1 is hydrogen or C_1-C_6 alkyl, and R_2 is hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or haloalkyl.

In still another aspect, the invention provides compounds of formula 8-11a, i.e. compounds of formula 8-11, where the B-ring and the C-ring together with the piperidine ring form an optionally substituted 4,5-dihydro-2H-pyrazolo[4,3-c][1,7]naphthyridine.

In still another aspect, the invention provides compounds of formula 8-11b, i.e. compounds of formula 8-11, where the B-ring and the C-ring together with the piperidine ring form an optionally substituted 4,5-dihydro-2H-pyrazolo[4,3-c][1,7]naphthyridine 7-oxide.

In still another aspect, the invention provides compounds of formula 8-11c, i.e. compounds of formula 8-11, where the B-ring and the C-ring together with the piperidine ring form an optionally substituted 4,5-dihydro-2H-pyrazolo[4,3-c][1,8]naphthyridine.

In still another aspect, the invention provides compounds of formula 8-11d, i.e. compounds of formula 8-11, where the B-ring and the C-ring together with the piperidine

ring form an optionally substituted 4,5-dihydro-2H-pyrazolo[4,3-c][1,8]naphthyridine 8-oxide.

In still another aspect, the invention provides compounds of formula 8-11c, i.e. compounds of any of the formula 8-12, 8-12a, 8-12b, 8-12c, 8-12d, where R_1 is H and R_2 is cycloalkyl. In one embodiment, R_2 is cyclopropyl, cyclopentyl, or cyclohexyl. In still another embodiment, R_2 is cyclopropyl. In another embodiment, the compound is racemic. In yet another embodiment, the compound is enantiomerically enriched.

In still another aspect, the invention provides compounds of formula 8-12, i.e. compounds of formula 8-5. 8-6, 8-7 or 8-8, wherein the B-ring is a pyrazolyl ring, the C-ring is a pyridyl ring or an N-oxide-pyridyl ring optionally substituted with halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, haloalkyl, haloalkoxy, OH or $OC(O)N(C_1$-C_6 alkyl$)_2$; and R_1 and R_2 together form a cycloalkyl, oxo or C=N-OR group where R is hydrogen, alkyl or phenyl.

In still another aspect, the invention provides compounds of formula 8-12a, i.e. compounds of formula 8-12, where the B-ring and the C-ring together with the piperidine ring form an optionally substituted 4,5-dihydro-2H-pyrazolo[4,3-c][1,7]naphthyridine.

In still another aspect, the invention provides compounds of formula 8-12b, i.e. compounds of formula 8-12, where the B-ring and the C-ring together with the piperidine ring form an optionally substituted 4,5-dihydro-2H-pyrazolo[4,3-c][1,7]naphthyridine 7-oxide.

In still another aspect, the invention provides compounds of formula 8-12c, i.e. compounds of formula 8-12, where the B-ring and the C-ring together with the piperidine ring form an optionally substituted 4,5-dihydro-2H-pyrazolo[4,3-c][1,8]naphthyridine.

In still another aspect, the invention provides compounds of formula 8-12d, i.e. compounds of formula 8-12, where the B-ring and the C-ring together with the piperidine ring form an optionally substituted 4,5-dihydro-2H-pyrazolo[4,3-c][1,8]naphthyridine 8-oxide.

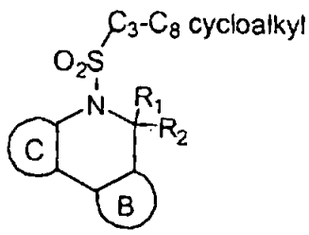
In still another aspect, the invention provides compounds of formula 8-13, i.e. compounds of any of the formula 8-12, 8-12a, 8-12b, 8-12c, 8-12d, where R_1 and R_2 together form a C_3-C_6 cycloalkyl ring.

In still another aspect, the invention provides compounds of formula 8-14, i.e. compounds of any of the formula 8-12, 8-12a, 8-12b, 8-12c, 8-12d, where R_1 and R_2 together are oxo.

In another aspect, the invention provides compounds of formula 9, i.e., compounds of formula I, wherein the A-ring is C_3-C_8 cycloalkyl, which is optionally substituted at a substitutable position with halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, hydroxyl, hydroxy-(C_1-C_4 alkyl), CN, NO_2, aryloxy (such as phenyloxy), aryl-(C_1-C_4alkoxy) (such as benzyloxy), -SO_2-(C_1-C_6 alkyl), -NR'R", C_1-C_6 alkanoyl, -C(O)OR', -(C_1-C_4 alkyl)-C(O)OR', pyridyl, phenyl, phenyl-(C_1-C_4 alkyl), -SO_2-NR'R", -C(O)NR'R", -OC(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", -NR'C(O)O-(C_1-C_6 alkyl), or NR'C(O)O-phenyl where each R' and R" is independently hydrogen or C_1-C_6 alkyl; and

the B-ring is pyrazolyl, imidazolyl, pyrrolyl, triazolyl, pyrrolidinyl, pyrazolidinyl, or imidazolidinyl, each of which is optionally substituted at a substitutable position with a group that is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, -NR'R", -SO_2-NR'R", -C(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, NO_2, CN, -C(O)OR', hydroxyl, hydroxy-(C_1-C_6 alkyl), -S(O)z (C_1-C_6 alkyl), -S(O)z aryl, halogen, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, benzyl or phenyl.

In still another aspect, the invention provides compounds of formula 10, i.e., compounds of formula 9 having the following formula:



Formula 10

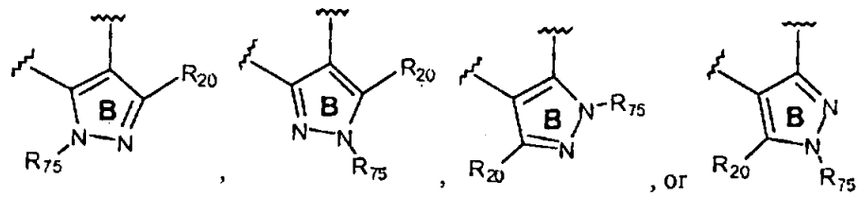
stereoisomers, tautomers, mixtures of stereoisomers and/or tautomers or pharmaceutically acceptable salts thereof, wherein

the cycloalkyl group is optionally substituted at a substitutable position with halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, hydroxyl, CN, NO_2, aryloxy, aryl-(C_1-C_4alkoxy), -SO_2-(C_1-C_6 alkyl), -NR'R", C_1-C_6 alkanoyl, -C(O)OR', -(C_1-C_4alkyl)-C(O)OR', pyridyl, phenyl, phenyl-(C_1-C_4 alkyl), -SO_2-NR'R", -C(O)NR'R", -OC(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", or -NR'C(O)OR', where each R' and R" is independently hydrogen or C_1-C_6 alkyl; and

the C-ring is cyclohexyl, phenyl, thienyl, imidazolinyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrrolyl, pyrazolyl, pyrimidyl, pyrazinyl or pyridyl, each of which is optionally substituted at each substitutable position with groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, aryloxy, aryl-(C_1-C_6 alkoxy), C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, hydroxyl, hydroxy-(C_1-C_6 alkyl), -NR'R", -(C_1-C_4 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, oxo, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -S(O)z aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl),or -S(O)z (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2 or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, CF_3, OCF_3, hydroxy, hydroxy-(C_1-C_4 alkyl), or -NR'R".

In still another aspect, the invention provides compounds of formula 10-1, i.e., compounds of formula 10, wherein the B-ring is pyrazolyl, imidazolyl, pyrrolyl, triazolyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, pyridyl, pyrimidyl, or isoxazolyl, each of which is unsubstituted.

In still another aspect, the invention provides compounds of formula 10-2, i.e., compounds of formula 10, wherein the B-ring has the formula:



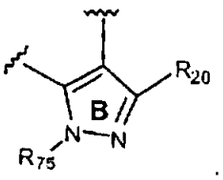
wherein

R_{20} is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, -NR'R", -(C_1-C_4 alkyl)-NR'R", -S(O)z (C_1-C_6 alkyl), hydroxyl, halogen, CN, NO_2, CH_2F, CHF_2, CF_3, -C(O)OR', -C(O)NR'R", -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", or phenyl, and

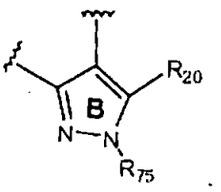
R_{75} is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl-(C_1-C_6 alkanoyl), -C(O)NR'R", -S(O)2(C_1-C_6 alkyl), -$S(O)_2$-aryl, -SO_2NR'R", phenyl, phenyl C_1-C_6 alkyl (preferably phenethyl or benzyl, more preferably, benzyl), phenylcarbonyl, benzylcarbonyl, or

heteroarylcarbonyl, where the heteroaryl group is pyridyl, pyrimidyl, thienyl or furanyl.

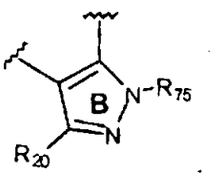
In still another aspect, the invention provides compounds of formula 10-3, i.e., compounds of formula 10-2, wherein the B-ring has the formula:



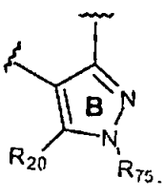
In still another aspect, the invention provides compounds of formula 10-4, i.e., compounds of formula 10-2, wherein the B-ring has the formula:



In still another aspect, the invention provides compounds of formula 10-5, i.e., compounds of formula 10-2, wherein the B-ring has the formula:



In still another aspect, the invention provides compounds of formula 10-6, i.e., compounds of formula 10-2, wherein the B-ring has the formula:



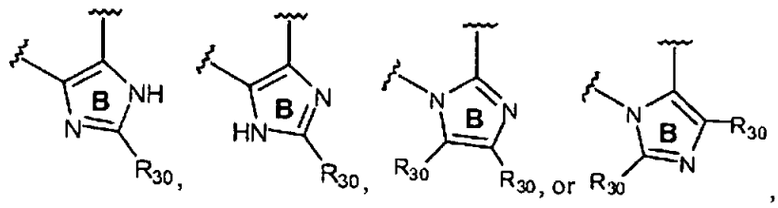
In a further aspect, the invention provides compounds of formula 10-6a, i.e., compounds according to any one of formulas 10-2, 10-3, 10-4, 10-5, or 10-6, wherein R_{20} is hydrogen, C_1-C_4 alkyl, CH_2F, CHF_2, CF_3, -C(O)OR', -$S(O)_Z$ (C_1-C_4 alkyl), or hydroxyl; and R_{75} is hydrogen, C_1-C_4 alkyl, or -$S(O)_Z$ –phenyl.

In another aspect, the invention provides compounds of formula 10-6b, i.e., compounds of formula 10-6a, wherein R_{20} is hydrogen or methyl, and R_{75} is hydrogen or methyl.

In yet another aspect, the invention provides compounds of formula 10-6c, i.e., compounds of formula 10-6a, wherein R_{20} is hydrogen or methyl, and R_{75} is hydrogen.

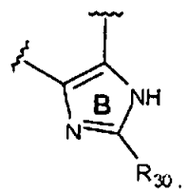
In still yet another aspect, the invention provides compounds of formula 10-6d, i.e., compounds of formula 10-6a, wherein R_{20} is hydrogen and R_{75} is hydrogen.

In still another aspect, the invention provides compounds of formula 10-7, i.e., compounds of formula 10, wherein the B-ring has the formula:

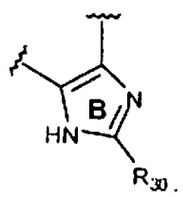


wherein R_{30} is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -NR'R", C_1-C_4 alkythio, hydroxyl, halogen, CH_2F, CHF_2, CF_3, or phenyl.

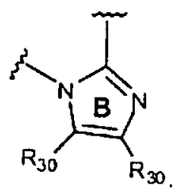
In still another aspect, the invention provides compounds of formula 10-8, i.e., compounds of formula 10-7, wherein the B-ring has the formula:



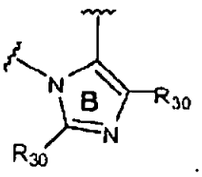
In still another aspect, the invention provides compounds of formula 10-9, i.e., compounds of formula 10-7, wherein the B-ring has the formula:



In still another aspect, the invention provides compounds of formula 10-10, i.e., compounds of formula 10-7, wherein the B-ring has the formula:



In still another aspect, the invention provides compounds of formula 10-11, i.e., compounds of formula 10-7, wherein the B-ring has the formula:

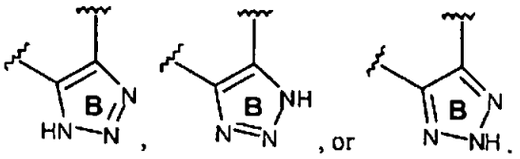


In a further aspect, the invention provides compounds of formula 10-11a, i.e., compounds according to any one of formulas 10-8, 10-9, 10-10, or 10-11, wherein each R_{30} is independently hydrogen, C_1-C_4 alkyl, CH_2F, CHF_2, or CF_3.

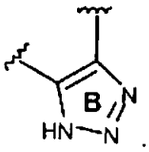
In another aspect, the invention provides compounds of formula 10-11b, i.e., compounds of formula 10-11a, wherein each R_{30} is independently hydrogen or methyl.

In still another aspect, the invention provides compounds of formula 10-11c, i.e., compounds of formula 10-11a, wherein each R_{30} is hydrogen.

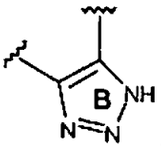
In still another aspect, the invention provides compounds of formula 10-12, i.e., compounds of formula 10, wherein the B-ring has the formula:



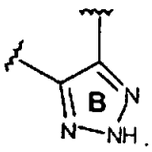
In still another aspect, the invention provides compounds of formula 10-13, i.e., compounds of formula 10-12, wherein the B-ring has the formula:



In still another aspect, the invention provides compounds of formula 10-14, i.e., compounds of formula 10-12, wherein the B-ring has the formula:



In still another aspect, the invention provides compounds of formula 10-15, i.e., compounds of formula 10-12, wherein the B-ring has the formula:



In yet another aspect, the invention provides compounds of formula 11, i.e., compounds of formula 9 or any one of formulas 10, 10-1, 10-2, 10-3, 10-4, 10-5, 10-6, 10-6a, 10-6b, 10-6c, 10-6d, 10-7, 10-8, 10-9, 10-10, 10-11, 10-11a, 10-11b, 10-11c, 10-12, 10-13, 10-14, or 10-15 wherein the C-ring is phenyl or cyclohexyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryloxy, aryl-(C_1-C_6 alkoxy), C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", -(C_1-C_4 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, oxo, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -S(O)z aryl, or -S(O)z (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1 or 2 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In one embodiment, the C-ring is an optionally substituted phenyl.

In yet another aspect, the invention provides compounds of formula 11-1, i.e., compounds of formula 11 wherein the C-ring is unsubstituted phenyl.

In yet another aspect, the invention provides compounds of formula 11-1a, i.e., compounds of formula 11 wherein the C-ring is unsubstituted cyclohexyl.

In yet another aspect, the invention provides compounds of formula 11-2, i.e., compounds of formula 11, wherein the C-ring is phenyl substituted with 1 or 2 groups that are independently Cl, F, methyl, ethyl, isopropyl, methoxy, ethoxy, CF_3, OCF_3, OH, CH_2OH, NH_2, $NH(CH_3)$, $N(CH_3)_2$ or -$OC(O)N(CH_3)_2$. In one embodiment, the C-ring is bis-substituted with at least one halogen. In another embodiment, the halogen is F. In still another embodiment, the halogen is Cl. In another embodiment, the C-ring is bis-substituted with two halogens, which are the same or different. In still another embodiment, the C-ring is substituted at least at position 7. In another embodiment, the C-ring is substituted at positions 7 and 8. In another embodiment, the C-ring is monosubstituted with a halogen. In another embodiment, the halogen is F. In still another embodiment, the halogen is Cl. In still another embodiment, the C-ring is substituted at position 7. In yet another embodiment, the C-ring is substituted at position 8.

In still yet another aspect, the invention provides compounds of formula 11-2a, i.e., compounds of formula 11, wherein the C-ring is phenyl substituted with 1 or 2 groups that are independently -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, phenyl, -S(O)z phenyl, or -S(O)z (C_1-C_6 alkyl), where the phenyl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In one embodiment, the C-ring is substituted at least at the 7-position. In another embodiment, the C-ring is substituted at least at the 8-position.

In still another aspect, the invention provides compounds of formula 11-2b, i.e., compounds of formula 11, wherein the C-ring is phenyl substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1 or 2 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_4 alkoxy. In one embodiment, the C-ring is substituted at least at the 7-position. In another embodiment, the C-ring is substituted at least at the 8-position.

In still another aspect, the invention provides compounds of formula 11-2c, i.e., compounds of formula 11, wherein the C-ring is phenyl substituted with 1 or 2 groups that are independently –C(O)OH, -C(O)O-(C_1-C_4 alkyl), NO_2, CN, or phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In one embodiment, the C-ring is substituted at least at the 7-position. In another embodiment, the C-ring is substituted at least at the 8-position.

In yet another aspect, the invention provides compounds of formula 11-2d, i.e., compounds of formula 11, wherein the C-ring is phenyl substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R", -NR'C(O)O-(C_1-C_6 alkyl), or -NR'C(O)O-phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In one embodiment, the C-ring is substituted at least at the 7-position. In another embodiment, the C-ring is substituted at least at the 8-position.

In yet another aspect, the invention provides compounds of formula 11-2e, i.e., compounds of formula 11, wherein the C-ring is cyclohexyl substituted with 1 or 2 groups that are independently Cl, F, methyl, ethyl, isopropyl, methoxy, ethoxy, CF_3, OCF_3, OH, CH_2OH, NH_2, $NH(CH_3)$, $N(CH_3)_2$, or $-OC(O)N(CH_3)_2$.

In still yet another aspect, the invention provides compounds of formula 11-2f, i.e., compounds of formula 11, wherein the C-ring is cyclohexyl substituted with 1 or 2 groups that are independently -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_4 alkyl)-C(O)OR', -(C_1-C_4 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, phenyl, -S(O)z phenyl, or -S(O)z (C_1-C_6 alkyl), where the phenyl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

In still another aspect, the invention provides compounds of formula 11-2g, i.e., compounds of formula 11, wherein the C-ring cyclohexyl substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1 or 2 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_4 alkoxy.

In still another aspect, the invention provides compounds of formula 11-2h, i.e., compounds of formula 11, wherein the C-ring is cyclohexyl substituted with 1 or 2 groups that are independently -C(O)OH, -C(O)O-(C_1-C_4 alkyl), NO_2, CN, or phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

In yet another aspect, the invention provides compounds of formula 11-2i, i.e., compounds of formula 11, wherein the C-ring is cyclohexyl substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R", -NR'C(O)O-(C_1-C_6 alkyl) or -NR'C(O)O-phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

In yet another aspect, the invention provides compounds of formula 11-3, i.e., compounds of formula 11, wherein the C-ring is phenyl or cyclohexyl substituted with 1 or 2 groups that are Cl, F, methyl, ethyl, isopropyl, methoxy, CF_3, OCF_3, OH, NH_2, $NH(CH_3)$, $N(CH_3)_2$ or $-OC(O)N(CH_3)_2$.

In yet still another aspect, the invention provides compounds of formula 11-3a, i.e., compounds according to any one of formulas 11, 11-1, 11-2, or 11-3, wherein R_2 is -X(CO)Y or $-(C(R_3)_2)_{1-4}X(CO)Y$.

In yet still another aspect, the invention provides compounds of formula 11-3a1, i.e., compounds according to any one of formulas 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-2e, 11-2f, 11-2g, 11-2h, 11-2i, or 11-3, wherein R_2 is hydrogen, C_1-C_3 alkyl or C_3-C_6-cycloalkyl.

In yet still another aspect, the invention provides compounds of formula 11-3a2, i.e., compounds according to any one of formulas 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-2e, 11-2f, 11-2g, 11-2h, 11-2i,or 11-3, wherein R_2 is NO_2 or CN.

In yet still another aspect, the invention provides compounds of formula 11-3a3, i.e., compounds according to any one of formulas 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-2e, 11-2f, 11-2g, 11-2h, 11-2i, or 11-3, wherein R_2 is C_2-C_6 alkenyl or C_2-C_6 alkynyl.

In yet still another aspect, the invention provides compounds of formula 11-3a4, i.e., compounds according to any one of formulas 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-2e, 11-2f, 11-2g, 11-2h, 11-2i, or 11-3, wherein R_2 is C_1-C_4 haloalkyl.

In still another aspect, the invention provides compounds of formula 11-3a5, i.e., compounds according to any one of formulas 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-2e, 11-2f, 11-2g, 11-2h, 11-2i, 11-3, 11-3a, 11-3a1, 11-3a2, 11-3a3, or 11-3a4, wherein R_1 is hydrogen.

In still yet another aspect, the invention provides compounds of formula 11-3a6, i.e., compounds according to any one of formulas 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-2e, 11-2f, 11-2g, 11-2h, 11-2i, or 11-3, wherein R_1 and R_2 combined are oxo.

In still yet another aspect, the invention provides compounds of formula 11-3a7, i.e., compounds according to any one of formulas 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-2e, 11-2f, 11-2g, 11-2h, 11-2i, or 11-3, wherein R_1 and R_2 combined are =N-OR, where R is hydrogen, C_1-C_6 alkyl, aryl (such as phenyl) or arylalkyl (such as benzyl or phenethyl).

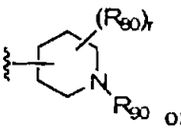
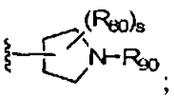
In yet another aspect, the invention provides compounds of formula 11-3a8, i.e., compounds according to any one of formulas 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-2c, 11-2f, 11-2g, 11-2h, 11-2i, or 11-3, wherein R_1 and R_2 together with the carbon to which they are attached form a C_3-C_6 cycloalkyl group.

In yet another aspect, the invention provides compounds of formula 11-3a9, i.e., compounds according to any one of formulas 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-

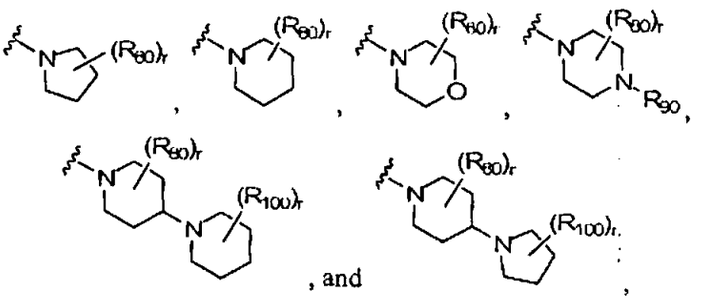
2d, 11-2e, 11-2f, 11-2g, 11-2h, 11-2i, or 11-3, wherein R_1 and R_2 together with the carbon to which they are attached form a cyclopropyl group.

In yet another aspect, the invention provides compounds of formula 11-3a10, i.e., compounds according to any one of formulas 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-2e, 11-2f, 11-2g, 11-2h, 11-2i, or 11-3, wherein R_1 is hydrogen and R_2 is cyclopropyl. In one embodiment, the compound is racemic. In another embodiment, the compound is enantiomerically enriched.

In yet still another aspect, the invention provides compounds of formula 11-3b, i.e., compounds of formula 11-3a, wherein,

X is O; and Y is $-NR_{60}R_{70}$ or $-N(R_{30})(CH_2)_{2\text{-}6}NR_{60}R_{70}$; where R_{60} and R_{70} are independently selected from: hydrogen, methyl, ethyl, (C_3 –C_8)cycloalkyl, aryl-(C_1-C_6alkyl) (such as benzyl or phenethyl), 4-pyridylmethyl,  or  ; or

R_{60} and R_{70} taken together with the nitrogen atom to which they are bound form a heterocycloalkyl group selected from



, and ,

where

each R_{80} is independently unsubstituted C_1-C_4 alkyl or C_1-C_4 alkyl substituted with hydroxy or halogen;

each R_{90} is independently hydrogen, unsubstituted C_1-C_4 alkyl, C_1-C_4 alkyl substituted with hydroxy or halogen, unsubstituted C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl substituted with one or more (e.g., 1-4) R_{50} groups, phenyl-(C_1-C_4 alkyl), pyridyl-(C_1-C_4 alkyl), thienyl-(C_1-C_4 alkyl), -C(O)O-(C_1-C_4 alkyl), -C(O)O-phenyl, $-SO_2$-(C_1-C_6alkyl), $-SO_2$-phenyl, unsubstituted phenyl, phenyl substituted with one or more (e.g., 1-4) R_{50} groups, pyridyl, thienyl, pyridyl substituted with one or more (e.g., 1-4) R_{50} groups, thienyl substituted with one or more (e.g., 1-4) R_{50} groups, where

each R_{50} is independently selected from: halogen, C_1-C_6 alkyl, - C_1-C_6 haloalkyl, -OH, -O (C_1-C_4 alkyl), -OCF_3, -CN, - $NR_{60}R_{70}$, -C(O)O-(C_1-C_4 alkyl), -$CONR_{60}R_{70}$, -(C_1-C_6 alkyl)-$NR_{60}R_{70}$, -$NR_{60}CO$-(C_1-C_4 alkyl), -$NR_{60}CO$-phenyl, -$NR_{60}CO$-pyridyl, -$NR_{60}CO$-thienyl, and -$NR_{60}CONR_{60}R_{70}$,

each R_{100} is independently hydrogen or C_1-C_4 alkyl;

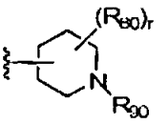
each r is 0 to 4; and

each s is 0 to 3.

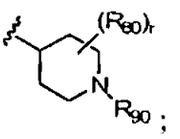
In yet still another aspect, the invention provides compounds of formula 11-3b1, i.e., compounds of formula 11-3a, wherein Y is –O-(C_1-C_6 alkyl). In one embodiment, Y is –O-(C_1-C_4 alkyl).

In yet still another aspect, the invention provides compounds of formula 11-3b2, i.e., compounds of formula 11-3a, wherein Y is –O-phenyl.

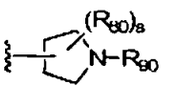
In yet still another aspect, the invention provides compounds of formula 11-3c, i.e., compounds of formula 11-3b, wherein said group



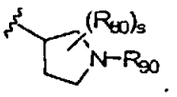
is a group of the formula:



and, said group



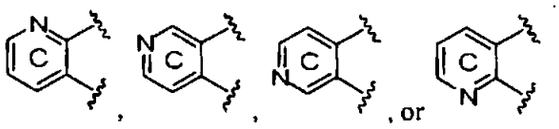
is a group of the formula:



In a further aspect, the invention provides compounds of formula 11-3d, i.e., compounds according to any one of formulas, 11-3b, 11-3b1, 11-3b2, or 11-3c, wherein R_1 is H or C_1-C_4 alkyl. In one embodiment, R_1 is H or methyl. In another embodiment, R_1 is H.

In yet another aspect, the invention provides compounds of formula 11-4, i.e., compounds according to formula 9 or any one of formulas 10, 10-1, 10-2, 10-3, 10-4, 10-5,

10-6, 10-6a, 10-6b, 10-6c, 10-6d, 10-7, 10-8, 10-9, 10-10, 10-11, 10-11a, 10-11b, 10-11c, 10-12, 10-13, 10-14, or 10-15 wherein the C-ring is

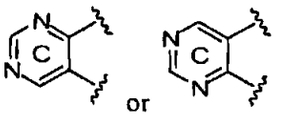


or N-oxide derivatives thereof,

each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryloxy, aryl-(C_1-C_6 alkoxy), C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", -(C_1-C_4 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -$S(O)_z$ aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl), or -$S(O)_z$ (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2 or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In another embodiment, the invention provides compounds of formula 11-4 wherein the C-ring is pyridyl or pyridyl N-oxide substituted with 1 or 2 groups that are independently -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, phenyl, -$S(O)_z$ aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl) or -$S(O)_z$ (C_1-C_6 alkyl) where the aryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In an alternative embodiment, the C-ring is pyridyl or pyridyl N-oxide substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1 or 2 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_4 alkoxy. In another alternative embodiment, the C-ring is pyridyl or pyridyl N-oxide substituted with 1 or 2 groups that are independently –C(O)OH, -C(O)O-(C_1-C_4 alkyl), NO_2, CN, or phenyl, where the phenyl group

is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In still another alternative embodiment, the C-ring is pyridyl or pyridyl N-oxide substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R"; -NR'C(O)O-(C_1-C_6 alkyl), or -NR'C(O)O-phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

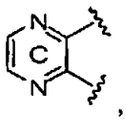
In still another aspect, the invention provides compounds of formula 11-4a, i.e., compounds of formula 9 or any one of formulas 10, 10-1, 10-2, 10-3, 10-4, 10-5, 10-6, 10-7, 10-8, 10-9, 10-10, 10-11, 10-12, 10-13, 10-14, or 10-15 wherein the C-ring is



each of which is optionally substituted with 1 or 2 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryloxy, aryl-(C_1-C_4 alkoxy), C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", -(C_1-C_4 alkyl)-NR'R",-NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -NR'C(O)R", NO_2, CN, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$ aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl), or -S(O)$_z$ (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2 or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In one embodiment, the invention provides compounds of formula 11-4a wherein the C-ring is pyrimidinyl substituted with 1 or 2 groups that are independently -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, phenyl, -S(O)$_z$ aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl) or -S(O)$_z$ (C_1-C_6 alkyl) where the aryl

portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In an alternative embodiment, the C-ring is pyrimidinyl substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1 or 2 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_4 alkoxy. In another alternative embodiment, the C-ring is pyrimidinyl substituted with 1 or 2 groups that are independently –C(O)OH, -C(O)O-(C_1-C_4 alkyl), NO_2, CN, or phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In still another alternative embodiment, the C-ring is pyrimidinyl substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R"; or -NR'C(O)O-(C_1-C_6 alkyl) or -NR'C(O)O-phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

In still another aspect, the invention provides compounds of formula 11-4b, i.e., compounds of formula 9 or any one of formulas 10, 10-1, 10-2, 10-3, 10-4, 10-5, 10-6, 10-6a, 10-6b, 10-6c, 10-6d, 10-7, 10-8, 10-9, 10-10, 10-11, 10-11a, 10-11b, 10-11c, 10-12, 10-13, 10-14, or 10-15 wherein the C-ring is

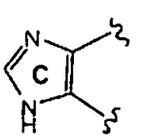


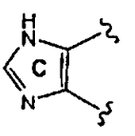
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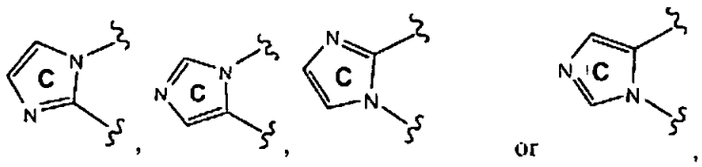
which is optionally substituted with 1 or 2 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryloxy, aryl-(C_1-C_4 alkoxy), C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", -(C_1-C_6 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -S(O)z aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl), or -S(O)z (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2 or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6

alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In one embodiment, the invention provides compounds of formula 11-4b wherein the C-ring is pyrazine substituted with 1 or 2 groups that are independently -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -C(O)OR', -C(O)NR'R", -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, phenyl, -$S(O)_Z$ aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl) or -$S(O)_Z$ (C_1-C_6 alkyl) where the aryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In an alternative embodiment, the C-ring is pyrazine substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1 or 2 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_4 alkoxy. In another alternative embodiment, the C-ring is pyrazine substituted with 1 or 2 groups that are independently –C(O)OH, -C(O)O-(C_1-C_4 alkyl), NO_2, CN, or phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In still another alternative embodiment, the C-ring is pyrazine substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R"; -NR'C(O)O-(C_1-C_6 alkyl), or -NR'C(O)O-phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

In still another aspect, the invention provides compounds of formula 11-4c, i.e., compounds of formula 9 or any one of formulas 10, 10-1, 10-2, 10-3, 10-4, 10-5, 10-6, 10-6a, 10-6b, 10-6c, 10-6d, 10-7, 10-8, 10-9, 10-10, 10-11, 10-11a, 10-11b, 10-11c, 10-12, 10-13, 10-14, or 10-15 wherein the C-ring is:

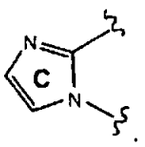




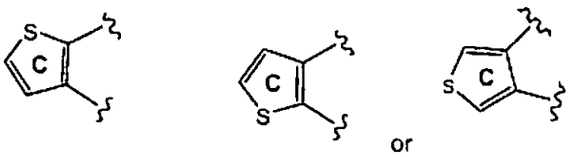


each of which is optionally substituted with 1 or 2 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryloxy, aryl-(C_1-C_4 alkoxy), C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", -(C_1-C_6 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -S(O)z aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl), or -S(O)z (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

In still another aspect, the invention provides compounds of formula 11-4c1, i.e., compounds of formula 11-4c wherein the C-ring is:



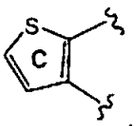
In still another aspect, the invention provides compounds of formula 11-4d, i.e., compounds of formula 9 or any one of formulas 10, 10-1, 10-2, 10-3, 10-4, 10-5, 10-6, 10-6a, 10-6b, 10-6c, 10-6d, 10-7, 10-8, 10-9, 10-10, 10-11, 10-11a, 10-11b, 10-11c, 10-12, 10-13, 10-14, or 10-15 wherein the C-ring is:



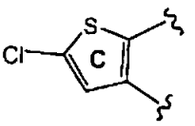
each of which is optionally substituted with 1 or 2 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryloxy, aryl-(C_1-C_4 alkoxy), C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl),

-NR'R", -(C_1-C_6 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -$S(O)_z$ aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl), or -$S(O)_z$ (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl) or -NR'R".

In still another aspect, the invention provides compounds of formula 11-4d1, i.e., compounds of formula 11-4d wherein the C-ring is:



In still another aspect, the invention provides compounds of formula 11-4d2, i.e., compounds of formula 11-4d wherein the C-ring is:

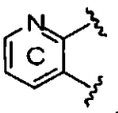


In another aspect, the invention provides compounds of formula 11-5, i.e., compounds of formula 11-4, 11-4a, 11-4b, 11-4c or 11-4d, wherein the C-ring is unsubstituted.

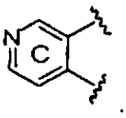
In another aspect, the invention provides compounds of formula 11-5a, i.e., compounds of formula 11-4, 11-4a, 11-4b, 11-4c or 11-4d wherein the C-ring is substituted with 1 or 2 groups that are independently Cl, F, methyl, ethyl, isopropyl, methoxy, ethoxy, CF_3, OCF_3, OH, or $C(O)CH_3$.

In yet another aspect, the invention provides compounds of formula 11-5b, i.e., compounds of formula 11-4, 11-4a, 11-4b, 11-4c or 11-4d, wherein the C-ring is substituted with 1 or 2 groups that are Cl, F, or methyl.

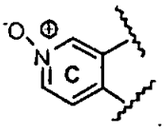
In still yet another aspect, the invention provides compounds of formula 11-5c, i.e., compounds according to any one of formulas 11-4, 11-5, 11-5a, or 11-5b, where the C-ring has the following structure:



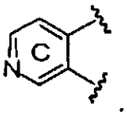
In still yet another aspect, the invention provides compounds of formula 11-5d, i.e., compounds according to any one of formulas 11-4, 11-5, 11-5a, or 11-5b, where the C-ring has the following structure:



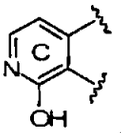
In still yet another aspect, the invention provides compounds of formula 11-5d1, i.e., compounds according to any one of formulas 11-4, where the C-ring has the following structure:



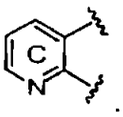
In still yet another aspect, the invention provides compounds of formula 11-5e, i.e., compounds according to any one of formulas 11-4, 11-5, 11-5a, or 11-5b, where the C-ring has the following structure:



In still yet another aspect, the invention provides compounds of formula 11-5e1, i.e., compounds according to formula 11-4, where the C-ring has the following structure:



In still yet another aspect, the invention provides compounds of formula 11-5f, i.e., compounds according to any one of formulas 11-4, 11-5, 11-5a, or 11-5b, where the C-ring has the following structure:



In a further aspect, the invention provides compounds of formula 11-5f1, i.e., compounds of formula 9 or any one of formulas 10, 10-1, 10-2, 10-3, 10-4, 10-5, 10-6, 10-6a, 10-6b, 10-6c, 10-6d, 10-7, 10-8, 10-9, 10-10, 10-11, 10-11a, 10-11b, 10-11c, 10-12, 10-13, 10-14, or 10-15 wherein the C-ring is thiazolyl, which is optionally substituted with 1 or 2 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryloxy, aryl-(C_1-C_4 alkoxy), C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", -(C_1-C_6 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$ aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl), or -S(O)$_z$ (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

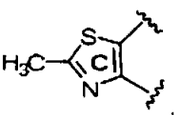
In another aspect, the invention provides compounds of formula 11-5f2, i.e., compounds of formula 11-5f1, wherein the thiazolyl ring is substituted with one group that is halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, or benzyl.

In still another aspect, the invention provides compounds of formula 11-5f3, i.e., compounds of formula 11-5f1, wherein the thiazolyl ring is substituted with C_1-C_4 alkyl.

In yet another aspect, the invention provides compounds of formula 11-5f4, i.e., compounds of formula 11-5f1, wherein the thiazolyl ring is substituted with C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", or -(C_1-C_6 alkyl)-NR'R".

In yet still another aspect, the invention provides compounds of formula 11-5f5, i.e., compounds of formula 11-5f1, wherein the thiazolyl ring is substituted with C_2-C_4 alkyl, -(C_1-C_4 alkyl)-C(O)OR', or -(C_1-C_4 alkyl)-C(O)NR'R".

In another aspect, the invention provides compounds of formula 11-5f6, i.e., compounds of formula 11-5f1, wherein the thiazolyl ring is:



In yet still another aspect, the invention provides compounds of formula 11-5g, i.e., compounds according to any one of formulas 11-4, 11-4a, 11-4b, 11-4c, 11-4c1, 11-4d, 11-4d1, 11-4d2, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, 11-5f, 11-5f1, 11-5f2, 11-5f3, 11-5f4, 11-5f5, or 11-5f6, wherein R_2 is -X(CO)Y or -$(C(R_3)_2)_{1-4}$X(CO)Y.

In still another aspect, the invention provides compounds of formula 11-5g1, i.e., compounds according to any one of formulas 11-4, 11-4a, 11-4b, 11-4c, 11-4c1, 11-4d, 11-4d1, 11-4d2, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, 11-5f, 11-5f1, 11-5f2, 11-5f3, 11-5f4, 11-5f5, or 11-5f6, wherein R_2 is H, C_1-C_3 alkyl or C_3-C_6 cyclopropyl.

In still another aspect, the invention provides compounds of formula 11-5g2, i.e., compounds according to any one of formulas 11-4, 11-4a, 11-4b, 11-4c, 11-4c1, 11-4d, 11-4d1, 11-4d2, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, 11-5f, 11-5f1, 11-5f2, 11-5f3, 11-5f4, 11-5f5, or 11-5f6, wherein R_2 is NO_2 or CN.

In still another aspect, the invention provides compounds of formula 11-5g3, i.e., compounds according to any one of formulas 11-4, 11-4a, 11-4b, 11-4c, 11-4c1, 11-4d, 11-4d1, 11-4d2, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, 11-5f, 11-5f1, 11-5f2, 11-5f3, 11-5f4, 11-5f5, or 11-5f6, wherein R_2 is C_2-C_6 alkenyl or C_2-C_6 alkynyl.

In still another aspect, the invention provides compounds of formula 11-5g4, i.e., compounds according to any one of formulas 11-4, 11-4a, 11-4b, 11-4c, 11-4c1, 11-4d, 11-4d1, 11-4d2, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, 11-5f, 11-5f1, 11-5f2, 11-5f3, 11-5f4, 11-5f5, or 11-5f6, wherein R_2 is C_1-C_4 haloalkyl.

In still another aspect, the invention provides compounds of formula 11-5g5, i.e., compounds according to any one of formulas 11-4, 11-4a, 11-4b, 11-4c, 11-4c1, 11-4d, 11-4d1, 11-4d2, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, 11-5f, 11-5f1, 11-5f2, 11-5f3, 11-5f4, 11-5f5, 11-5f6, 11-5g, 11-5g1, 11-5g2, 11-5g3, or 11-5g4, wherein R_1 is hydrogen.

In still yet another aspect, the invention provides compounds of formula 11-5g6, i.e., compounds according to any one of formulas 11-4, 11-4a, 11-4b, 11-4c, 11-4c1, 11-4d, 11-4d1, 11-4d2, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, 11-5f, 11-5f1, 11-5f2, 11-5f3, 11-5f4, 11-5f5, or 11-5f6, wherein R_1 and R_2 combined are oxo.

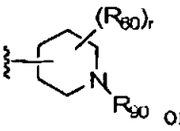
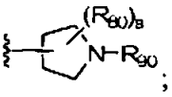
In still yet another aspect, the invention provides compounds of formula 11-5g7, i.e., compounds according to any one of formulas 11-4, 11-4a, 11-4b, 11-4c, 11-4c1, 11-4d, 11-4d1, 11-4d2, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, 11-5f, 11-5f1, 11-5f2, 11-5f3, 11-5f4, 11-5f5, or 11-5f6, wherein R_1 and R_2 combined are =N-OR, where R is hydrogen, C_1-C_6 alkyl, aryl (such as phenyl) or arylalkyl (such as benzyl or phenethyl).

In yet another aspect, the invention provides compounds of formula 11-5g8, i.e., compounds according to any one of formulas 11-4, 11-4a, 11-4b, 11-4c, 11-4c1, 11-4d, 11-4d1, 11-4d2, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, 11-5f, 11-5f1, 11-5f2, 11-5f3, 11-5f4, 11-5f5, or 11-5f6, wherein R_1 and R_2 together with the carbon to which they are attached form a C_3-C_6 cycloalkyl group.

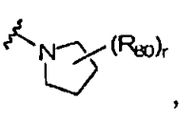
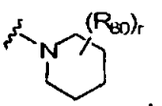
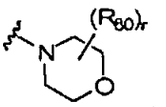
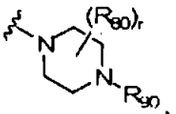
In yet another aspect, the invention provides compounds of formula 11-5g9, i.e., compounds according to any one of formulas 11-4, 11-4a, 11-4b, 11-4c, 11-4c1, 11-4d, 11-4d1, 11-4d2, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, 11-5f, 11-5f1, 11-5f2, 11-5f3, 11-5f4, 11-5f5, or 11-5f6, wherein R_1 and R_2 together with the carbon to which they are attached form a cyclopropyl group.

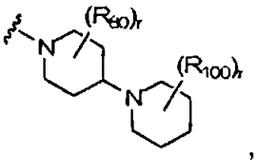
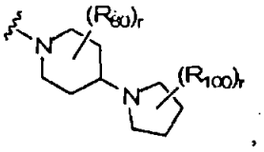
In yet another aspect, the invention provides compounds of formula 11-5g10, i.e., compounds according to any one of formulas 11-4, 11-4a, 11-4b, 11-4c, 11-4c1, 11-4d, 11-4d1, 11-4d2, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, 11-5f, 11-5f1, 11-5f2, 11-5f3, 11-5f4, 11-5f5, or 11-5f6, wherein R_1 is hydrogen and R_2 is cyclopropyl. In one embodiment, the compound is racemic. In another embodiment, the compound is enantiomerically enriched.

In yet still another aspect, the invention provides compounds of formula 11-5h, i.e., compounds of formula 11-5g wherein,

X is O; and Y is $-NR_{60}R_{70}$ or $-N(R_{30})(CH_2)_{2-6}NR_{60}R_{70}$; where R_{60} and R_{70} are independently selected from: hydrogen, methyl, ethyl, (C_3 –C_8)cycloalkyl, aryl-(C_1-C_6 alkyl) (such as benzyl or phenethyl), 4-pyridylmethyl,  or  ; or

R_{60} and R_{70} taken together with the nitrogen atom to which they are bound form a heterocycloalkyl group selected from

 ,  ,  ,  ,

 , and  ,

where

each R_{80} is independently unsubstituted C_1-C_4 alkyl or C_1-C_4 alkyl substituted with hydroxyl or halogen;

each R_{90} is independently hydrogen, unsubstituted C_1-C_4 alkyl, C_1-C_4 alkyl substituted with hydroxyl or halogen, unsubstituted C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl substituted with one or more (e.g., 1-4) R_{50} groups, phenyl-(C_1-C_4 alkyl)-, pyridyl-(C_1-C_4 alkyl)-, thienyl-(C_1-C_4 alkyl)-, -C(O)O-(C_1-C_4 alkyl), -C(O)O-phenyl, -SO_2-(C_1-C_6 alkyl) -SO_2-phenyl unsubstituted phenyl, phenyl substituted with one or more (e.g., 1-4) R_{50} groups, pyridyl, thienyl, pyridyl substituted with one or more (e.g., 1-4) R_{50} groups, thienyl substituted with one or more (e.g., 1-4) R_{50} groups, where

each R_{50} is independently selected from: halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -OH, -O C_1-C_4 alkyl, OCF_3, -CN, - $NR_{60}R_{70}$, -C(O)O-(C_1-C_4 alkyl), -$CONR_{60}R_{70}$, -(C_1-C_6 alkyl)-$NR_{60}R_{70}$, -$NR_{60}CO$-(C_1-C_4 alkyl), -$NR_{60}CO$-phenyl, -$NR_{60}CO$-pyridyl, -$NR_{60}CO$-thienyl, and -$NR_{60}CONR_{60}R_{70}$,

each R_{100} is independently hydrogen or C_1-C_4 alkyl;

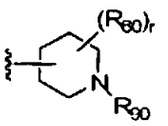
each r is 0 to 4; and

each s is 0 to 3.

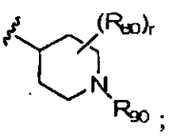
In yet still another aspect, the invention provides compounds of formula 11-5h1, i.e., compounds of formula 11-5g, wherein Y is –O-(C_1-C_6 alkyl). In one embodiment, Y is –O-(C_1-C_4 alkyl).

In yet still another aspect, the invention provides compounds of formula 11-5h2, i.e., compounds of formula 11-5g, wherein Y is –O-phenyl.

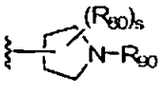
In yet still another aspect, the invention provides compounds of formula 11-5i, i.e., compounds of formula 11-5h, wherein said group



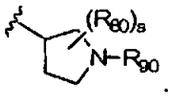
is a group of the formula:



and said group



is a group of the formula:



In a further aspect, the invention provides compounds of formula 11-5j, i.e., compounds according to any one of formulas, 11-5h, 11-5h1, 11-5h2, or 11-5i, wherein R_1 is H or C_1-C_4 alkyl. In one embodiment, R_1 is H or methyl. In another embodiment, R_1 is H.

In yet another aspect, the invention provides compounds of formula 11-6, i.e., compounds according to formula 9 or any one of formulas 10, 10-1, 10-2, 10-3, 10-4, 10-5, 10-6, 10-6a, 10-6b, 10-6c, 10-6d, 10-7, 10-8, 10-9, 10-10, 10-11, 10-11a, 10-11b, 10-11c, 10-12, 10-13, 10-14, or 10-15 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-2e, 11-2f, 11-2g, 11-2h, 11-2i, 11-3, 11-3a, 11-3a1, 11-3a2, 11-3a3, 11-3a4, 11-3a5, 11-3a6, 11-3a7, 11-3a8, 11-3a9, 11-3a10, 11-3b, 11-3b1, 11-3b2, 11-3c, 11-3d, 11-4, 11-4a, 11-4b, 11-4c, 11-4c1, 11-4d, 11-4d1, 11-4d2, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, 11-5f, 11-5f1, 11-5f2, 11-5f3, 11-5f4, 11-5f5, 11-5f6, 11-5g, 11-5g1, 11-5g2, 11-5g3, 11-5g4, 11-5g5, 11-5g6, 11-5g7, 11-5g8, 11-5g9, 11-5g10, 11-5h, 11-5h1, 11-5h2, 11-5i, or 11-5j, wherein the C_3-C_8 cycloalkyl (ring A of Formula I) group is cyclopropyl.

In yet another aspect, the invention provides compounds of formula 11-7, i.e., compounds according to formula 9 or any one of formulas 10, 10-1, 10-2, 10-3, 10-4, 10-5, 10-6, 10-6a, 10-6b, 10-6c, 10-6d, 10-7, 10-8, 10-9, 10-10, 10-11, 10-11a, 10-11b, 10-11c, 10-12, 10-13, 10-14, or 10-15 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-2e, 11-2f, 11-2g, 11-2h, 11-2i, 11-3, 11-3a, 11-3a1, 11-3a2, 11-3a3, 11-3a4, 11-3a5, 11-3a6, 11-3a7, 11-3a8, 11-3a9, 11-3a10, 11-3b, 11-3b1, 11-3b2, 11-3c, 11-3d, 11-4, 11-4a, 11-4b, 11-4c, 11-4c1, 11-4d, 11-4d1, 11-4d2, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, 11-5f, 11-5f1, 11-5f2, 11-5f3, 11-5f4, 11-5f5, 11-5f6, 11-5g, 11-5g1, 11-5g2, 11-5g3, 11-5g4, 11-5g5, 11-5g6, 11-5g7, 11-5g8, 11-5g9, 11-5g10, 11-5h, 11-5h1, 11-5h2, 11-5i, or 11-5j, wherein the C_3-C_8 cycloalkyl group (ring A of Formula I) is cyclobutyl.

In yet another aspect, the invention provides compounds of formula 11-8, i.e., compounds according to formula 9 or any one of formulas 10, 10-1, 10-2, 10-3, 10-4, 10-5, 10-6, 10-6a, 10-6b, 10-6c, 10-6d, 10-7, 10-8, 10-9, 10-10, 10-11, 10-11a, 10-11b, 10-11c, 10-12, 10-13, 10-14, or 10-15 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-2e, 11-2f, 11-2g, 11-2h, 11-2i, 11-3, 11-3a, 11-3a1, 11-3a2, 11-3a3, 11-3a4, 11-3a5, 11-3a6, 11-3a7,

11-3a8, 11-3a9, 11-3a10, 11-3b, 11-3b1, 11-3b2, 11-3c, 11-3d, 11-4, 11-4a, 11-4b, 11-4c, 11-4c1, 11-4d, 11-4d1, 11-4d2, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, 11-5f, 11-5f1, 11-5f2, 11-5f3, 11-5f4, 11-5f5, 11-5f6, 11-5g, 11-5g1, 11-5g2, 11-5g3, 11-5g4, 11-5g5, 11-5g6, 11-5g7, 11-5g8, 11-5g9, 11-5g10, 11-5h, 11-5h1, 11-5h2, 11-5i, or 11-5j, wherein the C_3-C_8 cycloalkyl group. (ring A of Formula I) is cyclopentyl.

In yet another aspect, the invention provides compounds of formula 11-9, i.e., compounds according to formula 9 or any one of formulas 10, 10-1, 10-2, 10-3, 10-4, 10-5, 10-6, 10-6a, 10-6b, 10-6c, 10-6d, 10-7, 10-8, 10-9, 10-10, 10-11, 10-11a, 10-11b, 10-11c, 10-12, 10-13, 10-14, or 10-15 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-2e, 11-2f, 11-2g, 11-2h, 11-2i, 11-3, 11-3a, 11-3a1, 11-3a2, 11-3a3, 11-3a4, 11-3a5, 11-3a6, 11-3a7, 11-3a8, 11-3a9, 11-3a10, 11-3b, 11-3b1, 11-3b2, 11-3c, 11-3d, 11-4, 11-4a, 11-4b, 11-4c, 11-4c1, 11-4d, 11-4d1, 11-4d2, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, 11-5f, 11-5f1, 11-5f2, 11-5f3, 11-5f4, 11-5f5, 11-5f6, 11-5g, 11-5g1, 11-5g2, 11-5g3, 11-5g4, 11-5g5, 11-5g6, 11-5g7, 11-5g8, 11-5g9, 11-5g10, 11-5h, 11-5h1, 11-5h2, 11-5i, or 11-5j, wherein the C_3-C_8 cycloalkyl group (ring A of Formula I) is cyclohexyl.

In yet another aspect, the invention provides compounds of formula 11-10, i.e., compounds according to any one of formulas formula 9 or 10, 10-1, 10-2, 10-3, 10-4, 10-5, 10-6, 10-6a, 10-6b, 10-6c, 10-6d, 10-7, 10-8, 10-9, 10-10, 10-11, 10-11a, 10-11b, 10-11c, 10-12, 10-13, 10-14, or 10-15 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-2e, 11-2f, 11-2g, 11-2h, 11-2i, 11-3, 11-3a, 11-3a1, 11-3a2, 11-3a3, 11-3a4, 11-3a5, 11-3a6, 11-3a7, 11-3a8, 11-3a9, 11-3a10, 11-3b, 11-3b1, 11-3b2, 11-3c, 11-3d, 11-4, 11-4a, 11-4b, 11-4c, 11-4c1, 11-4d, 11-4d1, 11-4d2, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, 11-5f, 11-5f1, 11-5f2, 11-5f3, 11-5f4, 11-5f5, 11-5f6, 11-5g, 11-5g1, 11-5g2, 11-5g3, 11-5g4, 11-5g5, 11-5g6, 11-5g7, 11-5g8, 11-5g9, 11-5g10, 11-5h, 11-5h1, 11-5h2, 11-5i, or 11-5j, wherein the C_3-C_8 cycloalkyl group (ring A of Formula I) is cycloheptyl.

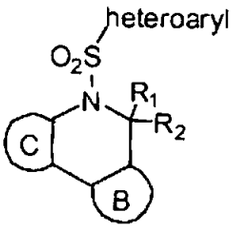
In still yet another aspect, the invention provides compounds of formula 11-11, i.e., compounds according to formula 9 or any one of formulas 10, 10-1, 10-2, 10-3, 10-4, 10-5, 10-6, 10-6a, 10-6b, 10-6c, 10-6d, 10-7, 10-8, 10-9, 10-10, 10-11, 10-11a, 10-11b, 10-11c, 10-12, 10-13, 10-14, or 10-15 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-2e, 11-2f, 11-2g, 11-2h, 11-2i, 11-3, 11-3a, 11-3a1, 11-3a2, 11-3a3, 11-3a4, 11-3a5, 11-3a6, 11-3a7, 11-3a8, 11-3a9, 11-3a10, 11-3b, 11-3b1, 11-3b2, 11-3c, 11-3d, 11-4, 11-4a, 11-4b, 11-4c, 11-4c1, 11-4d, 11-4d1, 11-4d2, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, 11-5f, 11-5f1, 11-5f2, 11-5f3, 11-5f4, 11-5f5, 11-5f6, 11-5g, 11-5g1, 11-5g2, 11-5g3, 11-5g4, 11-

5g5, 11-5g6, 11-5g7, 11-5g8, 11-5g9, 11-5g10, 11-5h, 11-5h1, 11-5h2, 11-5i, or 11-5j, wherein the C_3-C_8 cycloalkyl group (ring A of Formula I) is cyclooctyl.

In another aspect, the invention provides compounds of formula 12, i.e., compounds of formula I, wherein

the A-ring is heteroaryl, which is pyridyl, pyrimidyl, quinolinyl, isoquinolinyl, thienyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, or oxazolyl, each of which is optionally substituted at a substitutable position with halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, hydroxyl, hydroxy-(C_1-C_4 alkyl), CN, NO_2, aryloxy, aryl-(C_1-C_4 alkoxy) (such as benzyloxy),-SO_2-(C_1-C_6 alkyl), -NR'R", C_1-C_6 alkanoyl, -C(O)OR', -(C_1-C_4 alkyl)-C(O)OR', heteroaryl, aryl, aryl-(C_1-C_4 alkyl), -SO_2-NR'R", -C(O)NR'R", -OC(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", -NR'C(O)O-(C_1-C_6 alkyl) or -NR'C(O)O-phenyl, where each R' and R" is independently hydrogen or C_1-C_6 alkyl. In one embodiment, the B-ring is pyrazolyl, imidazolyl, pyrrolyl, triazolyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, pyridyl, pyrimidyl, or isoxazolyl, each of which is optionally substituted at a substitutable position with a group that is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, -NR'R", -SO_2-NR'R", -C(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, NO_2, CN, -C(O)OR', hydroxyl, hydroxy-(C_1-C_6 alkyl), -S(O)$_z$ (C_1-C_6 alkyl), -S(O)$_z$ aryl, halogen, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, benzyl or phenyl.

In still another aspect, the invention provides compounds of formula 13, i.e., compounds of formula I or 12 having the following formula:



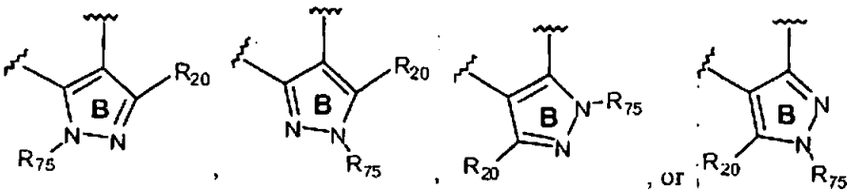
Formula 13

stereoisomers, tautomers, mixtures of stereoisomers and/or tautomers or pharmaceutically acceptable salts thereof. In one embodiment, the heteroaryl group is optionally substituted at a substitutable position with halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6

alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, hydroxyl, hydroxy-(C_1-C_4 alkyl), CN, NO_2, aryloxy, aryl-(C_1-C_4alkoxy), -SO_2-(C_1-C_6 alkyl), -NR'R", C_1-C_6 alkanoyl, -C(O)OR', -(C_1-C_4 alkyl)-C(O)OR', pyridyl, phenyl, phenyl-(C_1-C_4 alkyl), -SO_2-NR'R", -C(O)NR'R", -OC(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", or -NR'C(O)OR', where each R' and R" is independently hydrogen or C_1-C_6 alkyl. In another embodiment the heteroaryl group is optionally substituted as described immediately above and the C-ring is cyclohexyl, phenyl, thienyl, imidazolinyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrrolyl, pyrazolyl, pyrimidyl, pyrazinyl or pyridyl, each of which is optionally substituted at each substitutable position with groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, aryloxy, aryl-(C_1-C_4alkoxy), C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, hydroxyl, hydroxy-(C_1-C_6 alkyl), -NR'R", -(C_1-C_4 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, oxo, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$ aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl),or -S(O)$_z$ (C_1-C_6 alkyl) where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2 or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, CF_3, OCF_3, hydroxyl, hydroxy-(C_1-C_4 alkyl), or -NR'R".

In still yet another aspect, the invention provides compounds of formula 13-1, i.e., compounds of formula 13, wherein the B-ring is pyrazolyl, imidazolyl, pyrrolyl, triazolyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, pyridyl, pyrimidyl, or isoxazolyl, each of which is unsubstituted.

In still yet another aspect, the invention provides compounds of formula 13-2, i.e., compounds of formula 13, wherein the B-ring has the formula:

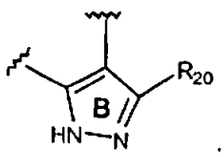


wherein

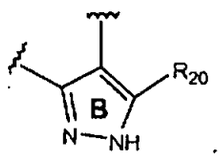
R_{20} is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, -NR'R", -(C_1-C_4 alkyl)-NR'R", -$S(O)_2$ (C_1-C_6 alkyl), halogen, hydroxyl, CN, NO_2, CH_2F, CHF_2, CF_3, -C(O)OR', -C(O)NR'R", -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", or phenyl, and

R_{75} is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl-C_1-C_6 alkanoyl, -C(O)NR'R", -$S(O)_2$-(C_1-C_6 alkyl), -$S(O)_2$-aryl, -SO_2NR'R", phenyl, phenyl-(C_1-C_6 alkyl) (preferably phenethyl or benzyl, more preferably, benzyl), phenylcarbonyl, benzylcarbonyl, or heteroarylcarbonyl, where the heteroaryl group is pyridyl, pyrimidyl, thienyl or furanyl.

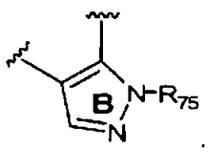
In still yet another aspect, the invention provides compounds of formula 13-3, i.e., compounds of formula 13-2, wherein the B-ring has the formula:



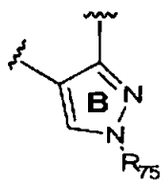
In still yet another aspect, the invention provides compounds of formula 13-4, i.e., compounds of formula 13-2, wherein the B-ring has the formula:



In still yet another aspect, the invention provides compounds of formula 13-5, i.e., compounds of formula 13-2, wherein the B-ring has the formula:



In still yet another aspect, the invention provides compounds of formula 13-6, i.e., compounds of formula 13-2, wherein the B-ring has the formula:



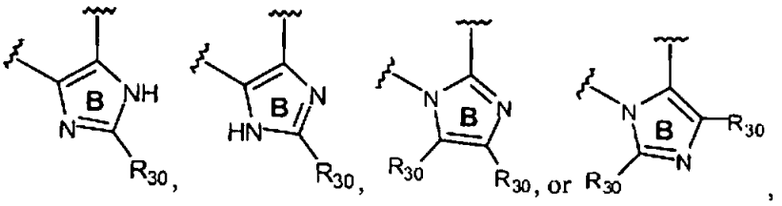
In a further aspect, the invention provides compounds of formula 13-6a, i.e., compounds according to any one of formulas 13-2, 13-3, or 13-4, wherein R_{20} is hydrogen, C_1-C_4 alkyl, CH_2F, CHF_2, CF_3, -C(O)OR', -$S(O)_2$ (C_1-C_4 alkyl), or hydroxyl.

In another aspect, the invention provides compounds of formula 13-6b, i.e., compounds of formula 13-6a, wherein R_{20} is hydrogen or methyl.

In yet another aspect, the invention provides compounds of formula 13-6c, i.e., compounds according to any one of formulas 13-2, 13-5 or 13-6, wherein R_{75} is hydrogen or methyl.

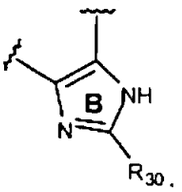
In still yet another aspect, the invention provides compounds of formula 13-6d, i.e., compounds according to any one of formulas 13-2, 13-5 or 13-6, wherein R_{75} is hydrogen. In one embodiment, R_{20} and R_{75} are both hydrogen.

In still yet another aspect, the invention provides compounds of formula 13-7, i.e., compounds of formula 13-2, wherein the B-ring has the formula:

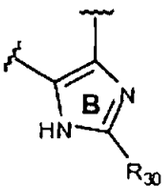


wherein R_{30} is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -NR'R", C_1-C_4 alkythio, halogen, hydroxy, CH_2F, CHF_2, CF_3, or phenyl.

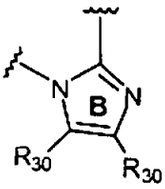
In still yet another aspect, the invention provides compounds of formula 13-8, i.e., compounds of formula 13-7, wherein the B-ring has the formula:



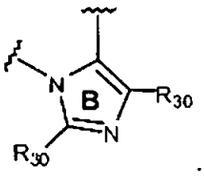
In still yet another aspect, the invention provides compounds of formula 13-9, i.e., compounds of formula 13-7, wherein the B-ring has the formula:



In still yet another aspect, the invention provides compounds of formula 13-10, i.e., compounds of formula 13-7, wherein the B-ring has the formula:



In still yet another aspect, the invention provides compounds of formula 13-11, i.e., compounds of formula 13-7, wherein the B-ring has the formula:

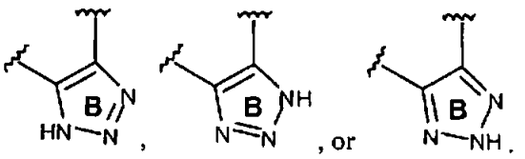


In a further aspect, the invention provides compounds of formula 13-11a, i.e., compounds according to any one of formulas 13-8, 13-9, 13-10, or 13-11, wherein each R_{30} is independently hydrogen, C_1-C_4 alkyl, CH_2F, CHF_2, or CF_3.

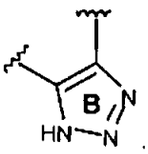
In another aspect, the invention provides compounds of formula 13-11b, i.e., compounds of formula 13-11a, wherein each R_{30} is independently hydrogen or methyl.

In still another aspect, the invention provides compounds of formula 13-11c, i.e., compounds of formula 13-11a, wherein each R_{30} is hydrogen.

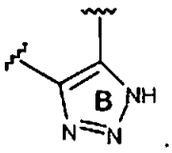
In still yet another aspect, the invention provides compounds of formula 13-12, i.e., compounds of formula 10, wherein the B-ring has the formula:



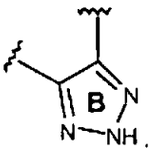
In still yet another aspect, the invention provides compounds of formula 13-13, i.e., compounds of formula 13-12, wherein the B-ring has the formula:



In still yet another aspect, the invention provides compounds of formula 13-14, i.e., compounds of formula 13-12, wherein the B-ring has the formula:



In still yet another aspect, the invention provides compounds of formula 13-15, i.e., compounds of formula 13-12, wherein the B-ring has the formula:



In yet still another aspect, the invention provides compounds of formula 14, i.e., compounds according to of formula 12 or any one of formulas 13, 13-1, 13-2, 13-3, 13-4, 13-5, 13-6, 13-6a, 13-6b, 13-6c, 13-6d, 13-7, 13-8, 13-9, 13-10, 13-11, 13-11a, 13-11b, 13-11c, 13-12, 13-13, 13-14, or 13-15, wherein the C-ring is phenyl or cyclohexyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryloxy, aryl-(C_1-C_4 alkoxy), C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", -(C_1-C_4 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -S(O)z aryl (such as phenyl), or -S(O)z (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1 or 2 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In one embodiment, the C-ring is an optionally substituted phenyl.

In yet still another aspect, the invention provides compounds of formula 14-1, i.e., compounds of formula 14 wherein the C-ring is unsubstituted phenyl.

In yet still another aspect, the invention provides compounds of formula 14-1a, i.e., compounds of formula 14 wherein the C-ring is unsubstituted cyclohexyl.

In yet still another aspect, the invention provides compounds of formula 14-2, i.e., compounds of formula 14 wherein the C-ring is phenyl substituted with 1 or 2 groups that are independently Cl, F, methyl, ethyl, isopropyl, methoxy, ethoxy, CF_3, OCF_3, OH, CH_2OH, NH_2, $NH(CH_3)$, $N(CH_3)_2$, or $-OC(O)N(CH_3)_2$. In one embodiment, the C-ring is bis-substituted with at least one halogen. In another embodiment, the halogen is F. In still another embodiment, the halogen is Cl. In another embodiment, the C-ring is bis-substituted with two halogens, which are the same or different. In still another embodiment, the C-ring is substituted at least at position 7. In another embodiment, the C-ring is substituted at positions 7 and 8. In another embodiment, the C-ring is monosubstituted with a halogen. In another embodiment, the halogen is F. In still another embodiment, the halogen is Cl. In still another embodiment, the C-ring is substituted at position 7. In yet another embodiment, the C-ring is substituted at position 8.

In still yet another aspect, the invention provides compounds of formula 14-2a, i.e., compounds of formula 14, wherein the C-ring is phenyl substituted with 1 or 2 groups that are independently -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, phenyl, -$S(O)_z$ phenyl, or -$S(O)_z$ (C_1-C_6 alkyl), where the phenyl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In one embodiment, the C-ring is substituted at least at the 7-position. In another embodiment, the C-ring is substituted at least at the 8-position.

In still another aspect, the invention provides compounds of formula 14-2b, i.e., compounds of formula 14, wherein the C-ring is phenyl substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1 or 2 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_4 alkoxy. In one embodiment, the C-ring is substituted at least at the 7-position. In another embodiment, the C-ring is substituted at least at the 8-position.

In still another aspect, the invention provides compounds of formula 14-2c, i.e., compounds of formula 14, wherein the C-ring is phenyl substituted with 1 or 2 groups that are independently –C(O)OH, -C(O)O-(C_1-C_4 alkyl), NO_2, CN, or phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3),

hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In one embodiment, the C-ring is substituted at least at the 7-position. In another embodiment, the C-ring is substituted at least at the 8-position.

In yet another aspect, the invention provides compounds of formula 14-2d, i.e., compounds of formula 14, wherein the C-ring is phenyl substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R"; or -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In one embodiment, the C-ring is substituted at least at the 7-position. In another embodiment, the C-ring is substituted at least at the 8-position.

In yet still another aspect, the invention provides compounds of formula 14-2e, i.e., compounds of formula 14 wherein the C-ring is cyclohexyl substituted with 1 or 2 groups that are independently Cl, F, methyl, ethyl, isopropyl, methoxy, ethoxy, CF_3, OCF_3, OH, CH_2OH, NH_2, $NH(CH_3)$, $N(CH_3)_2$, or $-OC(O)N(CH_3)_2$.

In still yet another aspect, the invention provides compounds of formula 14-2f, i.e., compounds of formula 14, wherein the C-ring is cyclohexyl substituted with 1 or 2 groups that are independently -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_4 alkyl)-C(O)OR', -(C_1-C_4 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, phenyl, -$S(O)_z$ phenyl, or -$S(O)_z$ (C_1-C_6 alkyl), where the phenyl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

In still another aspect, the invention provides compounds of formula 14-2g, i.e., compounds of formula 14, wherein the C-ring is cyclohexyl substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1 or 2 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_4 alkoxy.

In still another aspect, the invention provides compounds of formula 14-2h, i.e., compounds of formula 14, wherein the C-ring is cyclohexyl substituted with 1 or 2 groups that are independently –C(O)OH, -C(O)O-(C_1-C_4 alkyl), NO_2, CN, or phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6

alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

In yet another aspect, the invention provides compounds of formula 14-2i, i.e., compounds of formula 14, wherein the C-ring is cyclohexyl substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R"; -NR'C(O)O-(C_1-C_6 alkyl) or -NR'C(O)O-phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

In yet still another aspect, the invention provides compounds of formula 14-3, i.e., compounds of formula 14 wherein the C-ring is phenyl or cyclohexyl substituted with 1 or 2 groups that are Cl, F, methyl, isopropyl, methoxy, CF_3, OCF_3, OH, or -$OC(O)N(CH_3)_2$.

In yet still another aspect, the invention provides compounds of formula 14-3a, i.e., compounds according to any one of formulas 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2e, 14-2f, 14-2g, 14-2h, 14-2i, or 14-3, wherein R_2 is -X(CO)Y or -$(C(R_3)_2)_{1-4}$X(CO)Y.

In still another aspect, the invention provides compounds of formula 14-3a1, i.e., compounds according to any one of formulas 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2e, 14-2f, 14-2g, 14-2h, 14-2i, or 14-3, wherein R_2 is hydrogen, C_1-C_3 alkyl or C_3-C_6 cyclopropyl.

In still another aspect, the invention provides compounds of formula 14-3a2, i.e., compounds according to any one of formulas 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2e, 14-2f, 14-2g, 14-2h, 14-2i, or 14-3, wherein R_2 is NO_2 or CN.

In still another aspect, the invention provides compounds of formula 14-3a3, i.e., compounds according to any one of formulas 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2e, 14-2f, 14-2g, 14-2h, 14-2i, or 14-3, wherein R_2 is C_2-C_6 alkenyl or C_2-C_6 alkynyl.

In still another aspect, the invention provides compounds of formula 14-3a4, i.e., compounds according to any one of formulas 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2e, 14-2f, 14-2g, 14-2h, 14-2i, or 14-3, wherein R_2 is C_1-C_4 haloalkyl.

In still another aspect, the invention provides compounds of formula 14-3a5, i.e., compounds according to any one of formulas 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2e, 14-2f, 14-2g, 14-2h, 14-2i, 14-3, 14-3a, 14-3a1, 14-3a2, 14-3a3, or 14-3a4, wherein R_1 is hydrogen.

In still yet another aspect, the invention provides compounds of formula 14-3a6, i.e., compounds according to any one of formulas 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2e, 14-2f, 14-2g, 14-2h, 14-2i, or 14-3, wherein R_1 and R_2 combined are oxo.

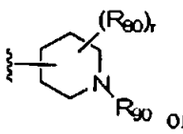
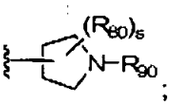
In still yet another aspect, the invention provides compounds of formula 14-3a7, i.e., compounds according to any one of formulas 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2e, 14-2f, 14-2g, 14-2h, 14-2i, or 14-3, wherein R_1 and R_2 combined are =N-OR, where R is hydrogen, C_1-C_6 alkyl, aryl (such as phenyl) or arylalkyl (such as benzyl or phenethyl).

In yet another aspect, the invention provides compounds of formula 14-3a8, i.e., compounds according to any one of formulas 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2e, 14-2f, 14-2g, 14-2h, 14-2i, or 14-3, wherein R_1 and R_2 together with the carbon to which they are attached form a C_3-C_6 cycloalkyl group.

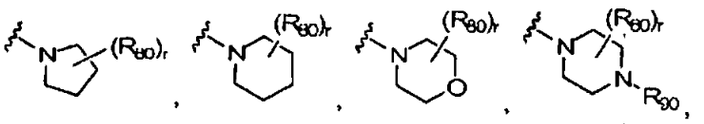
In yet another aspect, the invention provides compounds of formula 14-3a9, i.e., compounds according to any one of formulas 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2e, 14-2f, 14-2g, 14-2h, 14-2i, or 14-3, wherein R_1 and R_2 together with the carbon to which they are attached form a cyclopropyl group.

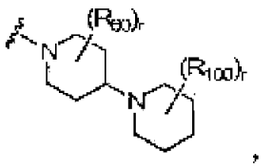
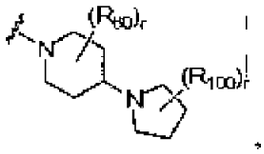
In yet another aspect, the invention provides compounds of formula 14-3a10, i.e., compounds according to any one of formulas 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2e, 14-2f, 14-2g, 14-2h, 14-2i, or 14-3, wherein R_1 is hydrogen and R_2 is cyclopropyl. In one embodiment, the compound is racemic. In another embodiment, the compound is enantiomerically enriched.

In yet still another aspect, the invention provides compounds of formula 14-3b, i.e., compounds of formula 14-3a, wherein

X is O; and Y is $-NR_{60}R_{70}$ or $-N(R_{30})(CH_2)_{2\text{-}6}NR_{60}R_{70}$; where R_{60} and R_{70} are independently selected from: hydrogen, methyl, ethyl, (C_3 –C_8)cycloalkyl, aryl-(C_1-C_6)alkyl (such as benzyl or phenethyl), 4-pyridylmethyl,  or  ; or

R_{60} and R_{70} taken together with the nitrogen atom to which they are bound form a heterocycloalkyl group selected from



, and

where,

each R_{80} is independently unsubstituted C_1-C_4 alkyl or C_1-C_4 alkyl substituted with hydroxyl or halogen;

each R_{90} is independently hydrogen, unsubstituted C_1-C_4 alkyl, C_1-C_4 alkyl substituted with hydroxyl or halogen, unsubstituted C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl substituted with one or more (e.g., 1-4) R_{50}, phenyl-(C_1-C_4 alkyl)-, pyridyl-(C_1-C_4 alkyl)-, thienyl-(C_1-C_4 alkyl), -C(O)O-(C_1-C_4 alkyl), -C(O)O-phenyl, -SO_2-(C_1-C_6 alkyl), -SO_2-phenyl, unsubstituted phenyl, phenyl substituted with one or more (e.g., 1-4) R_{50} groups, pyridyl, thienyl, pyridyl substituted with one or more (e.g., 1-4) R_{50} groups, thienyl substituted with one or more (e.g., 1-4) R_{50} groups, where

each R_{50} is independently selected from: halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -OH, -O (C_1-C_4 alkyl), OCF_3, -CN, - $NR_{60}R_{70}$, -C(O)O-(C_1-C_4 alkyl), -$CONR_{60}R_{70}$, -(C_1-C_6 alkyl)-$NR_{60}R_{70}$, -$NR_{60}CO$-(C_1-C_4 alkyl), -$NR_{60}CO$-phenyl, -$NR_{60}CO$-pyridyl, -$NR_{60}CO$-thienyl, and -$NR_{60}CONR_{60}R_{70}$,

each R_{100} is independently hydrogen or C_1-C_4 alkyl;

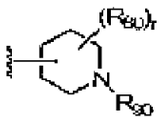
each r is 0 to 4; and

each s is 0 to 3.

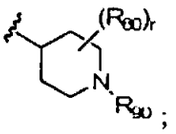
In yet still another aspect, the invention provides compounds of formula 14-3b1, i.e., compounds of formula 14-3a, wherein Y is –O-(C_1-C_6 alkyl). In one embodiment, Y is –O-(C_1-C_4 alkyl).

In yet still another aspect, the invention provides compounds of formula 14-3b2, i.e., compounds of formula 14-3a, wherein Y is –O-phenyl.

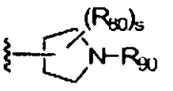
In yet still another aspect, the invention provides compounds of formula 14-3c, i.e., compounds of formula 14-3b, wherein said group



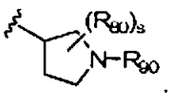
is a group of the formula:



and, said group

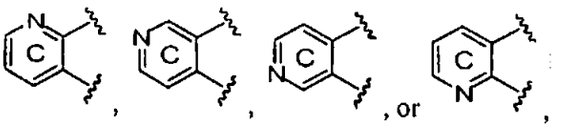


is a group of the formula:



In a further aspect, the invention provides compounds of formula 14-3c1, i.e., compounds according to any one of formulas, 14-3b, 14-3b1, 14-3b2, or 14-3c, wherein R_1 is H or C_1-C_4 alkyl. In one embodiment, R_1 is H or methyl. In another embodiment, R_1 is H.

In yet still another aspect, the invention provides compounds of formula 14-4, i.e., compounds according to formula 12 or any one of formulas 13, 13-1, 13-2, 13-3, 13-4, 13-5, 13-6, 13-6a, 13-6b, 13-6c, 13-6d, 13-7, 13-8, 13-9, 13-10, 13-11, 13-11a, 13-11b, 13-11c, 13-12, 13-13, 13-14, or 13-15 the C-ring is

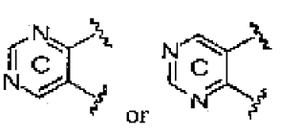


or N-oxide derivatives thereof,

each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryloxy, aryl-(C_1-C_4 alkoxy), C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", -(C_1-C_6 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$ aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl), or -S(O)$_z$ (C_1-C_6 alky), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2 or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl,

hydroxy-(C_1-C_6 alkyl), or -NR'R". In one embodiment, the invention provides compounds of formula 14-4 wherein the C-ring is pyridyl or pyridyl N-oxide substituted with 1 or 2 groups that are independently -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -C(O)OR', -C(O)NR'R", -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R"; NO_2, CN, phenyl, -$S(O)_z$ aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl) or -$S(O)_z$ (C_1-C_6 alkyl) where the aryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In an alternative embodiment, the C-ring is pyridyl or pyridyl N-oxide substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1 or 2 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_4 alkoxy. In another alternative embodiment, the C-ring is pyridyl or pyridyl N-oxide substituted with 1 or 2 groups that are independently -C(O)OH, -C(O)O-(C_1-C_4 alkyl), NO_2, CN, or phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In still another alternative embodiment, the C-ring is pyridyl or pyridyl N-oxide substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R"; or -NR'C(O)O-(C_1-C_6 alkyl), or -NR'C(O)O-phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-C_1-C_6 alkyl, or -NR'R".

In still another aspect, the invention provides compounds of formula 14-4a, i.e., compounds of formula 12 or any one of formulas 13, 13-1, 13-2, 13-3, 13-4, 13-5, 13-6, 13-6a, 13-6b, 13-6c, 13-6d, 13-7, 13-8, 13-9, 13-10, 13-11, 13-11a, 13-11b, 13-11c, 13-12, 13-13, 13-14, or 13-15, wherein the C-ring is

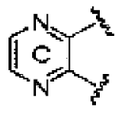


each of which is optionally substituted with 1 or 2 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_6 alkanoyl, aryloxy, aryl-(C_1-C_4 alkoxy), C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4

alkyl), -NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -$S(O)_z$ aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl), or -$S(O)_z$ (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2 or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In one embodiment, the invention provides compounds of formula 14-4a, wherein the C-ring is pyrimidinyl substituted with 1 or 2 groups that are independently -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, phenyl, -$S(O)_z$ aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl) or -$S(O)_z$ (C_1-C_6 alkyl) where the aryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In an alternative embodiment, the C-ring is pyrimidinyl substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1 or 2 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_4 alkoxy. In another alternative embodiment, the C-ring is pyrimidinyl substituted with 1 or 2 groups that are independently -C(O)OH, -C(O)O-(C_1-C_4 alkyl), NO_2, CN, or phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In still another alternative embodiment, the C-ring is pyrimidinyl substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R"; -NR'C(O)O-(C_1-C_6 alkyl), or -NR'C(O)O-phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

In still another aspect, the invention provides compounds of formula 14-4b, i.e., compounds of formula 12 or any one of formulas 13, 13-1, 13-2, 13-3, 13-4, 13-5, 13-6, 13-

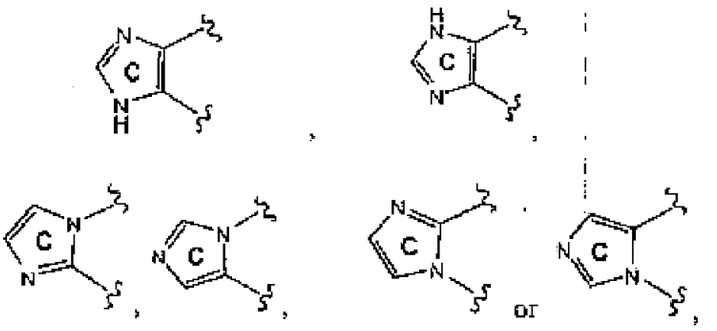
6a, 13-6b, 13-6c, 13-6d, 13-7, 13-8, 13-9, 13-10, 13-11, 13-11a, 13-11b, 13-11c, 13-12, 13-13, 13-14, or 13-15, wherein the C-ring is



which is optionally substituted with 1 or 2 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryloxy, aryl-(C_1-C_6 alkoxy), C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", -(C_1-C_4 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -$S(O)_z$ aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl), or -$S(O)_z$ (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2 or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In one embodiment, the invention provides compounds of formula 14-4b wherein the C-ring is pyrazine substituted with 1 or 2 groups that are independently -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, phenyl, -$S(O)_z$ aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl) or -$S(O)_z$ (C_1-C_6 alkyl) where the aryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In an alternative embodiment, the C-ring is pyrazine substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1 or 2 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_4 alkoxy. In another alternative embodiment, the C-ring is pyrazine substituted with 1 or 2 groups that are independently –C(O)OH, -C(O)O-(C_1-C_4 alkyl), NO_2, CN, or phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as

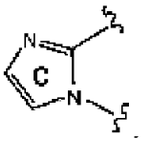
OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or =NR'R". In still another alternative embodiment, the C-ring is pyrazine substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R", -NR'C(O)O-(C_1-C_6 alkyl) or -NR'C(O)O-phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

In still another aspect, the invention provides compounds of formula 14-4c, i.e., compounds of formula 12 or any one of formulas 13, 13-1, 13-2, 13-3, 13-4, 13-5, 13-6, 13-6a, 13-6b, 13-6c, 13-6d, 13-7, 13-8, 13-9, 13-10, 13-11, 13-11a, 13-11b, 13-11c, 13-12, 13-13, 13-14, or 13-15, wherein the C-ring is:

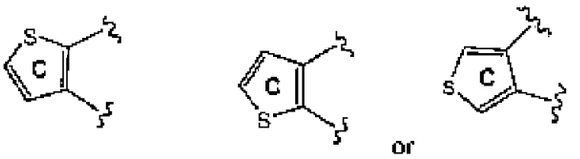


each of which is optionally substituted with 1 or 2 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryloxy, aryl-(C_1-C_4 alkoxy), C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", -(C_1-C_6 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -S(O)z aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl), or -S(O)z (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

In still another aspect, the invention provides compounds of formula 14-4c1, i.e., compounds of formula 14-4c wherein the C-ring is:



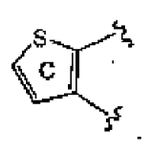
In still another aspect, the invention provides compounds of formula 14-4d, i.e., compounds of formula 12 or any one of formulas 13, 13-1, 13-2, 13-3, 13-4, 13-5, 13-6, 13-6a, 13-6b, 13-6c, 13-6d, 13-7, 13-8, 13-9, 13-10, 13-11, 13-11a, 13-11b, 13-11c, 13-12, 13-13, 13-14, or 13-15, wherein the C-ring is:



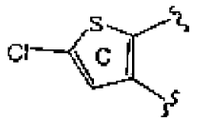
or

each of which is optionally substituted with 1 or 2 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryloxy, aryl-(C_1-C_4 alkoxy), C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", -(C_1-C_6 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R", -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$ aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl), or -S(O)$_z$ (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

In still another aspect, the invention provides compounds of formula 14-4d1, i.e., compounds of formula 14-4d wherein the C-ring is:



In still another aspect, the invention provides compounds of formula 14-4d2, i.e., compounds of formula 14-4d wherein the C-ring is:

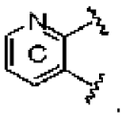


In yet still another aspect, the invention provides compounds of formula 14-5, i.e., compounds according to formula 14-4, 14-4a, 14-4b, 14-4c, or 14-4d, wherein the C-ring is unsubstituted.

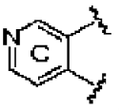
In another aspect, the invention provides compounds of formula 14-5a, i.e., compounds of formula 14-4, 14-4a, 14-4b, 14-4c, or 14-4d, wherein the C-ring is substituted with 1 or 2 groups that are independently Cl, F, methyl, ethyl, isopropyl, methoxy, ethoxy, CF_3, OCF_3, OH, CH_2OH, or $-C(O)CH_3$.

In yet another aspect, the invention provides compounds of formula 14-5b, i.e., compounds of formula 14-4, 14-4a, 14-4b, 14-4c, or 14-4d, wherein the C-ring is substituted with 1 or 2 groups that are independently Cl, F, or methyl.

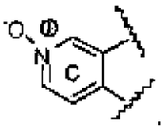
In still yet another aspect, the invention provides compounds of formula 14-5c, i.e., compounds according to any one of formulas 14-4, 14-5, 14-5a, or 14-4b, where the C-ring has the following structure:



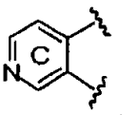
In still yet another aspect, the invention provides compounds of formula 14-5d, i.e., compounds according to any one of formulas 14-4, 14-5, 14-5a, or 14-5b, where the C-ring has the following structure:



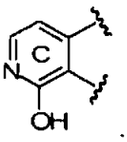
In still yet another aspect, the invention provides compounds of formula 14-5d1, i.e., compounds according to formula 14-4, where the C-ring has the following structure:



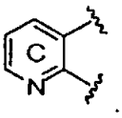
In still yet another aspect, the invention provides compounds of formula 14-5e, i.e., compounds according to any one of formulas 14-4, 14-5, 14-5a, or 14-5b, where the C-ring has the following structure:



In still yet another aspect, the invention provides compounds of formula 14-5e1, i.e., compounds according to formula 14-4, 14-5, 14-5a, or 14-5b, where the C-ring has the following structure:



In still yet another aspect, the invention provides compounds of formula 14-5f, i.e., compounds according to formula 14-4, where the C-ring has the following structure:



In a further aspect, the invention provides compounds of formula 14-5f1, i.e., compounds of formula 12 or any one of formulas 13, 13-1, 13-2, 13-3, 13-4, 13-5, 13-6, 13-6a, 13-6b, 13-6c, 13-6d, 13-7, 13-8, 13-9, 13-10, 13-11, 13-11a, 13-11b, 13-11c, 13-12, 13-13, 13-14, or 13-15, wherein the C-ring is thiazolyl, which is optionally substituted with 1 or 2 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryloxy, aryl-(C_1-C_4 alkoxy), C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", -(C_1-C_6 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -S(O)z aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl), or -S(O)z (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

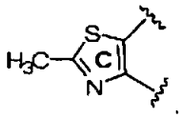
In another aspect, the invention provides compounds of formula 14-5f2, i.e., compounds of formula 14-5f1, wherein the thiazolyl ring is substituted with one group that is halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, or benzyl.

In still another aspect, the invention provides compounds of formula 14-5f3, i.e., compounds of formula 14-5f1, wherein the thiazolyl ring is substituted with C_1-C_4 alkyl.

In yet another aspect, the invention provides compounds of formula 14-5f4, i.e., compounds of formula 14-5f1, wherein the thiazolyl ring is substituted with C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", or -(C_1-C_6 alkyl)-NR'R".

In yet still another aspect, the invention provides compounds of formula 14-5f5, i.e., compounds of formula 14-5f1, wherein the thiazolyl ring is substituted with C_2-C_4 alkyl, -(C_1-C_4 alkyl)-C(O)OR', or -(C_1-C_4 alkyl)-C(O)NR'R".

In another aspect, the invention provides compounds of formula 14-5f6, i.e., compounds of formula 14-5f1, wherein the thiazolyl ring is:



In yet still another aspect, the invention provides compounds of formula 14-5g, i.e., compounds according to any one of formulas 14-4, 14-4a, 14-4b, 14-4c, 14-4c1, 14-4d, 14-4d1, 14-4d2, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, 14-5f, 14-5f1, 14-5f2, 14-5f3, 14-5f4, 14-5f5, or 14-5f6, wherein R_2 is -X(CO)Y or -$(C(R_3)_2)_{1-4}$X(CO)Y.

In still another aspect, the invention provides compounds of formula 14-5g1, i.e., compounds according to any one of formulas 14-4, 14-4a, 14-4b, 14-4c, 14-4c1, 14-4d, 14-4d1, 14-4d2, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, 14-5f, 14-5f1, 14-5f2, 14-5f3, 14-5f4, 14-5f5, or 14-5f6, wherein R_2 is hydrogen, C_1-C_3 alkyl or C_3-C_6 cycloalkyl.

In still another aspect, the invention provides compounds of formula 14-5g2, i.e., compounds according to any one of formulas 14-4, 14-4a, 14-4b, 14-4c, 14-4c1, 14-4d, 14-4d1, 14-4d2, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, 14-5f, 14-5f1, 14-5f2, 14-5f3, 14-5f4, 14-5f5, or 14-5f6, wherein R_2 is NO_2 or CN.

In still another aspect, the invention provides compounds of formula 14-5g3, i.e., compounds according to any one of formulas 14-4, 14-4a, 14-4b, 14-4c, 14-4c1, 14-4d, 14-4d1, 14-4d2, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, 14-5f, 14-5f1, 14-5f2, 14-5f3, 14-5f4, 14-5f5, or 14-5f6, wherein R_2 is C_2-C_6 alkenyl or C_2-C_6 alkynyl.

In still another aspect, the invention provides compounds of formula 14-5g4, i.e., compounds according to any one of formulas 14-4, 14-4a, 14-4b, 14-4c, 14-4c1, 14-4d, 14-4d1, 14-4d2, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, 14-5f, 14-5f1, 14-5f2, 14-5f3, 14-5f4, 14-5f5, or 14-5f6, wherein R_2 is C_1-C_4 haloalkyl.

In still another aspect, the invention provides compounds of formula 14-5g5, i.e., compounds according to any one of formulas 14-4, 14-4a, 14-4b, 14-4c, 14-4c1, 14-4d, 14-4d1, 14-4d2, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, 14-5f, 14-5f1, 14-5f2, 14-5f3, 14-5f4, 14-5f5, 14-5f6, 14-5g, 14-5g1, 14-5g2, 14-5g3, or 14-5g4 wherein R_1 is hydrogen.

In still yet another aspect, the invention provides compounds of formula 14-5g6, i.e., compounds according to any one of formulas 14-4, 14-4a, 14-4b, 14-4c, 14-4c1, 14-4d, 14-4d1, 14-4d2, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, 14-5f, 14-5f1, 14-5f2, 14-5f3, 14-5f4, 14-5f5, or 14-5f6, wherein R_1 and R_2 combined are oxo.

In still yet another aspect, the invention provides compounds of formula 14-5g7, i.e., compounds according to any one of formulas 14-4, 14-4a, 14-4b, 14-4c, 14-4c1, 14-4d, 14-4d1, 14-4d2, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, 14-5f, 14-5f1, 14-5f2, 14-5f3, 14-5f4, 14-5f5, or 14-5f6, wherein R_1 and R_2 combined are =N-OR, where R is hydrogen, C_1-C_6 alkyl, aryl (such as phenyl) or arylalkyl (such as benzyl or phenethyl).

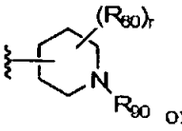
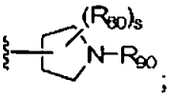
In yet another aspect, the invention provides compounds of formula 14-5g8, i.e., compounds according to any one of formulas 14-4, 14-4a, 14-4b, 14-4c, 14-4c1, 14-4d, 14-4d1, 14-4d2, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, 14-5f, 14-5f1, 14-5f2, 14-5f3, 14-5f4, 14-5f5, or 14-5f6, wherein R_1 and R_2 together with the carbon to which they are attached form a C_3-C_6 cycloalkyl group.

In yet another aspect, the invention provides compounds of formula 14-5g9, i.e., compounds according to any one of formulas 14-4, 14-4a, 14-4b, 14-4c, 14-4c1, 14-4d, 14-4d1, 14-4d2, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, 14-5f, 14-5f1, 14-5f2, 14-5f3, 14-5f4, 14-5f5, or 14-5f6, wherein R_1 and R_2 together with the carbon to which they are attached form a cyclopropyl group.

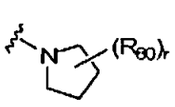
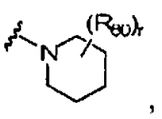
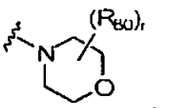
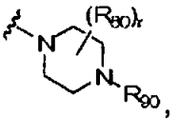
In yet another aspect, the invention provides compounds of formula 14-5g10, i.e., compounds according to any one of formulas 14-4, 14-4a, 14-4b, 14-4c, 14-4c1, 14-4d, 14-4d1, 14-4d2, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, 14-5f, 14-5f1, 14-5f2, 14-5f3, 14-5f4, 14-5f5, or 14-5f6, wherein R_1 is hydrogen and R_2 is cyclopropyl. In one embodiment, the compound is racemic. In another embodiment, the compound is enantiomerically enriched.

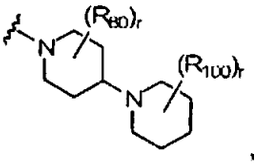
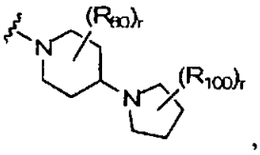
In yet another aspect, the invention provides compounds of formula 14-5g11, i.e., compounds according to any one of formulas 14-4, 14-4a, 14-4b, 14-4c, 14-4c1, 14-4d, 14-4d1, 14-4d2, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, 14-5f, 14-5f1, 14-5f2, 14-5f3, 14-5f4, 14-5f5, or 14-5f6, wherein R_2 is independently hydrogen, methyl, ethyl, propyl, isopropyl, or cyclopropyl; and R_1 is H or methyl.

In yet still another aspect, the invention provides compounds of formula 14-5h, i.e., compounds of formula 14-5g, wherein

X is O; and Y is $-NR_{60}R_{70}$ or $-N(R_{30})(CH_2)_{2\text{-}6}NR_{60}R_{70}$; where R_{60} and R_{70} are independently selected from: hydrogen, methyl, ethyl, (C_3 –C_8)cycloalkyl, aryl(C_1-C_6)alkyl (such as benzyl or phenethyl), 4-pyridylmethyl,  or  ; or

R_{60} and R_{70} taken together with the nitrogen atom to which they are bound form a heterocycloalkyl group selected from

 ,  ,  ,  ,

 , and  ,

where

each R_{80} is independently unsubstituted C_1-C_4 alkyl or C_1-C_4 alkyl substituted with hydroxyl or halogen;

each R_{90} is independently hydrogen, unsubstituted C_1-C_4 alkyl, C_1-C_4 alkyl substituted with hydroxyl or halogen, unsubstituted C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl substituted with one or more (e.g., 1-4) R_{50} groups, phenyl-(C_1-C_4 alkyl), pyridyl-(C_1-C_4 alkyl), thienyl-(C_1-C_4 alkyl), -C(O)O-(C_1-C_4 alkyl), -C(O)O-phenyl, $-SO_2$-(C_1-C_6 alkyl), $-SO_2$-phenyl, unsubstituted phenyl, phenyl substituted with one or more (e.g., 1-4) R_{50} groups, pyridyl, thienyl, pyridyl substituted with one or more (e.g., 1-4) R_{50} groups, thienyl substituted with one or more (e.g., 1-4) R_{50} groups, where

each R_{50} is independently selected from: halogen, C_1-C_6 alkyl, - C_1-C_6 haloalkyl, -OH, -O C_1-C_4 alkyl, OCF_3, -CN, - $NR_{60}R_{70}$, -C(O)O-(C_1-C_4 alkyl), $-CONR_{60}R_{70}$, -

(C_1-C_6 alkyl)-$NR_{60}R_{70}$, -NR_{60}CO-(C_1-C_4 alkyl), -NR_{60}CO-phenyl, -NR_{60}CO-pyridyl, -NR_{60}CO-thienyl, and -NR_{60}CO$NR_{60}R_{70}$,

each R_{100} is independently hydrogen or C_1-C_4 alkyl;

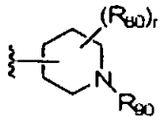
each r is 0 to 4; and

each s is 0 to 3.

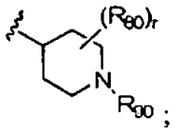
In yet still another aspect, the invention provides compounds of formula 14-5h1, i.e., compounds of formula 14-5g, wherein Y is –O-(C_1-C_6 alkyl). In one embodiment, Y is –O-(C_1-C_4 alkyl).

In yet still another aspect, the invention provides compounds of formula 14-5h2, i.e., compounds of formula 14-5g, wherein Y is –O-phenyl.

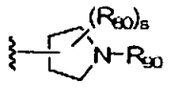
In yet still another aspect, the invention provides compounds of formula 14-5i, i.e., compounds of formula 14-5h, wherein said group



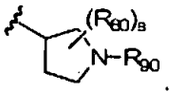
is a group of the formula:



and said group



is a group of the formula:



In a further aspect, the invention provides compounds of formula 14-5j, i.e., compounds according to any one of formulas, 14-5h, 14-5h1, 14-5h2, or 14-5i, wherein R_1 is H or C_1-C_4 alkyl. In one embodiment, R_1 is H or methyl. In another embodiment, R_1 is H.

In yet still another aspect, the invention provides compounds of formula 14-6, i.e., compounds according to any one of formulas 13, 13-1, 13-2, 13-3, 13-4, 13-5, 13-6, 13-6a, 13-6b, 13-6c, 13-6d, 13-7, 13-8, 13-9, 13-10, 13-11, 13-11a, 13-11b, 13-11c, 13-12, 13-13, 13-14, or 13-15, 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2e, 14-2f, 14-2g, 14-2h, 14-2i, 14-3, 14-3a, 14-3a1, 14-3a2, 14-3a3, 14-3a4, 14-3a5, 14-3a6, 14-3a7, 14-

3a8, 14-3a9, 14-3a10, 14-3b, 14-3c, 14-3c1, 14-4, 14-4a, 14-4b, 14-4c, 14-4c1, 14-4d, 14-4d1, 14-4d2, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, 14-5f, 14-5f1, 14-5f2, 14-5f3, 14-5f4, 14-5f5, 14-5f6, 14-5g, 14-5g1, 14-5g2, 14-5g3, 14-5g4, 14-5g5, 14-5g6, 14-5g7, 14-5g8, 14-5g9, 14-5g10, 14-5h, 14-5h1, 14-5h2, 14-5i, or 14-5j, wherein the heteroaryl group (ring A of Formula I) is pyridyl optionally substituted with 1 or 2 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, hydroxy, amino, or mono or di(C_1-C_4 alkyl)amino.

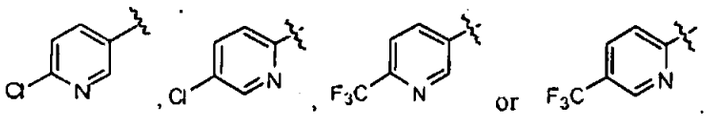
In yet still another aspect, the invention provides compounds of formula 14-7, i.e., compounds 14-6, wherein the pyridyl is substituted with one group that is halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, hydroxy, amino, or mono or di(C_1-C_4 alkyl)amino.

In yet still another aspect, the invention provides compounds of formula 14-8, i.e., compounds of formula 14-7, wherein the pyridyl is substituted at the 4-position.

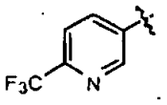
In yet still another aspect, the invention provides compounds of formula 14-8a, i.e., compounds of formula 14-7, wherein the pyridyl is substituted at the 2-position, i.e., immediately next to the pyridyl ring nitrogen. In one embodiment, the pyridyl ring is substituted at the 2-position, i.e., immediately next to the pyridyl ring nitrogen and the pyridyl ring is attached to the $-SO_2-$ group at the 5-position.

In yet still another aspect, the invention provides compounds of formula 14-9, i.e., compounds of formula 14-8, wherein the pyridyl is substituted with one group that is halogen (preferably chloro) or C_1-C_4 haloalkyl (preferably CF_3).

In yet still another aspect, the invention provides compounds of formula 14-10, i.e., compounds of formula 14-9, wherein the heteroaryl group has the following structures:



In yet still another aspect, the invention provides compounds of formula 14-10a, i.e., compounds of formula 14-9, wherein the heteroaryl group has the following structure:



In yet still another aspect, the invention provides compounds of formula 14-10b, i.e., compounds according to any one of formulas 13, 13-1, 13-2, 13-3, 13-4, 13-5, 13-6, 13-6a, 13-6b, 13-6c, 13-6d, 13-7, 13-8, 13-9, 13-10, 13-11, 13-11a, 13-11b, 13-11c, 13-12, 13-13,

13-14, or 13-15, 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2c, 14-2f, 14-2g, 14-2h, 14-2i, 14-3, 14-3a, 14-3a1, 14-3a2, 14-3a3, 14-3a4, 14-3a5, 14-3a6, 14-3a7, 14-3a8, 14-3a9, 14-3a10, 14-3b, 14-3c, 14-3c1, 14-4, 14-4a, 14-4b, 14-4c, 14-4c1, 14-4d, 14-4d1, 14-4d2, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, 14-5f, 14-5f1, 14-5f2, 14-5f3, 14-5f4, 14-5f5, 14-5f6, 14-5g, 14-5g1, 14-5g2, 14-5g3, 14-5g4, 14-5g5, 14-5g6, 14-5g7, 14-5g8, 14-5g9, 14-5g10, 14-5h, 14-5h1, 14-5h2, 14-5i, or 14-5j, wherein the heteroaryl group is pyridyl, or thienyl, each of which is optionally substituted with 1 or 2 groups that are independently halo, methyl, methoxy, CF_3, or OCF_3.

In yet still another aspect, the invention provides compounds of formula 14-11, i.e., compounds according to any one of formulas 13, 13-1, 13-2, 13-3, 13-4, 13-5, 13-6, 13-6a, 13-6b, 13-6c, 13-6d, 13-7, 13-8, 13-9, 13-10, 13-11, 13-11a, 13-11b, 13-11c, 13-12, 13-13, 13-14, or 13-15, 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2c, 14-2f, 14-2g, 14-2h, 14-2i, 14-3, 14-3a, 14-3a1, 14-3a2, 14-3a3, 14-3a4, 14-3a5, 14-3a6, 14-3a7, 14-3a8, 14-3a9, 14-3a10, 14-3b, 14-3c, 14-3c1, 14-4, 14-4a, 14-4b, 14-4c, 14-4c1, 14-4d, 14-4d1, 14-4d2, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, 14-5f, 14-5f1, 14-5f2, 14-5f3, 14-5f4, 14-5f5, 14-5f6, 14-5g, 14-5g1, 14-5g2, 14-5g3, 14-5g4, 14-5g5, 14-5g6, 14-5g7, 14-5g8, 14-5g9, 14-5g10, 14-5h, 14-5h1, 14-5h2, 14-5i, or 14-5j, wherein the heteroaryl group is an unsubstituted pyridyl.

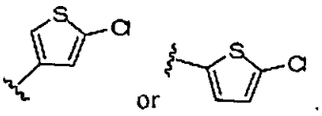
In yet still another aspect, the invention provides compounds of formula 14-12, i.e., compounds according to any one of formulas 13, 13-1, 13-2, 13-3, 13-4, 13-5, 13-6, 13-6a, 13-6b, 13-6c, 13-6d, 13-7, 13-8, 13-9, 13-10, 13-11, 13-11a, 13-11b, 13-11c, 13-12, 13-13, 13-14, or 13-15, 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2c, 14-2f, 14-2g, 14-2h, 14-2i, 14-3, 14-3a, 14-3a1, 14-3a2, 14-3a3, 14-3a4, 14-3a5, 14-3a6, 14-3a7, 14-3a8, 14-3a9, 14-3a10, 14-3b, 14-3c, 14-3c1, 14-4, 14-4a, 14-4b, 14-4c, 14-4c1, 14-4d, 14-4d1, 14-4d2, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, 14-5f, 14-5f1, 14-5f2, 14-5f3, 14-5f4, 14-5f5, 14-5f6, 14-5g, 14-5g1, 14-5g2, 14-5g3, 14-5g4, 14-5g5, 14-5g6, 14-5g7, 14-5g8, 14-5g9, 14-5g10, 14-5h, 14-5h1, 14-5h2, 14-5i, or 14-5j, wherein the heteroaryl group (ring A of Formula I) is thienyl optionally substituted with 1 or 2 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, hydroxy, amino, or mono or di(C_1-C_4 alkyl)amino.

In yet still another aspect, the invention provides compounds of formula 14-13, i.e., compounds of formula 14-12 where the thienyl group is substituted with one group that is halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, hydroxy, amino, or mono or di(C_1-C_4 alkyl)amino.

In yet still another aspect, the invention provides compounds of formula 14-13a, i.e., compounds of formula 14-12 where the thienyl group is substituted with one group that is optionally substituted heteroaryl (for example pyridyl).

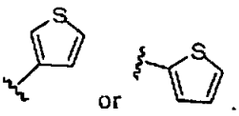
In yet still another aspect, the invention provides compounds of formula 14-14, i.e., compounds of formula 14-13, wherein the thienyl group is substituted with one halogen (preferably Cl).

In yet still another aspect, the invention provides compounds of formula 14-15, i.e., compounds of formula 14-14, wherein the thienyl group has the formula:



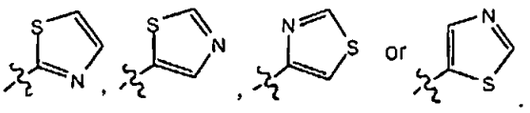
In yet still another aspect, the invention provides compounds of formula 14-16, i.e., compounds of formula 14-12, wherein the thienyl group is unsubstituted.

In yet still another aspect, the invention provides compounds of formula 14-17, i.e., compounds of formula 14-16, wherein the thienyl group has the formula:



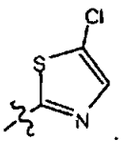
In yet still another aspect, the invention provides compounds of formula 14-18, i.e., compounds according to any one of formulas 13, 13-1, 13-2, 13-3, 13-4, 13-5, 13-6, 13-6a, 13-6b, 13-6c, 13-6d, 13-7, 13-8, 13-9, 13-10, 13-11, 13-11a, 13-11b, 13-11c, 13-12, 13-13, 13-14, or 13-15, 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2e, 14-2f, 14-2g, 14-2h, 14-2i, 14-3, 14-3a, 14-3a1, 14-3a2, 14-3a3, 14-3a4, 14-3a5, 14-3a6, 14-3a7, 14-3a8, 14-3a9, 14-3a10, 14-3b, 14-3c, 14-3c1, 14-4, 14-4a, 14-4b, 14-4c, 14-4c1, 14-4d, 14-4d1, 14-4d2, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, 14-5f, 14-5f1, 14-5f2, 14-5f3, 14-5f4, 14-5f5, 14-5f6, 14-5g, 14-5g1, 14-5g2, 14-5g3, 14-5g4, 14-5g5, 14-5g6, 14-5g7, 14-5g8, 14-5g9, 14-5g10, 14-5h, 14-5h1, 14-5h2, 14-5i, or 14-5j, wherein the heteroaryl group (ring A of Formula I) comprises thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, or oxazolyl optionally substituted with 1 or 2 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, hydroxy, amino, or mono or di(C_1-C_4 alkyl)amino.

In yet still another aspect, the invention provides compounds of formula 14-19, i.e., compounds of formula 14-18, wherein the thiazolyl group is unsubstituted and has the formula:

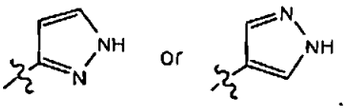


In yet still another aspect, the invention provides compounds of formula 14-19a, i.e., compounds of formula 14-18 where the heteroaryl group (ring A of Formula I) is a thiazolyl group that is substituted with one or two groups that are halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, hydroxy, amino, or mono or di(C_1-C_4 alkyl)amino.

In yet still another aspect, the invention provides compounds of formula 14-19b, i.e., compounds of formula 14-18, wherein the heteroaryl group (ring A of Formula I) is a thiazolyl group that has the formula:

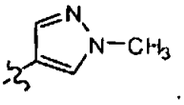


In yet still another aspect, the invention provides compounds of formula 14-20, i.e., compounds of formula 14-18, wherein the heteroaryl group (ring A of Formula I) is a pyrazolyl group that is unsubstituted and has the formula:

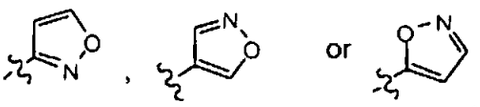


In yet still another aspect, the invention provides compounds of formula 14-20a, i.e., compounds of formula 14-18 where the heteroaryl group (ring A of Formula I) is a pyrazolyl group that is substituted with one or two groups that arehalogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkyoxy, hydroxy, amino, or mono or di(C_1-C_4 alkyl)amino.

In yet still another aspect, the invention provides compounds of formula 14-20b, i.e., compounds of formula 14-18, wherein the heteroaryl group (ring A of Formula I) is a pyrazolyl group that has the formula:

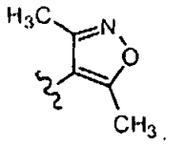


In yet still another aspect, the invention provides compounds of formula 14-21, i.e., compounds of formula 14-18, wherein the heteroaryl group (ring A of Formula I) is an isoxazolyl group that is unsubstituted and has the formula:

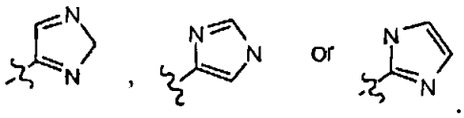


In yet still another aspect, the invention provides compounds of formula 14-21a, i.e., compounds of formula 14-18 where the heteroaryl group (ring A of Formula I) is an isoxazolyl group that is substituted with one or two groups that are halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, hydroxy, amino, or mono or di(C_1-C_4 alkyl)amino.

In yet still another aspect, the invention provides compounds of formula 14-21b, i.e., compounds of formula 14-18, wherein the heteroaryl group (ring A of Formula I) is an isoxazolyl group that has the formula:

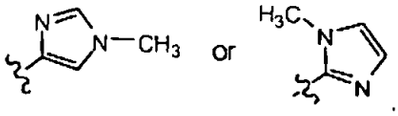


In yet still another aspect, the invention provides compounds of formula 14-22, i.e., compounds of formula 14-18, wherein the heteroaryl group (ring A of Formula I) is an imidazolyl group that is unsubstituted and has the formula:



In yet still another aspect, the invention provides compounds of formula 14-22a, i.e., compounds of formula 14-18 where the heteroaryl group (ring A of Formula I) is an imidazolyl group that is substituted with one or two groups that are halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, hydroxy, amino, or mono or di(C_1-C_4 alkyl)amino.

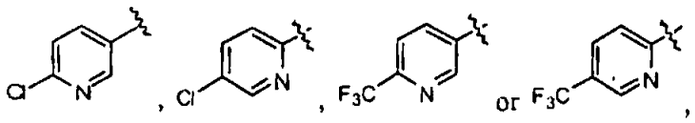
In yet still another aspect, the invention provides compounds of formula 14-22b, i.e., compounds of formula 14-18, wherein the heteroaryl group (ring A of Formula I) is an imidazolyl group that has the formula:



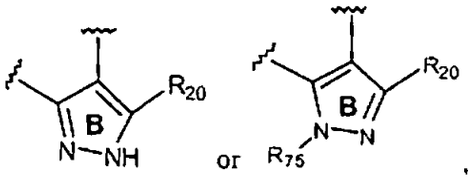
In yet still another aspect, the invention provides compounds of formula 14-23, i.e., compounds according to any one of formulas 12, 13, 13-1, 13-2, 13-3, 13-4, 13-5, 13-6, 13-6a, 13-6b, 13-6c, 13-6d, 13-7, 13-8, 13-9, 13-10, 13-11, 13-11a, 13-11b, 13-11c, 13-12, 13-13, 13-14, or 13-15, 14, 14-1, 14-2, 14-2a, 14-2b, 14-2c, 14-2d, 14-3, 14-4, 14-4a, 14-4b, 14-4c, 14-4c1, 14-4d, 14-4d1, 14-4d2, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, 14-5f, 14-5f1, 14-5f2, 14-5f3, 14-5f4, 14-5f5, or 14-5f6, wherein R_1 is H; R_2 is H, or C_3-C_6

cycloalkyl; R_{20} is H or methyl; R_{75} is H or methyl; and the C-ring is phenyl substituted with two halogens. In one embodiment, R_{20} and R_{75} are both hydrogen.

In another aspect, the invention provides compounds of formula 14-24, i.e., compounds according to formula 13, wherein the A-ring is a heteroaryl group, which has the following structures:



R_1 is hydrogen or methyl; R_2 is H, methyl, or cyclopropyl; the C-ring is phenyl substituted with 1 or 2 groups that are independently Cl, F, methyl, ethyl, isopropyl, methoxy, ethoxy, CF_3, OCF_3, OH, CH_2OH, NH_2, $NH(CH_3)$, or $N(CH_3)_2$; and the B-ring has the formula:



where R_{20} and R_{75} are independently H, methyl or ethyl. In one embodiment, the C-ring is bis-substituted with at least one halogen. In another embodiment, the halogen is F. In still another embodiment, the halogen is Cl. In another embodiment, the C-ring is bis-substituted with two halogens, which are the same or different. In still another embodiment, the C-ring is substituted at least at position 7. In another embodiment, the C-ring is substituted at positions 7 and 8. In yet another embodiment, the C-ring is substituted with two halogens, which are the same, and are attached to positions 7 and 8. In another embodiment, the C-ring is monosubstituted with a halogen. In another embodiment, the halogen is F. In still another embodiment, the halogen is Cl. In still another embodiment, the C-ring is substituted at position 7. In yet another embodiment, the C-ring is substituted at position 8.

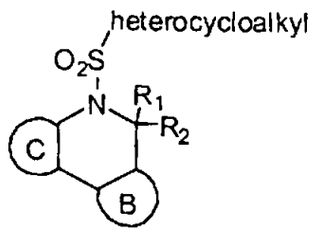
In another aspect, the invention provides compounds of formula 15, i.e., compounds of formula I, wherein

the A-ring is heterocycloalkyl, which is optionally substituted at a substitutable position with halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, hydroxyl, hydroxy-(C_1-C_4 alkyl), CN, aryloxy, aryl-(C_1-C_4alkoxy) such as benzyloxy, -SO_2-(C_1-C_6 alkyl), -NR'R", C_1-C_6 alkanoyl, -C(O)OR', -(C_1-C_4 alkyl)-C(O)OR', heteroaryl, aryl, aryl C_1-C_4 alkyl, -SO_2-NR'R", -C(O)NR'R",

-OC(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", -NR'C(O)O-(C_1-C_6 alkyl), or -NR'C(O)O-phenyl, where each R' and R" is independently hydrogen or C_1-C_6 alkyl; and

the B-ring is pyrazolyl, imidazolyl, pyrrolyl, triazolyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, pyridyl, pyrimidyl, or isoxazolyl, each of which is optionally substituted at a substitutable position with a group that is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, -NR'R", -SO_2-NR'R", -C(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, NO_2, CN, -C(O)OR', hydroxyl, hydroxy-(C_1-C_6 alkyl), -S(O)$_Z$ (C_1-C_6 alkyl), -S(O)$_Z$ aryl, halogen, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, benzyl, or phenyl.

In another aspect, the invention provides compounds of formula 16, i.e., compounds of either formula I or formula 15, having the structure



Formula 16

stereoisomers, tautomers, mixtures of stereoisomers and/or tautomers or pharmaceutically acceptable salts thereof, wherein

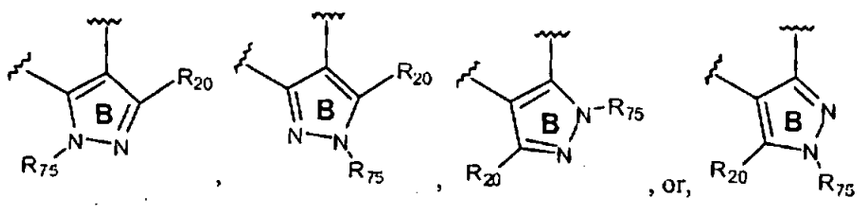
the heterocycloalkyl group is optionally substituted at each substitutable position with halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, hydroxyl, hydroxy-(C_1-C_4 alkyl), CN, NO_2, aryloxy, aryl-(C_1-C_4alkoxy),-SO_2-(C_1-C_6 alkyl), -NR'R", C_1-C_6 alkanoyl, -C(O)OR', -(C_1-C_4alkyl)-C(O)OR', pyridyl, phenyl, phenyl-(C_1-C_4 alkyl), -SO_2-NR'R", -C(O)NR'R", -OC(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", or -NR'CO(O)R', where each R' and R" is independently hydrogen or C_1-C_6 alkyl; and

wherein the C-ring is cyclohexyl, phenyl, thienyl, imidazolinyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrrolyl, pyrazolyl, pyrimidyl, pyrazinyl or pyridyl, each of which is optionally substituted at each substitutable position with groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, aryloxy, aryl-(C_1-C_4 alkoxy), C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, hydroxyl, hydroxy-(C_1-C_6 alkyl)-, -NR'R", -(C_1-C_6 alkyl)-NR'R", -NR'C(O)O-

(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, oxo, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -S(O)z aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl),or -S(O)z (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2 or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, CF_3, OCF_3, hydroxyl, hydroxy-(C_1-C_4 alkyl), or -NR'R".

In another aspect, the invention provides compounds of formula 16-1, i.e., compounds of formula 16, wherein the B-ring is pyrazolyl, imidazolyl, pyrrolyl, triazolyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, pyridyl, pyrimidyl, or isoxazolyl, each of which is unsubstituted.

In another aspect, the invention provides compounds of formula 16-2, i.e., compounds of formula 16, wherein the B-ring has the formula:

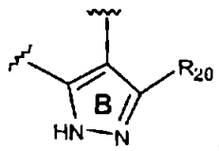


wherein

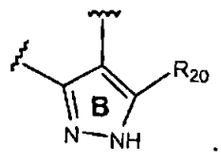
R_{20} is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, -NR'R", -(C_1-C_4 alkyl)-NR'R", -S(O)z (C_1-C_6 alkyl), hydroxyl, halogen, CN, NO_2, CH_2F, CHF_2, CF_3, -C(O)OR', -C(O)NR'R", -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", or phenyl, and

R_{75} is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl-(C_1-C_6 alkanoyl), -C(O)NR'R", -S(O)$_2$-(C_1-C_6) alkyl, -S(O)$_2$-aryl, -SO_2NR'R, phenyl, phenyl-(C_1-C_6 alkyl) (preferably phenethyl or benzyl, more preferably, benzyl), phenylcarbonyl, benzylcarbonyl, or heteroarylcarbonyl., where the heteroaryl group is pyridyl, pyrimidyl, thienyl or furanyl.

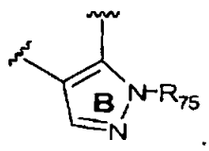
In another aspect, the invention provides compounds of formula 16-3, i.e., compounds of formula 16-2, wherein the B-ring has the formula:



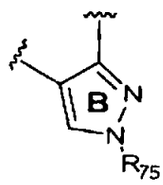
In another aspect, the invention provides compounds of formula 16-4, i.e., compounds of formula 16-2, wherein the B-ring has the formula:



In another aspect, the invention provides compounds of formula 16-5, i.e., compounds of formula 16-2, wherein the B-ring has the formula:



In another aspect, the invention provides compounds of formula 16-6, i.e., compounds of formula 16-2, wherein the B-ring has the formula:



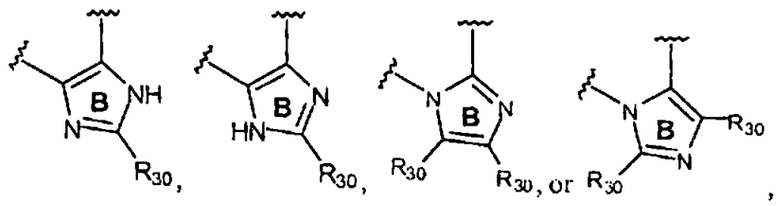
In a further aspect, the invention provides compounds of formula 16-6a, i.e., compounds according to any one of formulas 16-2, 16-3, or 16-4, wherein R_{20} is hydrogen, C_1-C_4 alkyl, CH_2F, CHF_2, CF_3, -C(O)OR', -S(O)z (C_1-C_4 alkyl), or hydroxyl.

In another aspect, the invention provides compounds of formula 16-6b, i.e., compounds of formula 16-6a, wherein R_{20} is hydrogen or methyl.

In yet another aspect, the invention provides compounds of formula 16-6c, i.e., compounds according to any one of formulas 16-2, 16-5 or 16-6, wherein R_{75} is hydrogen or methyl.

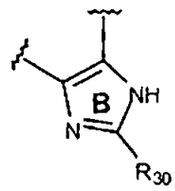
In still yet another aspect, the invention provides compounds of formula 16-6d, i.e., compounds according to any one of formulas 16-2, 16-5 or 16-6, wherein R_{75} is hydrogen.

In another aspect, the invention provides compounds of formula 16-7, i.e., compounds of formula 16, wherein the B-ring has the formula:

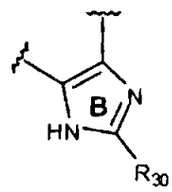


wherein R_{30} is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, -NR'R", C_1-C_4 alkythio, hydroxyl, halogen, CH_2F, CHF_2, CF_3, or phenyl.

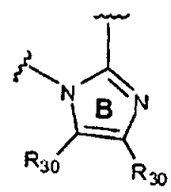
In another aspect, the invention provides compounds of formula 16-8, i.e., compounds of formula 16-7, wherein the B-ring has the formula:



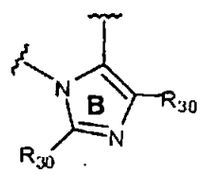
In another aspect, the invention provides compounds of formula 16-9, i.e., compounds of formula 16-7, wherein the B-ring has the formula:



In another aspect, the invention provides compounds of formula 16-10, i.e., compounds of formula 16-7, wherein the B-ring has the formula:



In another aspect, the invention provides compounds of formula 16-11, i.e., compounds of formula 16-7, wherein the B-ring has the formula:

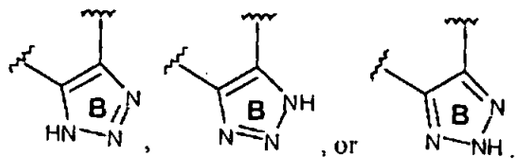


In a further aspect, the invention provides compounds of formula 16-11a, i.e., compounds according to any one of formulas 16-8, 16-9, 16-10, or 16-11, wherein each R_{30} is independently hydrogen, C_1-C_4 alkyl, CH_2F, CHF_2, or CF_3.

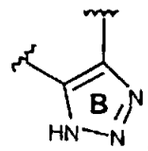
In another aspect, the invention provides compounds of formula 16-11b, i.e., compounds of formula 16-11a, wherein each R_{30} is independently hydrogen or methyl.

In still another aspect, the invention provides compounds of formula 16-11c, i.e., compounds of formula 16-11a, wherein each R_{30} is hydrogen.

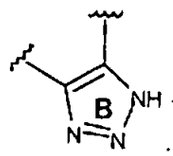
In another aspect, the invention provides compounds of formula 16-12, i.e., compounds of formula 16, wherein the B-ring has the formula:



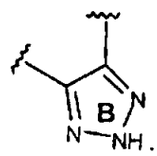
In another aspect, the invention provides compounds of formula 16-13, i.e., compounds of formula 16-12, wherein the B-ring has the formula:



In another aspect, the invention provides compounds of formula 16-14, i.e., compounds of formula 16-12, wherein the B-ring has the formula:



In another aspect, the invention provides compounds of formula 16-15, i.e., compounds of formula 16-12, wherein the B-ring has the formula:



In another aspect, the invention provides compounds of formula 17, i.e., compounds of formulas 15, 16, 16-1, 16-2, 16-3, 16-4, 16-5, 16-6, 16-6a, 16-6b, 16-6c, 16-6d, 16-7, 16-8, 16-9, 16-10, 16-11, 16-11a, 16-11b, 16-11c, 16-12, 16-13, 16-14, or 16-15 wherein the C-ring is phenyl or cyclohexyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryloxy, aryl-(C_1-C_6 alkoxy), C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", -(C_1-C_4 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R";

-(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, oxo, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -$S(O)_z$ aryl, or -$S(O)_z$ (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1 or 2 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In one embodiment, the C-ring is an optionally substituted phenyl.

In another aspect, the invention provides compounds of formula 17-1, i.e., compounds of formula 17 wherein the C-ring is unsubstituted phenyl.

In another aspect, the invention provides compounds of formula 17-1a, i.e., compounds of formula 17 wherein the C-ring is unsubstituted cyclohexyl.

In yet another aspect, the invention provides compounds of formula 17-2, i.e., compounds of formula 17 wherein the C-ring is phenyl substituted with 1 or 2 groups that are independently Cl, F, methyl, ethyl, isopropyl, methoxy, ethoxy, CF_3, OCF_3, OH, CH_2OH, NH_2, $NH(CH_3)$, or $N(CH_3)_2$, or -$OC(O)N(CH_3)_2$. In one embodiment, the C-ring is bis-substituted with at least one halogen. In another embodiment, the halogen is F. In still another embodiment, the halogen is Cl. In another embodiment, the C-ring is bis-substituted with two halogens, which are the same or different. In still another embodiment, the C-ring is substituted at least at position 7. In another embodiment, the C-ring is substituted at positions 7 and 8. In another embodiment, the C-ring is monosubstituted with a halogen. In another embodiment, the halogen is F. In still another embodiment, the halogen is Cl. In still another embodiment, the C-ring is substituted at position 7. In yet another embodiment, the C-ring is substituted at position 8.

In still yet another aspect, the invention provides compounds of formula 17-2a, i.e., compounds of formula 17, wherein the C-ring is phenyl substituted with 1 or 2 groups that are independently -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R", -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, phenyl, -$S(O)_z$ phenyl, or -$S(O)_z$ (C_1-C_6 alkyl), where the phenyl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-C_1-C_6 alkyl, or -NR'R". In one embodiment,

the C-ring is substituted at least at the 7-position. In another embodiment, the C-ring is substituted at least at the 8-position.

In still another aspect, the invention provides compounds of formula 17-2b, i.e., compounds of formula 17, wherein the C-ring is phenyl substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1 or 2 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_4 alkoxy. In one embodiment, the C-ring is substituted at least at the 7-position. In another embodiment, the C-ring is substituted at least at the 8-position.

In still another aspect, the invention provides compounds of formula 17-2c, i.e., compounds of formula 17, wherein the C-ring is phenyl substituted with 1 or 2 groups that are independently –C(O)OH, -C(O)O-(C_1-C_4 alkyl), NO_2, CN, or phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In one embodiment, the C-ring is substituted at least at the 7-position. In another embodiment, the C-ring is substituted at least at the 8-position.

In yet another aspect, the invention provides compounds of formula 17-2d, i.e., compounds of formula 17, wherein the C-ring is phenyl substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R", -NR'C(O)O-(C_1-C_6 alkyl) or -NR'C(O)O-phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In one embodiment, the C-ring is substituted at least at the 7-position. In another embodiment, the C-ring is substituted at least at the 8-position.

In yet another aspect, the invention provides compounds of formula 17-2e, i.e., compounds of formula 17 wherein the C-ring is cyclohexyl substituted with 1 or 2 groups that are independently Cl, F, methyl, ethyl, isopropyl, methoxy, ethoxy, CF_3, OCF_3, OH, CH_2OH, NH_2, $NH(CH_3)$, $N(CH_3)_2$, or -$OC(O)N(CH_3)_2$.

In still yet another aspect, the invention provides compounds of formula 17-2f, i.e., compounds of formula 17, wherein the C-ring is cyclohexyl substituted with 1 or 2 groups that are independently -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R", -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-

C(O)NR'R", -NR'C(O)R", NO_2, CN, phenyl, -S(O)2 aryl, or -S(O)2 (C_1-C_6 alkyl), where the phenyl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

In still another aspect, the invention provides compounds of formula 17-2g, i.e., compounds of formula 17, wherein the C-ring is cyclohexyl substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1 or 2 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_4 alkoxy.

In still another aspect, the invention provides compounds of formula 17-2h, i.e., compounds of formula 17, wherein the C-ring is cyclohexyl substituted with 1 or 2 groups that are independently –C(O)OH, -C(O)O-(C_1-C_4 alkyl), NO_2, CN, or phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

In yet another aspect, the invention provides compounds of formula 17-2i, i.e., compounds of formula 17, wherein the C-ring is cyclohexyl substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R", -NR'C(O)O-(C_1-C_6 alkyl) or -NR'C(O)O-phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

In yet another aspect, the invention provides compounds of formula 17-3, i.e., compounds of formula 17 wherein the C-ring is phenyl or cyclohexyl substituted with one or two groups that are Cl, F, methyl, ethyl, isopropyl, methoxy, CF_3, OCF_3, OH, or -OC(O)N(CH_3)2.

In yet still another aspect, the invention provides compounds of formula 17-3a, i.e., compounds according to any one of formulas 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, or 17-3, wherein R_2 is -X(CO)Y or -($C(R_3)_2$)1-4X(CO)Y.

In still another aspect, the invention provides compounds of formula 17-3a1, i.e., compounds according to any one of formulas 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, or 17-3, wherein R_2 is hydrogen, C_1-C_3 alkyl or C_3-C_6 cycloalkyl.

In still another aspect, the invention provides compounds of formula 17-3a2, i.e., compounds according to any one of formulas 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, or 17-3, wherein R_2 is NO_2 or CN.

In still another aspect, the invention provides compounds of formula 17-3a3, i.e., compounds according to any one of formulas 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, or 17-3, wherein R_2 is C_2-C_6 alkenyl or C_2-C_6 alkynyl.

In still another aspect, the invention provides compounds of formula 17-3a4, i.e., compounds according to any one of formulas 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, or 17-3, wherein R_2 is C_1-C_4 haloalkyl.

In still another aspect, the invention provides compounds of formula 17-3a5, i.e., compounds according to any one of formulas 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, 17-3, 17-3a, 17-3a1, 17-3a2, 17-3a3, or 17-3a4, wherein R_1 is hydrogen.

In still yet another aspect, the invention provides compounds of formula 17-3a6, i.e., compounds according to any one of formulas 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, or 17-3, wherein R_1 and R_2 combined are oxo.

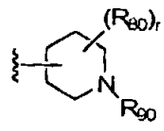
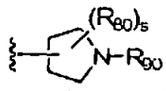
In still yet another aspect, the invention provides compounds of formula 17-3a7, i.e., compounds according to any one of formulas 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, or 17-3, wherein R_1 and R_2 combined are =N-OR, where R is hydrogen, C_1-C_6 alkyl, aryl (such as phenyl) or arylalkyl (such as benzyl or phenethyl).

In yet another aspect, the invention provides compounds of formula 17-3a8, i.e., compounds according to any one of formulas 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, or 17-3, wherein R_1 and R_2 together with the carbon to which they are attached form a C_3-C_6 cycloalkyl group.

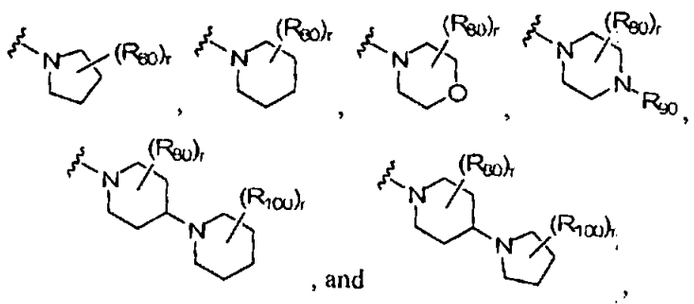
In yet another aspect, the invention provides compounds of formula 17-3a9, i.e., compounds according to any one of formulas 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, or 17-3, wherein R_1 and R_2 together with the carbon to which they are attached form a cyclopropyl group.

In yet another aspect, the invention provides compounds of formula 17-3a10, i.e., compounds according to any one of formulas 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, or 17-3, wherein R_1 is hydrogen and R_2 is cyclopropyl. In one embodiment, the compound is racemic. In another embodiment, the compound is enantiomerically enriched.

In yet still another aspect, the invention provides compounds of formula 17-3b, i.e., compounds of formula 17-3a, wherein

X is O; and Y is $-NR_{60}R_{70}$ or $-N(R_{30})(CH_2)_{2-6}NR_{60}R_{70}$; where R_{60} and R_{70} are independently selected from: hydrogen, methyl, ethyl, (C_3-C_8)cycloalkyl, aryl-(C_1-C_6 alkyl) (such as benzyl or phenethyl), 4-pyridylmethyl,  or  ; or

R_{60} and R_{70} taken together with the nitrogen atom to which they are bound form a heterocycloalkyl group selected from



, and

where

each R_{80} is independently unsubstituted C_1-C_4 alkyl or C_1-C_4 alkyl substituted with hydroxyl or halogen groups;

each R_{90} is independently hydrogen, unsubstituted C_1-C_4 alkyl, C_1-C_4 alkyl substituted with hydroxyl or halogen, unsubstituted C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl substituted with one or more (e.g., 1-4) R_{50}, phenyl-(C_1-C_4 alkyl), pyridyl-(C_1-C_4 alkyl), thienyl-(C_1-C_4 alkyl), -C(O)O-(C_1-C_4 alkyl), -C(O)O-phenyl, $-SO_2$-(C_1-C_6alkyl), $-SO_2$-phenyl, unsubstituted phenyl, phenyl substituted with one or more (e.g., 1-4) R_{50} groups, pyridyl, thienyl, pyridyl substituted with one or more (e.g., 1-4) R_{50} groups, thienyl substituted with one or more (e.g., 1-4) R_{50} groups, where

each R_{50} is independently selected from: halogen, C_1-C_6 alkyl, - C_1-C_6 haloalkyl, -OH, -O (C_1-C_4 alkyl), OCF_3, -CN, - $NR_{60}R_{70}$, -C(O)O-(C_1-C_4 alkyl), $-CONR_{60}R_{70}$, -(C_1-C_6 alkyl)-$NR_{60}R_{70}$, $-NR_{60}CO$-(C_1-C_4 alkyl), $-NR_{60}CO$-phenyl, $-NR_{60}CO$-pyridyl, $-NR_{60}CO$-thienyl, and $-NR_{60}CONR_{60}R_{70}$,

each R_{100} is independently hydrogen or C_1-C_4 alkyl;

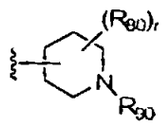
each r is 0 to 4; and

each s is 0 to 3.

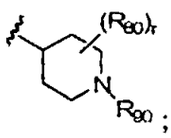
In yet still another aspect, the invention provides compounds of formula 17-3b1, i.e., compounds of formula 17-3a, wherein Y is –O-(C_1-C_6 alkyl). In one embodiment, Y is –O-(C_1-C_4 alkyl).

In yet still another aspect, the invention provides compounds of formula 17-3b2, i.e., compounds of formula 17-3a, wherein Y is –O-phenyl.

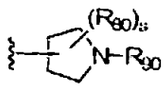
In yet still another aspect, the invention provides compounds of formula 17-3c, i.e., compounds of formula 17-3b, wherein said group



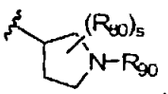
is a group of the formula:



and, said group

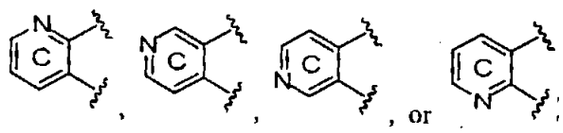


is a group of the formula:



In a further aspect, the invention provides compounds of formula 17-3d, i.e., compounds according to any one of formulas, 17-3b, 17-3b1, 17-3b2, or 17-3c, wherein R_1 is H or C_1-C_4 alkyl. In one embodiment, R_1 is H or methyl. In another embodiment, R_1 is H.

In yet another aspect, the invention provides compounds of formula 17-4, i.e., compounds according to any one of formulas 15, or any of the formulas 16, 16-1, 16-2, 16-3, 16-4, 16-5, 16-6, 16-6a, 16-6b, 16-6c, 16-6d, 16-7, 16-8, 16-9, 16-10, 16-11, 16-11a, 16-11b, 16-11c, 16-12, 16-13, 16-14, or 16-15, wherein the C-ring is

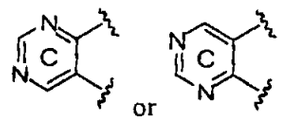


or N-oxide derivatives therof,

each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryloxy, aryl-(C_1-C_4 alkoxy), C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R",

-(C_1-C_4 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R", NO_2, CN, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$ aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl), or -S(O)$_z$ (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2 or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In one embodiment, the invention provides compounds wherein the C-ring is pyridyl or pyridyl N-oxide substituted with 1 or 2 groups that are independently -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -C(O)OR', -C(O)NR'R", -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R", NO_2, CN, phenyl, -S(O)$_z$ aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl) or -S(O)$_z$ (C_1-C_6 alkyl) where the aryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In an alternative embodiment, the C-ring is pyridyl or pyridyl N-oxide substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1 or 2 groups that are independently halogen, hydroxy, -NR'R" or C_1-C_4 alkoxy. In another alternative embodiment, the C-ring is pyridyl or pyridyl N-oxide substituted with 1 or 2 groups that are independently -C(O)O-(C_1-C_4 alkyl), NO_2, CN, or phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In still another alternative embodiment, the C-ring is pyridyl or pyridyl N-oxide substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, -C(O)NR'R", NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R", -NR'C(O)O-(C_1-C_6 alkyl) or -NR'C(O)O-phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

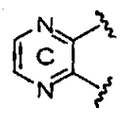
In still another aspect, the invention provides compounds of formula 17-4a, i.e., compounds of formula 15 or any one of formulas 15, 16, 16-1, 16-2, 16-3, 16-4, 16-5, 16-6, 16-6a, 16-6b, 16-6c, 16-6d, 16-7, 16-8, 16-9, 16-10, 16-11, 16-11a, 16-11b, 16-11c, 16-12, 16-13, 16-14, or 16-15, wherein the C-ring is



each of which is optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryloxy, aryl-(C_1-C_4 alkoxy), C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", -(C_1-C_4 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -S(O)z aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl), or -S(O)z (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2 or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In one embodiment, the invention provides compounds wherein the C-ring is pyrimidinyl substituted with 1 or 2 groups that are independently -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R", -(C_1- C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, phenyl, -S(O)z aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl) or -S(O)z (C_1-C_6 alkyl) where the aryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In an alternative embodiment, the C-ring is pyrimidinyl substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1 or 2 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_4 alkoxy. In another alternative embodiment, the C-ring is pyrimidinyl substituted with 1 or 2 groups that are independently –C(O)OH, -C(O)O-(C_1-C_4 alkyl), NO_2, CN, or phenyl, where

the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In still another alternative embodiment, the C-ring is pyrimidinyl substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R", -NR'C(O)O-(C_1-C_6 alkyl) or - NR'C(O)O-phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

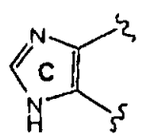
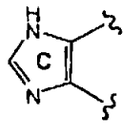
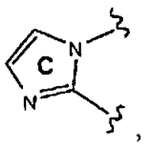
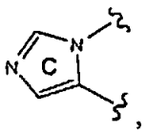
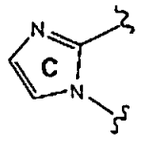
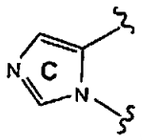
In still another aspect, the invention provides compounds of formula 17-4b, i.e., compounds of formula 15 or any one of formulas 15, 16, 16-1, 16-2, 16-3, 16-4, 16-5, 16-6, 16-6a, 16-6b, 16-6c, 16-6d, 16-7, 16-8, 16-9, 16-10, 16-11, 16-11a, 16-11b, 16-11c, 16-12, 16-13, 16-14, or 16-15, wherein the C-ring is



which is optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryloxy, aryl-(C_1-C_4 alkoxy), C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", -(C_1-C_4 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_4 alkyl)-C(O)OR', -(C_1-C_4 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, benzyl, phenyl, pyridyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -S(O)z aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl), or -S(O)z (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2 or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In one embodiment, the invention provides compounds wherein the C-ring is pyrazine substituted with 1 or 2 groups that are independently -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R", -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, phenyl, -S(O)z aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl) or -S(O)z (C_1-C_6 alkyl) where

the aryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In an alternative embodiment, the C-ring is pyrazine substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1 or 2 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_4 alkoxy. In another alternative embodiment, the C-ring is pyrazine substituted with 1 or 2 groups that are independently –C(O)OH, -C(O)O-(C_1-C_4 alkyl), NO_2, CN, or phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R". In still another alternative aspect, the C-ring is pyrazine substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R", or -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, where the phenyl group is optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

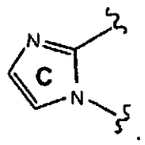
In still another aspect, the invention provides compounds of formula 17-4c, i.e., compounds of formula 15 or any of the formulas 15, 16, 16-1, 16-2, 16-3, 16-4, 16-5, 16-6, 16-6a, 16-6b, 16-6c, 16-6d, 16-7, 16-8, 16-9, 16-10, 16-11, 16-11a, 16-11b, 16-11c, 16-12, 16-13, 16-14, or 16-15, wherein the C-ring is:


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or

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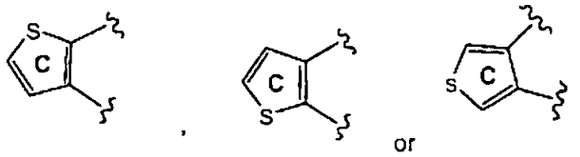
each of which is optionally substituted with 1 or 2 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryloxy, aryl-(C_1-C_4 alkoxy), C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", -(C_1-C_6 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6

alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -$S(O)_z$ aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl), or -$S(O)_z$ (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

In still another aspect, the invention provides compounds of formula 17-4c1, i.e., compounds of formula 17-4c wherein the C-ring is:



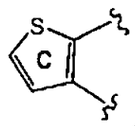
In still another aspect, the invention provides compounds of formula 17-4d, i.e., compounds of formula 15 or any of the formulas 15, 16, 16-1, 16-2, 16-3, 16-4, 16-5, 16-6, 16-6a, 16-6b, 16-6c, 16-6d, 16-7, 16-8, 16-9, 16-10, 16-11, 16-11a, 16-11b, 16-11c, 16-12, 16-13, 16-14, or 16-15, wherein the C-ring is


or

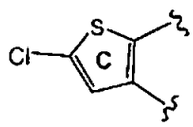
each of which is optionally substituted with 1 or 2 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryloxy, aryl-(C_1-C_4 alkoxy), C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", -(C_1-C_6 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -$S(O)_z$ aryl (where the aryl group is preferably naphthyl or phenyl, still more preferably, phenyl), or -$S(O)_z$ (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with

1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

In still another aspect, the invention provides compounds of formula 17-4d1, i.e., compounds of formula 17-4d wherein the C-ring is:



In still another aspect, the invention provides compounds of formula 17-4d2, i.e., compounds of formula 17-4d wherein the C-ring is:

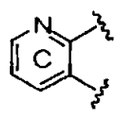


In another aspect, the invention provides compounds of formula 17-5, i.e., compounds according to formula 17-4, 17-4a, 17-4b, 17-4c, or 17-4d wherein the C-ring is unsubstituted.

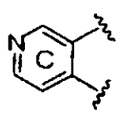
In another aspect, the invention provides compounds of formula 17-5a, i.e., compounds of formula 17-4, 17-4a, 17-4b, 17-4c, or 17-4d wherein the C-ring is substituted with 1 or 2 groups that are independently Cl, F, methyl, ethyl, isopropyl, methoxy, ethoxy, CF_3, OCF_3, OH, or $-C(O)CH_3$.

In yet another aspect, the invention provides compounds of formula 17-5b, i.e., compounds of formula 17-4, 17-4a, 17-4b, 17-4c, or 17-4d wherein the C-ring is substituted with 1 or 2 groups that are Cl, F, or methyl.

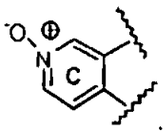
In still yet another aspect, the invention provides compounds of formula 17-5c, i.e., compounds according to any one of formulas 17-4, 17-5, 17-5a, or 17-5b, where the C-ring has the following structure:



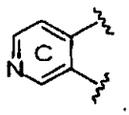
In still yet another aspect, the invention provides compounds of formula 17-5d, i.e., compounds according to any one of formulas 17-4, 17-5, 17-5a, or 17-5b, where the C-ring has the following structure:



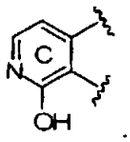
In still yet another aspect, the invention provides compounds of formula 17-5d1, i.e., compounds according to any one of formulas 17-4, 17-5, 17-5a, or 17-5b, where the C-ring has the following structure:



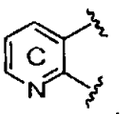
In still yet another aspect, the invention provides compounds of formula 17-5c, i.e., compounds according to any one of formulas 17-4, 17-5, 17-5a, or 17-5b, where the C-ring has the following structure:



In still yet another aspect, the invention provides compounds of formula 17-5c1, i.e., compounds according to formula 17-4, where the C-ring has the following structure:



In still yet another aspect, the invention provides compounds of formula 17-5f, i.e., compounds according to any one of formulas 17-4, 17-5, 17-5a, or 17-5b, where the C-ring has the following structure:



In a further aspect, the invention provides compounds of formula 17-5f1, i.e., compounds of formula 15 or any of the formulas 15, 16, 16-1, 16-2, 16-3, 16-4, 16-5, 16-6, 16-6a, 16-6b, 16-6c, 16-6d, 16-7, 16-8, 16-9, 16-10, 16-11, 16-11a, 16-11b, 16-11c, 16-12, 16-13, 16-14, or 16-15, wherein the C-ring is thiazolyl, which is optionally substituted with 1 or 2 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryloxy, aryl-(C_1-C_4 alkoxy), C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", -(C_1-C_6 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$ aryl (where the aryl group is preferably

naphthyl or phenyl, still more preferably, phenyl), or -S(O)$_z$ (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2, or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

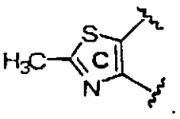
In another aspect, the invention provides compounds of formula 17-5f2, i.e., compounds of formula 17-5f1, wherein the thiazolyl ring is substituted with one group that is halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, or benzyl.

In still another aspect, the invention provides compounds of formula 17-5f3, i.e., compounds of formula 17-5f1, wherein the thiazolyl ring is substituted with C_1-C_4 alkyl.

In yet another aspect, the invention provides compounds of formula 17-5f4, i.e., compounds of formula 17-5f1, wherein the thiazolyl ring is substituted with C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", or -(C_1-C_6 alkyl)-NR'R".

In yet still another aspect, the invention provides compounds of formula 17-5f5, i.e., compounds of formula 17-5f1, wherein the thiazolyl ring is substituted with C_2-C_4 alkyl, -(C_1-C_4 alkyl)-C(O)OR', or -(C_1-C_4 alkyl)-C(O)NR'R".

In another aspect, the invention provides compounds of formula 17-5f6, i.e., compounds of formula 17-5f1, wherein the thiazolyl ring is:



In yet still another aspect, the invention provides compounds of formula 17-5g, i.e., compounds according to any one of formulas 17-4, 17-4a, 17-4b, 17-4c, 17-4c1, 17-4d, 17-4d1, 17-4d2, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, 17-5e1, 17-5f, 17-5f1, 17-5f2, 17-5f3, 17-5f4, 17-5f5, or 17-5f6, wherein R_2 is -X(CO)Y or -$(C(R_3)_2)_{1-4}$X(CO)Y.

In still another aspect, the invention provides compounds of formula 17-5g1, i.e., compounds according to any one of formulas 17-4, 17-4a, 17-4b, 17-4c, 17-4c1, 17-4d, 17-4d1, 17-4d2, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, 17-5e1, 17-5f, 17-5f1, 17-5f2, 17-5f3, 17-5f4, 17-5f5, or 17-5f6, wherein R_2 is hydrogen, C_1-C_3 alkyl or C_3-C_6 cycloalkyl.

In still another aspect, the invention provides compounds of formula 17-5g2, i.e., compounds according to any one of formulas 17-4, 17-4a, 17-4b, 17-4c, 17-4c1, 17-4d, 17-

4d1, 17-4d2, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, 17-5e1, 17-5f, 17-5f1, 17-5f2, 17-5f3, 17-5f4, 17-5f5, or 17-5f6, wherein R_2 is NO_2 or CN.

In still another aspect, the invention provides compounds of formula 17-5g3, i.e., compounds according to any one of formulas 17-4, 17-4a, 17-4b, 17-4c, 17-4c1, 17-4d, 17-4d1, 17-4d2, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, 17-5e1, 17-5f, 17-5f1, 17-5f2, 17-5f3, 17-5f4, 17-5f5, or 17-5f6, wherein R_2 is C_2-C_6 alkenyl or C_2-C_6 alkynyl.

In still another aspect, the invention provides compounds of formula 17-5g4, i.e., compounds according to any one of formulas 17-4, 17-4a, 17-4b, 17-4c, 17-4c1, 17-4d, 17-4d1, 17-4d2, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, 17-5e1, 17-5f, 17-5f1, 17-5f2, 17-5f3, 17-5f4, 17-5f5, or 17-5f6, wherein R_2 is C_1-C_4 haloalkyl.

In still another aspect, the invention provides compounds of formula 17-5g5, i.e., compounds according to any one of formulas 17-4, 17-4a, 17-4b, 17-4c, 17-4c1, 17-4d, 17-4d1, 17-4d2, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, 17-5e1, 17-5f, 17-5f1, 17-5f2, 17-5f3, 17-5f4, 17-5f5, 17-5f6, 17-5g, 17-5g1, 17-5g2, 17-5g3 or 17-5g4 wherein R_1 is hydrogen.

In still yet another aspect, the invention provides compounds of formula 17-5g6, i.e., compounds according to any one of formulas 17-4, 17-4a, 17-4b, 17-4c, 17-4c1, 17-4d, 17-4d1, 17-4d2, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, 17-5e1, 17-5f, 17-5f1, 17-5f2, 17-5f3, 17-5f4, 17-5f5, or 17-5f6, wherein R_1 and R_2 combined are oxo.

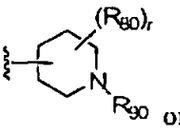
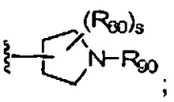
In still yet another aspect, the invention provides compounds of formula 17-5g7, i.e., compounds according to any one of formulas 17-4, 17-4a, 17-4b, 17-4c, 17-4c1, 17-4d, 17-4d1, 17-4d2, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, 17-5e1, 17-5f, 17-5f1, 17-5f2, 17-5f3, 17-5f4, 17-5f5, or 17-5f6, wherein R_1 and R_2 combined are =N-OR, where R is hydrogen, C_1-C_6 alkyl, aryl (such as phenyl) or arylalkyl (such as benzyl or phenethyl).

In yet another aspect, the invention provides compounds of formula 17-5g8, i.e., compounds according to any one of formulas 17-4, 17-4a, 17-4b, 17-4c, 17-4c1, 17-4d, 17-4d1, 17-4d2, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, 17-5e1, 17-5f, 17-5f1, 17-5f2, 17-5f3, 17-5f4, 17-5f5, or 17-5f6, wherein R_1 and R_2 together with the carbon to which they are attached form a C_3-C_6 cycloalkyl group.

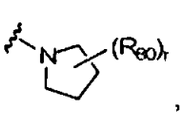
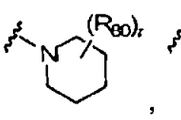
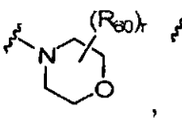
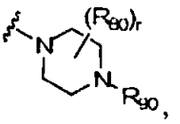
In yet another aspect, the invention provides compounds of formula 17-5g9, i.e., compounds according to any one of formulas 17-4, 17-4a, 17-4b, 17-4c, 17-4c1, 17-4d, 17-4d1, 17-4d2, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, 17-5e1, 17-5f, 17-5f1, 17-5f2, 17-5f3, 17-5f4, 17-5f5, or 17-5f6, wherein R_1 and R_2 together with the carbon to which they are attached form a cyclopropyl group.

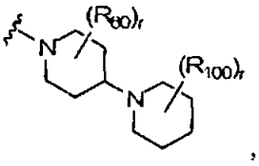
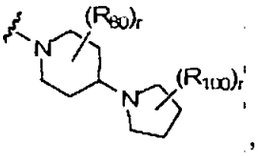
In yet another aspect, the invention provides compounds of formula 17-5g10, i.e., compounds according to any one of formulas 17-4, 17-4a, 17-4b, 17-4c, 17-4c1, 17-4d, 17-4d1, 17-4d2, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, 17-5e1, 17-5f, 17-5f1, 17-5f2, 17-5f3, 17-5f4, 17-5f5, or 17-5f6, wherein R_1 is hydrogen and R_2 is cyclopropyl. In one embodiment, the compound is racemic. In another embodiment, the compound is enantiomerically enriched.

In yet still another aspect, the invention provides compounds of formula 17-5h, i.e., compounds of formula 17-5g, wherein

X is O; and Y is $-NR_{60}R_{70}$ or $-N(R_{30})(CH_2)_{2-6}NR_{60}R_{70}$; where R_{60} and R_{70} are independently selected from: hydrogen, methyl, ethyl, (C_3-C_8)cycloalkyl, aryl-(C_1-C_6)alkyl (such as benzyl or phenethyl), 4-pyridylmethyl,  or  ; or

R_{60} and R_{70} taken together with the nitrogen atom to which they are bound form a heterocycloalkyl group selected from

 ,  ,  ,  ,

 , and  ,

where

each R_{80} is independently unsubstituted C_1-C_4 alkyl or C_1-C_4 alkyl substituted with hydroxyl or halgoen;

each R_{90} is independently hydrogen, unsubstituted C_1-C_4 alkyl, C_1-C_4 alkyl substituted with hydroxyl or halogen, unsubstituted C_2-C_8 cycloalkyl, C_3-C_8 cycloalkyl substituted with one or more (e.g., 1-4) R_5groups, phenyl-(C_1-C_4 alkyl), pyridyl-(C_1-C_4 alkyl), thienyl-(C_1-C_4 alkyl), -C(O)O-(C_1-C_4 alkyl), -C(O)O-phenyl, $-SO_2$-(C_1-C_6 alkyl), $-SO_2$-phenyl, unsubstituted phenyl, phenyl substituted with one or more (e.g., 1-4) R_{50} groups, pyridyl, thienyl, pyridyl substituted with one or more (e.g., 1-4) R_{50} groups, thienyl substituted with one or more (e.g., 1-4) R_{50} groups, where

each R_{50} is independently selected from: halogen, C_1-C_6 alkyl, - C_1-C_6 haloalkyl, -OH, -O- (C_1-C_4 alkyl), OCF_3, -CN, - $NR_{60}R_{70}$, -C(O)O-(C_1-C_4 alkyl), -$CONR_{60}R_{70}$, -(C_1-C_6 alkyl)-$NR_{60}R_{70}$, -$NR_{60}CO$-(C_1-C_4 alkyl), -$NR_{60}CO$-phenyl, -$NR_{60}CO$-pyridyl, -$NR_{60}CO$-thienyl, and -$NR_{60}CONR_{60}R_{70}$,

each R_{100} is independently hydrogen or C_1-C_4 alkyl;

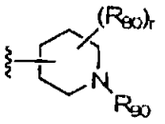
each r is 0 to 4; and

each s is 0 to 3.

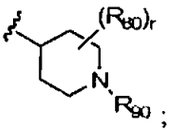
In yet still another aspect, the invention provides compounds of formula 17-5h1, i.e., compounds of formula 17-5g, wherein Y is –O-(C_1-C_6 alkyl). In one embodiment, Y is –O-(C_1-C_4 alkyl).

In yet still another aspect, the invention provides compounds of formula 17-5h2, i.e., compounds of formula 17-5g, wherein Y is –O-phenyl.

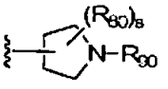
In yet still another aspect, the invention provides compounds of formula 17-5i, i.e., compounds of formula 17-5h, wherein said group



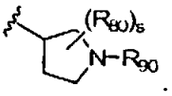
is a group of the formula:



and, said group



is a group of the formula:



In a further aspect, the invention provides compounds of formula 17-5j, i.e., compounds according to any one of formulas, 17-5h, 17-5h1, 17-5h2, or 17-5i, wherein R_1 is H or C_1-C_4 alkyl. In one embodiment, R_1 is H or methyl. In another embodiment, R_1 is H.

In yet another aspect, the invention provides compounds of formula 17-6, i.e., compounds of formulas 15, 16, 16-1, 16-2, 16-3, 16-4, 16-5, 16-6, 16-6a, 16-6b, 16-6c, 16-6d, 16-7, 16-8, 16-9, 16-10, 16-11, 16-11a, 16-11b, 16-11c, 16-12, 16-13, 16-14, or 16-15,

17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, 17-3, 17-3a, 17-3a1, 17-3a2, 17-3a3, 17-3a4, 17-3a5, 17-3a6, 17-3a7, 17-3a8, 17-3a9, 17-3a10, 17-3b, 17-3b1, 17-3b2, 17-3c, 17-3d, 17-4, 17-4a, 17-4b, 17-4c, 17-4c1, 17-4d, 17-4d1, 17-4d2, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, 17-5e1, 17-5f, 17-5f1, 17-5f2, 17-5f3, 17-5f4, 17-5f5, 17-5f6, 17-5g, 17-5g1, 17-5g2, 17-5g3, 17-5g4, 17-5g5, 17-5g6, 17-5g7, 17-5g8, 17-5g9, 17-5g10, 17-5h, 17-5h1, 17-5h2, or 17-5i, or 17-5j wherein the heterocycloalkyl group (ring A of Formula I) is morpholinyl optionally substituted with one or more groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, haloalkyl, haloalkoxy, hydroxyl, CN, aryloxy, -SO_2-(C_1-C_6 alkyl), -NR'R", C_1-C_6 alkanoyl, pyridyl, phenyl, or -SO_2-NR'R", where each R' and R" is independently hydrogen or C_1-C_6 alkyl.

In still another aspect, the invention provides compounds of formula 17-6a, i.e., compounds of formula 17-6 where the morpholinyl group is not attached to the sulfur of the SO_2 group via the ring nitrogen.

In still another aspect, the invention provides compounds of formula 17-6b, i.e., compounds of formula 17-6 where the morpholinyl group is attached to the sulfur of the SO_2 group via the ring nitrogen.

In yet another aspect, the invention provides compounds of formula 17-7, i.e., compounds of formulas 15, 16, 16-1, 16-2, 16-3, 16-4, 16-5, 16-6, 16-6a, 16-6b, 16-6c, 16-6d, 16-7, 16-8, 16-9, 16-10, 16-11, 16-11a, 16-11b, 16-11c, 16-12, 16-13, 16-14, or 16-15, 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, 17-3, 17-3a, 17-3a1, 17-3a2, 17-3a3, 17-3a4, 17-3a5, 17-3a6, 17-3a7, 17-3a8, 17-3a9, 17-3a10, 17-3b, 17-3b1, 17-3b2, 17-3c, 17-3d, 17-4, 17-4a, 17-4b, 17-4c, 17-4c1, 17-4d, 17-4d1, 17-4d2, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, 17-5e1, 17-5f, 17-5f1, 17-5f2, 17-5f3, 17-5f4, 17-5f5, 17-5f6, 17-5g, 17-5g1, 17-5g2, 17-5g3, 17-5g4, 17-5g5, 17-5g6, 17-5g7, 17-5g8, 17-5g9, 17-5g10, 17-5h, 17-5h1, 17-5h2, or 17-5i, or 17-5j wherein the heterocycloalkyl group (ring A of Formula I) is thiomorpholinyl optionally substituted with one or more groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, haloalkyl, haloalkoxy, hydroxyl, CN, aryloxy, -SO_2-(C_1-C_6 alkyl), -NR'R", C_1-C_6 alkanoyl, pyridyl, phenyl, or -SO_2-NR'R", where each R' and R" is independently hydrogen or C_1-C_6 alkyl.

In still another aspect, the invention provides compounds of formula 17-7a, i.e., compounds of formula 17-7 where the thiomorpholinyl group is not attached to the sulfur of the SO_2 group via the ring nitrogen.

In still another aspect, the invention provides compounds of formula 17-7b, i.e., compounds of formula 17-7 where the thiomorpholinyl group is attached to the sulfur of the SO_2 group via the ring nitrogen.

In yet another aspect, the invention provides compounds of formula 17-8, i.e., compounds of formulas 15, 16, 16-1, 16-2, 16-3, 16-4, 16-5, 16-6, 16-6a, 16-6b, 16-6c, 16-6d, 16-7, 16-8, 16-9, 16-10, 16-11, 16-11a, 16-11b, 16-11c, 16-12, 16-13, 16-14, or 16-15, 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, 17-3, 17-3a, 17-3a1, 17-3a2, 17-3a3, 17-3a4, 17-3a5, 17-3a6, 17-3a7, 17-3a8, 17-3a9, 17-3a10, 17-3b, 17-3b1, 17-3b2, 17-3c, 17-3d, 17-4, 17-4a, 17-4b, 17-4c, 17-4c1, 17-4d, 17-4d1, 17-4d2, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, 17-5e1, 17-5f, 17-5f1, 17-5f2, 17-5f3, 17-5f4, 17-5f5, 17-5f6, 17-5g, 17-5g1, 17-5g2, 17-5g3, 17-5g4, 17-5g5, 17-5g6, 17-5g7, 17-5g8, 17-5g9, 17-5g10, 17-5h, 17-5h1, 17-5h2, or 17-5i, or 17-5j, wherein the heterocycloalkyl group (ring A of Formula I) is thiomorpholinyl S,S-dioxide optionally substituted with one or more groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, haloalkyl, haloalkoxy, hydroxyl, CN, aryloxy, -SO_2-(C_1-C_6 alkyl), -NR'R", C_1-C_6 alkanoyl, pyridyl, phenyl, or -SO_2-NR'R", where each R' and R" is independently hydrogen or C_1-C_6 alkyl.

In still another aspect, the invention provides compounds of formula 17-8a, i.e., compounds of formula 17-8 where the thiomorpholinyl S,S-dioxide group is not attached to the sulfur of the SO_2 group via the ring nitrogen.

In still another aspect, the invention provides compounds of formula 17-8b, i.e., compounds of formula 17-8 where the thiomorpholinyl S,S-dioxide group is attached to the sulfur of the SO_2 group via the ring nitrogen.

In yet another aspect, the invention provides compounds of formula 17-9, i.e., compounds of formulas 15, 16, 16-1, 16-2, 16-3, 16-4, 16-5, 16-6, 16-6a, 16-6b, 16-6c, 16-6d, 16-7, 16-8, 16-9, 16-10, 16-11, 16-11a, 16-11b, 16-11c, 16-12, 16-13, 16-14, or 16-15, 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, 17-3, 17-3a, 17-3a1, 17-3a2, 17-3a3, 17-3a4, 17-3a5, 17-3a6, 17-3a7, 17-3a8, 17-3a9, 17-3a10, 17-3b, 17-3b1, 17-3b2, 17-3c, 17-3d, 17-4, 17-4a, 17-4b, 17-4c, 17-4c1, 17-4d, 17-4d1, 17-4d2, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, 17-5e1, 17-5f, 17-5f1, 17-5f2, 17-5f3, 17-5f4, 17-5f5, 17-5f6, 17-5g, 17-5g1, 17-5g2, 17-5g3, 17-5g4, 17-5g5, 17-5g6, 17-5g7, 17-5g8, 17-5g9, 17-5g10, 17-5h, 17-5h1, 17-5h2, or 17-5i, or 17-5j, wherein the heterocycloalkyl group (ring A of Formula I) is piperidinyl optionally substituted with one or more groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, haloalkyl, haloalkoxy, hydroxyl, CN,

aryloxy, -SO_2-(C_1-C_6 alkyl), -NR'R", C_1-C_6 alkanoyl, pyridyl, phenyl, or -SO_2-NR'R", where each R' and R" is independently hydrogen or C_1-C_6 alkyl.

In still another aspect, the invention provides compounds of formula 17-9a, i.e., compounds of formula 17-9 where the piperidinyl group is not attached to the sulfur of the SO_2 group via the ring nitrogen.

In still another aspect, the invention provides compounds of formula 17-9b, i.e., compounds of formula 17-9 where the piperidinyl group is attached to the sulfur of the SO_2 group via the ring nitrogen.

In yet another aspect, the invention provides compounds of formula 17-10, i.e., compounds of formulas 15, 16, 16-1, 16-2, 16-3, 16-4, 16-5, 16-6, 16-6a, 16-6b, 16-6c, 16-6d, 16-7, 16-8, 16-9, 16-10, 16-11, 16-11a, 16-11b, 16-11c, 16-12, 16-13, 16-14, or 16-15, 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, 17-3, 17-3a, 17-3a1, 17-3a2, 17-3a3, 17-3a4, 17-3a5, 17-3a6, 17-3a7, 17-3a8, 17-3a9, 17-3a10, 17-3b, 17-3b1, 17-3b2, 17-3c, 17-3d, 17-4, 17-4a, 17-4b, 17-4c, 17-4c1, 17-4d, 17-4d1, 17-4d2, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, 17-5e1, 17-5f, 17-5f1, 17-5f2, 17-5f3, 17-5f4, 17-5f5, 17-5f6, 17-5g, 17-5g1, 17-5g2, 17-5g3, 17-5g4, 17-5g5, 17-5g6, 17-5g7, 17-5g8, 17-5g9, 17-5g10, 17-5h, 17-5h1, 17-5h2, or 17-5i, or 17-5j wherein the heterocycloalkyl group (ring A of Formula I) is piperazinyl optionally substituted with one or more groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, haloalkyl, haloalkoxy, hydroxyl, CN, aryloxy, -SO_2-(C_1-C_6 alkyl), -NR'R", C_1-C_6 alkanoyl, pyridyl, phenyl, or -SO_2-NR'R", where each R' and R" is independently hydrogen or C_1-C_6 alkyl.

In still another aspect, the invention provides compounds of formula 17-10a, i.e., compounds of formula 17-10 where the piperazinyl group is not attached to the sulfur of the SO_2 group via the ring nitrogen.

In still another aspect, the invention provides compounds of formula 17-10b, i.e., compounds of formula 17-10 where the piperazinyl group is attached to the sulfur of the SO_2 group via the ring nitrogen.

In yet still another aspect, the invention provides compounds of formula 18, i.e., compounds according to any of the preceding formulas wherein, when R_2 is a cycloalkyl group, R_2 is cyclopropyl group.

In yet still another aspect, the invention provides compounds of formula 19, i.e., compounds according to any of the preceding formulas wherein, when R_2 is a cycloalkyl group, R_2 is cyclobutyl group.

In yet still another aspect, the invention provides compounds of formula 20, i.e., compounds according to any of the preceding formulas wherein, when R_2 is a cycloalkyl group, R_2 is cyclopentyl group.

In yet still another aspect, the invention provides compounds of formula 21 i.e., compounds according to any of the preceding formulas wherein, when R_2 is a cycloalkyl group, unless specifically identified as being other than cycloalkyl. In one embodiment, R_2 is cyclohexyl group. In a further embodiment, R_2 is cyclopentyl. In a still further embodiment, R_2 is cyclopropyl.

In another aspect, the invention provides compounds of formula 22, i.e., compounds according to any of the formulas 18, 19, 20, or 21 wherein R_1 is hydrogen, unless specifically identified as being other than hydrogen.

In another aspect, the invention provides compounds that are:

5-[(4-chlorophenyl)sulfonyl]-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline;

5-[(4-chlorophenyl)sulfonyl]-8-fluoro-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline;

5-[(4-chlorophenyl)sulfonyl]-7-fluoro-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline;

5-[(4-chlorophenyl)sulfonyl]-9-fluoro-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline;

5-[(4-chlorophenyl)sulfonyl]-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline;

5-[(4-chlorophenyl)sulfonyl]-7-methoxy-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline;

5-[(4-chlorophenyl)sulfonyl]-9-methoxy-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline;

5-[(4-chlorophenyl)sulfonyl]-3-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline;

6-(4-chlorophenylsulfonyl)-4-methoxy-5,6-dihydropyrimido[5,4-c]quinolin-2-amine;

5-[(4-chlorophenyl)sulfonyl]-3-(difluoromethyl)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline;

5-(4-Chloro-benzenesulfonyl)-8-fluoro-4,5-dihydro-isoxazolo[4,5-c]quinoline;

6-(4-chlorophenylsulfonyl)-5,6-dihydrobenzo[*j*][1,7]naphthyridine;

ethyl 5-[(4-chlorophenyl)-sulfonyl]-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline-3-carboxylate;

ethyl 5-[(4-chlorophenyl)-sulfonyl]-8-fluoro-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline-3-carboxylate;

5-[(4-chlorophenyl)sulfonyl]-3-(methylthio)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline;

5-[(4-chlorophenyl)sulfonyl]-3-(methylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline;

8-chloro-5-[(4-chlorophenyl)sulfonyl]-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline;

4-methyl-5-(pyridin-2-ylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline;

5-[(4-chlorophenyl)sulfonyl]-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinolin-3-ol;

{5-[(4-chlorophenyl)sulfonyl]-8-fluoro-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinolin-3-yl}methanol;

5-[(4-chlorophenyl)sulfonyl]-7,9-dimethoxy-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline;

5-[(4-chlorophenyl)sulfonyl]-8-fluoro-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline-3-carboxamide;

5-[(4-chlorophenyl)sulfonyl]-8-fluoro-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline-3-carboxylic acid;

6-(4-chlorophenylsulfonyl)-5-ethyl-5,6-dihydropyrazolo[1,5-c]quinazoline;

5-[(4-chlorophenyl)sulfonyl]-8-fluoro-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline-3-carbonitrile;

5-[(4-chlorophenyl)sulfonyl]-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline; (resolved enantiomer, with a retention time of about 9.3 min*;)

5-[(4-chlorophenyl)sulfonyl]-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline (resolved enantiomer, with a retention time of about 20.5 min*;)

5-[(4-chlorophenyl)sulfonyl]-8-fluoro-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline (racemate);

5-[(4-chlorophenyl)sulfonyl]-8-fluoro-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline (resolved enantiomer, with a retention time of about 9.8 min*;)

5-[(4-chlorophenyl)sulfonyl]-8-fluoro-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline (resolved enantiomer, with a retention time of about 27.1 min*;)

5-[(4-chlorophenyl)sulfonyl]-8-fluoro-4,4-dimethyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline;

8-fluoro-4-methyl-5-(pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline (racemate);

8-fluoro-4-methyl-5-(pyridin-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline;

4-methyl-5-(pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline;

8-fluoro-4-methyl-5-(pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline (resolved enantiomer, with a retention time of about 15.2 min*;)

8-fluoro-4-methyl-5-(pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline (resolved enantiomer, with a retention time of about 17.2 min*;)

5-[(4-chlorophenyl)sulfonyl]-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one;

5-[(4-chlorophenyl)sulfonyl]-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]-1,5-naphthyridine;

8-fluoro-4-methyl-5-(pyridin-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline; (resolved enantiomer, with a retention time of about 16.3 min*;)

5-(4-chlorophenylsulfonyl)-4-ethyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline; (resolved enantiomer, with a retention time of about 21.4 min*;)

5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinolin-7-ol;

5-(4-chlorophenylsulfonyl)-8-fluoro-1*H*-pyrazolo[4,3-c]quinolin-4(5*H*)-one;

5-(4-chlorophenylsulfonyl)-4-methyl-4,5,5a,6,7,8,9,9a-octahydro-1*H*-pyrazolo[4,3-c]quinoline;

5-(4-chlorophenylsulfonyl)-9-fluoro-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

5-(4-chlorophenylsulfonyl)-7-fluoro-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

8-fluoro-5-(4-fluorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

4-methyl-5-(pyridin-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline; (racemate and resolved enantiomer, with a retention time of about 7.9 min*.)5-(4-chlorophenylsulfonyl)-8-fluoro-4-deutero-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

9-fluoro-6-(4-fluorophenylsulfonyl)-5-methyl-5,6-dihydropyrimido[5,4-c]quinolin-2-amine;

5-(4-chlorophenylsulfonyl)-4-cyclopropyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

5-(4-chlorophenylsulfonyl)-4-(trifluoromethyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinolin-7-ol; (resolved enantiomer, with a retention time of about 13.4 min*;)5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinolin-7-ol; (resolved enantiomer, with a retention time of about 17.0 min*;)5-(4-chlorophenylsulfonyl)-4-isopropyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

1,5-bis(4-chlorophenylsulfonyl)-1*H*-pyrazolo[4,3-c]quinolin-4(5*H*)-one;

5-(4-chlorophenylsulfonyl)-4,5-dihydro-1*H*-imidazo[1,2-a]pyrazolo[4,3-e]pyrimidine;

8-fluoro-5-(4-fluorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline; (resolved enantiomer, with a retention time of about 7.6 min*;)

8-fluoro-5-(4-fluorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline; (resolved enantiomer, with a retention time of about 10.1 min*;)

5'-(4-chlorophenylsulfonyl)-2',5'-dihydrospiro[cyclopropane-1,4'-pyrazolo[4,3-c]quinoline];

5-(4-chlorophenylsulfonyl)-7,8-difluoro-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

7,8-difluoro-4-methyl-5-(thiophen-2-ylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-c][1,8]naphthyridine;

5-(4-chlorophenylsulfonyl)-4-ethyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline; (resolved enantiomer, with a retention time of about 6.0 min*;)

5-(4-chlorophenylsulfonyl)-4-ethyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline; (resolved enantiomer, with a retention time of about 9.3 min*;)

5-(5-chlorothiophen-2-ylsulfonyl)-7,8-difluoro-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinolin-7-yl dimethylcarbamate;

4-cyclopropyl-7,8-difluoro-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline; (resolved enantiomer, with a retention time of about 6.0 min*;)

4-cyclopropyl-7,8-difluoro-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline; (resolved enantiomer, with a retention time of about 9.3 min*;)

4-cyclopropyl-7,8-difluoro-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline; (racemate;)

7-chloro-4-methyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[3,4-d]thieno[2,3-b]pyridine;

5-(4-chlorophenylsulfonyl)-4-cyclopropyl-4,5-dihydro-1*H*-imidazo[1,2-a]pyrazolo[4,3-c]pyrimidine;

4-ethyl-7,8-difluoro-5-(5-(trifluoromethyl)pyridin-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

7,8-difluoro-4-methyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline; (resolved enantiomer, with a retention time of about 7.0 min*;)

7,8-difluoro-4-methyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline; (resolved enantiomer, with a retention time of about 9.5 min*;)

4-(4-cyclopropyl-1*H*-pyrazolo[4,3-c]quinolin-5(4*H*)-ylsulfonyl)benzonitrile;

5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-c][1,7]naphthyridine;

5'-(4-(trifluoromethyl)phenylsulfonyl)-1',5'-dihydrospiro[cyclopropane-1,4'-pyrazolo[4,3-c]quinoline];

5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-imidazo[1,2-a]pyrazolo[4,3-e]pyrimidine;

4-cyclopropyl-7,8-difluoro-5-(5-(trifluoromethyl)pyridin-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

5-(5-chlorothiophen-2-ylsulfonyl)-4-cyclopropyl-7,8-difluoro-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-7,8-difluoro-5-(4-fluorophenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c][1,8]naphthyridine;

4-cyclopropyl-5-(4-fluorophenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c][1,8]naphthyridine;

4-cyclopropyl-5-(4-fluorophenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-7,8-difluoro-1-(methoxymethyl)-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-7,8-difluoro-5-(thiophen-2-ylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-imidazo[1,2-a]pyrazolo[4,3-e]pyrimidine;

4-cyclopropyl-7,8-difluoro-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

5-(4-fluorophenylsulfonyl)-4-(trifluoromethyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c][1,8]naphthyridine;

7,8-difluoro-4-(pyridin-3-yl)-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-8-fluoro-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline; (racemate and resolved enantiomers, with a retention time of about 8.0 min* and 12.6;)

5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-2*H*-[1,3]dioxolo[4,5-g]pyrazolo[4,3-c]quinoline;

5-(5-chloropyridin-2-ylsulfonyl)-4-cyclopropyl-7,8-difluoro-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

5-(5-chlorothiophen-2-ylsulfonyl)-4-cyclopropyl-7,8-difluoro-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline; (resolved enantiomer, with a retention time of about 10.3 min*;)

5-(5-chlorothiophen-2-ylsulfonyl)-4-cyclopropyl-7,8-difluoro-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline; (resolved enantiomer, with a retention time of about 16.1 min*;)

4-cyclopropyl-7,8-difluoro-5-(4-fluorophenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline; (resolved enantiomer, with a retention time of about 16.9 min*;)

4-cyclopropyl-7,8-difluoro-5-(4-fluorophenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline; (resolved enantiomer, with a retention time of about 19.7 min*;)

4-cyclopropyl-8-fluoro-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline; (Enantiomer A)

4-cyclopropyl-8-fluoro-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline; (Enantiomer B)

4-cyclopropyl-7,8-difluoro-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline; (resolved enantiomer, with a retention time of about 17.3 min*;)

4-cyclopropyl-7,8-difluoro-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;(resolved enantiomer, with a retention time of about 13.0 min*;)

7,8-difluoro-4-isopropyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-7,8-difluoro-5-(4-(trifluoromethoxy)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

7,8-difluoro-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline-7,8-diol;

5-(5-chloropyridin-2-ylsulfonyl)-4-cyclopropyl-8-fluoro-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

(R)-4-cyclopropyl-7-(trifluoromethoxy)-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c][1,7]naphthyridine 7-oxide;

5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinolin-8-ol;

4-(8-fluoro-4-methyl-1*H*-pyrazolo[4,3-c]quinolin-5(4*H*)-ylsulfonyl)-3,5-dimethylisoxazole;

8-fluoro-4-methyl-5-(1-methyl-1*H*-pyrazol-4-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

8-fluoro-4-methyl-5-(5-(pyridin-2-yl)thiophen-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

(*R*)-2-tert-butyl-4-cyclopropyl-7,8-difluoro-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

(*R*)-1-tert-butyl-4-cyclopropyl-7,8-difluoro-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

(*R*)-4-cyclopropyl-7-(trifluoromethyl)-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

(*R*)-4-cyclopropyl-7-(trifluoromethoxy)-5-(4-(trifluoromethoxy)phenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

(*R*)-4-(4-cyclopropyl-7,8-difluoro-1*H*-pyrazolo[4,3-c]quinolin-5(4*H*)-ylsulfonyl)aniline;

(*R*)-4-cyclopropyl-7,8-difluoro-5-(4-nitrophenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline; (*R*)-4-cyclopropyl-8-(trifluoromethyl)-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

5-chloro-2-(4-cyclopropyl-7,8-difluoro-1*H*-pyrazolo[4,3-c]quinolin-5(4*H*)-ylsulfonyl)thiazole;

(*R*)-4-cyclopropyl-5-(4-(difluoromethoxy)phenylsulfonyl)-7,8-difluoro-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c][1,5]naphthyridine;

4-cyclopropyl-8-fluoro-5-(5-(trifluoromethyl)pyridin-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-8-fluoro-5-(5-(trifluoromethyl)pyridin-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-5-(4-(difluoromethoxy)phenylsulfonyl)-8-fluoro-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-7,8-difluoro-5-(5-(trifluoromethyl)pyridin-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline-7,8-diol;

8-fluoro-4-methyl-5-(1-methyl-1*H*-imidazol-4-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

(*R*)-1-tert-butyl-4-ethyl-7,8-difluoro-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

(*R*)-4-ethyl-7,8-difluoro-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

4-(4-(trifluoromethyl)phenylsulfonyl)-4,5,8,8b-tetrahydro-3a*H*-isothiazolo[4,5-b]pyrazolo[3,4-d]pyridine; and

7-methyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5,5a,7-tetrahydro-1*H*-oxazolo[5,4-b]pyrazolo[3,4-d]pyridine;

(R)-4-cyclopropyl-8-fluoro-5-(4-(trifluoromethoxy)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline

4-cyclopropyl-7-methyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[3,4-d]thiazolo[5,4-b]pyridine

(R)-4-cyclopropyl-8-fluoro-5-(4-methoxyphenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

and stereoisomers, tautomers, mixtures of stereoisomers and/or tautomers, or pharmaceutically acceptable salts thereof.

In another aspect, the invention provides a method of treating Alzheimer's disease comprising administering a therapeutically effective amount of a compound or salt of formula I, where formula I also encompasses:

5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline,

2-phenyl-5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline,

7-methoxy-2-phenyl-5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline,

8-methoxy-5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline,

8-methoxy-2-phenyl-5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline,
3-(methylthio)-5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline,
7-methoxy-5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline,
5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline,
ethyl 1-(4-sulfamoylphenyl)-5-tosyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline-3-carboxylate,
1-(4-sulfamoylphenyl)-5-tosyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline-3-carboxamide, and
ethyl 1-methyl-5-tosyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline-3-carboxylate;
to a patient in need of such treatment.

In still another aspect, the invention provides a composition comprising a compound or salt of formula I, where formula I further comprises 3-(methylthio)-5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline, 7-methoxy-5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline, and 5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline, and at least one pharmaceutically acceptable solvent, adjuvant, excipient, carrier, binder or disintegrant.

In still another aspect, the invention provides a method of treating Alzheimer's disease comprising administering a therapeutically effective amount of a compound or salt of formula I, where formula I also encompasses
5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline,
2-phenyl-5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline,
7-methoxy-2-phenyl-5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline,
8-methoxy-5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline,
8-methoxy-2-phenyl-5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline,
3-(methylthio)-5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline,
7-methoxy-5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline,
5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline,
ethyl 1-(4-sulfamoylphenyl)-5-tosyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline-3-carboxylate,
1-(4-sulfamoylphenyl)-5-tosyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline-3-carboxamide; and
ethyl 1-methyl-5-tosyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline-3-carboxylate
to a patient in need of such treatment.

In another aspect, the compounds of the invention have minimal interaction or preferably, no interaction with Notch.

Definitions

The definitions and explanations below are for the terms as used throughout this entire document including both the specification and the claims.

It should be noted that, as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to a composition containing "a compound" includes a mixture of two or more compounds. It should also be noted that the term "or" is generally employed in its sense including "and/or" unless the content clearly dictates otherwise.

Where multiple substituents are indicated as being attached to a structure, it is understood that the substituents can be the same or different. Thus for example "R_m optionally substituted with 1, 2 or 3 R_q groups" indicates that R_m is substituted with 1, 2, or 3 R_q groups where the R_q groups can be the same or different. It will be understood by those skilled in the art with respect to any group containing one or more substituents that such groups are not intended to introduce any substitution or substitution patterns that are sterically impractical and /or synthetically non-feasable.

APP, amyloid precursor protein, is defined as any APP polypeptide, including APP variants, mutations, and isoforms, for example, as disclosed in U.S. Patent No. 5,766,846.
A beta, amyloid beta peptide, is defined as any peptide resulting from beta-secretase mediated cleavage of APP, including peptides of 39, 40, 41, 42, and 43 amino acids, and extending from the beta-secretase cleavage site to amino acids 39, 40, 41, 42, or 43.

Pharmaceutically acceptable refers to those properties and/or substances that are acceptable to the patient from a toxicological and/or safety point of view.

A therapeutically effective amount is defined as an amount effective to reduce or lessen at least one symptom of the disease being treated or to reduce or delay onset of one or more clinical markers or symptoms of the disease.

By "A beta-related disease" is meant diseases or disorders which are associated with extracellular accumulation of A beta (amyloid) in various organs and tissues of the body and includes diseases, disorders, conditions, pathologies, and other abnormalities of the structure or function of the brain, including components thereof, such as the stroma, including the vasculature or the parenchyma including functional or anatomical regions, or neurons themselves, in which the causative agent is A beta (amyloid). The 4 kDa beta-amyloid (A beta) protein, a 39-43 amino-acid protein, is a major component of cerebral and cerebrovascular deposits, such as plaques, found in, among others, Alzheimer's disease, cerebral amyloid angiopathy, mild cognitive impairment (MCI), and Down's syndrome and is derived from the proteolytic cleavage of a larger, membrane-bound precursor, the A beta precursor protein (APP) by several aspartyl proteases, one of which is gamma secretase.

By "alkanoyl" is meant an acyl radical Alk-C(O)-, wherein Alk is an alkyl radical as defined herein. Examples of alkanoyl include acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, 2-methyl-butyryl, 2,2-dimethylpropionyl, valeryl, hexanoyl, heptanoyl, octanoyl and the like. By "C_1-C_6 alkanoyl" in the present invention is meant an acyl radical Alk-C(O)-, wherein Alk is a straight or branched chain alkyl group having 1-6 carbon atoms.

By "alkyl" and "C_1-C_6 alkyl" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, such as, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. It is understood that in cases where an alkyl chain of a substituent (e.g. of an alkyl, alkoxy or alkenyl group) is shorter or longer than 6 carbons, it will be so indicated in the second "C" as, for example, "C_1-C_{10}" indicates a maximum of 10 carbons. Alkyl groups may be mono or di-radicals. The meaning will be clear to one of skill in the art. The term also includes substituted alkyl groups, and refers to an alkyl group in which 1 or more hydrogen atoms is replaced by a substituent independently selected from the group: acyl, acyloxy, alkoxy, amino (wherein the amino group may be a cyclic amine), aryl, heteroaryl, heterocycoalkyl, carboxyl, oxo, amido, cyano, cycloalkyl, cycloalkenyl, halogen, hydroxyl, nitro, sulfamoyl, sulfanyl, sulfinyl, sulfonyl, and sulfonic acid.

By "alkylene" is meant a diradical alkyl group, whereby alkyl is as defined above.

By "alkoxy" and "C_1-C_6 alkoxy" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, attached through at least one divalent oxygen atom, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, isopentoxy, neopentoxy, hexoxy, and 3-methylpentoxy.

By the term "halogen" in the present invention is meant fluorine, bromine, chlorine, and/or iodine.

"Alkenyl" and "C_2-C_6 alkenyl" means straight and branched hydrocarbon radicals having from 2 to 6 carbon atoms and from one to three double bonds and includes, for example, ethenyl, propenyl, 1-but-3-enyl, 1-pent-3-enyl, 1-hex-5-enyl and the like. The term also includes substituted alkenyl groups, and refers to an alkenyl group in which 1 or more hydrogen atoms is replaced by a substituent independently selected from the group: acyl, acyloxy, alkoxy, amino (wherein the amino group may be a cyclic amine), aryl, heteroaryl, heterocycloalkyl, carboxyl, oxo, amido, cyano, cycloalkyl, cycloalkenyl, halogen, hydroxyl, nitro, sulfamoyl, sulfanyl, sulfinyl, sulfonyl, and sulfonic acid, for example 1*H*-pyrrol-2-ylmethylene.

"Alkynyl" and "C_2-C_6 alkynyl" means straight and branched hydrocarbon radicals having from 2 to 6 carbon atoms and one or two triple bonds and includes ethynyl, propynyl, butynyl, pentyn-2-yl and the like. The term also includes substituted alkynyl groups, and refers to an alkynyl group in which 1 or more hydrogen atoms is replaced by a substituent independently selected from the group: acyl, acyloxy, alkoxy, amino (wherein the amino group may be a cyclic amine), aryl, heteroaryl, heterocyclyl, carboxyl, oxo, amido, cyano, cycloalkyl, cycloalkenyl, halogen, hydroxyl, nitro, sulfamoyl, sulfanyl, sulfinyl, sulfonyl, and sulfonic acid.

As used herein, the term "cycloalkyl" refers to saturated carbocyclic radicals having three to twelve carbon atoms. The cycloalkyl can be monocyclic, a polycyclic fused system, or a bi or polycyclic bridged system, such as adamantyl or bicyclo[2.2.1] heptyl. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Preferred cycloalkyl groups are cyclopentyl, cyclohexyl, and cycloheptyl. The cycloalkyl groups herein are unsubstituted or, substituted in one or more substitutable positions with various groups. For example, such cycloalkyl groups may be optionally substituted with, for example, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxyl, oxo, cyano, nitro, amino, mono(C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, amino(C_1-C_6)alkyl, mono(C_1-C_6)alkylamino(C_1-C_6)alkyl or di(C_1-C_6)alkylamino(C_1-C_6)alkyl.

By "aryl" is meant an aromatic carbocyclic group having a single ring (e.g., phenyl) or multiple condensed rings in which at least one is aromatic, (e.g., 1,2,3,4-tetrahydronaphthyl, naphthyl), which is optionally substituted at one or more substitutable positions. Preferred aryl groups of the present invention are phenyl, 1-naphthyl, 2-naphthyl, indanyl, indenyl, dihydronaphthyl, fluorenyl, tetralinyl or 6,7,8,9-tetrahydro-5H-benzo[a]cycloheptenyl. More preferred aryl groups include phenyl and naphthyl. The most preferred aryl group is phenyl. The aryl groups herein are unsubstituted or, substituted in one or more substitutable positions with various groups. For example, such aryl groups may be optionally substituted with, for example, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxyl, cyano, nitro, amino, mono(C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, amino(C_1-C_6)alkyl, mono(C_1-C_6)alkylamino(C_1-C_6)alkyl or di(C_1-C_6)alkylamino(C_1-C_6)alkyl.

By "arylalkyl" or "aralkyl" is meant the group -alkylene-aryl, or –alkyl-aryl, wherein alkylene, alkyl, and aryl are defined herein.

By "aryloxy" is meant the group -O-aryl wherein the term aryl is as defined herein.

By "arylalkyloxy" "arylalkyloxy" or "aralkyloxy" is meant the group -O-C_{1-4}-alkylene-aryl, or -O-C_{1-4}-alkyl-aryl, wherein the terms aryl, alkyl, and alkylene are as defined herein. An example of arylalkyloxy is benzyloxy (or -O-CH_2-phenyl).

By the term "halogen" or "halo" in the present invention is meant fluorine, bromine, chlorine, and/or iodine.

By "haloalkyl" is meant an alkyl radical having the meaning as defined above wherein one or more hydrogens are replaced by a halogen. Examples of such haloalkyls include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1,1,1-trifluoroethyl and the like.

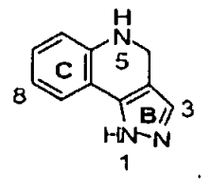
By "heteroaryl" is mean at least one or more aromatic ring systems of 5-, 6-, or 7-membered rings which includes fused ring systems of 9-11 atoms containing at least one and up to four heteroatoms selected from nitrogen, oxygen, or sulfur. A heteroaryl ring may be a mono-radical, or di-radical. For example, when the B-ring is pyrazolyl, the pyrazolyl ring is fused to the piperidine ring in the core, and the pyrazolyl ring is a diradical. The meaning will be apparent to one of ordinary skill in the art. Preferred heteroaryl groups of the present invention include pyridyl, pyrimidinyl, quinolinyl, benzothienyl, indolyl, indolinyl, pryidazinyl, pyrazinyl, isoindolyl, isoquinolyl, quinazolinyl, quinoxalinyl, phthalazinyl, imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indolizinyl, indazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, isothiazolyl, naphthyridinyl, isochromanyl, chromanyl, tetrahydroisoquinolinyl, isoindolinyl, isobenzotetrahydrofuranyl, isobenzotetrahydrothienyl, isobenzothienyl, benzoxazolyl, pyridopyridyl, benzotetrahydrofuranyl, benzotetrahydrothienyl, purinyl, benzodioxolyl, triazinyl, pteridinyl, benzothiazolyl, imidazopyridyl, imidazothiazolyl, dihydrobenzisoxazinyl, benzisoxazinyl, benzoxazinyl, dihydrobenzisothiazinyl, benzopyranyl, benzothiopyranyl, chromonyl, chromanonyl, pyridyl-N-oxide, tetrahydroquinolinyl, dihydroquinolinyl, dihydroquinolinonyl, dihydroisoquinolinonyl, dihydrocoumarinyl, dihydroisocoumarinyl, isoindolinonyl, benzodioxanyl, benzoxazolinonyl, pyrrolyl N-oxide,, pyrimidinyl N-oxide, pyridazinyl N-oxide, pyrazinyl N-oxide, quinolinyl N-oxide, indolyl N-oxide, indolinyl N-oxide, isoquinolyl N-oxide, quinazolinyl N-oxide, quinoxalinyl N-oxide, phthalazinyl N-oxide, imidazolyl N-oxide, isoxazolyl N-oxide, oxazolyl N-oxide, thiazolyl N-oxide, indolizinyl N-oxide, indazolyl N-oxide, benzothiazolyl N-oxide, benzimidazolyl N-oxide, pyrrolyl N-oxide, oxadiazolyl N-oxide, thiadiazolyl N-oxide, triazolyl N-oxide, tetrazolyl N-oxide, benzothiopyranyl S-oxide, benzothiopyranyl S,S-dioxide. Preferred heteroaryl groups include pyridyl, pyridazinyl, pyrimidyl, pyrazinyl,

pyrrolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, oxazolyl, isoxazolyl, thienyl, furanyl, quinolinyl, and isoquinolinyl. The heteroaryl groups herein are unsubstituted or substituted in one or more substitutable positions with various groups. For example, such heteroaryl groups may be optionally substituted with, for example, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxyl, cyano, nitro, amino, mono(C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, amino(C_1-C_6)alkyl, mono(C_1-C_6)alkylamino(C_1-C_6)alkyl or di(C_1-C_6)alkylamino(C_1-C_6)alkyl.

By "heterocycle", "heterocycloalkyl" or "heterocyclyl" is meant one or more carbocyclic ring systems of 4-, 5-, 6-, or 7-membered rings which includes fused ring systems of 9-11 atoms containing at least one and up to four heteroatoms selected from nitrogen, oxygen, or sulfur. Preferred heterocycles of the present invention include morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, piperazinyl, homopiperazinyl, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl, piperidinyl, tetrahydrofuranyl, tetrahydrothienyl, homopiperidinyl, homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S,S-dioxide, oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl, dihydropyrazolyl, dihydropyridyl, dihydropyrimidinyl, dihydrofuryl, dihydropyranyl, tetrahydrothienyl, tetrahydrothienyl S-oxide, tetrahydrothienyl S,S-dioxide and homothiomorpholinyl S-oxide. The heterocycle groups herein are unsubstituted or substituted in one or more substitutable positions with various groups. For example, such heterocycle groups may be optionally substituted with, for example, C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxyl, oxo, cyano, nitro, amino, mono(C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, amino(C_1-C_6)alkyl, mono(C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl or oxo.

By "hydroxyalkyl" is meant an alkyl substituted with a hydroxyl, such as hydroxymethyl, 1-hydroxypropyl, 2-hydroxyethyl, 3-hydroxyethyl, or 3-hydroxybutyl.

Numbering on the tricyclic core when the C-ring is a phenyl and the B-ring is pyrazolyl:



Most compounds were named using Autonom 2000 4.01.305, which is available from Beilstein Information Systems, Inc, Englewood, Colorado, or ChemDraw v.10.0, (available

from Cambridgesoft at 100 Cambridge Park Drive, Cambridge, MA 02140). Alternatively, the names were generated based on the IUPAC rules.

The compounds of this invention may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates, chiral non-racemic or diastereomers. In these situations, the single enantiomers, i.e., optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent; chromatography, using, for example a chiral HPLC column; or derivatizing the racemic mixture with a resolving reagent to generate diastereomers, separating the diastereomers via chromatography, and removing the resolving agent to generate the original compound in enantiomerically enriched form. Any of the above procedures can be repeated to increase the enantiomeric purity of a compound.

Non-toxic pharmaceutically acceptable salts include, but are not limited to salts of inorganic acids such as hydrochloric, sulfuric, phosphoric, diphosphoric, hydrobromic, and nitric or salts of organic acids such as formic, citric, malic, maleic, fumaric, tartaric, succinic, acetic, lactic, methanesulfonic, p-toluenesulfonic, 2-hydroxyethylsulfonic, salicylic, besylate and stearic. Similarly, pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium and ammonium. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts. The invention also encompasses prodrugs of the compounds of Formula I.

The invention also encompasses the prodrugs of the compounds of Formula I. Those skilled in the art will recognize various synthetic methodologies that may be employed to prepare non-toxic pharmaceutically acceptable prodrugs of the compounds encompassed by Formula I. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable solvates, such as water, ethanol, mineral oil, vegetable oil, and dimethylsulfoxide... The invention also encompasses the acylated prodrugs of the compounds of Formula I. Those skilled in the art will recognize various synthetic methodologies, which may be employed to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the compounds encompassed by Formula I.

The term "acid prodrug group" denotes a moiety that is converted in vivo into an active carboxylic acid compound of formula I. Such prodrug groups are generally known in the art and include ester forming groups, to form an ester prodrug, such as benzyloxy, di(C_1-C_6)alkylaminoethyloxy, acetoxymethyl, pivaloyloxymethyl, phthalidoyl,

ethoxycarbonyloxyethyl, 5-methyl-2-oxo-1,3-dioxol-4-yl methyl, and (C_1-C_6)alkoxy optionally substituted by N-morpholino and amide-forming groups such as di(C_1-C_6)alkylamino. Preferred prodrug groups include C_1-C_6 alkoxy forming an ester, and O^-M^+ where M^+ represents a cation to form a salt of the acid. Preferred cations include sodium, potassium, and ammonium. Other cations include magnesium and calcium. Further preferred prodrug groups include O^-M^{++} where M^{++} is a divalent cation such as magnesium or calcium.

It is understood by those practicing the art that the definition of compounds of Formula I contain asymmetric carbons, encompass all possible stereoisomers, mixtures and regioisomers thereof which possess the activity discussed below. Such regioisomers may be obtained pure by standard separation methods known to those skilled in the art. The definition encompasses any optical isomers and diastereomers as well as the racemic and resolved enantiomercially pure R and S stereoisomers as well as other mixtures of the R and S stereoisomers and pharmaceutically acceptable salts thereof, which possess the activity discussed below. Optical isomers may be obtained in pure form by standard separation techniques or enantiomer specific synthesis. It is understood that this invention encompasses all crystalline forms of compounds of Formula I.

When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless otherwise specified, it is intended that the compounds include the cis, trans, Z- and E- configurations. Likewise, all tautomeric forms are also intended to be included.

The compounds of general Formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes percutaneous, subcutaneous, intravascular (e.g., intravenous), intramuscular, or intrathecal injection or infusion techniques and the like. In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula I and a pharmaceutically acceptable carrier. One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants, and if desired other active ingredients. The pharmaceutical compositions containing compounds of general Formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preservative agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques. In some cases such coatings may be prepared by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monosterate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules, wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Formulations for oral use may also be presented as lozenges.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents or suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil or a mineral oil or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol, glucose or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general Formula I may also be administered in the form of suppositories, e.g., for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

Compounds of general Formula I may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

For disorders of the eye or other external tissues, e.g., mouth and skin, the formulations are preferably applied as a topical gel, spray, ointment or cream, or as a suppository, containing the active ingredients in a total amount of, for example, 0.075 to 30% w/w, preferably 0.2 to 20% w/w and most preferably 0.4 to 15% w/w. When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base.

Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs. The compounds of this invention can also be administered by a transdermal device. Preferably topical administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane. The transdermal patch may include the compound in a suitable solvent system with an adhesive system, such as an acrylic emulsion, and a polyester patch. The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or oil or with both a fat and an oil. Preferably, a hydrophilic

emulsifier is included together with a lipophilic emulsifier, which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base, which forms the oily, dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, and sodium lauryl sulfate, among others. The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active ingredients. The anti-inflammatory active ingredients are preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w. For therapeutic purposes, the active compounds of this combination invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. The compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene

glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient. The daily dose can be administered in one to four doses per day. In the case of skin conditions, it may be preferable to apply a topical preparation of compounds of this invention to the affected area two to four times a day.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

For administration to non-human animals, the composition may also be added to the animal feed or drinking water. It may be convenient to formulate the animal feed and drinking water compositions so that the animal takes in a therapeutically appropriate quantity of the composition along with its diet. It may also be convenient to present the composition as a premix for addition to the feed or drinking water.

The disclosures in this document of all articles and references, including patents, are incorporated herein by reference in their entirety.

The invention is illustrated further by the following examples, which are not to be construed as limiting the invention in scope or spirit to the specific procedures described in them.

The starting materials and various intermediates may be obtained from commercial sources, prepared from commercially available compounds, and/or prepared using known synthetic methods.

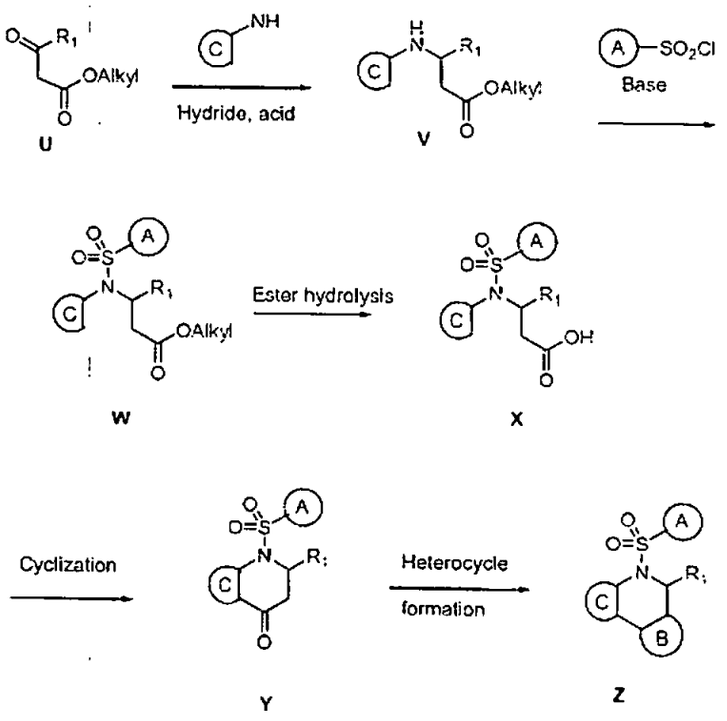
General Synthetic Procedures

The compounds of the invention can be prepared using methods known in the art of organic synthesis. For example, the compounds of the invention, as well as all intermediates, can be synthesized by known processes using either solution or solid phase techniques as shown below. Representative procedures for preparing compounds of the invention are outlined in the following schemes.

Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups as well as suitable conditions for protecting and deprotecting particular functional groups are well known in the art. For example, numerous protecting groups are described in T. W. Greene and G. M. Wuts, Protecting Groups in Organic Synthesis, Second Edition, Wiley, New York, 1991, and references cited therein.

Scheme 1:

Example A



Compounds V'can be prepared by reductive amination of an appropriate aniline and a β-keto ester U in an appropriate solvent such as dichloromethane, 1,2-dichlorocthanc, benzene, toluenc, tetrahydrofuran, or chloroform, an acid source such as acetic acid, propionic acid, formic acid, hydrochloric acid, or trifluoroacetic acid, and a hydride source such as sodium borohydride, sodium cyanoborohydridc, sodium triacetoxyborohydride, decaborane, or dibutyl chloride hydride complex. After reaction completion, the excess hydride can bc quenched with a base such as saturated aqueous $NaHCO_3$ or saturated aqueous Na_2CO_3, or saturated aqueous K_2CO_3, and the resulting solution or biphasic mixture is then treated by standard extraction procedures to isolate the products V.

Compounds W can be prepared by reacting compounds V with a sulfonyl chloride in a suitable solvent such as dichloromethane, 1,2-dichloroethane, benzenc, toluene, tetrahydrofuran, chloroform, or pyridine and a suitable base such as triethylamine, diisopropylethylamine, pyridine, or dimethylamino pyridine. The reaction mixture can then bc concentrated and the residue taken up in a suitable solvent for aqueous extraction such as diethyl ether, ethyl acetate, chloroform, or dichloromethane and then treated by standard extraction procedures to isolate the products W.

Compounds X can be prepared by standard acid or base catalyzed ester hydrolysis methods or by other methods as outlined in 'Protective Groups in Organic Synthesis' third edition by Greene and Wuts, Wiley interscience, 1999.

Compounds Y can be prepared by cyclization of compounds X by heating in trifluoroacetic anhydride and trifluoroacetic acid (3:1 mixture) followed by addition of water and standard aqueous workup, or by the Inverse Friedel-Crafts Method described in W.S. Johnson and H.J. Glenn, JACS, 71, 1092 (1949).

Compounds Z can bc prepared by a variety of methods for construction of the desired ring B-ring. Compounds Z were the B-ring is pyrazolyl can be made by treatment of compounds Y with acylating agents such as dimethylformamide dimethyl acetal, ethyl formate, or dimethylacetamide dimethyl acetal followed by cyclization with hydrazines in a suitable solvent such as acetic acid to obtain compounds Z.

In the above scheme, each of the variables independently contains the definitions as described above, while P is a protecting group. One of ordinary skill in the art will appreciate that the above scheme can be used to selectively produce a single diastereomer and/or a single enantiomer.

Compounds may be deprotected by standard means appropriate to the type of protection utilized as described in Greene, Theodora W.; Wuts, Peter G. M. Protective Groups in Organic Synthesis. 2nd Ed. (1991). 473 pp. (treatment with trimethylsilyl iodide, catalytic hydrogenation, sodium alkoxide, etc.)

Experimental Procedures

Certain compounds of this invention are prepared from other compounds of this invention via-known reactions and functional group transformations. Examples of such transformations include ester hydrolysis, amide formation, and reductive alkylation; examples of these are described in the preparations below. Starting materials are obtained from commercial sources or prepared by known methods as described in the examples below.

Compounds included in this invention are exemplified by the following examples, which should not be construed as limiting the scope of this disclosure. Analogous structures and alternative synthetic routes within the scope of the invention will be apparent to those skilled in the art.

Examples

The following synthetic and biological examples are offered to illustrate this invention and are not to be construed in any way as limiting the scope of this invention. Unless otherwise stated, all temperatures are in degrees Celsius

Reagents and solvents obtained from commercial suppliers were used without further purification unless otherwise stated. Thin layer chromatography was performed on precoated 0.25 mm silica gel plates (E. Merck, silica gel 60, F_{254}). Visualization was achieved using UV illumination or staining with phosphomolybdic acid, ninhydrin or other common staining reagents. Flash chromatography was performed using either a Biotage Flash 40 system and prepacked silica gel columns or hand packed columns (E. Merck silica gel 60, 230-400 mesh). Preparatory HPLC was performed on a Varian Prepstar high performance liquid chromatograph. ^{1}H NMR spectra were recorded on either a Varian Gemini 300 MHz spectrometer or a Bruker Avance 300 MHz spectrometer. Chemical shifts are reported in ppm (δ) and were calibrated using the undeuterated solvent resonance as internal standard. Mass spectra were recorded on an Agilent series 1100 mass spectrometer connected to an Agilent series 1100 HPLC.

In the examples below, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

BSA	=	bovine serum albumin
DBU	=	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	=	1,2-dichloroethane
DEAD	=	diethyl azodicarboxylate
DMAP	=	4-dimethylaminopyridine
DME	=	1,2-dimethoxyethane
DMF	=	dimethylformamide
DMF-DMA	=	*N,N*-dimethylformamide dimethyl acetal
DMSO	=	dimethylsulfoxide
DPPA	=	diphenylphosphoryl azide
EDTA	=	ethylenediamine tetraacetic acid
EtOAc	=	ethyl acetate
EtOH	=	ethanol
Et_3N	=	triethylamine
HBSS	=	Hank's balanced salt solution
HEPES	=	4-(2-hydroxyethyl)-1-piperazinecthanesulfonic acid
HOAc	=	Acetic acid
HPLC	=	high performance liquid chromatography
i-PrOH	=	*iso*-propanol
LC/MS	=	liquid chromatography/mass spectroscopy
MTBE	=	methyl tert-butylether
PBS	=	phosphate buffered saline
PBS++	=	PBS with calcium and magnesium
R_f	=	retention factor (ratio of distance traveled by substance/distance traveled by solvent front)
R_t	=	retention time
SEM	=	2-(trimethylsilyl)ethoxymethyl
TFA	=	trifluoroacetic acid
THF	=	tetrahydrofuran
TLC	=	thin layer chromatography

Exemplary HPLC Procedures

Purity of compounds were determined by HPLC/MS analysis employing a variety of analytical methods:

Method 1 = 20% [B]: 80% [A] to 70% [B]: 30% [A] gradient in 1.75 min, then hold, at 2 mL/min, where [A]=0.1% trifluoroacetic acid in water; [B]=0.1% trifluoroacetic acid in acetonitrile on a Phenomenex Luna C18 (2) 4.6-mm X 30-cm column, 3 micron packing, 210 nm detection, at 35 °C.

Method 2 = 50% [B]: 50% [A] to 95% [B] : 5% [A] gradient in 2.5 min, then hold, at 2 mL/min, where [A]=0.1% trifluoroacetic acid in water; [B]=0.1% trifluoroacetic acid in acetonitrile on a Phenomenex Luna C18 (2) 4.6-mm X 30-cm column, 3 micron packing, 210 nm detection, at 35 °C.

Method 3 = 5% [B]: 95% [A] to 20% [B]: 80% [A] gradient in 2.5 min, then hold, at 2 mL/min, where [A]=0.1% trifluoroacetic acid in water; [B]=0.1% trifluoroacetic acid in acetonitrile on a Phenomenex Luna C18 (2) 4.6-mm X 30-cm column, 3 micron packing, 210 nm detection, at 35 °C.

Method 4 = 20% [B]: 80% [A] to 70% [B]: 30% [A] gradient in 2.33 min, then hold, at 1.5 mL/min, where [A]=0.1% trifluoroacetic acid in water; [B]=0.1% trifluoroacetic acid in acetonitrile on a Phenomenex Luna C18 (2) 4.6-mm X 30-cm column, 3 micron packing, 210 nm detection, at 35 °C.

Method 5 = 50% [B]: 50% [A] to 95% [B] : 5% [A] gradient in 3.33 min, then hold, at 1.5 mL/min, where [A]=0.1% trifluoroacetic acid in water; [B]=0.1% trifluoroacetic acid in acetonitrile on a Phenomenex Luna C18 (2) 4.6-mm X 30-cm column, 3 micron packing, 210 nm detection, at 35 °C.

Method 6 = 5% [B]: 95% [A] to 20% [B] : 80% [A] gradient in 3.33 min, then hold, at 1.5 mL/min, where [A]=0.1% trifluoroacetic acid in water; [B]=0.1% trifluoroacetic acid in acetonitrile on a Phenomenex Luna C18 (2) 4.6-mm X 30-cm column, 3 micron packing, 210 nm detection, at 35 °C.

Method 7= 20% [B]: 80% [A] to 70% [B]: 30% [A] gradient in 10.0 min, then hold, at 1.5 mL/min, where [A]=0.1% trifluoroacetic acid in water; [B]=0.1% trifluoroacetic acid in acetonitrile on a Phenomenex Luna C18 (2) 4.6-mm X 3-cm column, 3 micron packing, 210 nm detection, at 35 °C.

Method 8= 10% [B]: 90% [A] to 40% [B]: 60% [A] gradient in 10.0 min, then hold, at 1.5 mL/min, where [A]=0.1% trifluoroacetic acid in water; [B]=0.1% trifluoroacetic acid in acetonitrile on a Phenomenex Luna C18 (2) 4.6-mm X 3-cm column, 3 micron packing, 210 nm detection, at 35 °C.

Method 9 = 23% [B]: 77% [A] to 30% [B]: 70% [A] gradient in 15.0 min, then hold, at 1.0 mL/min, where [A]=0.1% trifluoroacetic acid in water; [B]=0.1% trifluoroacetic acid in acetonitrile on a Zorbex SB-phenyl C18 2.1-mm X 5-cm column, 5 micron packing, 210 nm detection, at 30 °C.

Method 10 = 5%[A]: 95% [B] isocrat, 1.0 mL/min, where [A]=isopropanol; [B]=hexanes; on a Chiral Technologies AD column (4.6 x 250 mm), 10 micron packing, 220 nm detection at ambient temperature.

Method 11 = 10%[A]: 90% [B] isocrat, 1.0 mL/min, where [A]=ethanol; [B]=hexanes; on a Chiral Technologies AD column (4.6 x 250 mm), 10 micron packing, 220 nm detection at ambient temperature.

Method 12 = 10%[A]: 90% [B] isocrat, 0.8 mL/min, where [A]=ethanol; [B]=hexanes; on a Chiral Technologies IA column (4.6 x 250 mm), 5 micron packing, 220 nm detection at ambient temperature.

Method 13 = 10%[A]: 90% [B] isocrat, 1.0 mL/min, where [A]=isopropanol; [B]=hexanes; on a Chiral Technologies IA column (4.6 x 250 mm), 5 micron packing, 220 nm detection at ambient temperature.

Method 14 = 10%[A]: 90% [B] isocrat, 1.0 mL/min, where [A]=isopropanol; [B]=hexanes; on a Chiral Technologies IB column (4.6 x 250 mm), 5 micron packing, 220 nm detection at ambient temperature.

Method 15 = 10%[A]: 90% [B] isocrat, 1.0 mL/min, where [A]=ethanol; [B]=hexanes; on a Chiral Technologies OD column (4.6 x 250 mm), 10 micron packing, 220 nm detection at ambient temperature.

Method 16 = 10%[A]: 90% [B] isocrat, 1.0 mL/min, where [A]=isopropanol; [B]=hexanes; on a Chiral Technologies OD column (4.6 x 250 mm), 10 micron packing, 220 nm detection at ambient temperature.

Method 17 = 15%[A]: 85% [B] isocrat, 1.0 mL/min, where [A]=ethanol; [B]=hexanes; on a Chiral Technologies OD column (4.6 x 250 mm), 10 micron packing, 220 nm detection at ambient temperature.

Method 18 = 5%[A]: 95%[B] isocrat, 55 mL/min, where [A]=isopropanol; [B]=hexanes on a Chiral Technologies AD column (5 x 50 cm), 20 micron packing, 220 nM detection at ambient temperature

Method 19 = 10%[A]: 90%[B] isocrat, 0.8 mL/min, where [A]=ethanol; [B]=hexanes; on a Chiral Technologies IB column (4.6 x 250 mm), 10 micron packing, 220 nm detection at ambient temperature.

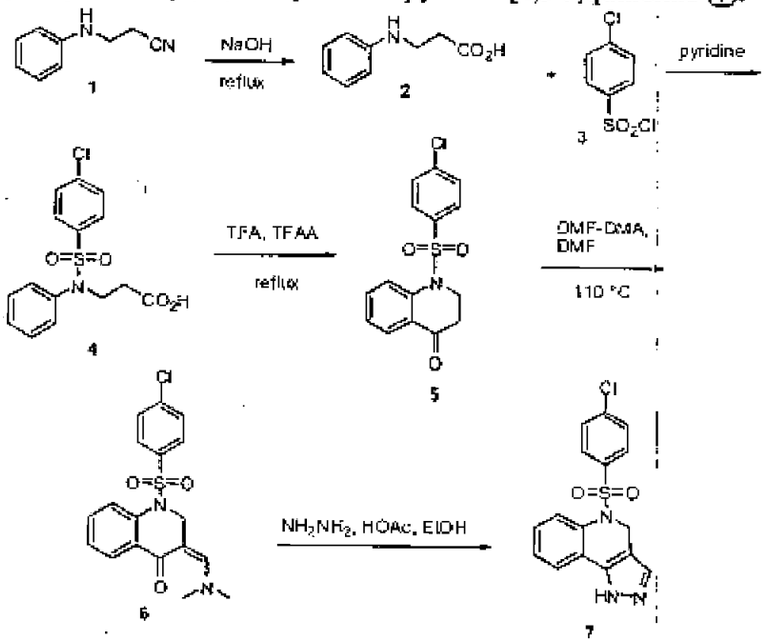
Method 20 = 10%[A]: 90% [B] isocrat, 1.0 mL/min, where [A]=ethanol; [B]=hexanes; on a Chiral Technologies OD-H column (4.6 x 250 mm), 5 micron packing, 220 nm detection at ambient temperature.

Method 21 = 20%[A]: 80% [B] isocrat, 1.0 mL/min, where [A]=ethanol; [B]=hexanes; on a Chiral Technologies OD column (4.6 x 250 mm), 10 micron packing, 220 nm detection at ambient temperature.

Method 22 = 20%[A]: 80% [B] isocrat, 1.0 mL/min, where [A]=isopropanol; [B]=hexanes; on a Chiral Technologies OD column (4.6 x 250 mm), 10 micron packing, 220 nm detection at ambient temperature.

Example 1

5-[(4-Chlorophenyl)sulfonyl]-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline (7).



3-(Phenylamino)propanoic acid (2).

To a 10% aqueous solution of NaOH (120 mL) was added 3-anilinopropionitrile (1) (10.3 g, 10.7 mmol). The suspension was heated at reflux for 6 h and the resulting homogenous solution cooled to room temperature and stirred overnight. The solution was washed with ether (3 x 50 mL) and the pH of the aqueous phase was then adjusted to approximately 3 with conc. HCl. The aqueous phase was extracted with EtOAc (4 x 100 mL) and the combined organic phase was washed with water (1 x 50 mL), brine (1 x 50 mL), dried ($MgSO_4$), filtered and concentrated to yield (2) (11.6 g, 100%) as a brown solid. ^1H

NMR ($CDCl_3$) δ 7.20 (2 H, t, J = 8.2 Hz), 6.77 (1H, t, J = 8.8 Hz), 6.69 (2H, d, J = 7.7 Hz), 3.46, (2H, t, J = 6.6 Hz), 2.67 (2H, t, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ178.5, 147.1, 129.4, 118.5, 113.6, 39.4, 33.5; MS *m/z*: 166 $(M+H)^+$.

3-(4-Chloro-*N*-phenylphenylsulfonamido)propanoic acid (4).

To a solution of (2) (2.0 g, 12.3 mmol) in pyridine (70 mL) at 0 °C was added 4-chlorobenzenesulfonyl chloride (3) (2.6 g, 12.3 mmol) portionwise. The reaction was warmed to room temperature and stirred for 3 hours. The reaction mixture was then concentrated and the residue taken up in EtOAc (100 mL). The organic phase was washed with 1N HCl (5 x 100 mL), water (1 x 100 mL), brine (1 x 50 mL), dried ($MgSO_4$), filtered, and concentrated to yield (4) (3.2g, 77%) as a tan solid. ^1H NMR ($CDCl_3$) δ 7.58-7.54 (2H, m), 7.48-7.45 (2H, m), 7.38-7.36 (3H, m), 7.08-7.06 (2H, m), 3.39 (2H, t, J = 7.5 Hz), 2.64 (2H, t, J = 7.2 Hz); MS *m/z* 340 $(M+H)^+$.

1-(4-Chlorophenylsulfonyl)-2,3-dihydroquinolin-4(1*H*)-one (5).

Trifluoroacetic acid (5 mL) and trifluoroacetic anhydride (2 mL) were added to (4) (1.64 g, 4.83 mmol). The homogenous solution was heated at reflux for 3.5 hours, cooled and poured into ice water and the product extracted with EtOAc (1 x 50 mL, 2 x 10 mL). The combined organic phase was washed with water (1 x 20 mL), saturated aqueous $NaHCO_3$ (5 x 50 mL), brine (1 x 10 mL), dried ($MgSO_4$), filtered, and concentrated to yield (5) (1.48 g, 95%) as a tan solid. TLC: Rf = 0.30 (3:1 hexanes/EtOAc, silica gel). ^1H NMR ($CDCl_3$) δ 7.98 (1H, dd, J = 7.7, 1.6 Hz), 7.86 (1H, d, J = 8.2 Hz), 7.65-7.61 (3H, m), 7.45-7.42 (2 H, m), 7.31 (1H, d, J = 8.2 Hz), 4.27 (2H, t, J = 6.6 Hz), 2.48 (2H, t, J = 6.6 Hz); MS *m/z* 322 $(M+H)^+$.

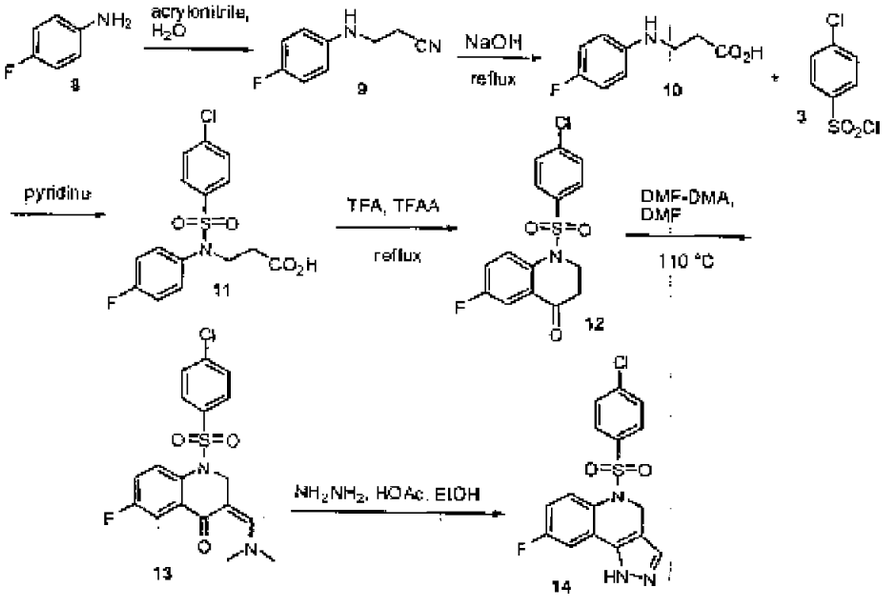
5-(4-Chlorophenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline (7).

To a DMF (800 μL) solution of (5) (151 mg, 0.470 mmol) was added dimethylformamide dimethyl acetal (62 μL, 0.470 mmol). The reaction was heated at 110 °C for 4 hours and then cooled to room temperature and set aside overnight. HPLC/MS analysis of the reaction mixture determined compound (6) to be present, (M+H)+ = 377, with no remaining (5). Volatiles were removed under a stream of nitrogen and the crude product was used directly in the next reaction. To an EtOH/glacial HOAc solution (25:1, 2 mL) of crude (6) (177 mg, 0.470 mmol) was added hydrazine hydrate (73 μL, 2.34 mmol). The reaction mixture was stirred overnight at room temperature, concentrated and the residue taken up in

EtOAc (10 mL). The organic phase was washed with sat. aq. $NaHCO_3$ (3 x 20 mL), brine (1 x 10 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by reverse phase HPLC to give (7) (26 mg, 12% from (5)) as a yellow TFA salt. TLC: Rf = 0.35 (1:1 hexanes/EtOAc, silica gel). ^1H NMR (DMSO-d_6) δ 7.68-7.62 (2H, m), 7.46-7.41 (3H, m), 7.32 (2H, d, J = 8.2 Hz), 7.16 (2H, d, J = 8.8 Hz), 4.93 (2H, s); ^{13}C NMR (DMSO-d_6) δ 138.9, 137.1, 135.0, 129.6, 129.5, 129.3, 128.9, 128.6, 123.3, 112.3, 44.2; MS *m/z* 346 $(M+H)^+$

Example 2

5-[(4-Chlorophenyl)sulfonyl]-8-fluoro-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline (14).



3-(4-Fluorophenylamino)propanoic acid (10).

Acrylonitrile (7.89 mL, 120 mmol) was added to 4-fluoroaniline (8), (11.1 g, 100 mmol), and H_2O (80 mL). The biphasic mixture was heated to reflux and stirred overnight. The reaction mixture was cooled to room temp. HPLC/MS analysis of the reaction mixture confirmed compound (9) to be present, $(M+H)^+ = 165.1$. NaOH (12 g, 300 mmol) was added to the reaction mixture, and the reaction was heated to reflux for 1.5 hours. HPLC/MS analysis of the reaction mixture confirmed compound (10), to be present with no remaining (9). The reaction was cooled to room temperature and extracted with diethyl ether (3 x 50 mL). The pH was adjusted to approximately 3 with 3N aqueous HCl and then the aqueous layer was extracted with EtOAc (2 x 50 mL). The aqueous layer was then adjusted to pH 5

with 1 N NaOH and extracted with EtOAc (1 x 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to yield (10) as a brown solid, (16 g, 87.6 mmol, 87%) MS *m/z* 184.1 $(M+H)^+$.

3-(4-Chloro-*N*-(4-fluorophenyl)phenylsulfonamido)propanoic acid (11).

To a rapidly stirring room temperature pyridine (0.5 M, 166 mL) solution of (10) (15.19 g, 83 mmol) was added 4-chlorobenzenesulfonyl chloride (3), (17.5 g, 83 mmol). After 30 minutes, pyridine was removed and the residue was taken into EtOAc, and washed with water (5 x 50 mL), brine (2 x 50 mL), and 1M HCl (3 x 50 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated to yield (11) as a tan solid (22.2 g, 62.3 mmol, 75 %). MS *m/z* 357.9 $(M+H)^+$, 379.9 $(M+Na)^+$.

1-(4-Chlorophenylsulfonyl)-6-fluoro-2,3-dihydroquinolin-4(1*H*)-one (12).

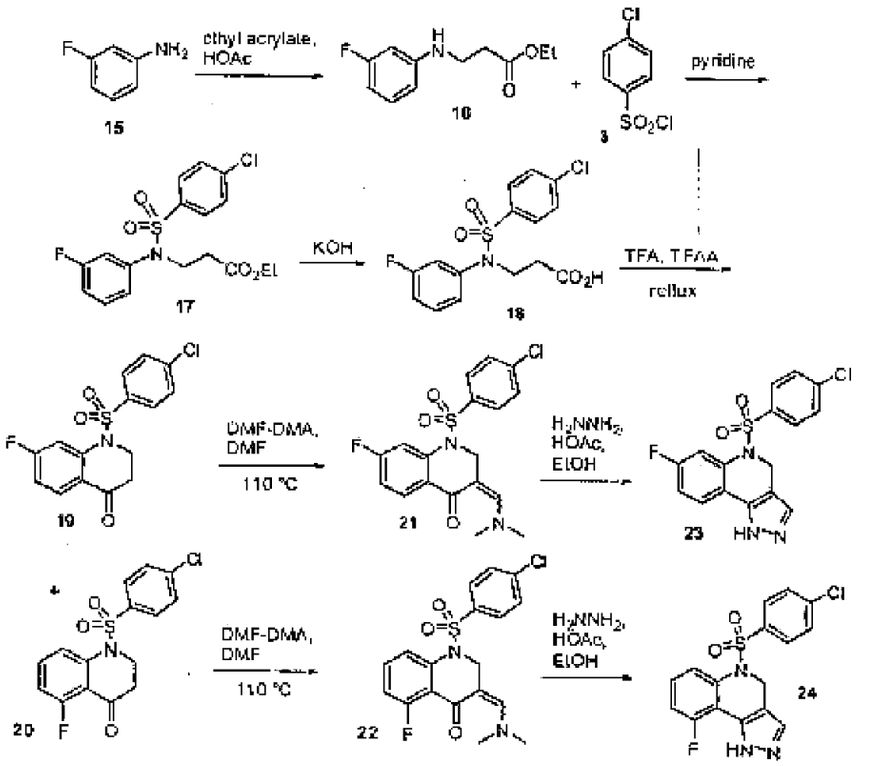
Trifluoroacetic acid (10 mL) and trifluoroacetic anhydride (3.2 mL) were added to (11) (3.3 g, 9.2 mmol). The homogenous solution was heated to 80 °C for 6 hours, cooled and poured into ice water. The product was extracted with EtOAc. The organic phase was washed with sat. aq. $NaHCO_3$ (3 x 25 mL), and concentrated. The residue was triturated with diethyl ether, and then chromatographed with EtOAc to afford (12) (0.8 g, 26%). MS *m/z* 339.9 $(M+H)^+$.

5-(4-Chlorophenylsulfonyl)-8-fluoro-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline (14).

Dimethylformamide dimethyl acetal (2 mL) was added to (12) (454 mg, 1.34 mmol). The reaction was heated at 103 °C for 20 minutes and then cooled to room temperature. HPLC/MS analysis of the reaction mixture determined compound (13) was present, $(M+H)^+$ = 394.9, with no remaining (12). Volatiles were removed and the crude product was used directly in the next reaction. To an HOAc solution (4 mL) of crude (13) (1.34 mmol) was added hydrazine hydrate (78 µL, 1.61 mmol). The reaction mixture was heated to 95 °C for 1 hour. Solvent was removed and the residue was chromatographed with 1:1 hexane/EtOAc to afford (14) (432 mg, 89%). MS *m/z* 364 $(M+H)^+$. ^1H NMR (CD_3OD) δ 7.77-7.74 (dd, J = 8.9, 5.0 Hz, 1H), 7.40(s, 1H), 7.36-7.33 (dd, J = 8.8, 3.0 Hz, 1H), 7.20-7.14 (m, 5H), 4.95 (s, 2H); ^{13}C NMR (CD_3OD) δ 163.6, 160.3, 138.8, 136.0, 130.8, 130.7, 128.6, 128.1, 114.6, 114.3, 112.2, 108.7, 108.4, 43.0.

Example 3

5-[(4-Chlorophenyl)sulfonyl]-7-fluoro-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline (23) and 5-[(4-Chlorophenyl)sulfonyl]-9-fluoro-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline (24).



Ethyl 3-(3-fluorophenylamino)propanoate (16).

A mixture of 3-fluoroaniline (15), 10 g, 90 mmol), ethyl acrylate (9.9 g, 10.8 mL, 95 mmmol) and HOAc (400 µL) was heated at reflux for 17 h. The mixture was cooled to ambient temperature then distilled (b.p 120-130 °C at 0.25 Torr) to give (16), 12.35 g (65%).

Ethyl 3-(4-chloro-*N*-(3-fluorophenyl)phenylsulfonamido)propanoate (17).

Ethyl 3-(3'-fluoroanilinyl)propionate (16), 12.3 g, 58.2 mmol) was dissolved in pyridine (125 mL) and cooled in an ice bath. 4-Chlorobenzenesulfonyl chloride (3), 13.5 g, 64 mmol) was added in portions over 30 min. The mixture was stirred for 1 h in an ice bath and then allowed to warm to ambient temperature for 1h. The volatiles were removed *in vacuo* and the residue was diluted with water (200 mL) and then extracted with EtOAc (2 x 200 mL). The combined organic extracts were washed with 1N aq HCl (2 x 100) then dried (Na_2SO_4), filtered and evaporated *in vacuo* to give 23.2 g of (17) (quantitative).

3-(4-Chloro-*N*-(3-fluorophenyl)phenylsulfonamido)propanoic acid (18).

The ethyl ester (17) (23.2 g, 58 mmol) was taken up into MeOH (200 mL) and treated dropwise with a solution of potassium hydroxide (4.10 g, 73 mmol) in water (75 mL). The mixture was then stirred for 1 h until TLC analysis indicated the consumption of starting material. The mixture was concentrated *in vacuo*, diluted with water (200 mL), then made acidic with 6 N aq. HCl. The mixture was extracted with EtOAc (2 x 200 mL) and the combined organic extracts were washed with water (2 x 100 mL), then dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a residue of (18). The residue was recrystallized from EtOAc/hexanes to give two small crops of crystals (2.35g, 1.21 g), but the remaining mother liquors were concentrated *in vacuo* to give a residue (16 g), which was taken on to the next step.

1-(4-Chlorophenylsulfonyl)-7-fluoro-2,3-dihydroquinolin-4(1*H*)-one (19) and 1-(4-Chlorophenylsulfonyl)-5-fluoro-2,3-dihydroquinolin-4(1*H*)-one (20).

The carboxylic acid (18) (16 g) was taken up into trifluoroacetic acid (75 mL) and treated with trifluoroacetic anhydride (30 mL). The mixture was heated to reflux for 3 hours before cooling to ambient temperature. The volatiles were removed *in vacuo* to give a residue which was combined with two earlier reactions and purified by silica gel chromatography (twice, eluted 4:1 hexanes/EtOAc) to give (19) (5.5 g) and (20) (1.05 g).

5-(4-Chlorophenylsulfonyl)-7-fluoro-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline (23).

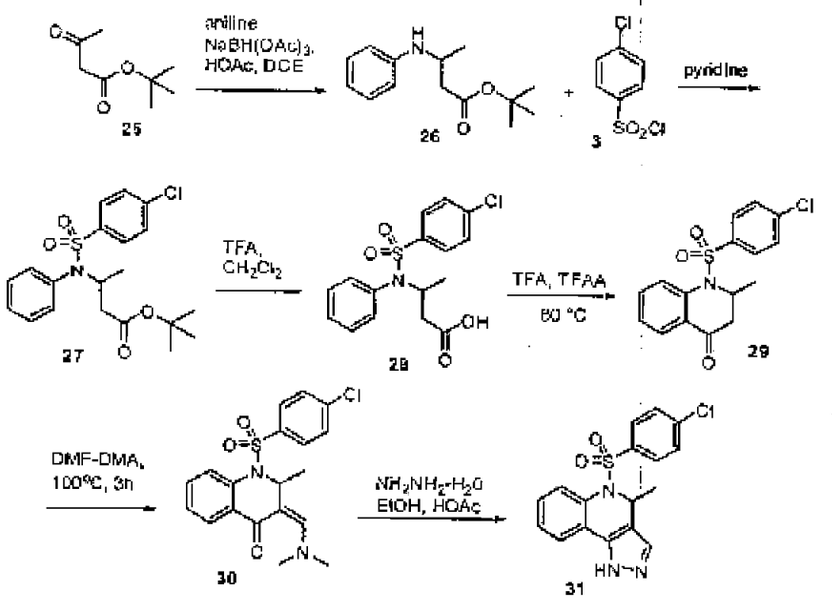
Dimethylformamide dimethyl acetal (2 mL) was added to (19) (518 mg, 1.53 mmol). The reaction was heated at 103 °C for 20 minutes and then cooled to room temperature. HPLC/MS analysis of the reaction mixture determined compound (21) present, $(M+H)^+$ = 394.9, with no remaining (19). Volatiles were removed and the crude product was used directly in the next reaction. To an acetic acid solution (4 mL) of crude (21) (1.53 mmol) was added hydrazine hydrate (74 µL, 1.53 mmol). The reaction mixture was heated to 95 °C for 1 hour. Solvent was removed and the residue was chromatographed with HPLC to afford (23) (272 mg, 0.75 mmol). MS *m/z* 363.9 $(M+H)^+$. ^1H NMR (CD_3OD) δ 7.68-7.63 (dd, J = 8.6, 6.2 Hz, 1H), 7.53-7.49(dd, J = 10.1, 2.6 Hz, 1H), 7.38 (s, 1H), 7.22-7.14 (m, 5H), 4.96 (s, 2H); ^{13}C NMR (CD_3OD) δ 163.4, 160.2, 139.0, 136.6, 136.4.8, 136.2, 128.5, 128.2, 123.7, 123.6, 115.7, 115.4, 114.8, 114.5, 43.1.

5-(4-Chlorophenylsulfonyl)-9-fluoro-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline (24).

Dimethylformamide dimethyl acetal (2 mL) was added to (20) (530 mg, 1.56 mmol). The reaction was heated at 103 °C for 20 minutes and then cooled to room temperature. HPLC/MS analysis of the reaction mixture determined compound (22) present, $(M+H)^+$ = 394.9, with no remaining (20). Volatiles were removed and the crude product was used directly in the next reaction. To an acetic acid solution (4 mL) of crude (22) (1.56 mmol) was added hydrazine hydrate (76 µL, 1.56 mmol). The reaction mixture was heated to 95 °C for 1 hour. Solvent was removed and the residue was chromatographed with HPLC to afford (24) (253 mg, 45 %). MS *m/z* 364.0 $(M+H)^+$. ^{1}H NMR (CD_3OD) δ 7.64-7.61 (d, J = 7.7 Hz, 1H), 7.47-7.39 (m, 2H), 7.24-7.19 (m, 5H), 4.96 (s, 2H); ^{13}C NMR (CD_3OD) δ 159.2, 155.9, 139.0, 136.2, 128.5, 128.3, 128.2, 127.7, 124.5, 124.4, 114.8, 114.5, 112.7, 43.0.

Example 4

5-(4-Chlorophenylsulfonyl)-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline (31).



tert-Butyl 3-(phenylamino)butanoate (26).

To a 1,2-dichloroethane solution (100 mL) of aniline (2.52 g, 27.1 mmol) was added *t*-butyl acetoacetate (25), 4.49 mL, 27.1 mmol) and glacial acetic acid (2.0 mL, 35.2 mmol). Sodium triacetoxyborohydride (8.60 g, 40.6 mmol) was added in portions and the reaction was stirred overnight at room temperature. Saturated aqueous $NaHCO_3$ (200 mL) was slowly added and the biphasic solution was well stirred for 45 min. The aqueous solution was extracted with dichloroethane (1 x 30 mL) and the combined organic portions were washed

with brine (1 x 20 mL), dried ($MgSO_4$), filtered and concentrated to yield (26) (5.2, 81%) as an oil which solidified upon standing. MS *m/z* 236.2 $(M+H)^+$.

tert-Butyl 3-(4-chloro-*N*-phenylphenylsulfonamido)butanoate (27).

To a solution of (26) (2.34 g, 9.94 mmol) in pyridine (25 mL) at 0 °C was added 4-chlorobenzenesulfonyl chloride (3), (6.29 g, 29.8 mmol) portionwise. The reaction was warmed to room temperature and then heated at 70 °C for 5 hours, cooled, and stirred overnight at room temperature. The reaction mixture was then concentrated and the residue taken up in EtOAc (150 mL). The organic phase was washed with cold 1N HCl (5 x 100 mL), water (1 x 50 mL), sat. aq. $NaHCO_3$ (3 x 50 mL), brine (1 x 20 mL), dried ($MgSO_4$), filtered, and concentrated to an oil. ^1H NMR revealed the presence of unreacted 4-chlorobenzenesulfonyl chloride, so the product was dissolved in pyridine (25 mL) and dimethylaminopropylamine (35 mL) was added and the resulting solution was stirred overnight. The reaction mixture was concentrated and the residue taken up in EtOAc (150 mL) and washed with cold 1N HCl (6 x 60 mL), water (1 x 50 mL), sat. aq. $NaHCO_3$ (3 x 60 mL), brine (1 x 20 mL), dried ($MgSO_4$), filtered, and concentrated to yield (27) (3.7 g, 91%) as a light yellow oil. MS *m/z*: 432.1 $(M+Na)^+$.

3-(4-Chloro-*N*-phenylphenylsulfonamido)butanoic acid (28).

To a solution of (27) (3.35 g, 8.17 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added TFA (45 mL). The reaction mixture was allowed to warm to room temperature. After stirring for 72 hours the reaction mixture was concentrated to give (28) (2.63 g, 91%) as a light yellow oil which solidified upon standing. MS *m/z* 354.1$(M+H)^+$.

5-(4-Chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline (31).

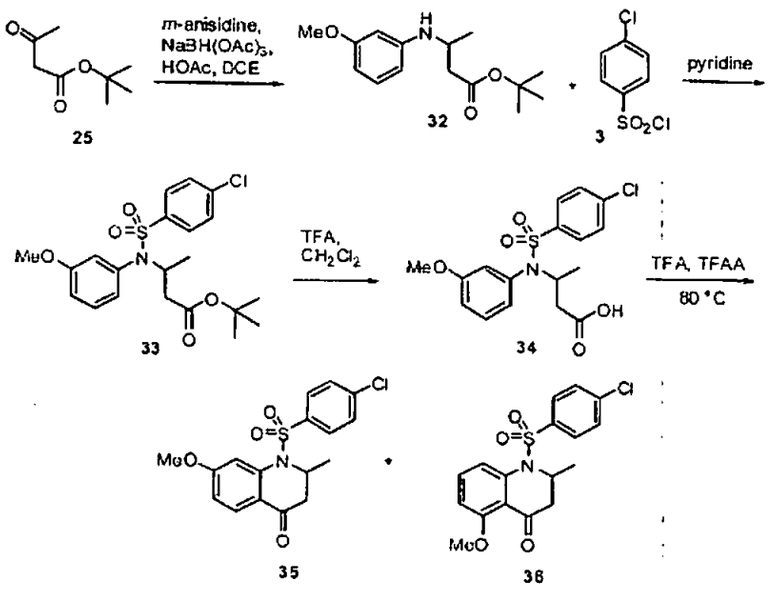
To a solution of (28) (1.02 g, 2.89 mmol) in TFA (3 mL) was added trifluoroacetic anhydride (1.2 mL, 8.8 mmol). The reaction mixture was heated at 80 °C for one hour, cooled and pour onto cracked ice. The product was extracted with EtOAc (3 x 15 mL) and the combined organic portion was washed with water (1 x 20 mL), sat. aq. $NaHCO_3$ (3 x 40 mL), brine (1 x 20 mL), dried ($MgSO_4$), filtered, and concentrated to a tacky yellow solid. The crude product was purified by flash chromatography eluting with 6:1 hexanes/EtOAc to give impure (29) (351 mg) as a light yellow foam. MS *m/z*: 336.1 $(M+H)^+$.

A dimethylformamide dimethyl acetal (1.5 mL) solution of (29) (263 mg, 0.782 mmol) was heated at 100 °C for 3 hours. HPLC/MS analysis of the reaction mixture determined no starting material remained so the reaction was cooled to room temperature.

Following concentration, the crude product (30) was used directly in the next reaction. To an EtOH/glacial acetic acid solution (25:1 v/v, 2 mL) of (30) (306 mg, 0.782 mmol) was added hydrazine hydrate (189 μL, 3.91 mmol). The reaction mixture was stirred overnight at room temperature, concentrated, and the residue taken up in EtOAc (10 mL). The organic phase was washed with sat. aq. $NaHCO_3$ (3 x 20 mL), brine (1 x 10 mL), dried over $MgSO_4$, filtered and concentrated to a semi-solid. The crude product was purified by flash chromatography eluting with 10:1 hexanes/EtOAc and then 2:1 hexanes/EtOAc to give (31) as a light golden solid. MS *m/z* 360.0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.82 (1H, dd), 7.66 (1H, dd), 7.44-7.33 (2H, m), 7.21 (1H, *s*), 7.12-7.02 (4H, m), 5.62 (1H, q), 1.30 (3H, d) ^{13}C NMR ($CDCl_3$) δ 138.9, 136.0, 132.4, 129.8, 128.6, 128.4, 128.3, 127.8, 124.8, 122.4, 118.0, 49.8, 23.1.

Example 5

1-(4-Chlorophenylsulfonyl)-7-methoxy-2-methyl-2,3-dihydroquinolin-4(1*H*)-one (35) and 1-(4-Chlorophenylsulfonyl)-5-methoxy-2-methyl-2,3-dihydroquinolin-4(1*H*)-one (36).



tert-Butyl 3-(3-methoxyphenylamino)butanoate (32).

To a solution of *m*-anisidine (1.00 g, 8.12 mmol) in CH_2Cl_2 (10 mL) was added *tert*-butyl acetoacetate (25), (1.28 g, 8.12 mmol), followed by HOAc (0.47 mL, 8.12 mmol). The reaction mixture was stirred for 45 minutes. Sodium triacetoxyborohydride (2.41 g, 11.3

mmol) was added and the reaction mixture was stirred overnight at room temperature. The reaction mixture was quenched by the slow addition of saturated aqueous $NaHCO_3$. The two layers were separated. The aqueous solution was extracted with CH_2Cl_2 (10 mL). The combined organic layers were washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography (20% EtOAc in hexanes) to afford (32) (1.09 g, 51%) MS *m/z* 266.1 $(M+H)^+$.

tert-Butyl 3-(4-chloro-*N*-(3-methoxyphenyl)phenylsulfonamido) butanoate (33).

To a solution of (32) (1.00 g, 3.76 mmol) in pyridine (10 mL) was added 4-chlorobenzenesulfonyl chloride (3), (0.79 g, 3.76 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated, and the resulting residue was dissolved in ClH_2Cl_2 (15 mL). The organic phase was washed with water (10 mL), and saturated aqueous NaCl (10 mL), then dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography (20% EtOAc in hexanes) to afford (33) (1.32 g, 80%) MS *m/z* 462.1 $(M+Na)^+$.

3-(4-Chloro-*N*-(3-methoxyphenyl)phenylsulfonamido)butanoic acid (34).

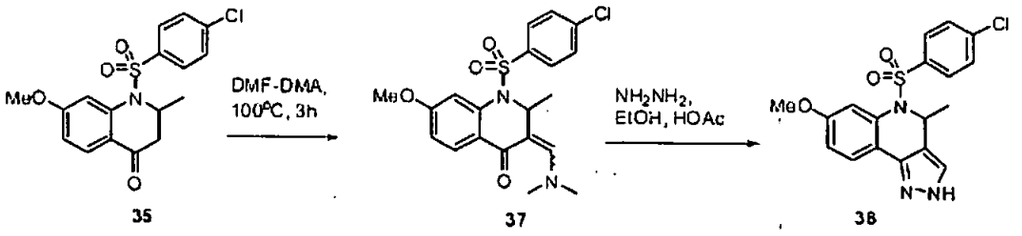
To a solution of (33) (1.25 g, 2.86 mmol) in CH_2Cl_2 (10 mL) was added TFA (10 mL). The reaction mixture was stirred at room temperature overnight, and then concentrated. The resulting residue was dissolved in CH_2Cl_2 (10 mL) and washed with water (5 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated to afford (34) (0.93g, 85%), which solidified upon standing. MS *m/z* 384.1 $(M+H)^+$.

1-(4-Chlorophenylsulfonyl)-7-methoxy-2-methyl-2,3-dihydroquinolin-4(1*H*)-one (35) and 1-(4-Chlorophenylsulfonyl)-5-methoxy-2-methyl-2,3-dihydroquinolin-4(1*H*)-one (36).

To a solution of (34) (0.93 g, 2.43 mmol) in trifluoroacetic acid (5 mL) was added trifluoroacetic anhydride (2 mL). The reaction mixture was heated to 80 °C for 3h, and then cooled to room temperature. The reaction mixture was poured into water and crushed ice. The product was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (3 x 15mL), saturated aqueous NaCl (15 mL), dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography (20% EtOAc in hexanes) to yield the two regioisomers (35) (0.66 g, 69%) MS *m/z* 366.0 $(M+H)^+$, and (36) (0.06 g, 6%) MS *m/z* 366.0 $(M+H)^+$.

Example 6

5-(4-Chlorophenylsulfonyl)-7-methoxy-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline (38).

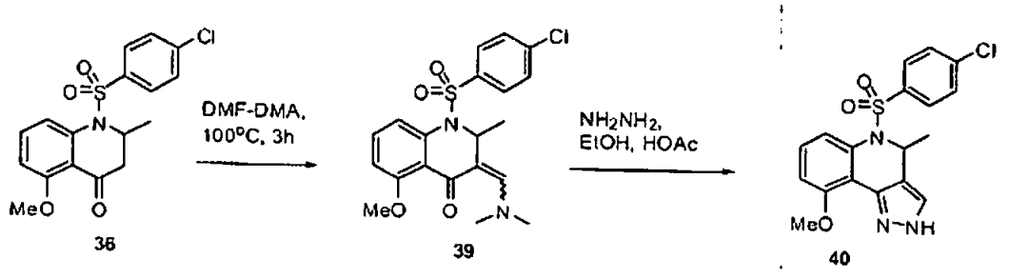


5-(4-Chlorophenylsulfonyl)-7-methoxy-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline (38).

To (35) (0.25 g, 0.68 mmol) was added dimethylformamide dimethylacetal (5 mL). The reaction mixture was heated to 100 °C for 3h, then cooled to room temperature and concentrated. The resulting residue of crude (37) was used without purification in the next reaction. To a solution of (37) in MeOH (5 mL) was added HOAc (0.12 mL, 2.05 mmol), followed by anhydrous hydrazine (0.06 g, 2.05 mmol). The reaction mixture was stirred at room temperature overnight, then concentrated. The resulting residue was dissolved in EtOAc (15 mL), washed with saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous NaCl (10 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography (30% EtOAc in hexanes) to yield (38) (0.16 g, 61%); ^{1}H NMR ($CDCl_3$) δ 7.55 (d, J = 8.3 Hz, 1H), 7.39 (d, J = 2.5 Hz, 1H), 7.16 (m, 3H), 7.03 (d, J = 8.7 Hz, 2H), 6.91 (dd, J = 8.5, 2.5 Hz, 1H), 5.60 (q, J = 6.9 Hz, 1H), 3.91 (s, 3H), 1.32 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 159.7, 139.0, 136.1, 133.9, 128.5, 128.3, 123.3, 117.7, 116.9, 114.6, 114.4, 60.5, 55.7, 50.1, 23.2, 14.2; MS *m/z* 389.0 $(M+H)^+$.

Example 7

5-(4-Chlorophenylsulfonyl)-9-methoxy-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline (40).

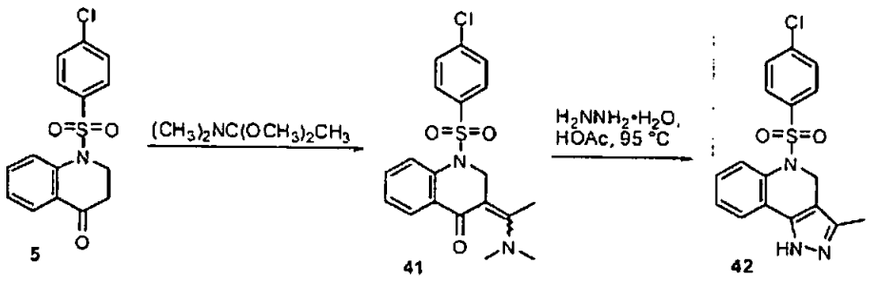


5-(4-Chlorophenylsulfonyl)-9-methoxy-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline (40).

To (36) (0.06 g, 0.15 mmol) was added dimethylformamide dimethylacetal (2 mL). The reaction mixture was heated to 100 °C for 3h, then cooled to room temperature and concentrated. The resulting residue of crude (39) was used without purification in the next reaction. To a solution of (39) in MeOH (2 mL) was added HOAc (0.02 mL, 0.45 mmol), followed by anhydrous hydrazine (0.02 g, 045 mmol). The reaction mixture was stirred at room temperature overnight, then concentrated. The resulting residue was dissolved in EtOAc (15 mL), washed with saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous NaCl (10 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography (30% EtOAc in hexanes) to yield (40) (0.03 g, 59%); ^{1}H NMR ($CDCl_3$) δ 7.52 (dd, J, 8.1, 0.8 Hz, 1H), 7.36 (d, J = 8.3 Hz, 1H), 7.28 (s, 1H), 7.17 (m, 4H), 6.92 (dd, J = 8.3, 0.5 Hz, 1H), 5.68 (q, J = 6.9 Hz, 1H), 3.96 (s, 3H), 1.28 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 139.0, 136.1, 134.0, 132.7, 129.5, 128.7, 122.3, 117.5, 111.3, 109.5, 60.5, 56.1, 50.5, 23.0, 14.3; MS *m/z* 390.0 $(M+H)^+$.

Example 8

5-[(4-Chlorophenyl)sulfonyl]-3-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline (42).



5-(4-Chlorophenylsulfonyl)-3-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline (42).

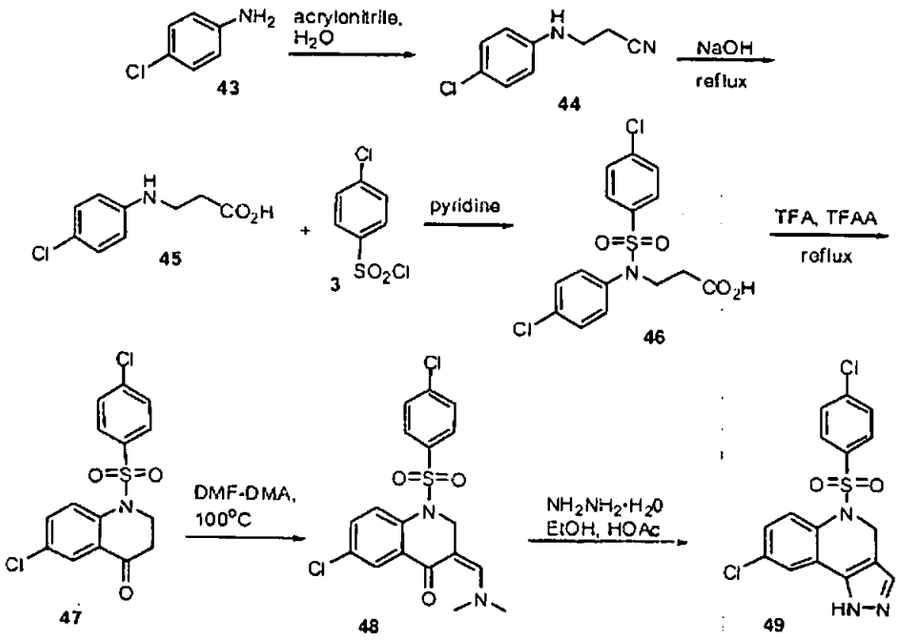
Ketone (5) (357 mgs, 1.11 mmol) was warmed to dissolution in neat *N,N*-dimethylacetamide dimethyl acetal (1.63 mL, 11.11 mmol) and stirred under nitrogen at 103 °C for 30 min. The amber solution was cooled to ambient temperature and subsequently dried via rotary evaporation to afford compound (41) MS (ES) *m/z* 391.0 $(M+H)^+$.

To a suspension of intermediate (41) (156 mgs, 0.4 mmol) and glacial HOAc (8 mL) was added hydrazine hydrate (82.4 μL, 1.0 mmol). The solution was stirred under nitrogen and heated at 95 °C for 18h. Additional hydrazine hydrate was then added (82.4 μL, 1.0 mmol) and the reaction stirred for an additional 4h at 95 °C. Upon complete consumption of

(41) (0.3h-22h LC-MS), the reaction mixture was cooled to ambient temperature and the solvent was removed by rotary evaporation. The resulting residue was dissolved in CH_2Cl_2 (20 mL), washed with water (2 x 20 mL) and dried over $MgSO_4$. After filtration and concentration by rotary evaporation, the residue was dissolved in MeOH (6 mL) and purified by reverse-phase preparative HPLC, resulting in 33 mgs of (42). MS (ES) *m/z* 359.9 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.81-7.78 (dd, J = 6.2, 1.5 Hz, 1H), 7.66-7.63 (dd, J = 5.4, 1.6 Hz, 1H), 7.43-7.32 (m, 2H), 7.16-7.07 (m, 4H), 4.81 (s, 2H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.3, 156.2, 143.7, 138.9, 136.5, 135.2, 134.8, 128.7, 128.3, 128.2, 128.1, 127.8, 125.7, 122.4, 109.9, 43.0, 9.6.

Example 9

5-(4-Chlorophenylsulfonyl)-9-methoxy-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline (49).



3-(4-Chlorophenylamino)propanenitrile (44).

Acrylonitrile (10.3 mL, 157 mmol) was added to 4-fluoroaniline (43), (10 g, 78 mmol), and H_2O (62 mL). The biphasic mixture was heated to reflux and stirred for 4 days. An additional 10 mL of acrylonitrile was added to the reaction mixture and reflux continued overnight. Cooled reaction was extracted with CH_2Cl_2 (100 mL) and organic phase was

washed with 0.1 M aqueous citric acid (25 mL) and dried over $MgSO_4$ to obtain compound (44) (12.7 g, 90%) MS *m/z* 181$(M+H)^+$.

3-(4-Chlorophenylamino)propanoic acid (45).

To (44) (12.7 g, 70.8 mmol) was added 1M aqueous NaOH (71 mL), and the reaction was heated to reflux for 4 hours. HPLC/MS analysis of reaction mixture confirmed compound (45), to be present with no remaining (44). The reaction was cooled to room temperature and the precipitate was filtered. The pH was adjusted to approximately 5 with 37% HCl and the product was filtered yielding (45) as a white solid, (10.0 g, 72%) MS *m/z* 200(M+H)+.

3-(4-Chloro-*N*-(4-chlorophenyl)phenylsulfonamido)propanoic acid (46).

To a rapidly stirring 0 °C pyridine (0.5 M, 166 mL) solution of (45) (15.19 g, 83 mmol) was added 4-chlorobenzenesulfonyl chloride (3), 17.5 g, 83 mmol). After 1 h pyridine was removed and the residue was taken into EtOAc, washed with water (2 x 50 mL) and dried ($MgSO_4$), filtered, and concentrated. The sample was crystallized with 1:1 hexane:EtOAc and (46) (1.6 g, 46 %) was obtained MS *m/z* 395.9 $(M+Na)^+$.

6-Chloro-1-(4-chlorophenylsulfonyl)-2,3-dihydroquinolin-4(1*H*)-one (47).

Trifluoroacetic acid (10 mL) and trifluoroacetic anhydride (3.2 mL) were added to (46) (0.8 g, 2.14 mmol). The homogenous solution was heated to reflux for 7 hours, cooled and poured into ice water. The product was extracted with EtOAc. The organic phase was washed with saturated aqueous $NaHCO_3$ (3 x 25 mL), dried over $MgSO_4$, and concentrated. The residue was chromatographed with HPLC to afford (47) (0.192 g, 25%). MS *m/z* 355.9 $(M+H)^+$.

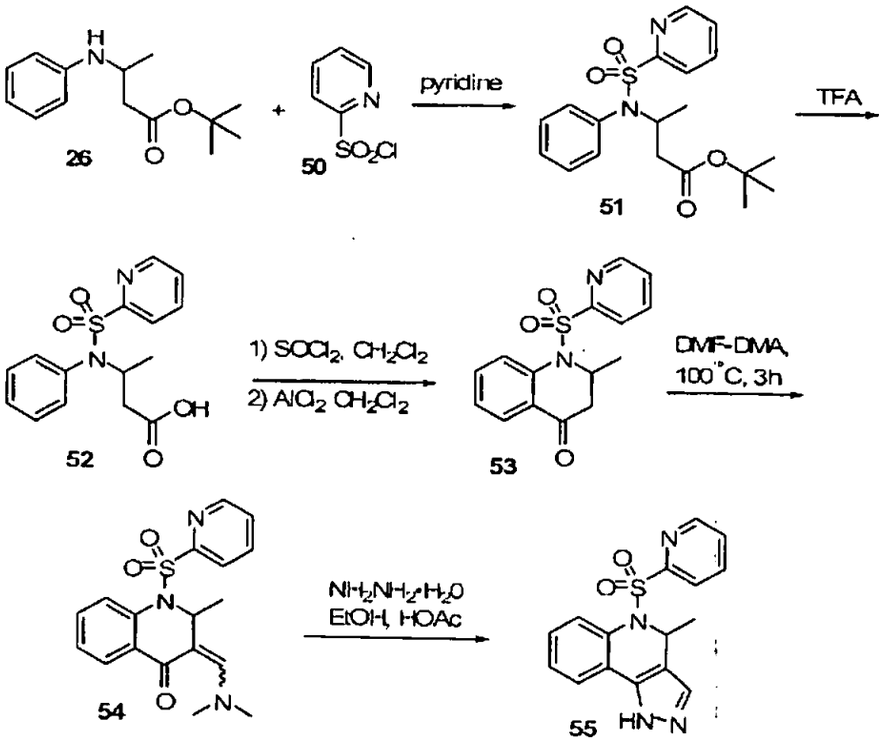
8-Chloro-5-(4-chlorophenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline (49).

Dimethylformamide dimethyl acetal (1 mL) was added to (47) (192 mg, 0.54 mmol). The reaction was heated at 103 °C for 20 minutes and then cooled to room temperature. HPLC/MS analysis of the reaction mixture determined compound (48) present, $(M+H)^+$ = 394.9, with no remaining (47). Volatiles were removed and the crude product was used directly in the next reaction. To an acetic acid solution (1.35 mL) of crude (48) was added hydrazine hydrate (26 µL, 0.54 mmol). The reaction mixture was heated at 95 °C for 1 hour.

Solvent was removed and the residue was chromatographed on HPLC to afford (49) (153 mg, 75 %). MS *m/z* 379.9 $(M+H)^+$. ^1H NMR (CD_3OD) δ 7.75-7.72 (d, J = 8.6 Hz, 1H), 7.64-7.63(d, J = 2.4 Hz, 1H) 7.44-7.40(m 2H), 7.19-7.18 (m, 4H), 4.95 (s, 2H); ^{13}C NMR (CD_3OD) δ 138.9, 136.1, 133.5, 133.4, 130.1, 128.5, 128.2, 127.6, 121.9, 112.3, 43.0.

Example 10

4-Methyl-5-(pyridin-3-ylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline (55).



tert-Butyl 3-(*N*-phenylpyridine-2-sulfonamido)butanoate (51).

To a solution of (26) (2.74 g, 11.6 mmol) in pyridine (46 mL) at 0 °C was added 2-pyridylsulfonyl chloride (50), (5 g, 23.4 mmol). The reaction was warmed to room temperature and stirred overnight. The reaction mixture was then concentrated and the residue taken up in diethyl ether (150 mL). The organic phase was washed with water (1 x 200 mL), 3N HCl (1 x 50 mL), sat. aq. $NaHCO_3$ (1 x 50 mL), water (1 x 50mL), brine (1 x 20 mL), dried ($MgSO_4$), filtered, and concentrated to yield (51) (4.192 g, 96%) as a light yellow oil. MS *m/z* 377.1 $(M+H)^+$.

3-(*N*-Phenylpyridine-2-sulfonamido)butanoic acid (52).

To (51) (4.19 g, 11.1 mmol) was added TFA (8.5 mL) at room temperature and the mixture was sonicated to form a homogeneous solution. After stirring for 1.5 hours the reaction mixture was concentrated, then dissolved in CH_2Cl_2 (200 mL) and extracted with sat. aq. $NaHCO_3$ (4 x 100 mL). Collected aqueous extracts were extracted with CH_2Cl_2 and then the pH was adjusted to 1. The aqueous layer was then extracted with EtOAc (4 x 100 mL). Collected organic extracts were dried over $MgSO_4$, filtered, and concentrated to afford (52) (3.26 g, 92%). MS *m/z* 321.0 $(M+H)^+$.

2-Methyl-1-(pyridin-2-ylsulfonyl)-2,3-dihydroquinolin-4(1*H*)-one (53):

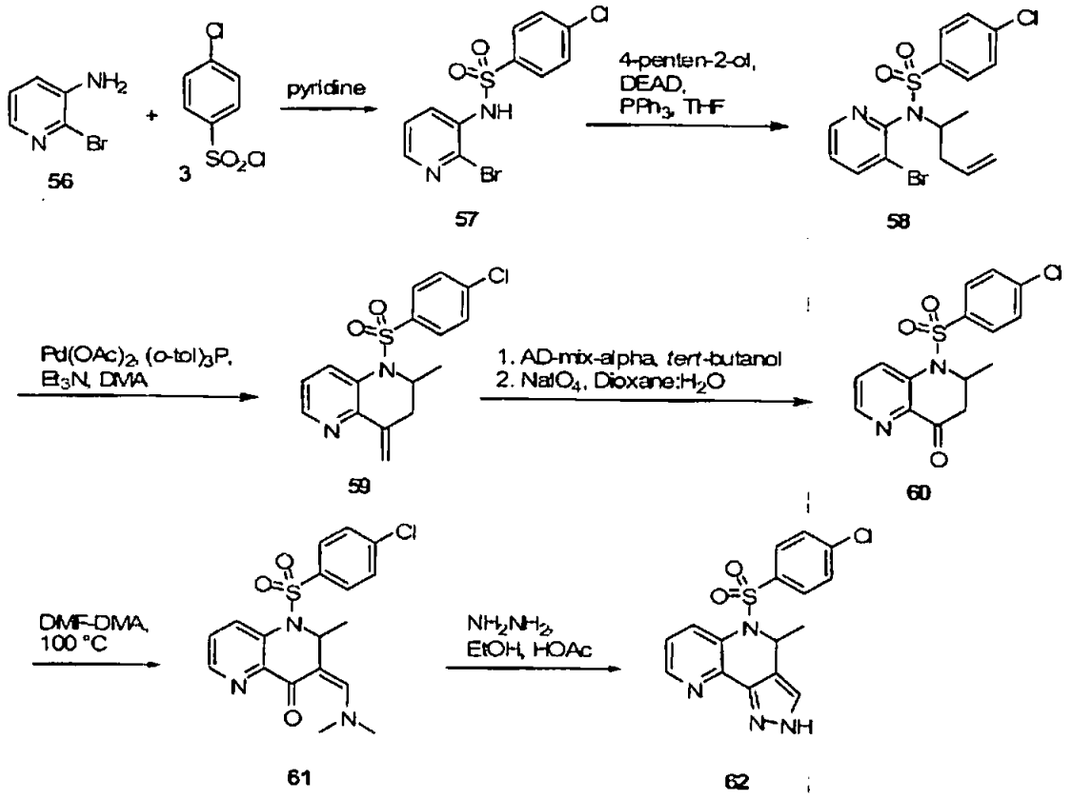
To a solution of (52) (1.32 g, 4.11 mmol) in CH_2Cl_2 (30 mL) was added thionylchloride (0.45 mL, 6.16 mmol). After 20 min at room temperature, the reaction mixture was transferred over 15 min to a 0 °C CH_2Cl_2 (40 mL) solution of $AlCl_3$ (1.36 g, 10.27 mmol). The reaction mixture was then allowed to warm to room temperature and stirred overnight. In the morning, 6N HCl (30 mL) was slowly added to the reaction mixture at 0 °C. The resulting biphasic mixture was rapidly stirred for 1.5 hours, and then the layers were separated. The organic phase was washed with water (1 x 50 mL), sat. aq. $NaHCO_3$ (1 x 50 mL), water (1 x 50 mL), brine (1 x 50 mL), dried ($MgSO_4$), filtered, and concentrated to obtain (53) (1.22 g, 98%) MS *m/z* 303.0 $(M+H)^+$.

4-Methyl-5-(pyridin-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline (55).

A dimethylformamide dimethyl acetal (6.5 mL) solution of (53) (1.46 g, 4.83 mmol) was heated at 100 °C for 2.5 hours. HPLC/MS analysis of the reaction mixture determined no starting material remained so the reaction was cooled to room temperature and concentrated to obtain the crude product (54), which was used directly in the next reaction. To a glacial acetic acid solution (12 mL) of (54) was added hydrazine hydrate (257 µL, 5.31 mmol). The reaction mixture was heated to 80 °C for 45 min, concentrated, and the residue taken up in diethyl ether (100 mL). The organic phase was washed with water (1 x 25 mL), sat. aq. $NaHCO_3$ (1 x 20 mL), brine (1 x 25 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by preparative HPLC chromatography to obtain (55) as a light yellow solid. MS *m/z* 327.0 : $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.45-8.43 (m, 2H), 7.86-7.83 (dd, J = 7.8, 1.3 Hz, 1H), 7.66-7.63 (dd, J = 7.4, 1.6 Hz, 1H), 7.47-7.28 (m, 4H), 7.03-6.99 (m, 1H), 5.75-5.68 (q, J = 6.9 Hz, 1H), 1.35-1.33 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 155.7, 149.3, 137.0, 132.5, 129.3, 128.4, 127.3, 126.4, 124.6, 122.6, 122.1, 118.7, 50.2, 23.1.

Example 11

5-(4-Chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c][1,5]naphthyridine (62).



56 3 57 58 59 60 61 62

N-(2-Bromopyridin-3-yl)-4-chlorobenzenesulfonamide (57).

To a solution of 3-amino-2-bromopyridine (56), (2.00 g, 11.6 mmol) in pyridine (10 mL) was added *p*-chlorobenzenesulfonyl chloride (3), 2.44 g, 11.6 mmol). The reaction mixture was stirred at room temperature for 24h, and then filtered and concentrated. The resulting residue was dissolved in CH_3CN (10 mL) and purified by reverse-phase HPLC. The resulting residue was dissolved in CH_2Cl_2 (20 mL) and washed with saturated aqueous $NaHCO_3$ (2 x 30 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated to afford (57) (0.59 g, 25%). MS (ES) *m/z* 348.8 $(M+H)^+$.

N-(3-Bromopyridin-2-yl)-4-chloro-*N*-(pent-4-en-2-yl)benzenesulfonamide (58).

To a solution of (57) (1.71 g, 4.93 mmol) in THF (10 mL) was added 4-penten-2-ol (0.51 mL, 4.93 mmol), followed by triphenylphosphine (1.55 g, 5.92 mmol). Diethyl

azodicarboxylate (1.08 mL, 5.92 mmol) was added drop-wise to the reaction mixture. The reaction mixture was stirred at room temperature for 24h, and then concentrated. The resulting residue was dissolved in CH_3CN (10 mL) and purified by reverse-phase HPLC. The resulting residue was dissolved in CH_2Cl_2 (20 mL) and washed with saturated aqueous $NaHCO_3$ (2 x 30 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to afford (58) (0.68 g, 33%). MS (ES) *m/z* 416.9 $(M+H)^+$.

1-(4-Chlorophenylsulfonyl)-2-methyl-4-methylene-1,2,3,4-tetrahydro-1,5-naphthyridine (59).

To a solution of (58) (0.68 g, 1.64 mmol) in DMA (5 mL) was added palladium acetate (0.03 g, 0.16 mmol), tri(*o*-tolyl)phosphine (0.16 g, 0.54 mmol), and triethylamine (0.41 mL, 2.95 mmol). The reaction mixture was heated to 150 °C for 8h. The reaction mixture was then cooled to room temperature, diluted with CH_2Cl_2 (10 mL), and washed with H_2O (15 mL) and brine (15 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography (20% EtOAc in hexanes) to afford (59) (0.31 g, 57%). MS (ES) *m/z* 335.0 $(M+H)^+$.

1-(4-Chlorophenylsulfonyl)-2-methyl-2,3-dihydro-1,5-naphthyridin-4(1*H*)-one (60).

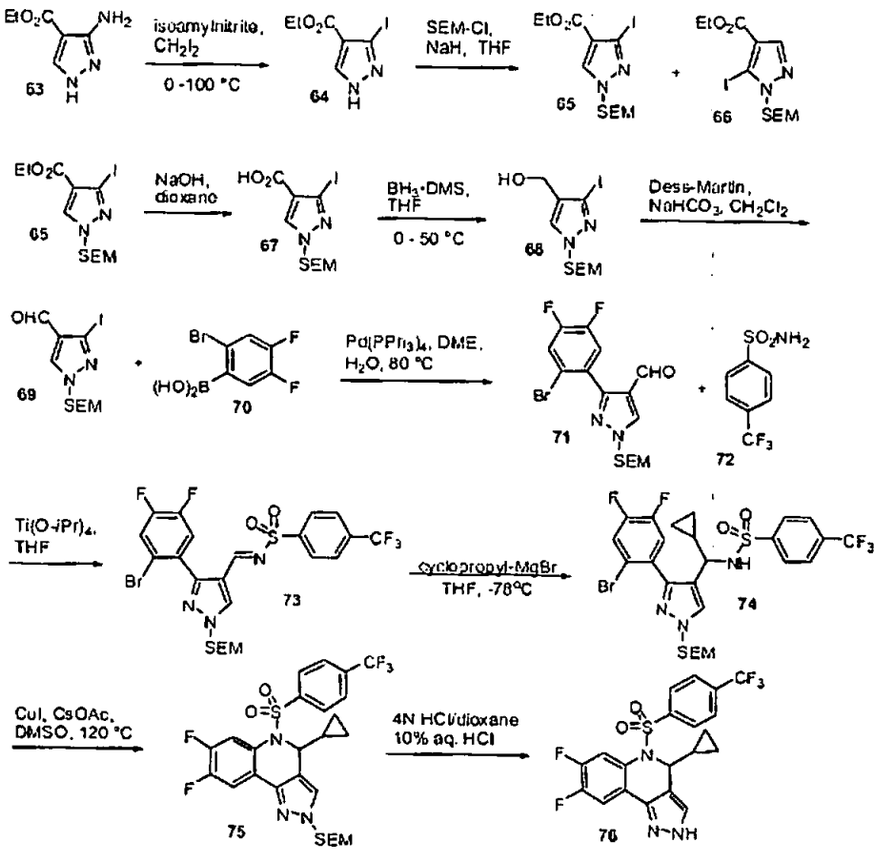
To a solution of (59) (0.21 g, 0.63 mmol) in a 1:1 mix of *tert*-butanol (3 mL) and H_2O (3 mL) at 0 °C was added AD-mix-α (0.88 g, 1.4 g/mmol). The reaction mixture was stirred for 24h while slowly warming to room temperature. The temperature was then decreased to 0 °C and sodium sulfite (1.51 g, 1.5 g/mmol) was added. After 10 minutes at 0 °C, the ice bath was removed and the reaction mixture was stirred at room temperature for 45 minutes. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL) and the two layers were separated. The organic layer was washed with brine (15 mL), dried over $MgSO_4$, filtered and concentrated. The resulting residue was dissolved in a 1:1 mixture of dioxane (2 mL) and H_2O (2 mL), and sodium periodate (0.13 g, 0.63 mmol) was added. The reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL) and the two layers were separated. The organic layer was dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography (70% EtOAc in hexanes) to afford (60) (0.13 g, 61%). MS (ES) *m/z* 337.0 $(M+H)^+$.

5-(4-Chlorophenylsulfonyl)-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-c][1,5]naphthyridine (62).

Dimethylformamide dimethylacetal (1 mL) and (60) (0.09 g, 0.28 mmol) were combined and heated to 100 °C for 2h. The reaction mixture was then cooled to room temperature and concentrated. The resulting residue was dissolved in CH_2Cl_2 (15 mL) and washed with H_2O (10 mL) and brine (15 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated. The resulting residue (61) was dissolved in MeOH (1 mL) and the temperature was decreased to 0 °C. Anhydrous hydrazine (0.02 mL, 0.55 mmol) was added to the reaction mixture, followed by HOAc (0.03 mL, 0.55 mmol). The reaction mixture was stirred for 18h while warming to room temperature. The reaction mixture was concentrated. The resulting residue was dissolved in CH_2Cl_2 (15 mL) and washed with H_2O (15 mL), saturated aqueous $NaHCO_3$ (15 mL), and brine (15 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography on alumina (5% MeOH in CH_2Cl_2) to afford (62) (0.03 g, 32%); ^{1}H NMR ($CDCl_3$) δ 8.64 (dd, J = 4.8, 1.5 Hz, 1H), 8.21 (dd, J = 8.2, 1.5 Hz, 1H), 7.38 (dd, J = 8.2, 4.8 Hz, 1H), 7.36 (s, 1H), 7.17 (m, 2H), 7.09 (m, 2H), 5.67 (q, J = 7.0 Hz, 1H), 1.37 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 147.7, 141.6, 139.6, 137.0, 136.0, 135.3, 129.2, 128.8, 128.3, 123.2, 121.0, 50.7, 23.8. MS (ES) *m/z* 361.0 $(M+H)^+$.

Example 12

4-Cyclopropyl-7,8-difluoro-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline (76).



Ethyl 3-iodo-1*H*-pyrazole-4-carboxylate (64).

Isoamylnitrite (400 mL, 2.98 mol) was added to a heterogenous mixture of ethyl 3-amino-1*H*-pyrazole-4-carboxylate (63), 47.69 g, 307 mmol) in diiodomethane (800 mL) at -10 °C over a period of 30 minutes. The heterogeneous mixture was placed into a preheated oil bath at 100 °C for 2 hours. The solution was cooled to ambient temperature, diluted with saturated aqueous sodium sulfite, and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was flash chromatographed on silica using 9:1, 4:1, 7:3, 3:2, and 1:1 hexanes:EtOAc as the eluant to yield 53.85 g (66%) of (64) as a light yellow solid.

Method 1: Retention time 1.26 min by HPLC. MS *m/z* 267 $(M+H)^+$.

Ethyl 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carboxylate (65) and Ethyl 5-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carboxylate (66).

Sodium hydride (6.00 g, 150 mmol) as a 60% dispersion in mineral oil was added to a solution of ethyl 3-iodo-1*H*-pyrazole-4-carboxylate (64), (28.21 g, 106 mmol) in tetrahydrofuran (400 mL). After stirring for 1 hour, (2-(chloromethoxy)ethyl)trimethylsilane (25.0 mL, 142 mmol) was added. After stirring for 18 hours, the heterogeneous mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with diethyl ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was flash chromatographed with 49:1, 24:1, 23:2, 22:3, 21:4 and 4:1 hexanes:EtOAc as the eluant to yield 22.50 g (54%) of (65) as a light yellow liquid and 18.00 g (43%) of (66) as a light yellow liquid.

^{1}H NMR ($CDCl_3$) δ 8.02 (s, 1H), 5.58 (s, 2H), 4.33 (q, J=7.2 Hz, 2H), 3.60 (t, J=8.1 Hz, 2H), 1.37 (t, J=7.2 Hz, 3H), 0.91 (t, J=8.1 Hz, 2H), -0.03 (s, 9H).

^{1}H NMR ($CDCl_3$) δ 7.97 (s, 1H), 5.40 (s, 2H), 4.31 (q, J=7.2 Hz, 2H), 3.58 (t, J=8.4 Hz, 2H), 1.35 (t, J=7.2 Hz, 3H), 0.90 (t, J=8.4 Hz, 2H), -0.03 (s, 9H).

3-Iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carboxylic acid (67).

Ethyl 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carboxylate (65), (22.50 g, 56.8 mmol) and 3N aqueous sodium hydroxide (50.0 mL, 150 mmol) in dioxane (200 mL) was stirred for four days. The solution was brought to pH=3 and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield 20.91 g (100%) of (67) as a light yellow solid.

Method 7: Retention time 6.22 min by HPLC. MS *m/z* 369 $(M+H)^+$, 391 $(M+Na)^+$.

3-Iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)methanol (68).

Neat borane dimethylsulfide *ca.* 10M (25 mL, 250 mmol) was slowly added to 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carboxylic acid (67), (20.91 g, 56.8 mmol) in THF (250 mL) at 0 °C. After stirring for 30 minutes, the solution was placed into a preheated oil bath at 50 °C. After stirring for 18 hours, the solution was cooled to 0 °C and ice was added. After stirring for 30 minutes, saturated aqueous NH_4Cl was added and stirred for an additional 30 minutes. The solution was extracted with CH_2Cl_2 and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield 19.50 g (97%) of (68) as a light yellow liquid.

Method 7: Retention time 5.72 min by HPLC MS *m/z* 355 $(M+H)^+$.

3-Iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carbaldehyde (69).

Dess-Martin periodinane (13.80 g, 32.5 mmol) was added to a heterogeneous mixture of (3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)methanol (68), 7.19 g, 20.3 mmol) and $NaHCO_3$ (17.44 g, 208 mmol) in CH_2Cl_2 (200 mL). After stirring for 24 hours, the heterogeneous mixture was diluted with saturated aqueous sodium sulfite and water, and then extracted with diethyl ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was flash chromatographed on silica using 99:1 49:1, 24:1, 23:2, 22:3, 21:4, and 4:1 hexanes:EtOAc as the eluant to yield 7.15 g (100%) of (69) as a white solid.

Method 1: Retention time 2.43 min by HPLC. MS *m/z* 353, 375$(M+Na)^+$.

^1H NMR ($CDCl_3$) δ 9.71 (s, 1H), 8.00 (s, 1H), 5.44 (s, 2H), 3.58 (m, 2H), 1.35 0.90 (m, 2H), -0.03 (s, 9H).

3-(2-Bromo-4,5-difluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carbaldehyde (71).

Tetrakis(triphenylphosphine)palladium(0) (1.29 g, 1.12 mmol), 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carbaldehyde (69), 3.53 g, 10.0 mmol), 2-bromo-4,5-difluorophenylboronic acid (70), 10.17 g, 42.9 mmol), and K_2CO_3 (15.91 g, 115 mmol) was placed into a flask that was then evacuated and refilled with nitrogen three times. Water (40 mL) and 1,2-dimethoxyethane (40 mL) were added and the solution placed into a preheated oil bath at 80 °C. After stirring for 18 hours, the solution was extracted with diethyl ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was flash chromatographed on silica using 49:1, 24:1, 23:2, 22:3, 21:4, and 4:1 hexanes:EtOAc as the eluant to yield 2.10 g pure (50%) and 1.00 g slightly impure (<24%) of (71) as an orange oil.

Method 2: Retention time 2.04 min by HPLC MS *m/z* 359 and 361$(M+H)^+$.

N-((3-(2-Bromo-4,5-difluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)(cyclopropyl)methyl)-4-(trifluoromethyl)benzenesulfonamide (74).

Titanium(IV) isopropoxide (3.0 mL, 10.2 mmol) was added to a solution of 3-(2-bromo-4,5-difluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carbaldehyde (71), (1.00 g, 2.40 mmol) and 4-(trifluoromethyl)benzenesulfonamide (72), (970 mg, 4.31 mmol) in THF (10 mL). After stirring for 18 hours, the solution was diluted with CH_2Cl_2, then

water, and the heterogeneous solution was filtered through Celite. The filtrate was extracted with CH_2Cl_2, the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was flash chromatographed on silica using 9:1, 4:1, 7:3, and 3:2 hexanes:EtOAc as the eluant to afford a mixture of products containing (73), which was used without further purification.

Method 2: Retention time 2.58 min by HPLC (M+=624 and 626).

A 1.0M solution of cyclopropyl magnesium bromide in THF (20.0 mL, 20.0 mmol) was slowly added along the walls of the flask to a solution of (73) in THF (20 mL) at -78 °C. After stirring for 30 minutes, the dry ice/acetone bath was removed and saturated aqueous NH_4Cl was added followed by water until the heterogeneous mixture became homogeneous. The biphasic solution was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was flash chromatographed on silica using 9:1, 4:1, 7:3, and 3:2 hexanes:EtOAc as the eluant to yield 1.13 g (>60%, two steps) of (74) as a yellow oil.

Method 2: Retention time 2.55 min by HPLC. MS *m/z* 666 and 668$(M+H)^+$

4-Cyclopropyl-7,8-difluoro-5-(4-(trifluoromethyl)phenylsulfonyl)-2-((2-(trimethylsilyl)ethoxy)-methyl)-4,5-dihydro-2*H*-pyrazolo[4.3-*c*]quinoline (75).

Cesium acetate (2.71g, 14.1 mmol), cuprous iodide (797 mg, 4.19 mmol), and *N*-((3-(2-bromo-4,5-difluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)(cyclopropyl)methyl)-4-(trifluoromethyl)benzenesulfonamide (74), 1.13 g, 1.69 mmol) were placed into a flask that was then evacuated and refilled with nitrogen. Degassed DMSO (1.7 mL) was added and the heterogeneous mixture was placed into a preheated oil bath at 120 °C. After stirring for 2 hours, the solution was cooled to ambient temperature. The solid that formed was washed with CH_2Cl_2, and filtered. The filtrate was concentrated and the residue was flash chromatographed on silica using 19:1, 9:1, 17:3, and 4:1 hexanes:EtOAc as the eluant to yield 645 mg (65%) of (75) as a yellow oil.

Method 2: Retention time 2.82 min by HPLC MS *m/z* 586 $(M+H)^+$ 608, $(M+Na)^+$.

4-Cyclopropyl-7,8-difluoro-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline (76).

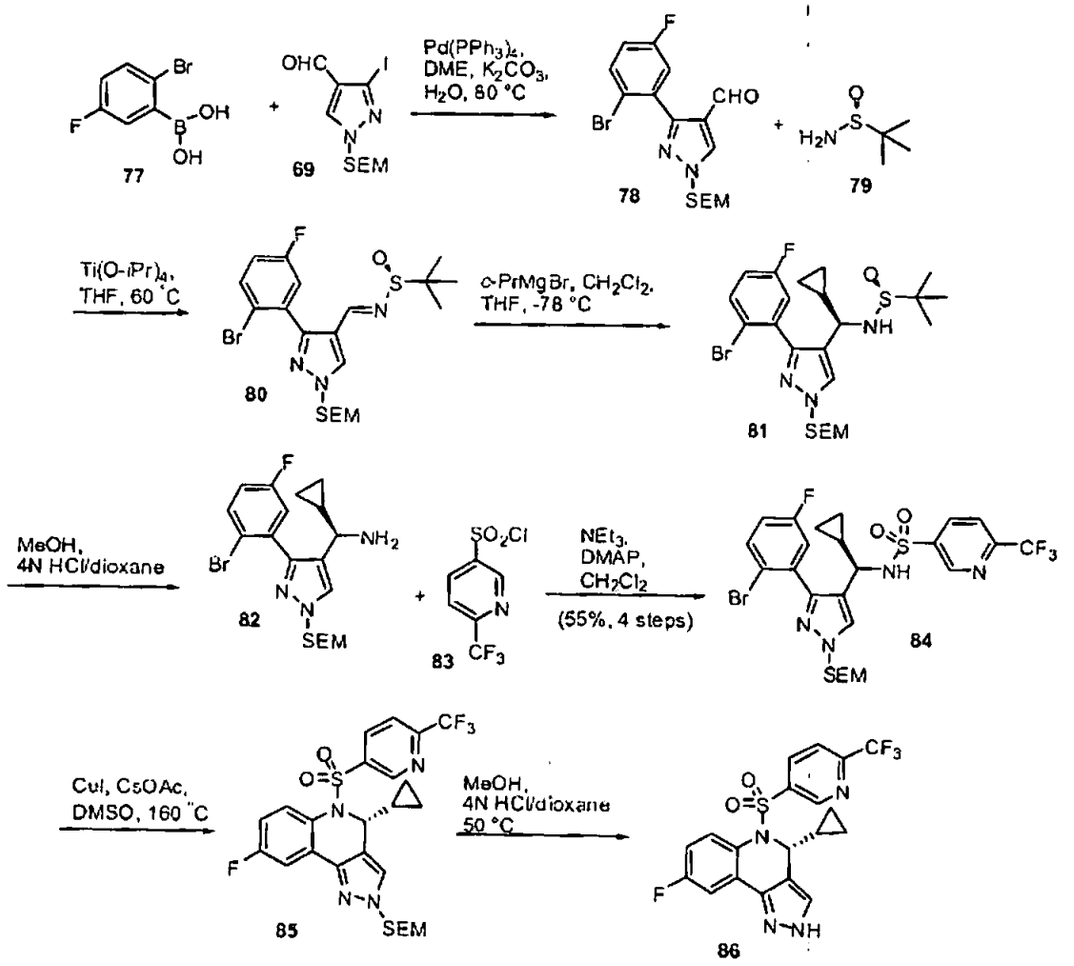
4-Cyclopropyl-7,8-difluoro-5-(4-(trifluoromethyl)phenylsulfonyl)-2-((2-(trimethylsilyl)ethoxy)methyl)-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline (75), 645 mg, 1.10 mmol) was stirred in 4N HCl in dioxane (10 mL) and 10% aqueous HCl (2 mL) for 18 hours.

The solution was concentrated to yield (76) as a light yellow solid. Method 7: Retention time 8.34 min by HPLC. MS *m/z* 456.0$(M+H)^+$, 478$(M+Na)^+$.

^{1}H NMR ($CDCl_3$) δ 7.76 (dd, J = 11.1, 7.2 Hz, 1H), 7.47 (m, J = 10.2, 8.7 Hz, 1H), 7.39 (d, J = 8.7 Hz, 2H), 7.32 (d, J = 8.7 Hz, 2H), 7.20 (s, 1H), 4.95f (d, J = 7.8 Hz, 1H), 1.03 (m, 1H), 0.54 (m, 1H), 0.41 (m, 2H), 0.08 (m, 1H).

Example 13

(*R*)-4-Cyclopropyl-8-fluoro-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline (86).



3-(2-Bromo-5-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carbaldehyde (78).

Tetrakis(triphenylphosphine)palladium(0) (224 mg, 194 μmol), 3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carbaldehyde (69), (1.71 g, 10.0 mmol), 2-bromo-5-fluorophenylboronic acid (77), 1.36 g, 6.23 mmol), and K_2CO_3 (2.86 g, 20.7 mmol) were placed into a flask that was evacuated and refilled with nitrogen three times. Water (5 mL) and 1,2-dimethoxyethane (5 mL) were added and the solution placed into a preheated oil bath at 80 °C. After stirring for 18 hours, the solution was extracted with diethyl ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was flash chromatographed on silica using 49:1, 24:1, 23:2, 22:3, 21:4, and 4:1 hexanes:EtOAc as eluant to yield 590 mg (73%) of (78) as a brown oil.
Method 2: Retention time 1.92 min by HPLC MS *m/z* 399 and 401 $(M+H)^+$.

(*S*)-(*E*)-*N*-((3-(2-Bromo-5-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)methylene)-2-methylpropane-2-sulfinamide (80).

Titanium(IV) isopropoxide (1.1 mL, 3.75 mmol) was added to a solution of 3-(2-bromo-5-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-4-carbaldehyde (78), 590 mg, 1.48 mmol) and (*S*)-(-)-*tert*-butanesulfinamide (79), 254 mg, 2.10 mmol) in THF (10 mL). After stirring for 18 hours, the solution was placed into a preheated oil bath at 60 °C. After stirring for 2 hours, the solution was cooled to ambient temperature, diluted with CH_2Cl_2, then water, and the heterogeneous solution was filtered through Celite. The filtrate was extracted with CH_2Cl_2, the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to yield (80) as an oil which was used without further purification.
Method 2: Retention time 2.28 min by HPLC. MS *m/z* 502 and 504$(M+H)^+$.

(*S*)-*N*-((*R*)-(3-(2-Bromo-5-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)(cyclopropyl)methyl)-2-methylpropane-2-sulfinamide (81).

A 1.0M solution of cyclopropyl magnesium bromide in THF (15.0 mL, 15.0 mmol) was slowly added dropwise to a solution of (*S*)-(*E*)-*N*-((3-(2-bromo-5-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)methylene)-2-methylpropane-2-sulfinamide (80) in CH_2Cl_2 (15 mL) at -78 °C. After stirring for 30 minutes, the dry ice/acetone bath was removed and saturated aqueous $NaHCO_3$ was added followed by water until the heterogeneous mixture became homogeneous. The biphasic solution was extracted with CH_2Cl_2, the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to yield (81) as a brown oil which was used without further purification.

Method 7: Retention time 9.63 min by HPLC, MS *m/z* 544 and 546 $(M+H)^+$. for the major diastereomer and 10.03 min by HPLC, MS *m/z* 544 and 546$(M+H)^+$. for the minor diastereomer.

(*R*)-(3-(2-Bromo-5-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)(cyclopropyl)methanamine (82).

4 N HCl in dioxane (1 mL) was added to a solution of (*S*)-*N*-((*R*)-(3-(2-bromo-5-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)(cyclopropyl)methyl)-2-methylpropane-2-sulfinamide (81) in MeOH (20 mL). After stirring for 1 hour, the solution was concentrated. The residue was diluted with 1 N aqueous NaOH, extracted with CH_2Cl_2, the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to yield (82) as a brown oil which was used without further purification.
Method 7: Retention time 5.57 min by HPLC MS *m/z* 423 and 425 $(M-NH_2)^+$ and MS *m/z* 440 and 442$(M+H)^+$.

(*R*)-*N*-((3-(2-Bromo-5-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)(cyclopropyl)methyl)-6-(trifluoromethyl)pyridine-3-sulfonamide (84).

4-(Trifluoromethyl)benzene-1-sulfonyl chloride (83), (835 mg, 3.40 mmol) was added to a solution of (*R*)-(3-(2-bromo-5-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)(cyclopropyl)methanamine (82) and DMAP (120 mg, 982 µmol) in CH_2Cl_2 (5 mL) and triethylamine (1 mL). After stirring for 18 hours, the solution was concentrated, and the residue was flash chromatographed on silica using 9:1, 4:1, 7:3, and 3:2 hexanes:EtOAc as eluant to yield 525 mg (55%, 4 steps) of (84) as an oil.
Method 7: Retention time 11.00 min by HPLC MS *m/z* 649 and 651$(M+H)^+$.

(*R*)-4-Cyclopropyl-8-fluoro-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-2-((2-(trimethylsilyl)ethoxy)methyl)-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline (85).

Cesium acetate (1.46 g, 7.61 mmol), cuprous iodide (446 mg, 2.34 mmol), and (*R*)-*N*-((3-(2-bromo-5-fluorophenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)(cyclopropyl)methyl)-6-(trifluoromethyl)pyridine-3-sulfonamide (84), 613 mg, 944 µmol) were placed into a flask that was evacuated and refilled with nitrogen. Degassed DMSO (1.0 mL) was added and the heterogeneous mixture was placed into a preheated oil bath at 160 °C. After stirring for 30 minutes, the solution was cooled to ambient temperature; the solid that formed was washed with CH_2Cl_2, and filtered through Celite. The filtrate was concentrated

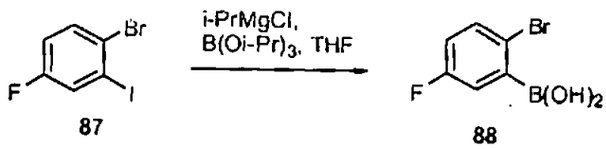
and the residue was flash chromatographed on silica using 19:1, 9:1, 17:3, 4:1, and 3:1 hexanes: EtOAc as eluant to yield 405 mg (75%) of (85) as a yellow oil.
Method 2: Retention time 2.66 min by HPLC MS *m/z* 569 $(M+H)^+$, 591$(M+Na)^+$.

(*R*)-4-Cyclopropyl-8-fluoro-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4.3-c]quinoline (86).

4 N HCl in dioxane (10 mL) was added to a solution of (*R*)-4-cyclopropyl-8-fluoro-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-2-((2-(trimethylsilyl)ethoxy)methyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline (85), (1.30 g, 2.29 mmol) in MeOH (20 mL) was placed into a preheated oil bath at 50 °C. After stirring for 1.5 hours, the solution was concentrated. The residue was diluted with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was flash chromatographed on silica using 9:1, 4:1, 7:3, and 3:2 hexanes:EtOAc as eluant to yield 1.00 g of (86) as a light yellow oil.
Method 7: Retention time 7.04 min by HPLC MS *m/z* 439 $(M+H)^+$; 461$(M+Na)^+$.
^1H NMR ($CDCl_3$) δ 10.13 (broad s, 1H), 8.51 (s, 1H), 7.85 (dd, J=12.0 and 6.4 Hz, 1H), 7.40 (m, 2H), 7.36 (d, J=3.0 Hz, 1H), 7.28 (s, 1H), 7.14 (dt, J=3.0 and 8.7 Hz, 1H), 4.99 (d, J=7.8 Hz, 1H), 1.01 (m, 1H), 0.54 (m, 1H), 0.39 (m, 2H), 0.09 (m, 1H).
Separation of the major and minor enantiomers was achieved using HPLC Method 18.

Example 14

2-Bromo-5-fluorophenylboronic acid (88).



87 88

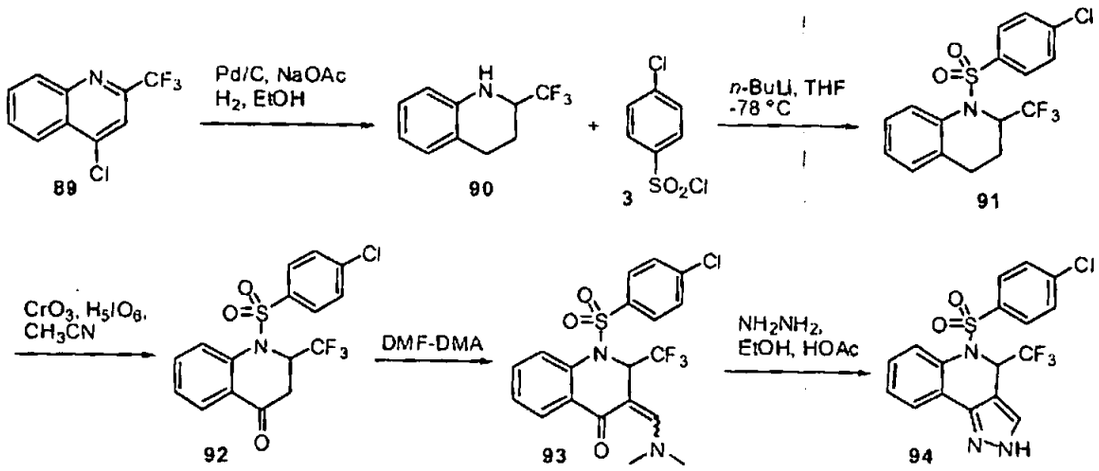
2-Bromo-5-fluorophenylboronic acid (88).

Isopropylmagnesium chloride (36.5 mmol, 2.0 M in THF) was slowly added to a -42 °C THF (2.0 M) solution of 1-bromo-4-fluoro-2-iodobenzene (87), (10 g, 33.2 mmol) under N_2, and stirred at -42 °C for 2 h. Triisopropylborate (11.4 mL, 49.8 mmol) was added and the reaction was warmed to room temperature and stirred overnight. 1N NaOH (20 mL) was added and the mixture stirred for 1h. The pH was adjusted to 3 with 3N HCl, and the sample was extracted (2 x 20 mL) with EtOAc. The combined organics were dried over $MgSO_4$,

filtered through Celite, and the solvent was removed to obtain (5.75 g, 26.39 mmol) of 2-bromo-5-fluorophenylboronic acid (88) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.68-7.64 (1H, dd, J = 9.1, 3.2 Hz), 7.54-7.49 (1H, dd, J = 8.8, 4.8 Hz), 7.08-7.01 (1H, m), 5.76 (2H, s).

Example 15

5-(4-chlorophenylsulfonyl)-4-(trifluoromethyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline (94).



2-(Trifluoromethyl)-1,2,3,4-tetrahydroquinoline (90).

An ethanol solution (70 mL) of 4-chloro-2-(trifluoromethyl)quinoline (89) (5.48 g, 23.66 mmol), NaOAc (3.88 g, 47.32 mmol) and 10% Pd/C (500 mg) was placed under 45 psi of H_2 for one day. The reaction mixture was then filtered through a pad of Celite and the filtrate was concentrated. The residue was taken-up in EtOAc and washed with water (3 x 50 ml), brine (1 x 10 ml), dried over $MgSO_4$, filtered and concentrated to yield (90) (4.43 g, 93%) as a clear oil that solidified upon standing and was used without further purification. ^{1}H NMR ($CDCl_3$) δ 7.07-7.02 (m, 2H), 6.75-6.70 (m, 1H), 6.60 (d, J = 8.0Hz, 1H), 4.09 (br s, 1H), 3.92-3.84 (m, 1H), 2.85-2.81 (m, 2H), 2.15-2.08 (m, 2H); MS *m/z* 202.1 $(M+H)^+$.

1-(4-Chlorophenylsulfonyl)-2-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline (91).

To a THF solution (5.5 mL) of (90) (271 mg, 1.34 mmol) at -78 °C was added *n*-BuLi (2.5M in hexanes, 566 μL, 1.41 mmol). After 10 minutes a THF ,solution (2mL) of 4-chlorobenzenesulfonyl chloride (341 mg, 1.62 mmol) was added over a 5 minute period to give a black solution. The reaction mixture was held at -78 °C one hour and then warmed to -30 °C. After 30 minutes the mixture was cooled to -78 °C, quenched with the addition of

saturated NH_4Cl, warmed to room temperature and diluted with EtOAc and water. The organic portion was washed with 0.2 N citric acid (3 x 15 mL), water (1 x 15 mL), sat. $NaHCO_3$ (3 x 15 mL), brine (1 x 10 mL), dried over $MgSO_4$, filtered and concentrated to yield the crude product which was purified by flash chromatography eluting with 25:1 hexanes/EtOAc to give (91) (178mg, 35%).

^1H NMR ($CDCl_3$) δ 7.59 (d, J = 7.7 Hz, 1H), 7.42-7.27 (m, 5H), 7.22-7.18 (m, 1H), 7.00, (d, J = 7.1 Hz, 1H), 4.91-4.84 (m, 1H), 2.40-2.27 (m, 2H), 1.81-1.67 (m, 1H), 1.51-1.42 (m, 1H); MS *m/z* 376.0 $(M+H)^+$.

1-(4-Chlorophenylsulfonyl)-2-(trifluoromethyl)-2,3-dihydroquinolin-4(1*H*)-one (92).

To a solution of H_5IO_6 (594 mg, 2.61mmol) in CH_3CN (3 mL) was added CrO_3 (7 mg, 70.1 μmol). After stirring for a few minutes (91) (178 mg, 0.47 mmol) was added to the reddish solution to give a heterogeneous reaction mixture solution. TLC analysis (10:1 hexane/EtOAc) after 6 hours determined no starting material remained so the reaction mixture was diluted with EtOAc (10 mL) and washed with water (2 x 10 mL), 5% $NaHSO_3$ (2 x 10 mL), brine (1 x 20 mL), dried over $MgSO_4$, filtered and concentrated to give the crude product. Purification by preparative TLC (2:1 hexanes/EtOAc) gave 92 (37.6 mg, 20%). ^1H NMR ($CDCl_3$) δ 7.95-7.92 (m, 1H), 7.86-7.83 (m, 1H), 7.66-7.56 (m, 3H), 7.45-7.32 (m, 3H), 5.28-5.23 (m, 1H), 2.84 (dd, J = 19.9, 1.6 Hz, 1H), 2.64 (dd, J = 18.7, 7.70 Hz, 1H); MS *m/z* 390.0 $(M+H)^+$.

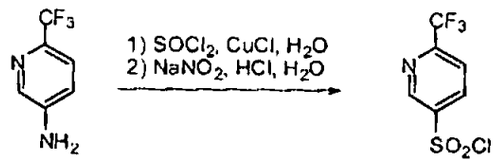
5-(4-Chlorophenylsulfonyl)-4-(trifluoromethyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline (94).

A dimethylformamide dimethyl acetal (173 μL) solution of (92) (34 mg, 87 μmol) was heated at 100 °C for 1 hour. HPLC/MS analysis of the reaction mixture determined no starting material remained so the reaction was cooled to room temperature and diluted with EtOAc (5 mL). The organic phase was washed with water (3 x 10 mL), brine (1 x 20 mL), dried over $MgSO_4$, filtered and concentrated to give (93) which was used directly in the next reaction. To an EtOH/glacial HOAc solution (25:1 v/v, 400 μL) of (93) (39 mg, 90 μmol) was added hydrazine hydrate (21 μL, 0.45 mmol). The reaction mixture was stirred 5 days at room temperature, transferred to a sealed tube and heated at 75 °C for 5 days. The reaction mixture was then cooled to room temperature, concentrated, and the residue taken up in EtOAc (10 mL). The organic phase was washed with sat. $NaHCO_3$ (3 x 20 mL), brine (1 x 10 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by preparative HPLC

to give (94) (6.7 mg, 19% over two steps) as a white powder. ^{1}H NMR ($CDCl_3$) δ 7.88 (dd, J = 7.70, 1.1 Hz, 1H), 7.67 (dd, J = 8.5, 1.6 Hz, 1H), 7.53 (s, 1H), 7.43-7.36 (m, 2H), 7.25-7.17 (m, 4H), 6.03 (q, J = 7.1 Hz, 1H); MS *m/z* 414.0 $(M+H)^+$.

Example 16

6-(Trifluoromethyl)pyridine-3-sulfonyl chloride (83).



95 83

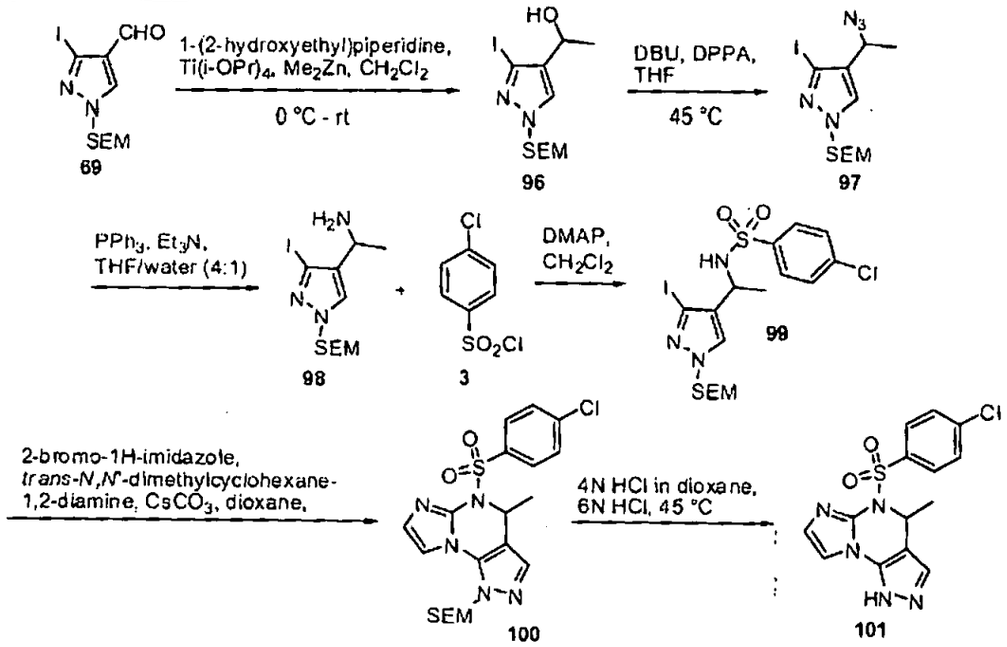
6-(Trifluoromethyl)pyridine-3-sulfonyl chloride (83).

Thionyl chloride (31 mL, 0.43 mol) was slowly added to 175 mL of water at 0 °C. During the addition the temperature was maintained between 0-5 °C. After addition the solution was warmed to 15 °C and 0.47 g (4.8 mmol) of CuCl was added. The solution was diluted with 100 mL of water and cooled back to 0 °C.

A solution of 7.21 g (0.10 mol) of $NaNO_2$ in 100 mL of water was slowly added to a solution of 15.39 g (0.10 mol) of 5-amino-2-(trifluoromethyl)pyridine (95) in 125 mL of conc. HCl at 0 °C. During addition the temperature was maintained between 0-5 °C. This mixture was then slowly added to the above prepared solution so as to maintain a temperature between 0-5 °C. A voluminous precipitate formed. The mixture was stirred for an additional 30 min after addition and the solid was then collected by filtration. The solid was washed with water and dissolved in $CHCl_3$. The solution was dried over $MgSO_4$, filtered and the solvent was removed to afford 18.03 g (77%) of sulfonyl chloride (83) as a tan solid. ^{1}H NMR ($CDCl_3$) δ 9.34 (d, J = 2.2 Hz, 1H), 8.53 (dd, J = 8.4, 2.2 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H).

Example 17

5-(4-Chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-imidazo[1,2-a]pyrazolo[4,3-e]pyrimidine (104).



1-(3-Iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)ethanol (96).

To a stirring mixture of 1-(2-hydroxyethyl)piperidine (149 mg, 1.09 mmol) in dry CH_2Cl_2 (25 mL) under N_2 at room temperature was added $Ti(iOPr)_4$. After 1 h of stirring, the reaction mixture was cooled to 0 °C and a 2.0 M solution of dimethyl zinc in toluene (17 mL, 33 mmol) was added. After 30 min, a solution of aldehyde (69) (1.45 g, 5.45 mmol) in CH_2Cl_2 (2 mL) was added and the reaction was stirred overnight. The reaction mixture was quenched with 1N HCl and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was flash chromatographed with 9:1, 4:1, and 3:1 hexanes:EtOAc as the eluant to yield 1.3 g (85%) of (96) as a colorless oil. The product was analyzed by HPLC/MS using Method 1. Retention time = 2.199 min. MS *m/z* 369.0 $(M+H)^+$. ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (s, 1H), 5.38 (s, 2H), 4.79 (q, J = 6.1 Hz, 1H), 3.58 (t, J = 7.7 Hz, 2H), 1.53 (d, J = 6.1 Hz, 3H), 0.91 (t, J = 8.2 Hz, 2H), -0.03 (s, 9H).

4-(1-Azidoethyl)-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (97).

To a stirring mixture of the alcohol (96) (1.2 g, 3.26 mmol) in THF (0.5 M, 6.5 mL) at room temperature was added DBU (843 mg, 5.54 mmol), followed by DPPA (1.5 g, 5.54

mmol). The resulting mixture slowly turned dark brown, and it was slowly warmed up to 45 °C. The reaction mixture was cooled to room temperature and then diluted with CH_2Cl_2 and quenched with brine. The layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was flash chromatographed with 10:1 and 9:1 hexanes:EtOAc as eluant to yield 1.1 g of (97) as a colorless oil. The product was analyzed by HPLC/MS using Method 1. Retention time = 2.076 min. MS *m/z* 394.0 $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (s, 1H), 5.41 (s, 2H), 4.47 (q, *J* = 7.0 Hz, 1H), 3.58 (t, *J* = 8.1 Hz, 2H), 1.53 (d, *J* = 6.6 Hz, 3H), 0.91 (t, *J* = 8.2 Hz, 2H), -2.0 (s, 9H).

1-(3-Iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)ethanamine (98).

To a stirring mixture of the azide (97) (270 mg, 0.7 mmol) in THF/water was added PPh_3 (545 mg, 2.08 mmol) and Et_3N (0.58 mL, 4.15 mmol). The reaction mixture was warmed to 50 °C and stirred overnight. The reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was flash chromatographed with 2:1, 1:1 hexanes/EtOAc and 10:1:0.1 EtOAc/MeOH/NH_4OH to give 240 mg of compound (98) as a colorless oil. The product was analyzed by HPLC/MS using Method 1. Retention time = 1.576 min. MS *m/z* 368.1 $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (s, 1H), 5.37 (s, 2H), 4.17 (q, *J* = 6.9 Hz, 1H), 3.59 (t, *J* = 7.8 Hz, 2H), 1.56 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 8.2 Hz, 2H), -1.3 (s, 9H).

4-Chloro-N-(1-(3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)ethyl)benzenesulfonamide (99).

To a stirring mixture of amine (98) (100 mg, 0.27 mmol) in CH_2Cl_2 (1.0 mL) at room temperature was added 4-chlorobenzenesulfonyl chloride (3), (111 mg, 0.55 mmol), Et_3N, and DMAP (4 mg). The reaction mixture was reacted for 4 h or until all the starting material was consumed. The resulting mixture was diluted with $NaHCO_3$ and extracted with EtOAc. The residue was flash chromatographed with 2:1, 1:1 and 1:2 hexanes/EtOAc to give 70 mg of (99) as a colorless oil. The product was analyzed by HPLC/MS using Method 1. Retention time = 2.906 min. MS *m/z* 564.0 $(M+Na)^+$.

5-(4-Chlorophenylsulfonyl)-4-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-4,5-dihydro-1*H*-imidazo[1,2-a]pyrazolo[4,3-e]pyrimidine (100).

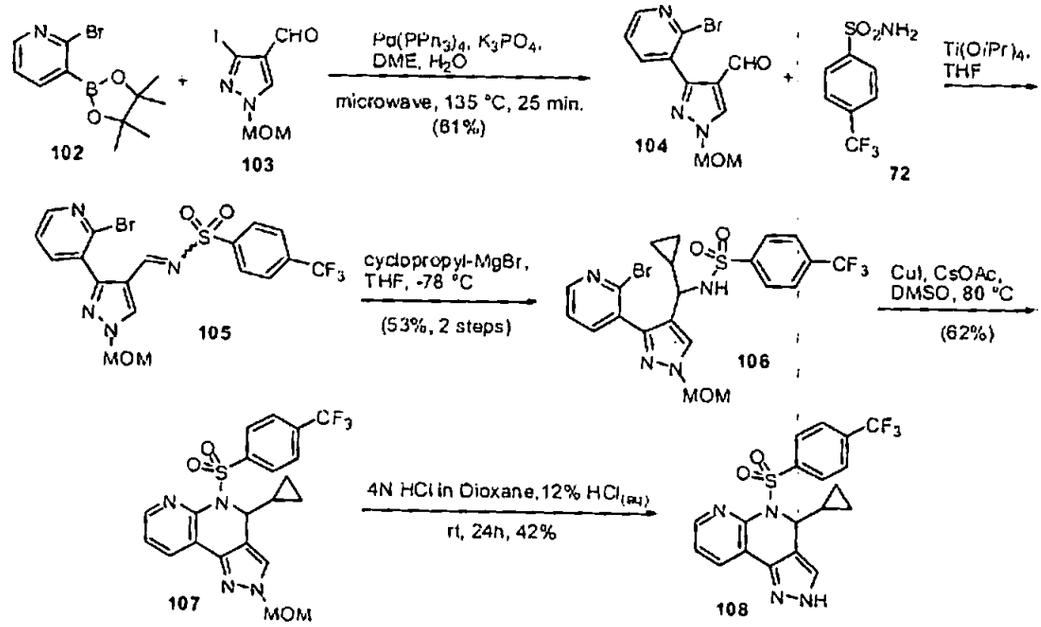
To a stirring mixture of sulfonamide (99) (110 mg, 0.2 mmol) in deoxygenated dioxane (0.5 M) was added *trans-N,N'*-dimethylcyclohexane-1,2-diamine (114 mg, 0.812 mmol), CuI (38 mg, 0.2 mmol), $CsCO_3$ (263 mg, 0.81 mmol), and 2-bromo-1*H*-imidazole (38 mg, 0.24 mmol). The reaction mixture was quickly warmed to 110 °C and stirred for 1 h. The crude mixture was directly loaded onto a silica gel column and chromatographed to give 78 mg (80%) of (100) as a colorless oil. The product was analyzed by HPLC/MS using Method 2. Retention time = 1.429 min. MS *m/z* 480.1 $(M+H)^+$.

5-(4-Chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-imidazo[1,2-a]pyrazolo[4,3-c]pyrimidine (101).

Pyrimidine (100) was stirred in 4N HCl in dioxane (10 mL) and 6 N aqueous HCl (2 mL) for 18 hours. The solution was concentrated to yield compound (101) as a yellow solid. The desired product was further purified by preparative HPLC using the specified column type and analyzed using Method 1 to give a white solid. MS(ESI) *m/z* 350.0 $(M+H)^+$. Retention time = 1.139 min. ^1H NMR (300 MHz, $CDCl_3$) δ 7.74-7.72 (m, 2H), 7.37-7.35 (m, 2H), 7.32 (s, 2H), 7.08-7.07 (m, 1H), 5.78 (q, *J* = 5.7 Hz, 1H), 1.36 (d, *J* = 6.6 Hz, 3H).

Example 18

4-Cyclopropyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c][1,8]naphthyridine (108).



3-(2-Bromopyridin-3-yl)-1-(methoxymethyl)-1*H*-pyrazole-4-carbaldehyde (104).

To a solution of potassium phosphate (4.78 g, 22.5 mmol) in a 1:1 ethylene glycol dimethylether (10 mL) and H_2O (10 mL) mixture was added 2-bromopyridine-3-boronic acid pinacol ester (102) (2.13 g, 7.52 mmol). The reaction mixture was stirred at room temperature for 10 minutes before aldehyde (103) (1.00 g, 3.75 mmol) and palladium tetrakistriphenylphosphine (0.43 g, 0.37 mmol) were added. The reaction mixture was microwaved at 125 °C for 25 minutes. The reaction mixture was then diluted with EtOAc (25 mL) and the two layers were separated. The organic layer was washed with saturated aqueous NaCl (15 mL), dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography (50% EtOAc in hexanes) to afford (104) (0.68 g, 61%). MS (ES) *m/z* 295.9, 297.9 $(M+H)^+$.

N-((3-(2-Bromopyridin-3-yl)-1-(methoxymethyl)-1*H*-pyrazol-4-yl)(cyclopropyl)methyl)-4-(trifluoromethyl)benzenesulfonamide (106).

To a solution of (104) (0.68 g, 2.30 mmol) in THF (10 mL) was added sulfonamide (72) (0.77 g, 3.45 mmol), followed by titanium (IV) isopropoxide (1.30 g, 4.6 mmol). The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was then diluted with EtOAc (15 mL), and then quenched with saturated aqueous NaCl (3 mL). The mixture was stirred for 10 minutes, and then was filtered through a pad of Celite. The two layers were separated. The organic layer was dried over $MgSO_4$, filtered and concentrated. The resulting imine, (105), was used in the next reaction without purification. To a solution of (105) in THF at -78 °C was added slowly cyclopropylmagnesium bromide (0.5M in THF, 9.20 mL, 4.60 mmol). The reaction mix was stirred for 2 h at -78 °C, then diluted with EtOAc (20 mL) and quenched with saturated aqueous NH_4Cl (10 mL). The mixture was warmed to room temperature and the two layers were separated. The organic layer was washed with saturated aqueous NaCl (15mL), dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography (50% EtOAc in hexanes) to afford (106) (0.66 g, 53% over two steps). MS (ES) *m/z* 544.8 and 546.8 $(M+H)^+$.

4-Cyclopropyl-2-(methoxymethyl)-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c][1,8]naphthyridine (107).

Sulfonamide (106) (0.30 g, 0.55 mmol) was dissolved in DMSO (1 mL) and nitrogen was bubbled through the solution for 1 h. In a separate flame-dried flask, copper iodide (0.42 g, 2.20 mmol) and cesium acetate (1.05 g, 5.50 mmol) were combined. The reaction flask

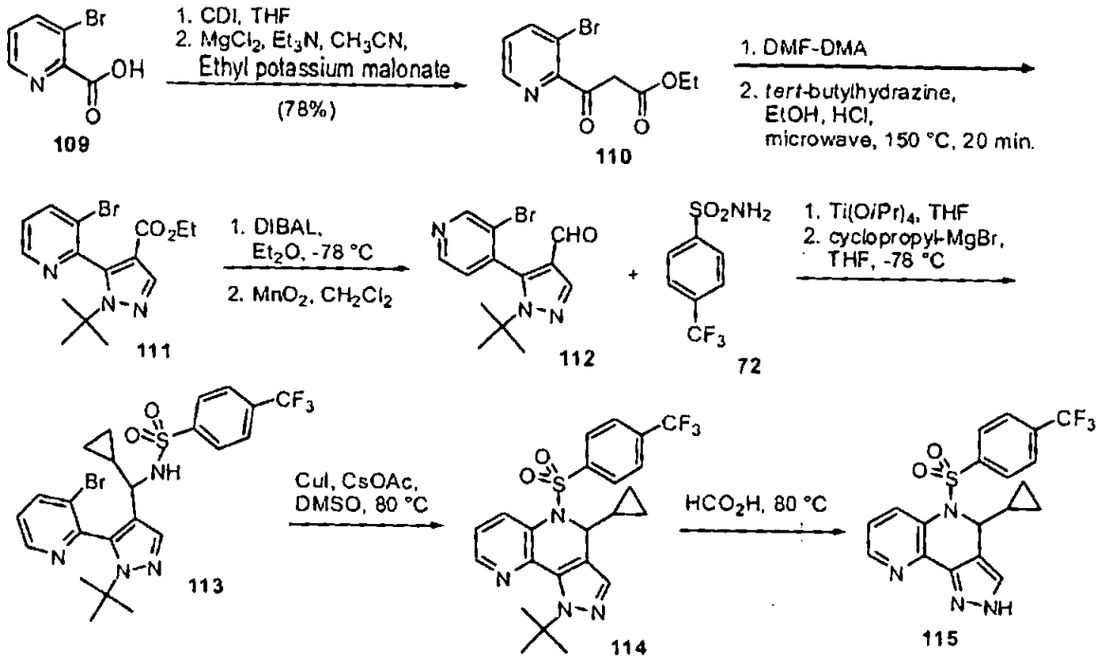
was evacuated, then refilled with nitrogen. This pump/purge process was repeated three times. The DMSO solution of sulfonamide (106) was added to the reaction flask and the flask was plunged into a preheated, 80 °C oil bath. The reaction mixture was stirred for 2 h at 80 °C, and then cooled to room temperature. The mixture was diluted with Et_2O (15 mL) and washed with H_2O (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography (50% EtOAc in hexanes) to afford (107) (0.16 g, 62%). MS (ES) *m/z* 464.9 $(M+H)^+$.

4-Cyclopropyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c][1,8]naphthyridine (108).

To a solution of pyrazolonaphthyridine (107) (0.21 g, 0.45 mmol) in 4N HCl in dioxane (5 mL) was added 12% HCl (0.15 mL). The reaction mixture was stirred for 18 h at room temperature. The reaction mixture was diluted with EtOAc (15 mL), and the temperature was decreased to 0 °C. The reaction mixture was quenched with the addition of 1M NaOH until pH 7. The two layers were separated. The aqueous layer was washed with EtOAc (20 mL, 3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography (50% EtOAc in hexanes) to afford (108) (0.14 g, 42%). ^1H NMR ($CDCl_3$) δ 8.32 (dd, J = 4.8, 1.6 Hz, 1H), 8.19 (d, J = 8.3 Hz, 2H), 8.07 (dd, J = 7.6, 1.5 Hz, 1H), 7.72 (d, J = 8.3 Hz, 2H), 7.52 (s, 1H), 7.16 (dd, J = 7.6, 4.9 Hz, 1H), 5.45 (d, J = 8.1 Hz, 1H), 1.15 (m, 1H), 0.51 (m, 2H), 0.38 (m, 1H), 0.21 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 148.5, 148.1, 144.7, 141.2, 134.6, 134.2, 131.4, 128.9, 126.3, 125.8, 125.7, 121.5, 120.9, 116.0, 57.7, 18.0, 5.07, 2.67. MS (ES) *m/z* 420.9 $(M+H)^+$.

Example 19

4-Cyclopropyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c][1,5]naphthyridine (115).



Ethyl 3-(3-bromopyridin-2-yl)-3-oxopropanoate (110).

To a suspension of 3-bromo-2-pyridine-carboxylic acid (109) (2.00 g, 9.90 mmol) in THF (10 mL) was added carbonyl diimidazole (1.61 g, 9.90 mmol). The reaction mix was stirred for 18 h at room temperature. In a separate, flame-dried flask, potassium ethylmalonate (3.37 g, 19.8 mmol) was suspended in CH_3CN (40 mL) and Et_3N (3.00 g, 29.7 mmol) was added. The temperature was decreased to 0 °C. Magnesium chloride (2.35 g, 24.7 mmol) was added in two portions and the reaction mix was stirred at room temperature for 5 h. The temperature was then decreased to 0 °C and the THF solution of (109) was added slowly. The reaction mix was stirred at 0 °C for 10 minutes, then was warmed to room temperature and stirred for 18 h. The reaction mix was concentrated, and the resulting residue was suspended in toluene (70 mL). The temperature was decreased to 0 °C and the reaction mix was quenched by the slow addition of 12% HCl (50 mL). The reaction mix was warmed to room temperature and stirred for 30 minutes. The two layers were separated, and the aqueous layer was washed with EtOAc (50 mL, 3x). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL), dried over $MgSO_4$, filtered and

concentrated. The resulting residue was purified by flash chromatography (30% EtOAc in hexanes) to afford (110) (2.09 g, 78%). MS (ES) *m/z* 271.9, 273.9 $(M+H)^+$.

Ethyl 5-(3-bromopyridin-2-yl)-1-*tert*-butyl-1*H*-pyrazole-4-carboxylate (111).

The β-ketoester (110) (0.90 g, 3.31 mmol) was dissolved in dimethylformamide dimethylacetal (3 mL), and was heated to 50 °C for 15 min. The reaction mix was cooled to room temperature and concentrated. The resulting residue was dissolved in EtOH (15 mL) and *tert*-butylhydrazine hydrochloride (0.49 g, 4.97 mmol) was added followed by three drops of concentrated HCl. The reaction mix was stirred at room temperature for 10 minutes, and then was microwaved at 150 °C for 25 min. The reaction mixture was concentrated. The resulting residue was dissolved in EtOAc (25 mL) and was washed with H_2O (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography (20% EtOAc in hexanes) to afford (111) (1.47 g, 60%). MS (ES) *m/z* 351.9, 353.9 $(M+H)^+$.

5-(3-Bromopyridin-4-yl)-1-*tert*-butyl-1*H*-pyrazole-4-carbaldehyde (112).

To a solution of (111) (1.00 g, 2.83 mmol) in Et_2O (10 mL) at -78 °C was added diisobutylaluminum hydride (1M in toluene, 7.09 mmol). The reaction mix was stirred at -78 °C for 1.5 h, and then was quenched with a 1:1 mixture of Celite and $Na_2S_2O_3 \cdot 5H_2O$ (2.5 g). The reaction mix was stirred while warming to room temperature and then was filtered and concentrated. The resulting residue was dissolved in CH_2Cl_2 (20 mL) and MnO_2 (2.46 g, 28.3 mmol) was added. The reaction mix was stirred at room temperature for 48 h. The reaction mixture was filtered through a pad of Celite and was concentrated. The resulting residue was purified by flash chromatography (50% EtOAc in hexanes) to afford (112) (0.27 g, 32%). MS (ES) *m/z* 307.9, 309.9 $(M+H)^+$.

N-((5-(3-Bromopyridin-2-yl)-1-*tert*-butyl-1*H*-pyrazol-4-yl)(cyclopropyl)methyl)-4-(trifluoromethyl)benzenesulfonamide (113).

To a solution of (112) (0.25 g, 0.81 mmol) in THF (5 mL) was added sulfonamide (72) (0.27 g, 1.21 mmol), followed by titanium (IV) isopropoxide (0.46 g, 1.62 mmol). The reaction mix was stirred at room temperature for 18 h. The reaction mix was diluted with EtOAc (10 mL), and then quenched with saturated aqueous NaCl (3 mL). The reaction mix was stirred for 10 minutes, and then was filtered through a pad of Celite. The two layers were separated. The organic layer was dried with $MgSO_4$, filtered and concentrated. To a solution of the resulting residue THF (5 mL) at -78 °C was added slowly cyclopropylmagnesium

bromide (0.5M in THF, 16.2 mL, 8.11 mmol). The reaction mixture was stirred for 2 h at –78 °C, then diluted with EtOAc (20 mL) and was quenched with saturated $NH_4Cl_{(aq)}$ (10 mL). The reaction mix was warmed to room temperature and the two layers were separated. The organic layer was washed with saturated aqueous NaCl (15 mL), dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography (30% EtOAc in hexanes) to afford (113) (0.17 g, 45% over two steps). MS (ES) *m/z* 556.9 and 558.9 $(M+H)^+$.

1-*tert*-Butyl-4-cyclopropyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c][1,5]naphthyridine (114).

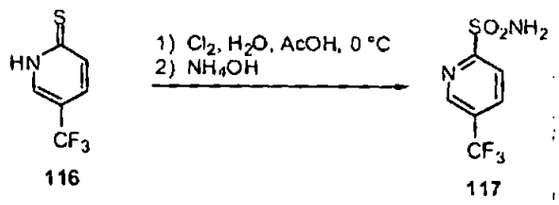
Sulfonamide (113) (0.82 g, 0.15 mmol) was dissolved in DMSO (1 mL) and nitrogen was bubbled through for 1 h. In a separate flame-dried flask, copper iodide (0.11 g, 0.59 mmol) and cesium acetate (0.28 g, 1.48 mmol) were combined. The reaction flask was evacuated, and then refilled with nitrogen. The pump/purge process was repeated three times. The DMSO solution of sulfonamide (113) was added to the reaction flask and the flask was plunged into a preheated, 80 °C oil bath. The reaction mixture was stirred for 1 h at 80 °C, and then cooled to room temperature. The reaction mixture was diluted with Et_2O (15 mL) and washed with water (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography (30% EtOAc in hexanes) to afford (114) (0.05 g, 66%). MS (ES) *m/z* 477.0 $(M+H)^+$.

4-Cyclopropyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c][1,5]naphthyridine (115).

A solution of (114) (0.05 g, 0.09 mmol) in formic acid (1 mL) was plunged into a preheated 80 °C oil bath. The reaction mixture stirred for 2 h at 80 °C and then cooled to room temperature. The mixture was concentrated and the resulting residue was dissolved in CH_2Cl_2 (10 mL) and washed with water (5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography (50% EtOAc in hexanes) to afford (115) (0.03 g, 63%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.62 (dd, J = 4.8, 1.2 Hz, 1H), 8.27 (dd, J = 8.2, 1.2 Hz, 1H), 7.36 (m, 6H), 5.12 (d, J = 7.5 Hz, 1H), 1.05 (m, 1H), 0.45 (m, 2H), 0.19 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7, 141.6, 141.0, 136.7, 135.6, 133.5, 129.9, 127.3, 125.5, 125.4, 123.2, 117.7, 58.7, 30.3, 17.0, 3.32, 2.82; MS (ES) *m/z* 420.9 $(M+H)^+$.

Example 20

5-(Trifluoromethyl)pyridine-2-sulfonamide (117).

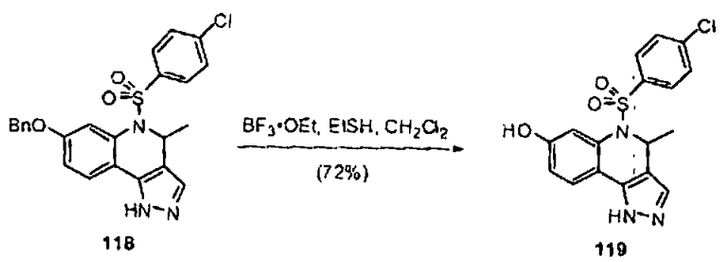


116 117

5-(Trifluoromethyl)pyridine-2(1*H*)-thione (116), 10.0g, 55.8 mmol) was placed in a flask containing 100 mL of water and 50 mL of acetic acid. The mixture was cooled to 0 °C and chlorine gas was bubbled into the mixture for 45-60 minutes. Water (100 mL) was added and a precipitate formed which was collected by filtration. This solid was cooled in an ice bath and in a separate flask 100 mL of conc. NH_4OH was also cooled in an ice bath. After 10 minutes, the cooled NH_4OH solution was added to the solid and the mixture was stirred overnight at room temperature. The mixture was then extracted with Et_2O (100 mL). The aqueous layer was collected and concentrated to give crude product that was purified by column chromatography on silica gel using EtOAc/hexanes gradients to afford 1.30 g of (117) (10%) as an off-white solid.

Example 21

5-(4-Chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinolin-7-ol (119).



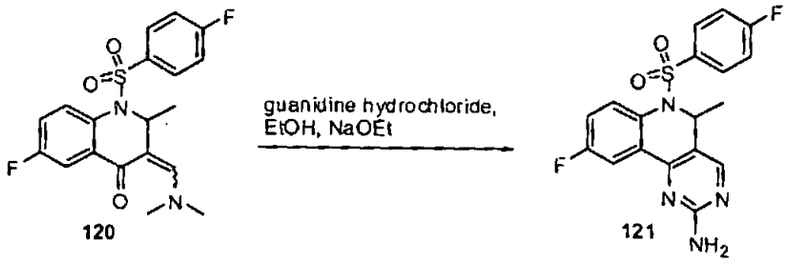
118 119

To a solution of (118) (0.37 g, 0.78 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added ethane thiol (1 mL) and BF_3•Et_2O (0.39 mL, 3.15 mmol). The reaction mixture was stirred for 18 h while warming to room temperature. A second aliquot of BF_3•Et_2O (0.39 mL, 3.15 mmol) was added and the reaction mixture was heated to 50 °C for 3 h. The mixture was then cooled to room temperature, diluted with EtOAc (10 mL), and washed with water (10 mL) and saturated aqueous NaCl (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by preparative HPLC to afford (119) (0.21 g, 72%). ^{1}H NMR (CD_3CN) δ 7.44 (d, J = 8.4 Hz, 1H), 7.27 (s, 1H), 7.17 (d, J = 2.5 Hz, 1H),

7.17 (s, 4H), 6.83 (dd, J = 8.4, 2.5 Hz, 1H), 6.38 (bs, 1H), 5.57 (q, J = 6.9 Hz, 1H), 1.21 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, CD_3CN) δ 158.1, 139.5, 137.0, 134.8, 129.6, 129.2, 127.2, 124.6, 118.2, 117.8, 117.2, 116.0, 55.2, 50.9, 23.3; MS (ES) *m/z* 375.9 $(M+H)^+$.

Example 22

9-Fluoro-6-(4-fluorophenylsulfonyl)-5-methyl-5,6-dihydropyrimido[5,4-c]quinolin-2-amine (121).

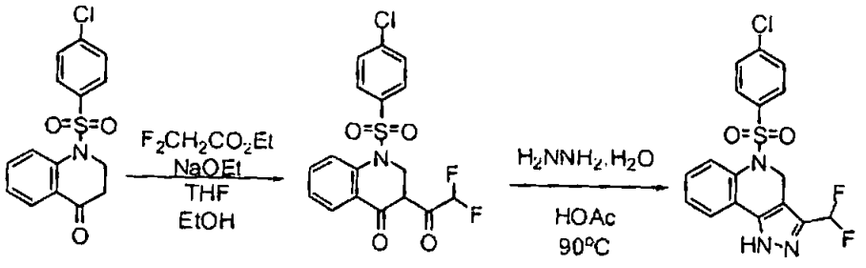


120 121

A solution of guanidine hydrochloride (0.49 mmol) and NaOEt (21% wt in EtOH, 1.34 mmol) was added to a reaction vial containing compound (120) (0.45 mmol) in EtOH (1.5 ml). The vial was heated for 5 minutes at 100 °C in a microwave and was subsequently filtered and purified by preparative HPLC to afford compound (121) (27%). ^{1}H NMR (CD_3OD) δ 8.13 (s, 1H), 7.85-7.79 (m, 2H), 7.51-7.45 (m, 1H), 7.34-7.29 (m, 2H), 7.17-7.12 (m, 1H), 7.02-6.96 (m, 2H), 6.76-6.69 (m, 1H), 5.57-5.50 (q, J = 6.9 Hz, 1H), 1.31-1.28 (m, 3H). MS *m/z* 388.9 $(M+H)^+$.

Example 23

5-(4-Chlorophenylsulfonyl)-3-(difluoromethyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline (123)



5 122 123

1-(4-Chlorophenylsulfonyl)-3-(2,2-difluoroacetyl)-2,3-dihydroquinolin-4(1*H*)-one (122).

Ketone (5) (481 mgs, 1.5 mmol) was dissolved in ethyl difluoroacetate (3.15 mL, 30 mmol), THF (1 mL) and dry ethanol (1 mL). To the reaction mixture was added 21% sodium

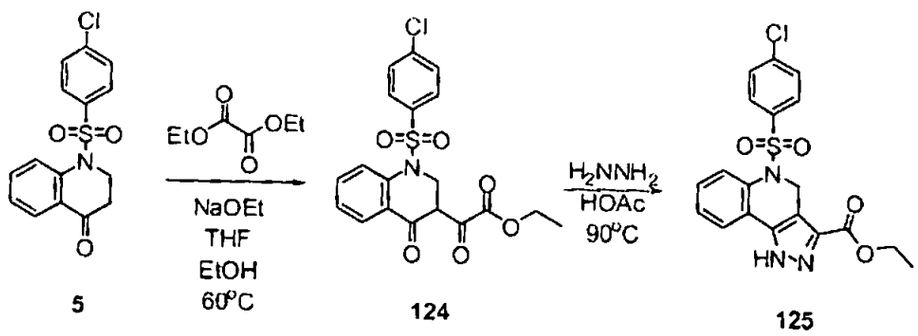
ethoxide in ethanol (1.68 mL, 4.5 mmol). The solution was then stirred at ambient temperature. After 4h, LC-MS analysis showed partial conversion and the reaction continued at room temperature for an additional 14h. Evaporation of the amber reaction mixture under a stream of nitrogen resulted in intermediate (122), MS (ES) *m/z* 422.0 $(M+Na)^+$.

5-(4-Chlorophenylsulfonyl)-3-(difluoromethyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline (123).

To a suspension of intermediate (122) (239 mgs, 0.6 mmol) and glacial acetic acid (3 mL) was added anhydrous hydrazine (30 µL, 0.6 mmol). The solution was stirred under nitrogen and heated at 90 °C for 3h, followed by cooling to ambient temperature. Upon complete consumption of (87) by LC-MS, the reaction mixture was evaporated by rotary evaporation. The resulting residue was dissolved in acetonitrile (5 mL) and purified by reverse-phase preparative HPLC, resulting in 172 mgs of compound (123). MS (ES) *m/z* 396.0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.90-7.83 (m, 2H), 7.52-7.43 (m, 1H), 7.42-7.35 (m, 2H), 7.27 (m, 1H), 7.19-7.04 (m, 3H), 5.05 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 139.2, 138.8, 135.8, 134.4, 129.5, 129.4, 128.4, 128.3, 128.0, 122.1, 121.7, 113.9, 110.8, 110.7, 107.7, 50.6, 42.8.

Example 24

Ethyl 5-(4-chlorophenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline-3-carboxylate (125)



Ethyl 2-(1-(4-chlorophenylsulfonyl)-4-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-2-oxoacetate (124).

The ketone (5) (963 mgs, 3.0 mmol) was dissolved in diethyl oxalate (4.1 mL, 30 mmol), THF (2 mL) and dry ethanol (2 mL). To the reaction mixture was added 1% sodium ethoxide in ethanol (3.36 mL, 9.0 mmol). The solution was placed under nitrogen and allowed to stir at ambient temperature for 1h, followed by heating at 60 °C for 1h. The

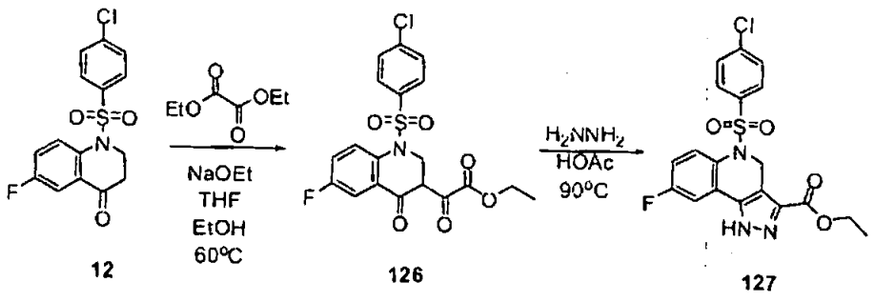
resulting mixture was concentrated by rotary evaporation, dissolved in MeOH (14 mL) and purified by reverse-phase preparative HPLC to afford 260 mgs of compound (124). MS (ES) *m/z* 421.9 $(M+H)^+$.

Ethyl 5-(4-chlorophenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline-3-carboxylate (125).

To a suspension of intermediate (124) (260 mgs, 0.62 mmol) and glacial acetic acid (2 mL) was added anhydrous hydrazine (35 µL, 0.62 mmol). The solution was stirred under nitrogen and heated at 90 °C for 6h, followed by cooling to ambient temperature. Upon complete consumption of (124) by LC-MS, the reaction mixture was evaporated by rotary evaporation. The resulting residue was dissolved in methanol (6 mL) and purified by reverse-phase preparative HPLC, resulting in 107 mgs of compound (125). MS (ES) *m/z* 417.9 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.84-7.80 (dd, 2H), 7.74-7.74 (dd, 2H), 7.49-7.38 (m, 2H), 7.17-7.04 (m, 2H), 5.10 (s, 2H), 4.54-4.47 (q, 2H), 1.53-1.48 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 159.0, 145.2, 139.4, 136.0, 134.9, 129.9, 129.7, 129.3, 129.0, 128.4, 128.3, 128.2, 128.1, 124.3, 122.7, 115.6, 62.0, 43.1, 14.4.

Example 25

Ethyl 5-(4-chlorophenylsulfonyl)-8-fluoro-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline-3-carboxylate (127).



12 126 127

Ethyl 2-(1-(4-chlorophenylsulfonyl)-6-fluoro-4-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-2-oxoacetate (126).

The ketone (12) (1017 mgs, 3.0 mmol) was heated to dissolution in diethyl oxalate (4.1 mL, 30 mmol), THF (2 mL) and dry ethanol (2 mL). To the reaction mixture was added 21% sodium ethoxide in ethanol (3.36 mL, 9.0 mmol). The solution was stirred under nitrogen at ambient temperature for 1h, followed by heating at 60 °C for 1h. The resulting

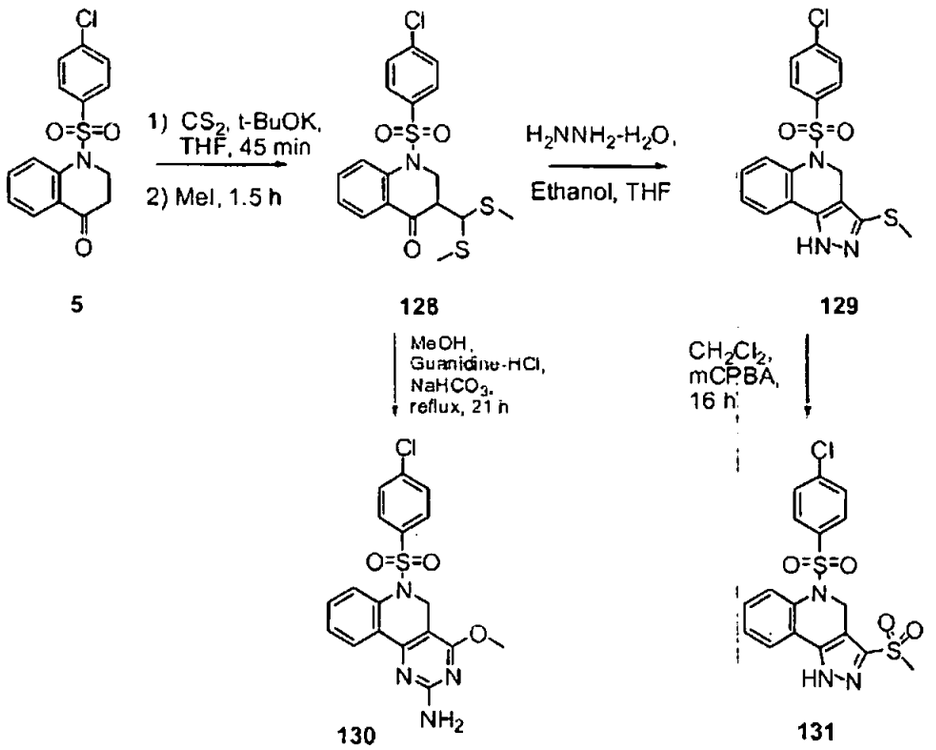
mixture was concentrated by rotary evaporation and carried forward crude. Compound (126) MS (ES) *m/z* 440.0 $(M+H)^+$.

Ethyl 5-(4-chlorophenylsulfonyl)-8-fluoro-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline-3-carboxylate (127).

To a suspension of intermediate (126) (3.0 mmol) and glacial acetic acid (10 mL) was added anhydrous hydrazine (168 µL, 3.0 mmol). The solution was stirred under nitrogen and heated at 90 °C for 5h, followed by cooling to ambient temperature. Upon complete consumption of (126) by LC-MS, the reaction mixture was evaporated by rotary evaporation. The resulting residue was dissolved in methanol (12 mL) and purified by reverse-phase preparative HPLC, resulting in 379 mgs of compound (127). MS (ES) *m/z* 435.9 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.81-7.76 (dd, 2H), 7.47-7.43 (dd, 2H), 7.16-7.06 (m, 3H), 5.07 (s, 2H), 4.54-4.46 (q, 2H), 1.53-1.48 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 163.5, 160.2, 159.0, 139.4, 135.8, 131.0, 130.9, 130.7, 128.4, 128.3, 116.0, 115.7, 115.6, 109.7, 109.4, 61.9, 50.8, 43.1, 14.4.

Example 26

5-(4-Chlorophenylsulfonyl)-3-(methylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline (131).



5 128 129

130 131

3-(Bis(methylthio)methyl)-1-(4-chlorophenylsulfonyl)-2,3-dihydroquinolin-4(1*H*)-one (128)

A solution of (5) (506 mg, 1.57 mmol) and carbon disulfide (239 mg, 0.189 mL, 3.15 mmol) in tetrahydrofuran (10 mL) was treated with potassium *tert*-butoxide (441 mg, 3.93 mmol) and stirred for 45 min. The mixture was then treated with iodomethane (1.12g, 0.49 mL), 7.9 mmol) and stirred at ambient temp for 1.5 h. The mixture was diluted with sat. aq sodium bicarbonate (25 mL) and extracted with ethyl acetate (2 x 25 mL). The combined organic extracts were washed with water (20 mL) and brine (10 mL), then dried (sodium sulfate), filtered and evaporated *in vacuo* to give (128) as a yellow oil (645 mg, 92% crude).

5-(4-Chlorophenylsulfonyl)-3-(methylthio)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline (129)

The ketene dithioacetal (128) (615 mg, 1.44 mmol) was taken up into ethanol (10 mL) and treated with hydrazine hydrate (87 mg, 0.084 mL, 1.73 mmol). Tetrahydrofuran (2 mL) was added to give a homogeneous solution, which was stirred for 4 h. The mixture was diluted with water (25 mL) and extracted with ethyl acetate (2 X 25 mL). The combined organic extracts were washed with water (25 mL) and brine (10 mL), then dried (sodium sulfate), filtered and evaporated *in vacuo* to give a crude residue which was purified by silica gel flash chromatography (eluted 2:1 hexanes/ethyl acetate) to give (129) (373 mg, 66%) as a

tan solid. Mass spectrum: MS (ES) *m/z* 392.0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.81 (d, *J* = 7.7 Hz, 1H), 7.60 (m, 1H), 7.45-7.34 (m, 2H), 7.16 (d, *J* = 8.2 Hz, 2H), 7.08 (d, *J* = 8.2 Hz, 2H), 4.87 (s, 2H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 139.2, 136.3, 134.9, 129.1, 128.9, 128.4, 128.0, 122.4, 42.7.

5-(4-Chlorophenylsulfonyl)-3-(methylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline (131)

A solution of (129) (307 mg, 0.78 mmol) in methylene chloride (10 mL) was treated with mCPBA (assay: 77%, 527 mg, 2.35 mmol) and stirred for 16 h. The mixture was diluted with ethyl acetate (50 mL) and washed with diluted aq sodium bicarbonate (2 x 25 mL). The volatiles were removed *in vacuo* and the residue was purified by silica gel flash chromatography (eluted 1:1 hexanes/ethyl acetate) to give (131) as a white solid (290 mg, 87%) Mass spectrum: MS (ES) *m/z* 424.0 $(M+H)^+$. ^1H NMR (DMSO d_6) δ 7.75 (m, 1H), 7.65-7.54 (m, 3H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.12 (d, *J* = 8.2 Hz, 2H), 5.11 (s, 2H), 3.33 (s, 3H). ^{13}C NMR (DMSO d_6) δ 133.7,130.7, 128.7, 128.1, 124.8, 124.1, 124.1, 123.8, 123.7, 123.3, 117.9, 38.6, 37.6.

6-(4-Chlorophenylsulfonyl)-4-methoxy-5,6-dihydropyrimido[5,4-c]quinolin-2-amine (130)

The ketene dithioacetal (128) (0.58g, 1.36 mmol) was taken up into methanol (10 mL) and treated with guanidine hydrochloride (0.260 g, 2.77 mmol) the mixture was stirred for 16 h whereupon TLC analysis indicated no condensation had taken place. Sodium bicarbonate (300 mg) was added and the mixture was heated to reflux for 21 h. The mixture was cooled to ambient temp and diluted with water (15 mL); then extracted with ethyl acetate (3 x 25 mL). The extracts were dried (sodium sulfate), filtered and concentrated *in vacuo* to give a residue, which was purified by silica gel chromatography (eluted 1:1 hexanes/ethyl acetate) to give 190 mg of (130) . MS *m/z* 403.0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.98 (dd, *J* = 1.1, 7.7 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.51 (m, 1H), 7.39 (m, 1H), 7.18 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 2H), 4.87 (br s, 2H), 4.76 (s,2H), 3.92 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 166.0, 162.9, 156.6, 139.5, 137.8, 136.5, 131.1, 128.9, 128.6, 128.2, 128.0, 127.7, 125.3, 99.9, 53, 7, 42.4.

Example 27

5-(4-Chlorophenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinolin-3-ol.

Prepared by treatment of ethyl 1-(4-chlorophenylsulfonyl)-4-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate, which was prepared from compound (5) using triethyl phosphonoformate and NaH in THF, with hydrazine in AcOH. MS *m/z* 361.9 $(M+H)^+$. ^1H NMR (CD_3OD) δ 7.74 (m, 1H), 7.42-7.37 (m, 3H), 7.25-7.16 (m, 4H), 4.82 (s, 4H).

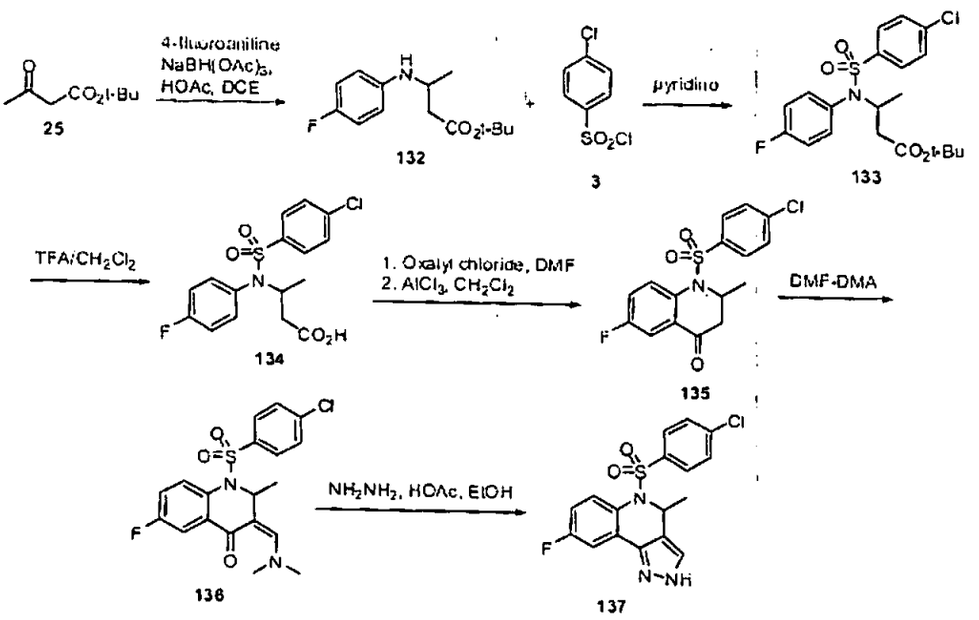
Example 28

8-Fluoro-4-methyl-5-(pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline.

Prepared as described in Example 10 using 3-pyridinesulfonyl chloride and tert-butyl 3-(4-fluorophenylamino)butanoate, which was prepared from compound (25) and 4-fluoroaniline as described for compound (26) in Example 4. MS *m/z* 345.0 $(M+H)^+$. ^1H NMR (CD_3OD) δ 8.52-8.50 (dd, J = 4.9, 1.3 Hz, 1H), 8.30-8.29 (d, J = 1.8 Hz, 1H), 7.81-7.77 (dd, J = 8.9, 4.9 Hz, 1H), 7.61-7.57 (m, 1H), 7.46 (s, 1H), 7.37-7.33 (dd, J = 8.7, 3.0 Hz, 1H), 7.27-7.17 (m, 2H), 5.76-5.73 (q, J = 6.9 Hz, 1H), 1.29-1.27 (d, J = 6.9 Hz, 3H).

Example 29

5-(4-Chlorophenylsulfonyl)-8-fluoro-4-methyl-4,5-dihydro-2H-pyrazolo[4,3-c]quinoline (149).



tert-Butyl 3-(4-fluorophenylamino)butanoate (132). To a 1,2-dichloroethane solution (146 mL) of 4-fluoroaniline (4.06 g, 36.5 mmol) was added *tert*-butyl acetoacetate (25) (6.05 mL, 36.5 mmol) and glacial acetic acid (3.0 mL, 47.5 mmol). Sodium triacetoxyborohydride (11.6 g, 54.8 mmol) was added in portions and the reaction was stirred overnight at room temperature. Saturated aqueous $NaHCO_3$ (250 mL) was slowly added and the two phase solution was well stirred. The separated organic portion was washed with sat. aq. $NaHCO_3$ (1 x 100 mL), water (1 x 100 mL), brine (1 x 20 mL), dried ($MgSO_4$), filtered and concentrated to yield 132 (9.03 g, 98%) as an oil. MS *m/z*: $(M+H)^+ = 254.1$.

tert-Butyl 3-(4-chloro-*N*-(4-fluorophenyl)phenylsulfonamido)butanoate (133). To a solution of compound 132 (3.08 g, 12.2 mmol) in pyridine (35 mL) at 0 °C was added 4-chlorobenzenesulfonyl chloride (3) (8.98 g, 42.6 mmol) portionwise. The reaction was warmed to room temperature and then heated at 70 °C for 5.5 hours then cooled to room temperature. Dimethylaminopropylamine (~ 40 mL) was added to the reaction mixture which was then stirred overnight. The reaction mixture was then concentrated and the residue taken up in EtOAc (120 mL). The organic phase was washed with cold 1N HCl (6 x 100 mL), water (1 x 100 mL), sat. aq. $NaHCO_3$ (3 x 100 mL), brine (1 x 100 mL), dried ($MgSO_4$), filtered, and concentrated to yield ester 133 (5.2 g, 99%) as an oil. MS *m/z*: $(M+Na)^+ = 450.1$.

3-(4-Chloro-*N*-(4-fluorophenyl)phenylsulfonamido)butanoic acid (134). To a solution of ester 133 (5.19 g, 12.13 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added TFA (35 mL). The reaction mixture was allowed to warm to room temperature, stirred overnight and then concentrated to give 134 (4.7 g, 105%) as an oil. MS *m/z*: $(M+H)^+ = 372.1$.

1-(4-Chlorophenylsulfonyl)-6-fluoro-2-methyl-2,3-dihydroquinolin-4(1H)-one (135). To an ice chilled solution of 134 (3.91 g, 10.52 mmol) in CH_2Cl_2 (45 mL) and DMF (4 drops) was added oxalyl chloride (3.67 mL, 42.10 mmol) dropwise. The resulting solution was stirred at -5 °C for 15 minutes and then warmed to room temperature and stirred for 3 hours. The reaction mixture was then concentrated and the residue taken-up in diethyl ether, filtered through a plug of glass wool, and concentrated to give the acid chloride (4.09, 99%). A CH_2Cl_2 (20 mL) solution of the acid chloride was added dropwise over a 20 minute period to a chilled (-5 °C) suspension of $AlCl_3$ (1.81 g, 13.6 mmol) in CH_2Cl_2 (20 mL). After stirring for 0 °C for one hour the reaction was warmed to room temperature and stirred overnight.

The reaction mixture was then chilled in an ice bath to which was added 10% HCl (15 mL) dropwise over 15 minutes. The organic portion was washed with 10% HCl (2 x 50 ml), water (1 x 20 mL), sat. aq. $NaHCO_3$ (3 x 50 mL), brine (1 x 20 mL), dried ($MgSO_4$), filtered, and concentrated. The crude product was then dissolved in THF (40 mL) to which was added sat. aq. $NaHCO_3$ (40 mL). This mixture was stirred for 7 hours and then concentrated. The residue was taken-up in water and EtOAc. The aqueous layer was extracted with EtOAc (4 x 30 mL) and the combined EtOAc extracts were washed with brine (1 x 20 mL), dried ($MgSO_4$) filtered, and concentrated to the give the crude product which was purified by flash chromatography eluting with 8:1 hexanes/EtOAc to give 135 (980 mg, 26%). MS *m/z*: $(M+H)^+ = 354.2$.

5-(4-Chlorophenylsulfonyl)-8-fluoro-4-methyl-4,5-dihydro-2H-pyrazolo[4,3-c]quinoline (137). A dimethylformamide dimethyl acetal (5.2 mL) solution of 135 (922 mg, 2.61 mmol) was heated at 100 °C for 3 hours. HPLC/MS analysis of the reaction mixture determined that no starting material remained so the reaction was cooled to room temperature and poured into EtOAc (50 mL) and water (50 mL). The organic portion was washed with water (3 x 50 mL), brine (1 x 20 mL), dried ($MgSO_4$), filtered and concentrated to give 136 as a red foam which was used directly in the next reaction. To an EtOH/glacial HOAc solution (25:1 v/v, 12 mL) of 136 (982 mg, 2.40 mmol) was added hydrazine hydrate (582 mL, 12.0 mmol). The reaction mixture was stirred overnight at room temperature, concentrated, and the residue taken up in EtOAc (20 mL). The organic phase was washed with sat. aq. $NaHCO_3$ (3 x 25 mL), brine (1 x 20 mL), dried ($MgSO_4$), filtered and concentrated. The crude product was purified by flash chromatography eluting with 2:1 hexanes/EtOAc to give 137 as a yellow solid. ^1H NMR ($CDCl_3$) δ 7.81-7.76 (m, 1H), 7.37 (dd, J = 8.5, 2.7 Hz, 1H), 7.21 (s, 1H), 7.13-7.04 (m, 5H), 5.60 (q, J = 6.6 Hz), 1.28 (d, J = 7.1 Hz, 3H); MS: $(M+H)^+ = 378.0$.

Example 30

8-Fluoro-4-methyl-5-(pyridin-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 10 using tert-butyl 3-(4-fluorophenylamino)butanoate, which was prepared from compound (25) and 4-fluoroaniline as described for compound (26) in Example 4. MS *m/z* 345 $(M+H)^+$. ^1H NMR (CD_3OD) δ 8.25-8.24 (m, 1H), 7.78-7.68 (m, 2H), 7.44-7.32 (m, 4H), 7.22-7.10 (m, 2H), 5.75-5.68 (q, J = 6.9 Hz, 1H), 1.28-1.26 (d, J = 6.9 Hz, 3H).

Example 31

5-(4-Chlorophenylsulfonyl)-8-fluoro-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. (Enantiomers A and B) Prepared as described in Example 4 using 4-fluoroaniline followed by chromatographic separation using the specified column type and analyzed using Method 16. Enantiomer A Retention time = 9.8 min. Enantiomer B Retention time = 27.1 min. MS *m/z* 378.0 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ 7.81-7.76 (m, 1H), 7.37 (dd, J = 8.5, 2.7 Hz, 1H), 7.21 (s, 1H), 7.13-7.04 (m, 5H), 5.60 (q, J = 6.6 Hz), 1.28 (t, J = 7.1 Hz, 3H).

Example 32

4-Methyl-5-(pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 10 using 3-pyridinesulfonyl chloride in place of compound (50). MS *m/z* 327.0 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 8.45-8.43 (m, 2H), 7.86-7.83 (dd, J = 7.8, 1.3 Hz, 1H), 7.66-7.63 (dd, J = 7.4, 1.6 Hz, 1H), 7.47-7.28 (m, 4H), 7.03-6.99 (m, 1H), 5.75-5.68 (q, J = 6.9 Hz, 1H), 1.35-1.33 (d, J = 6.9 Hz, 3H).

Example 33

8-Fluoro-4-methyl-5-(pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. (Enantiomers A and B) Prepared as described in Example 10 using 3-pyridinesulfonyl chloride and tert-butyl 3-(4-fluorophenylamino)butanoate, which was prepared from compound (25) and 4-fluoroaniline as described for compound (26) in Example 4 followed by chromatographic separation using the specified column type and analyzed using Method 15. Enantiomer A Retention time = 15.2 min. Enantiomer B Retention time = 17.5 min. MS *m/z* 345 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 10.16 (s, 1H), 8.48-8.45 (d, J = 10.4 Hz, 2H), 7.83-7.79 (dd, J = 8.9, 5.0 Hz, 1H), 7.36-7.28 (m, 3H), 7.16-7.05 (m, 2H), 5.75-5.68 (q, J = 6.9 Hz, 1H), 1.34-1.31 (d, J = 6.9 Hz, 3H).

Example 34

5-(Pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 1 using 3-pyridinesulfonyl chloride in place of compound (3). ^{1}H-NMR ($CDCl_3$) δ 8.47 (br s, 2H), 7.82 (d, J = 7.6 Hz, 1H), 7.66 (d, J = 6.0 Hz, 1H), 7.45-7.39 (m, 2H), 7.31-7.28 (m, 3H), 7.03-6.99 (m, 1H), 4.99 (s, 2H).

Example 35

8-Fluoro-5-(pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 2 using 3-pyridinesulfonyl chloride in place of compound (3). ^{1}H NMR (CD_3OD) δ 8.50-8.49 (1H, d), 8.27 (1H, s), 7.82-7.77 (1H, dd), 7.56-7.53 (1H, d), 7.46 (1H, s), 7.35-7.32 (1H, d), 7.24-7.17 (2H, m), 5.00 (2H, s).

Example 36

8-Fluoro-4-methyl-5-(pyridin-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. (Enantiomers A and B) Prepared as described in Example 10 using *tert*-butyl 3-(4-fluorophenylamino)butanoate, which was prepared from compound (25) and 4-fluoroaniline as described for compound (26) in Example 4. Enantiomers were then separated using the specified column type and analyzed using Method 15. Enantiomer A Retention time = 16.3 min. Enantiomer B Retention time = 21.4 min. MS *m/z* 345.0 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 8.31-8.30 (d, J = 4.6 Hz, 1H), 7.83-7.78 (dd, J = 8.9, 5.1 Hz, 1H), 7.60-7.55 (td, J = 7.8, 1.6 Hz, 1H), 7.39-7.33 (m, 2H), 7.23-7.19 (m, 1H), 7.10-7.04 (td, J = 8.7, 2.9 Hz, 1H), 5.83-5.76 (q, J = 6.9 Hz, 1H), 1.34-1.32 (d, J = 6.9 Hz, 3H).

Example 37

4-Methyl-5-(pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. (Enantiomers A and B) Prepared as described in Example 10 using 3-pyridinesulfonyl chloride in place of compound (50) followed by chromatographic separation using the specified column type and analyzed using Method 15. Enantiomer A Retention time = 13.5 min. Enantiomer B Retention time = 14.6 min. MS *m/z* 326.9 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 9.44 (s, 1H) 8.48-8.43 (m, 2H), 7.86-7.83 (dd, J = 8.0, 1.3 Hz, 1H), 7.64-7.61 (dd, J = 7.4, 1.6 Hz, 1H), 7.47-7.28 (m, 4H), 7.04-7.00 (dd, J = 8.0, 4.9 Hz, 1H), 5.75-5.68 (q, J = 6.9 Hz, 1H), 1.35-1.33 (d, J = 6.9 Hz, 3H).

Example 38

8-Fluoro-5-(4-fluorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 4 using 4-fluoroaniline and 4-fluorophenylsulfonyl chloride. MS *m/z* 361.9 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 7.84-7.79 (dd, J = 5.1, 3.8 Hz, 1H), 7.38-7.34 (dd, J = 5.5, 2.9 Hz, 1H), 7.23 (s, 1H), 7.22-7.16 (m, 2H), 7.15-7.08 (dt, J = 5.7, 2.9 Hz, 1H), 6.80-6.75 (m, 2H), 5.67-5.60 (q, J = 6.9 Hz, 1H), 1.33-1.30 (d, J = 6.8, 3H).

Example 39

4-Methyl-5-(pyridin-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 10 followed by chromatographic separation using the specified column type and analyzed using Method 21. Retention time = 7.9. MS *m/z* 373.9 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.31-8.30 (d, J = 4.6 Hz, 1H), 7.84-7.81 (dd, J = 8.0, 1.0 Hz, 1H), 7.65-7.62 (dd, J = 7.4, 1.5 Hz, 2H), 7.57-7.51 (td, J = 7.8, 1.7 Hz, 1H), 7.41-7.30 (m, 3H), 7.20-7.16 (m, 1H), 5.85-5.78 (q, J = 6.9 Hz, 1H), 1.35-1.33 (d, J = 6.9 Hz, 3H).

Example 40

5-(4-Chlorophenylsulfonyl)-4-cyclopropyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 12 using 2-bromophenylboronic acid in place of compound (70). MS *m/z* 386 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.88 (s, 1H), 7.91 (dd, J=7.8, 1.2 Hz, 1H), 7.62 (dd, J=7.8, 1.5 Hz, 1H), 7.49 (dt, J=7.8, 1.5 Hz, 1H), 7.39 (dt, J=7.8, 1.2 Hz, 1H), 7.34 (s, 1H), 7.06 (s, 4H), 4.95 (d, J=8.4 Hz, 1H), 1.02 (m, 1H), 0.44 (broad m, 3H), 0.14 (m, 1H).

Example 41

5-(4-Chlorophenylsulfonyl)-4-isopropyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 12 using 2-bromophenylboronic acid and isopropylmagnesium bromide. MS *m/z* 388.0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.86 (dd, J=7.5, 0.9 Hz, 1H), 7.58 (dd, J=7.5, 1.5 Hz, 1H), 7.48 (dt, J=7.5, 1.5 Hz, 1H), 7.39 (dt, J=7.5, 0.9 Hz, 1H), 7.33 (s, 1H), 7.05 (s, 4H), 4.94 (d, J=9.6 Hz, 1H), 1.51 (m, 1H) 1.09 (d, J=7.2 Hz, 3H), 0.83 (d, J=6.3 Hz, 3H).

Example 42

8-Fluoro-5-(4-fluorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. (Enantiomers A and B) Prepared as described in Example 4 using 4-fluoroaniline and 4-fluorophenylsulfonyl chloride followed by chromatographic separation using the specified column type and analyzed using Method 17. Enantiomer A Retention time = 7.6 min. Enantiomer B Retention time = 10.1 min. MS *m/z* 361.9 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.83-7.78 (dd, J = 5.1, 3.8 Hz, 1H), 7.34-7.30 (dd, J = 5.5, 2.9 Hz, 1H), 7.22 (s, 1H), 7.20-7.18 (m, 2H), 7.14-7.07 (m, 1H), 6.79-6.73 (m, 2H), 5.67-5.61 (q, J = 6.9 Hz, 1H), 1.32-1.29 (d, J = 6.9 Hz, 3H).

Example 43

5-(4-Chlorophenylsulfonyl)-7,8-difluoro-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 12 using methylmagnesium bromide and 4-chlorophenylsulfonamide. MS *m/z* 396.0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.73 (dd, J=11.1, 7.5 Hz, 1H), 7.42 (dd, J=10.2, 8.4 Hz, 1H), 7.30 (s, 1H), 7.13 (broad m, 5H), 5.62 (q, J=6.9 Hz, 1H), 1.31 (q, J=6.9 Hz, 3H).

Example 44

7,8-Difluoro-4-methyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 12 using methylmagnesium bromide. MS *m/z* 430.0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.84 (broad s, 1H), 7.74 (dd, J=11.1, 7.5 Hz, 1H), 7.41 (m, 3H), 7.32 (d, J=9.0 Hz, 2H), 7.29 (s, 1H), 5.63 (q, J=6.9 Hz, 1H), 1.32 (q, J=6.9 Hz, 3H).

Example 45

5-(5-Chlorothiophen-2-ylsulfonyl)-7,8-difluoro-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 12 using 5-chlorothiophene-2-sulfonamide and methylmagnesium bromide. MS *m/z* 402.0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.66 (dd, J=11.4, 7.5 Hz, 1H), 7.55 (dd, J=10.5, 8.1 Hz, 1H), 7.33 (s, 1H), 6.73 (d, J=3.9 Hz, 1H), 6.57 (d, J=3.9 Hz, 1H), 6.14 (broad s, 1H), 5.63 (q, J=6.9 Hz, 1H), 1.32 (q, J=6.9 Hz, 3H).

Example 46

7,8-Difluoro-4-methyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. (Enantiomers A and B) Prepared as described in Example 12 using methylmagnesium bromide followed by chromatographic separation using the specified column type and analyzed using Method 15. Enantiomer A Retention time = 7.0 min. Enantiomer B Retention time = 9.5 min. MS *m/z* 430.0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.84 (broad s, 1H), 7.74 (dd, J=11.1, 7.5 Hz, 1H), 7.41 (m, 3H), 7.32 (d, J=9.0 Hz, 2H), 7.29 (s, 1H), 5.63 (q, J=6.9 Hz, 1H), 1.32 (q, J=6.9 Hz, 3H).

Example 47

4-Cyclopropyl-7,8-difluoro-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. (Enantiomers A and B) Prepared as described in Example 12

followed by chromatographic separation using the specified column type and analyzed using Method 16. Enantiomer A Retention time = 6.0 min. Enantiomer B Retention time = 9.3 min. MS *m/z* 456.0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.76 (dd, J = 11.1, 7.2 Hz, 1H), 7.47 (m, J = 10.2, 8.7 Hz, 1H), 7.39 (d, J = 8.7 Hz, 2H), 7.32 (d, J = 8.7 Hz, 2H), 7.20 (s, 1H), 4.95f (d, J = 7.8 Hz, 1H), 1.03 (m, 1H), 0.54 (m, 1H), 0.41 (m, 2H), 0.08 (m, 1H).

Example 48

4-(4-Cyclopropyl-1H-pyrazolo[4,3-c]quinolin-5(4*H*)-ylsulfonyl)benzonitrile. Prepared as described in Example 12 using 2-bromophenylboronic acid and 4-cyanobenzenesulfonamide. MS *m/z* 377,2 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.91-7.88 (m, 1H), 7.66-7.63 (m, 1H), 7.50-7.33 (m, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.27 (s, 1H), 7.25 (d, J = 8.4 Hz, 2H), 4.95 (d, J = 8.3 Hz, 1H), 1.07-0.98 (m, 1H), 0.57-0.54 (m, 1H), 0.51-0.39 (m, 2H), 0.17-0.09 (m, 1H).

Example 49

4-Cyclopropyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1H-pyrazolo[4,3-c]quinoline. Prepared as described in Example 12 using 2-bromophenylboronic acid and 4-(trifluoromethyl)benzenesulfonamide. MS *m/z* 420.1 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.90 (dd, J = 9.2, 2.0 Hz, 1H), 7.64 (dd, J = 7.0, 1.5 Hz, 1H), 7.48-7.32 (m, 4H), 7.28-7.25 (m, 2H), 7.21 (s, 1H), 4.95 (d, J = 7.8 Hz, 1H), 1.06-1.033 (m, 1H), 0.52-0.34 (m, 3H), 0.15-0.05 (m, 1H).

Example 50

5-(5-Chlorothiophen-2-ylsulfonyl)-4-cyclopropyl-7,8-difluoro-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 12 using 5-chlorothiophene-2-sulfonamide. MS *m/z* 457.0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 9.97 (broad s, 1H), 7.70 (dd, J = 11.4, 7.2 Hz, 1H), 7.57 (dd, J = 10.2, 8.7 Hz, 1H), 7.31 (s, 1H), 6.70 (d, J = 4.8 Hz, 1H), 6.56(d, J = 4.8 Hz, 1H), 4.98 (d, J = 7.5 Hz, 1H), 1.03 (m, 1H), 0.53 (m, 1H), 0.40 (m, 2H), 0.10 (m, 1H).

Example 51

4-Cyclopropyl-7,8-difluoro-5-(4-fluorophenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 12 using 4-fluorophenylsulfonamide. MS *m/z* 406.0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 9.73 (broad s, 1H), 7.77 (dd, J = 11.1, 7.2 Hz, 1H),

7.43 (dd, J = 9.9, 8.4 Hz, 1H), 7.27 (s, 1H), 7.21 (dd, J = 8.7, 5.4 Hz, 1H), 6.80(t, J = 8.7 Hz, 1H), 4.96 (d, J = 7.8 Hz, 1H), 1.01 (m, 1H), 0.52 (m, 1H), 0.40 (m, 2H), 0.09 (m, 1H).

Example 52

4-Cyclopropyl-5-(4-fluorophenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 12 using 2-bromophenylboronic acid and 4-fluorophenylsulfonamide. MS *m/z* 371.0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.91 (d, J = 8.6 Hz, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.48-7.35 (m, 2H), 7.30-7.28 (m, 2H), 7.18-7.11 (m, 1H), 6.74 (dd, J = 9.1, 7.2 Hz, 2H), 4.96 (d, J = 7.6 Hz, 1H), 1.14-0.08 (m, 1H), 0.58-0.32 (m, 3H), 0.20-0.11, 1H).

Example 53

5-(5-Chlorothiophen-2-ylsulfonyl)-4-cyclopropyl-7,8-difluoro-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. (Enantiomers A and B) Prepared as described in Example 12 using 5-chlorothiophene-2-sulfonamide followed by chromatographic separation using the specified column type and analyzed using Method 22. Enantiomer A Retention time = 10.3 min. Enantiomer B Retention time = 16.1 min. MS *m/z* 428.0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 9.97 (broad s, 1H), 7.70 (dd, J = 11.4, 7.2 Hz, 1H), 7.57 (dd, J = 10.2, 8.7 Hz, 1H), 7.31 (s, 1H), 6.70 (d, J = 4.8 Hz, 1H), 6.56(d, J = 4.8 Hz, 1H), 4.98 (d, J = 7.5 Hz, 1H), 1.03 (m, 1H), 0.53 (m, 1H), 0.40 (m, 2H), 0.10 (m, 1H).

Example 54

4-Cyclopropyl-7,8-difluoro-5-(4-fluorophenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline. (Enantiomers A and B) Prepared as described in Example 12 using 4-fluorophenylsulfonamide followed by chromatographic separation using the specified column type and analyzed using Method 13. Enantiomer A Retention time = 16.9. Enantiomer B Retention time = 19.7. MS *m/z* 406.0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 9.73 (broad s, 1H), 7.77 (dd, J = 11.1, 7.2 Hz, 1H), 7.43 (dd, J = 9.9, 8.4 Hz, 1H), 7.27 (s, 1H), 7.21 (dd, J = 8.7, 5.4 Hz, 1H), 6.80(t, J = 8.7 Hz, 1H), 4.96 (d, J = 7.8 Hz, 1H), 1.01 (m, 1H), 0.52 (m, 1H), 0.40 (m, 2H), 0.09 (m, 1H).

Example 55

5-(5-Chloropyridin-2-ylsulfonyl)-4-cyclopropyl-8-fluoro-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 12 using 5-chloro-2-pyridinesulfonamide. MS *m/z* 404.9 $(M+H)^+$. ^1H NMR (DMSO-d_6) δ 8.36-8.35 (d, J = 2.2 Hz, 1H), 7.95-7.92 (dd, J = 8.4, 2.3 Hz, 3H), 7.71-7.67 (m, 1H), 7.50-7.44 (m, 1H), 7.38-7.34 (dd, J = 8.8, 2.9 Hz, 1H), 7.24-7.19 (dt, J = 8.7, 2.6 Hz, 1H), 4.90-4.88 (d, J = 7.7 Hz, 1H), 0.93-0.87 (m, 1H), 0.45-0.40 (m, 1H), 0.28-0.15 (m, 3H).

Example 56

5-(4-Chlorophenylsulfonyl)-4-ethyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared by cyclization of 3-(4-chloro-N-phenylphenylsulfonamido)pentanoic acid, which was prepared as described for compound (27) using methyl 3-oxopentanoate followed by hydrolysis with NaOH, in the manner described for compound 55 followed by pyrazole formation as shown in Example 10. MS *m/z* 373.9 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.90 – 7.87 (dd, J = 8.1, 0.9 Hz, 1H), 7.66 – 7.63 (dd, 7.7, 1.4 Hz, 1H), 7.56 – 7.39 (m, 3H), 7.14 – 7.11 (m, 4H), 5.39 – 5.34 (ABq, J = 8.5, 6.8 Hz, 1H), 1.67 - 1.43 (m, 2H), 1.02 – 0.95 (t, J = 7.3 Hz, 3H).

Example 57

5-(4-Chlorophenylsulfonyl)-4-methyl-4,5,5a,6,7,8,9,9a-octahydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared by sulfonylation of 2-methyloctahydroquinolin-4(1H)-one followed by pyrazole formation as described in Example 1. MS *m/z* 365.9 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.80-7.76 (m, 2H), 7.55 (s, 1H), 7.49-7.45 (m, 2H), 4.21-4.15 (m, 1H), 3.15-3.06 (dt, J = 7.9, 2.4 Hz, 1H), 2.95-2.88 (dt, J = 7.9, 2.4 Hz, 1H), 1.95-1.92 (m, 1H), 1.80-1.70 (m, 3H), 1.56-1.55 (m, 1H), 1.51-1.48 (d, J = 7.0 Hz, 3H), 1.40-1.28 (m, 3H).

Example 58

5-(4-Chlorophenylsulfonyl)-9-fluoro-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 4 using 3-fluoroaniline. MS *m/z* 378.0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.70 (d, J = 8.10 Hz, 1H), 7.37 (m, 1H), 7.32 (s, 1H), 7.16-7.04 (m, 5H), 5.70 (q, J = 6.90 Hz, 1H), 1.33 (d, J = 6.93 Hz, 3H).

Example 59

5-(4-Chlorophenylsulfonyl)-7-fluoro-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 4 using 3-fluoroaniline. MS *m/z* 378.0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 10.40 (br s, 1H), 7.58-7.69 (m, 2H), 7.28-7.16 (m, 3H), 7.11-7.05 (m, 3H), 5.65 (q, J = 6.90 Hz, 1H), 1.33 (d, J = 6.90 Hz, 3H).

Example 60

5-(4-Chlorophenylsulfonyl)-4-cyclopropyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 12 using 2-bromophenylboronic acid in place of compound (70). MS *m/z* 386.0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.88 (s, 1H), 7.91 (dd, J=7.8, 1.2 Hz, 1H), 7.62 (dd, J=7.8, 1.5 Hz, 1H), 7.49 (dt, J=7.8, 1.5 Hz, 1H), 7.39 (dt, J=7.8, 1.2 Hz, 1H), 7.34 (s, 1H), 7.06 (s, 4H), 4.95 (d, J=8.4 Hz, 1H), 1.02 (m, 1H), 0.44 (broad m, 3H), 0.14 (m, 1H).

Example 61

5-(4-Chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinolin-7-ol. (Enantiomers A and B) Prepared as described in Example 21 followed by chromatographic separation using the specified column type and analyzed using Method 15. Enantiomer A Retention time = 13.4 min. Enantiomer B Retention time = 17.0 min. MS *m/z* 375.9$(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.42 (d, J = 8.4 Hz, 1H), 7.23 (s, 1H), 7.18 (d, J = 2.4 Hz, 1H), 7.14 (m, 4H), 6.85 (dd, J = 8.4, 2.5 Hz, 1H), 5.59 (q, J = 6.9 Hz, 1H), 1.22 (d, J = 6.9 Hz, 3H).

Example 62

5-(4-Chlorophenylsulfonyl)-4,5-dihydro-1*H*-imidazo[1,2-a]pyrazolo[4,3-e]pyrimidine. Prepared by reductive amination of aldehyde (69) with 4-chlorobenzenesulfonamide as described for compound (26) in Example 4 to afford 4-chloro-N-((3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)methyl)benzenesulfonamide. This was then coupled to 2-bromo-1*H*-imidazole and deproteced as described for compound (100) in Example 17. MS *m/z* 336.0$(M+H)^+$. ^1H NMR (CD3OD) δ 7.66 (d, J = 1.65 Hz, 1H), 7.61 (d, J = 8.79 Hz, 2H), 7.52 (s, 1H), 7.46 (d, J = 8.79 Hz, 2H), 7.35 (d, J = 1.65 Hz, 1H), 5.36 (s, 2H).

Example 63

5-(4-Chlorophenylsulfonyl)-4-ethyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. (Enantiomers A and B) Prepared by cyclization of 3-(4-chloro-N-phenylphenylsulfonamido)pentanoic acid, which was prepared as described for compound (27) using methyl 3-oxopentanoate followed by hydrolysis with NaOH, in the manner described for compound (53) followed by pyrazole formation as shown in Example 10. Enantiomers were then separated using the specified column type and analyzed using Method 17. Enantiomer A Retention time = 6.0 min. Enantiomer B Retention time = 9.3 min. MS *m/z* 373.9$(M+H)^+$. ^{1}H NMR (CD_3OD) δ 7.77-7.74 (d, J = 7.3 Hz, 1H), 7.65 (s, 1H) 7.44-7.35 (m, 3H), 7.14 (s, 4H), 5.36-5.31 (t, J = 8.3 Hz, 1H), 1.51-1.44 (m, 2H), 1.02-0.98 (t, J = 7.2 Hz, 3H).

Example 64

5-(4-Chlorophenylsulfonyl)-7-methyl-4,5-dihydro-1*H*-imidazo[1,2-a]pyrazolo[4,3-e]pyrimidines and 5-(4-chlorophenylsulfonyl)-8-methyl-4,5-dihydro-1*H*-imidazo[1,2-a]pyrazolo[4,3-e]pyrimidine. Prepared by reductive amination of aldehyde (69) with 4-chlorobenzenesulfonamide as described for compound 26 in Example 4 to afford 4-chloro-N-((3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)methyl)benzenesulfonamide. This was then coupled to 2-bromo-4-methyl-1*H*-imidazole and deprotected as described for compound (100) in Example 18 to give a mixture of regioisomers. MS *m/z* 350.0 $(M+H)^+$. ^{1}H NMR (CD_3OD) δ 7.39-7.31 (m, 10H), 7.13-7.11 (s, 1H), 6.75-6.73 (m, 1H), 4.98 (s, 2H), 4.97 (s, 2H), 2.41-2.40 (m, 3H), 2.67-2.50 (m, 3H).

Example 65

5-(4-Chlorophenylsulfonyl)-4-cyclopropyl-4,5-dihydro-1*H*-imidazo[1,2-a]pyrazolo[4,3-e]pyrimidine. Prepared by imine formation using aldehyde 69 and 4-chlorobenzenesulfonamide as described for compound 73 in Example 12 to afford 4-chloro-*N*-((3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)methylene)benzenesulfonamide. This was then reacted with isopropylmagnesium bromide as described for compound 74 in Example 12 to afford 4-chloro-*N*-(cyclopropyl(3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)methyl)benzenesulfonamide which was then coupled to 2-bromo-1*H*-imidazole and deprotected as described in Example 17. MS *m/z* 376.0 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 7.82 (d, J = 6.90 Hz, 2H), 7.71 (s, 1H), 7.40 (d, J = 6.6

Hz, 2H), 6.80 (s, 1H), 6.70 (s, 1H), 3.95 (d, J = 7.6 Hz, 1H), 1.10 – 1.04 (m, 1H), 0.59 – 0.51 (m, 2H), 0.48- 0.41 (m, 1H), 0.21 – 0.13 (m, 1H).

Example 66

5-(4-Chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c][1,7]naphthyridine. Prepared as described in Example 18 using 3-bromopyridin-4-ylboronic acid, 4-chlorobenzenesulfonamide and methylmagnesium bromide. MS *m/z* 362.0 $(M+H)^+$. 1H NMR (CDCl3) δ 8.99 (bs, 1H), 8.62 (bs, 1H), 8.03 (bs, 1H), 7.42 (s, 1H), 7.29 (m, 2H), 7.23 (m, 2H), 5.73 (q, J = 6.8 Hz, 1H), 1.28 (d, J = 6.9 Hz, 3H).

Example 67

4-Cyclopropyl-7,8-difluoro-5-(5-(trifluoromethyl)pyridin-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 12 using aldehyde (103) and sulfonamide (117). MS *m/z* 457.0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.53 (s, 1H), 7.89 (dd, J = 10.6, 8.0 Hz, 1H), 7.82 (dd, J = 18.6, 11.3, 1H), 7.60 (d, J = 8.2 Hz, 1H), 7.45 (dd, J = 18.6, 10.0, 1H), 7.38 (s, 1H), 5.11 (d, J = 8.0 Hz, 1H), 1.06 (m, 1H), 0.58 (m, 1H), 0.47 (m, 2H), 0.20 (m, 1H).

Example 68

5-(5-Chlorothiophen-2-ylsulfonyl)-4-cyclopropyl-7,8-difluoro-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 12 using 5-chlorothiophene-2-sulfonamide. MS *m/z* 428.0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 9.97 (broad s, 1H), 7.70 (dd, J = 11.4, 7.2 Hz, 1H), 7.57 (dd, J = 10.2, 8.7 Hz, 1H), 7.31 (s, 1H), 6.70 (d, J = 4.8 Hz, 1H), 6.56(d, J = 4.8 Hz, 1H), 4.98 (d, J = 7.5 Hz, 1H), 1.03 (m, 1H), 0.53 (m, 1H), 0.40 (m, 2H), 0.10 (m, 1H).

Example 69

4-Cyclopropyl-5-(4-fluorophenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c][1,8]naphthyridine. Prepared as described in Example 18 using 4-fluorobenzenesulfonamide. MS *m/z* 371.0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.42 (dd, J = 4.9, 1.6 Hz, 1H), 8.10 (dd, J = 7.6, 1.6 Hz, 1H), 7.98 (m, 2H), 7.58 (s, 1H), 7.22 (dd, J = 7.6, 4.9 Hz, 1H), 7.08 (m, 2H), 5.42 (d, J = 8.0 Hz, 1H), 1.14 (m, 1H), 0.46 (m, 3H), 0.21 (m, 1H).

Example 70

4-Cyclopropyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-imidazo[1,2-a]pyrazolo[4,3-e]pyrimidines. Prepared by imine formation using aldehyde (69) and 4-(trifluoromethyl)benzenesulfonamide as described for compound (73) in Example 12 to afford 4-chloro-*N*-((3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)methylene)benzenesulfonamide. This was then reacted with isopropylmagnesium bromide as described for compound (74) in Example 12 to afford 4-chloro-*N*-(cyclopropyl(3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)methyl)benzenesulfonamide which was then coupled to 2-bromo-1*H*-imidazole and deprotected as described in Example 17. . MS *m/z* 410.0 $(M+H)^+$. ^1H NMR (CD_3OD) δ 8.05 (d, J = 8.3 Hz, 2H), 7.78 (d, J = 9.4 Hz, 2H), 7.76 (s, 1H), 6.86 (dd, J = 13.0, 2.6 Hz, 2H), 3.80 (d, J = 8.2 Hz, 1H), 1.05-1.03 (m, 1H), 0.42-0.37 (m, 1H), 0.31-0.24 (m, 1H), 0.21-0.13 (m, 1H), 0.54-0.14 (m, 1H).

Example 71

4-Cyclopropyl-7,8-difluoro-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 12 using aldehyde (103) and sulfonamide (83). MS *m/z* 457.0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.57 (s, 1H), 7.76 (m, J = 11.0, 7.6 Hz, 1H), 7.52 (m, 3H), 7.43 (d, J = 8.3 Hz, 1H), 7.33 (s, 1H), 5.03 (d, J = 7.6 Hz, 1H), 1.05 (m, 1H), 0.56 (m, 1H), 0.42 (m, 2H), 0.11 (m, 1H).

Example 72

5-(4-Fluorophenylsulfonyl)-4-(trifluoromethyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c][1,8]naphthyridine. Prepared as described in Example 18 using methyl trifluoromethanesulfonate in place of cyclopropymagnesium bromide. MS *m/z* 399.0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.30 (dd, J = 4.9, 1.9 Hz, 1H), 8.15 (dd, J = 7.6, 1.9 Hz, 1H), 8.05 (m, 2H), 7.82 (s, 1H), 7.22 (m, 3H), 6.58 (q, J = 7.4 Hz, 1H).

Example 73

7,8-Difluoro-4-(pyridin-3-yl)-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared by addition of 3-lithiopyridine (Ota, T.; Terashima, M. J. Heterocycl. Chem. 1987, 24(2), 377) to compound (73) followed by pyrazole formation as described in Example 12. MS *m/z* 493.0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.52 (d, J = 3.8 Hz, 1H), 8.33 (s, 1H), 7.72-7.48 (m, 7H), 7.40-7.33 (m, 2H), 6.71 (s, 1H).

Example 74

4-Cyclopropyl-8-fluoro-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 12 using 2-bromo-5-fluorophenylboronic acid in place of compound (70). MS *m/z* 437.9 $(M+H)^+$. ^1H NMR (CD_3OD) δ 7.85-7.80 (dd, J = 8.9, 5.1 Hz, 1H), 7.50-7.46 (m, 2H) 7.40-7.34 (m, 4H), 7.22-7.16 (td, J = 8.7, 2.9 Hz, 1H), 5.07-5.04 (d, J = 7.5 Hz, 1H), 1.02-0.94 (m, 1H), 0.54-0.47 (m, 1H), 0.41-0.31 (m, 2H), 0.17-0.12 (m, 1H).

Example 75

4-Cyclopropyl-7,8-difluoro-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. (Enantiomers A and B) Prepared as described in Example 13 using boronic acid (70) and sulfonyl chloride (83). Enantiomers were then separated using HPLC Method 19. Enantiomer A Retention time = 17.3 min. Enantiomer B Retention time = 13.0 min. MS *m/z* 457.0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 10.03 (br s, 1H), 8.58 (s, 1H), 7.76 (dd, J=11.0, 7.2 Hz, 1H), 7.49 (m, 2H), 7.44 (s, 1H), 5.03 (d, J=7.6 Hz), 1.04 (m, 1H), 0.56 (m, 1H), 0.41 (m, 2H), 0.11 (m, 1H).

Example 76

7,8-Difluoro-4-isopropyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 12 using isopropylmagnesium bromide. The product was analyzed by HPLC using Method 7. Retention time = 8.77 min. MS *m/z* 458.0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.73 (dd, J = 11.1, 7.5 Hz, 1H), 7.35 (broad m, 5H), 7.25 (s, 1H), 4.92 (d, J = 9.9 Hz, 1H), 4.48 (broad s, 1H), 1.50 (m, 1H), 1.09 (d, J = 6.9 Hz, 3H), 0.83 (d, J = 6.9 Hz, 3H).

Example 77

4-Cyclopropyl-7,8-difluoro-5-(4-(trifluoromethoxy)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 12 using 4-trifluoromethoxybenzensulfonamide in place of compound (72). MS *m/z* 472.0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.78 (dd, J = 10.8, 6.8 Hz, 1H), 7.43 (dd, J = 9.8, 8.2 Hz, 1H), 7.26 (s, 1H), 7.23 (d, J = 9.3 Hz, 2H), 6.96 (d, J = 7.9 Hz, 2H), 4.93 (d, J = 7.6 Hz, 1H), 1.07-0.96 (m, 1H), 0.61-0.50 (m, 1H), 0.47-0.37 (m, 2H), 0.13-0.06 (m, 1H).

Example 78

4-Cyclopropyl-8-fluoro-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. (Enantiomers A and B) Prepared as described in Example 12 using 2-bromo-5-fluorophenylboronic acid in place of compound (70). Enantiomers were then separated using the specified column type and analyzed using Method 15. Enantiomer A Retention time = 8.0 min. Enantiomer B Retention time = 12.6 min. MS *m/z* 437.9 $(M+H)^+$. ^1H NMR (CD_3OD) δ 7.85-7.80 (dd, J = 8.9, 5.1 Hz, 1H), 7.50-7.46 (m, 2H) 7.40-7.34 (m, 4H), 7.22-7.16 (td, J = 8.7, 2.9 Hz, 1H), 5.07-5.04 (d, J = 7.5 Hz, 1H), 1.02-0.94 (m, 1H), 0.54-0.47 (m, 1H), 0.41-0.31 (m, 2H), 0.17-0.12 (m, 1H).

Example 79

5-(5-Chloropyridin-2-ylsulfonyl)-4-cyclopropyl-8-fluoro-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 12 using 5-chloro-2-pyridinesulfonamide. MS *m/z* 405 $(M+H)^+$. ^1H NMR (DMSO-D6) δ 8.36-8.35 (d, J = 2.2 Hz, 1H), 7.95-7.92 (dd, J = 8.4, 2.3 Hz, 3H), 7.71-7.67 (m, 1H), 7.50-7.44 (m, 1H), 7.38-7.34 (dd, J = 8.8, 2.9 Hz, 1H), 7.24-7.19 (dt, J = 8.7, 2.6 Hz, 1H), 4.90-4.88 (d, J = 7.7 Hz, 1H), 0.93-0.87 (m, 1H), 0.45-0.40 (m, 1H), 0.28-0.15 (m, 3H).

Example 80

4-Cyclopropyl-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 13 using 2-bromoboronic acid and sulfonyl chloride (83). Enantiomers were then separated using the specified column type and analyzed using Method 17. MS *m/z* 421.1 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.51 (s, 1H), 7.87 (d, J = 9.7, 1H), 7.68 (d, J = 7.7 Hz, 1H), 7.49-7.26 (m, 5H), 5.00 (d, J = 7.6 Hz, 1H), 1.07-1.00 (m, 1H), 0.56-0.31 (m, 3H), 0.17-0.08 (m, 1H).

Example 81

5-(4-Chlorophenylsulfonyl)-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinolin-8-ol. Prepared from 8-(benzyloxy)-5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline as described for compound 119 in Example 21. MS *m/z* 376 $(M+H)^+$. 1H NMR (CD3OD) δ 7.55 (d, J = 8.7 Hz, 1H), 7.45 (s, 1H), 7.11 (m, 4H), 6.84 (dd, J = 8.7, 2.8 Hz, 1H), 5.60 (q, J = 6.9 Hz, 1H), 1.25 (d, J = 7.0 Hz, 3H).

Example 82

(*R*)-4-(4-Cyclopropyl-7,8-difluoro-1*H*-pyrazolo[4,3-c]quinolin-5(4*H*)-ylsulfonyl)aniline. Prepared as described in Example 13 using boronic acid (70) and 4-nitrobenzenesulfonyl chloride followed by reduction of the nitro group using hydrogen over Pt_2O in MeOH. MS *m/z* 403.1 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.77 (dd, J = 11.2, 7.4 Hz, 1H), 7.41 (dd, J = 10.0, 8.0 Hz, 1H), 7.29 (s, 1H), 6.94 (d, J = 8.4 Hz, 2H), 6.27 (d, J = 9.0 Hz, 2H), 4.95 (d, J = 7.7 Hz, 1H), 1.05-0.96 (m, 1H), 0.54-0.48 (m, 1H), 0.44-0.33 (m, 2H), 0.13-0.04 (m, 1H).

Example 83

(*R*)-4-Cyclopropyl-7,8-difluoro-5-(4-nitrophenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 13 using boronic acid (70) and 4-nitrobenzenesulfonyl chloride. MS *m/z* 432.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.78 (dd, J = 11.0, 7.0 Hz,1H), 7.41 (dd, J = 9.7, 8.0 Hz, 1H), 7.28 (s, 1H), 6.95 (d, J = 8.9 Hz, 2H), 6.17 (d, J = 8.6 Hz, 2H) 4.97 (d, J = 7.1 Hz, 1H), 1.04-0.94 (m, 1H), 0.57-0.47 (m, 1H), 0.45-0.31 (m, 2H), 0.129 - 0.05 (m, 1H).

Example 84

5-Chloro-2-(4-cyclopropyl-7,8-difluoro-1*H*-pyrazolo[4,3-c]quinolin-5(4*H*)-ylsulfonyl)thiazole. Prepared as described in Example 13 using boronic acid (70), aldehyde (103), and 5-chlorothiazole-2-sulfonyl chloride. MS *m/z* 429 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.71 (dd, J = 11.2, 7.4 Hz, 1H), 7.58 (dd, J = 10.3, 8.8 Hz, 1H), 7.38 (s, 1H), 7.33 (s, 1H), 5.07 (d, J = 7.5 Hz, 1H), 1.09-1.02 (m, 1H), 0.56-0.32 (m, 2H), 0.21-0.08 (m, 1H).

Example 85

(*R*)-4-Cyclopropyl-5-(4-(difluoromethoxy)phenylsulfonyl)-7,8-difluoro-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 13 using boronic acid (70) and 4-(difluoromethoxy)benzenesulfonyl chloride. MS *m/z* 454.1 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.78 (dd, J = 7.9, 4.3 Hz, 1H), 7.42 (dd, J = 9.9, 8.1 Hz, 1H), 7.27 (s, 1H), 7.20 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.9 Hz, 2H), 6.45 (t, J = 72.6 Hz, 1H), 4.94 (d, J = 7.7 Hz, 1H), 1.05-0.96 (m, 1H), 0.60-0.49 (m, 1H), 0.46 - 0.35 (m, 2H), 0.15-0.06 (m, 1H).

Example 86

4-Cyclopropyl-8-fluoro-5-(5-(trifluoromethyl)pyridin-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. (Enantiomers A and B) Prepared as described in Example 12

using boronic acid (77) and sulfonamide (117). Enantiomers were then separated using the specified column type and analyzed using Method 20.

Enantiomer A Retention time = 7.6 min.

Enantiomer B Retention time = 13.7 min.

MS *m/z* 439.1 $(M+H)^+$. ^1H NMR (300 MHz, $CDCl_3$) δ 10.14 (br s, 1H), 8.53 (m, 1H), 7.86 (dd, J=9.3 Hz and 5.7 Hz, 1H), 7.81 (m, 1H), 7.46 (d, J=8.2 Hz, 1H), 7.38 (dd, J=8.5 Hz and 3.2 Hz, 1H), 7.10 (m, 1H), 5.10 (m, J=7.8 Hz, 1H), 1.06 (m, 1H), .48 (m, 3H), .16 (m, 1H).

Example 87

4-Cyclopropyl-5-(4-(difluoromethoxy)phenylsulfonyl)-8-fluoro-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 13 using 4-(difluoromethoxy)benzenesulfonyl chloride in place of compound 83. MS *m/z* 436.1 $(M+H)^+$. ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (dd, J = 8.5, 4.8 Hz, 1H), 7.29 (d, J = 8.5 Hz, 2H), 7.21-7.12 (m, 1H), 7.14 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.7 Hz, 1H), 6.65 (s, 1H), 6.44 (t, J = 7.25 Hz, 1H), 4.93 (d, J = 8.2 Hz, 1H), 1.02-0.99 (m, 1H), 0.54-0.51 (m, 1H), 0.46-0.37 (m, 2H), 0.13 - 0.11 (m, 1H).

Example 88

7-(Benzyloxy)-5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 4 using 3-benzyloxyaniline. MS *m/z* 467.8 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.47 (m, 4H), 7.35 (m, 3H), 7.19 (s, 1H), 7.01 (m, 5H), 5.62 (q, J = 6.87 Hz, 1H), 5.16 (s, 2H), 1.30 (d, J = 6.93 Hz, 3H).

Example 89

5-(4-Fluorophenylsulfonyl)-4-methyl-4,5,5a,6,7,8,9,9a-octahydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared by sulfonylation of 2-methyloctahydroquinolin-4(1H)-one followed by pyrazole formation as described in Example 1. MS *m/z* 350 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.88-7.83 (m, 2H), 7.56 (s, 1H), 7.20-7.15 (m, 2H), 5.16-5.09 (q, J = 6.8 Hz, 1H), 4.21-4.14 (m, 1H), 2.77 (m, 1H), 2.40-2.35 (m, 1H), 1.80-1.73 (m, 1H), 1.70-1.69 (m, 2H), 1.65-1.63 (d, J = 6.0 Hz, 3H), 1.55-1.52 (m, 1H), 1.44-1.27 (m, 2H), 1.08-0.99 (m, 1H).

The following compounds were prepared essentially according to the above methods and schemes described above.

Example 90

5'-(4-(Trifluoromethyl)-phenylsulfonyl)-1',5'-dihydrospiro[cyclopropane-1,4'-pyrazolo[4,3-c]quinoline]. MS *m/z* 439.1 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.75-7.73 (m, 1H), 7.61-7.45 (m, 3H), 7.36 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 7.0 (s, 1H), 2.70-2.60 (m, 1H), 1.68-1.60 (m, 1H), 1.29-1.19 (m, 1H), 0.58-0.51 (m, 1H).

Example 91

5'-(4-Chlorophenylsulfonyl)-1',5'-dihydrospiro[cyclopropane-1,4'-pyrazolo[4,3-c]quinoline]. MS *m/z* 372.1 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.72 – 7.69 (m, 1H), 7.64 – 7.61 (m, 1H), 7.52 – 7.42 (m, 2H), 7.28 – 7.25 (m, 2H), 7.08 – 7.04 (m, 2H), 7.0 (s, 1H), 2.64 – 2.56 (m, 1H), 1.64 – 1.56 (m, 1H), 1.29 – 1.19 (m, 1H), 0.56 – 0.52 (m, 1H).

Example 92

7,8-Difluoro-4-methyl-5-(thiophen-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. MS *m/z* 368 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.72 (dd, J=10.8, 7.2 Hz, 1H), 7.57 (dd, J=9.9, 8.1 Hz, 1H), 7.29 (m, 2H), 6.98 (dd, J=3.9, 1.2 Hz, 1H), 6.75 (d, J=4.8, 3.9 Hz, 1H), 5.84 (broad s, 1H), 5.69 (q, J=7.2 Hz, 1H), 1.32 (q, J=7.2 Hz, 3H).

Example 93

5-(4-Chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c][1,8]naphthyridine. Prepared as described in Example 18 using methylmagnesium bromide in place of cyclopropylmagnesium bromide. MS *m/z* 368 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.30 (dd, J = 4.9, 1.8 Hz, 1H), 8.07 (dd, J = 7.6, 1.8 Hz, 1H), 7.95 (m, 2H), 7.43 (s, 1H), 7.38 (m, 2H), 7.10 (dd, J = 7.6, 4.9 Hz, 1H).

Example 94

5-(4-Chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinolin-7-yl dimethylcarbamate. MS *m/z* 447$(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.65 (d, J=11.7 Hz, 1H), 7.64 (s, 1H), 7.22 (s, 1H), 7.18 (d, J=8.6 Hz, 1H) 7.17 (d, J=8.8 Hz, 2H), 7.06 (d, J=8.8 Hz, 2H), 5.64 (q, J=6.8 Hz, 1H), 3.17 (s, 3H), 3.07 (s, 3H), 1.32 (d, J=7.0 Hz, 3H).

Example 95

7-Chloro-4-methyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[3,4-d]thieno[2,3-b]pyridine. MS *m/z* 434.0(M+H)$^+$. ^{1}H NMR ($CDCl_3$) δ 8.58 (s, 1H), 7.62 (d, J=9.0 Hz, 2H), 7.54 (dd, J=9.0 Hz, 2H), 7.36 (s, 1H), 7.03 (s, 1H), 5.66 (q, J=6.3 Hz, 1H), 1.43 (q, 6.3 Hz, 3H).

Example 96

4-Ethyl-7,8-difluoro-5-(5-(trifluoromethyl)pyridin-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. MS *m/z* 445.0(M+H)$^+$. ^{1}H NMR ($CDCl_3$) δ 8.53 (s, 1H), 7.89 (dd, J = 10.6, 8.0 Hz, 1H), 7.74 (dd, J = 18.6, 11.3, 1H), 7.60 (d, J = 8.2 Hz, 1H), 7.46 (dd, J = 18.6, 10.0, 1H), 7.34 (s, 1H), 5.45 (dd, J = 15.3, 8.5 Hz, 1H), 1.64 (m, 1H), 1.50 (m, 1H), 1.00 (t, J=7.3 Hz, 3H).

Example 97

4-Cyclopropyl-7,8-difluoro-5-(thiophen-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. MS *m/z* 394.0 (M+H)$^+$. ^{1}H NMR ($CDCl_3$) δ 7.75 (dd, J = 11.4, 7.5 Hz, 1H), 7.57 (dd, J = 10.5, 8.7 Hz, 1H), 7.29 (m, 2H), 7.08 (broad s, 1H), 6.96 (dd, J = 3.9, 1.2 Hz, 1H), 6.73 (d, J = 5.1, 3.9 Hz, 1H), 5.01 (d, J = 8.1 Hz, 1H), 1.03 (m, 1H), 0.53 (m, 1H), 0.40 (m, 2H), 0.11 (m, 1H).

Example 98

7,8-Difluoro-5-(4-(trifluoromethyl)-phenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline. MS *m/z* 416 (M+H)$^+$. ^{1}H NMR ($CDCl_3$) δ 7.69 (dd, J=11.1, 7.2 Hz, 1H), 7.48 (dd, J=10.2, 8.4 Hz, 1H), 7.38 (d, 11.4 Hz, 4H), 7.20 (s, 1H), 4.93 (s, 2H), 2.69 (broad s, 1H).

Example 99

4-Cyclopropyl-7-(trifluoromethoxy)-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 13 using 2-bromo-4-(trifluoromethoxy)phenylboronic acid. MS *m/z* 506.1 (M+H)$^+$. ^{1}H NMR (CD_3OD) δ 8.45 (s, 1H), 7.78-7.73 (m, 3H), 7.62-7.59 (m, 1H), 7.47 (s, 1H), 7.41-7.37 (m, 1H), 5.18-5.16 (d, J = 7.6 Hz, 1H), 1.06-0.98 (m, 1H), 0.60-0.52 (m, 1H), 0.45-0.34 (m, 2H), 0.23-0.14 (m, 1H).

Example 100

(*R*)-4-cyclopropyl-7-(trifluoromethyl)-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 13 using 2-bromo-4-(trifluoromethyl)phenylboronic acid and sulfonyl chloride 83. MS *m/z* 488.9 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.53 (s, 1H), 8.17 (s, 1H), 7.84-7.81 (m, 1H) 7.68-7.65 (m, 1H), 7.50-7.28 (m, 3H), 5.08-5.05 (d, J = 7.7 Hz, 1H), 1.09-0.93 (m, 1H), 0.64-0.55 (m, 1H), 0.50-0.36 (m, 2H), 0.18-0.13 (m, 1H).

Example 101

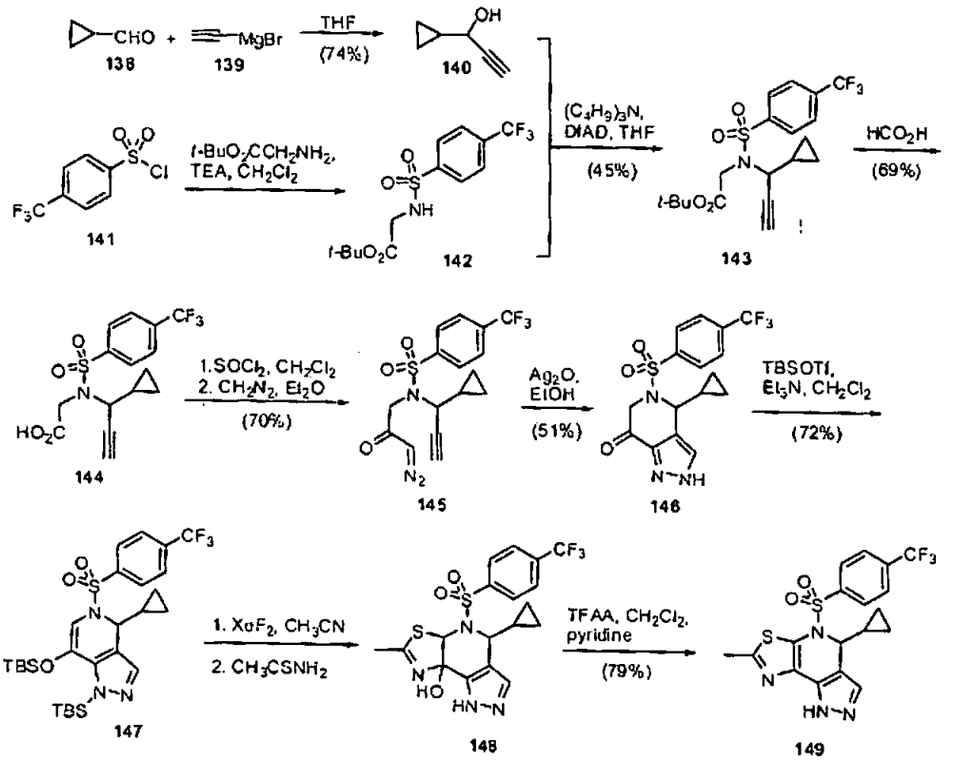
(*R*)-4-Cyclopropyl-7-(trifluoromethoxy)-5-(4-(trifluoromethoxy)phenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 13 using 2-bromo-4-(trifluoromethoxy)phenylboronic acid and 4-(trifluoromethoxy)benzenesulfonyl chloride. MS *m/z* 520.1 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.85 (s, 1H), 7.71-7.68 (m, 1H), 7.43 (s, 1H), 7.31-7.24 (m, 3H) 6.99-6.96 (m, 2H), 5.02-4.99 (d, J = 8.0 Hz, 1H), 1.09-1.00 (m, 1H), 0.66-0.57 (m, 1H), 0.55-0.40 (m, 2H), 0.23-0.16 (m, 1H).

Example 102

(*R*)-4-cyclopropyl-8-(trifluoromethyl)-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 13 using 2-bromo-5-(trifluoromethyl)phenylboronic acid. MS *m/z* 489.1 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.59 (s, 1H), 8.11-8.08 (m, 1H), 7.91 (s, 1H) 7.82-7.79 (m, 1H), 7.61-7.49 (m, 3H), 5.08-5.05 (d, J = 8.0 Hz, 1H), 1.08-1.01 (m, 1H), 0.67-0.58 (m, 1H), 0.55-0.44 (m, 2H), 0.23-0.17 (m, 1H).

Example 103

4-Cyclopropyl-7-methyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1H-pyrazolo[3,4-d]thiazolo[5,4-b]pyridine (149).



1-Cyclopropylprop-2-yn-1-ol (140). To a solution of aldehyde 138 (5.00 g, 71.3 mmol) in THF (50 mL) at 0 °C was added ethynylmagnesium bromide (139) (0.5M in THF, 178 mL, 89.2 mmol), dropwise via a pressure equalizing addition funnel. The reaction mixture was stirred for 3 h at 0 °C, and then quenched with saturated aqueous NH_4Cl (100 mL) and warmed to room temperature. The reaction mixture was filtered through a pad of Celite. The filtrate was diluted with EtOAc (100 mL) and the layers were separated. The organic layer was washed with saturated aqueous NaCl (100 mL), dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography (20% EtOAc in hexanes) to afford 6.15 g of alcohol 140 (90%). ^1H NMR (300 MHz, $CDCl_3$) δ 4.20 (bd, J = 5.6 Hz, 1H), 2.44 (d, J = 2.1 Hz, 1H), 1.90 (bs, 1H), 1.25 (m, 1H), 0.57 (m, 2H), 0.52 (m, 2H).

tert-Butyl 2-(4-(trifluoromethyl)phenylsulfonamido)acetate (142). To a solution of glycine *tert*-butyl ester (10.0 g, 76.2 mmol) in CH_2Cl_2 (150 mL) at 0 °C was added triethylamine (12.7 mL, 91.5 mmol) followed by sulfonyl chloride 141 (18.6 g, 76.2 mmol). The reaction mixture was stirred for 18 h while warming to room temperature. The reaction mixture was quenched with the addition of H_2O (100 mL), and the two layers were separated. The organic

layer was dried over $MgSO_4$, filtered and concentrated to provide 25.9 g of 142 (100%). MS (ES) *m/z:* 340.0 $(M+H)^+$.

tert-Butyl 2-(*N*-(1-cyclopropylprop-2-ynyl)-4-(trifluoromethyl)phenylsulfonamido)acetate (143). To a solution of 142 in THF (150 mL) at 0 °C was added tributylphosphine (29.1 g, 143.6 mmol) and alcohol 140 (5.06 g, 52.6 mmol). Diisopropyl azodicarboxylate (27.8 mL, 143.6 mmol) was then added in a drop wise manner. The reaction mixture was stirred at 0 °C for 2 h, and then concentrated. The resulting residue was purified by flash chromatography (10% EtOAc and 10% CH_2Cl_2 in hexanes) to afford 9.84 g of 143 (45%). MS (ES) *m/z:* 440.2 $(M+Na)^+$.

2-(*N*-(1-Cyclopropylprop-2-ynyl)-4-(trifluoromethyl)phenylsulfonamido)acetic acid (144). Compound 143 (8.34 g, 20.0 mmol) was dissolved in formic acid and allowed to stand for 24 h at room temperature. A white precipitate formed, which was isolated by filtration. The solid was washed with cold EtOAc (10 mL) to provide 5.08 g of 144 (69%). MS (ES) *m/z:* 362.0 $(M+H)^+$.

N-(1-Cyclopropylprop-2-ynyl)-*N*-(3-diazo-2-oxopropyl)-4-(trifluoromethyl)benzenesulfonamide (145). To thionyl chloride (2 mL) was added compound 144 (0.50 g, 1.38 mmol). The reaction mixture was heated to 70 °C for 2 h. The reaction mixture was cooled to room temperature and concentrated. The resulting residue was dissolved in Et_2O (5 mL) and added to a solution of freshly prepared diazomethane in Et_2O (30 mL) at 0 °C. The diazomethane was prepared in the following manner; to a solution of 40% $KOH_{(aq)}$ (15 mL) and Et_2O (30 mL) at 0 °C was added 1-methyl-3-nitro-1-nitrosoguanadine (1.01 g, 6.91 mmol). The reaction mixture was allowed to stand at 0 °C for 45 minutes. The temperature was decreased to -40 °C, and the aqueous layer was frozen. The organic layer was decanted into a fresh vial at 0 °C containing solid KOH (2.50 g). The reaction mixture was allowed to stand at 0 °C for 15 minutes. The reaction mixture was then decanted into a clean vial at 0 °C, at which time the Et_2O solution of acid chloride was added. The reaction mixture was allowed to stand for 30 minutes at 0 °C, and then quenched with acetic acid (2 mL). The reaction mixture was warmed to room temperature and diluted with EtOAc (25 mL) and H_2O (25 mL). The two layers were separated. The organic layer was washed with saturated $NaHCO_3$ (2x 30 mL) and saturated aqueous NaCl (30 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. The resulting residue was

purified by flash chromatography (20% EtOAc in hexanes) to afford 0.37 g of 145 (70%). MS (ES) *m/z:* 408.1 $(M+Na)^+$.

4-Cyclopropyl-5-(4-(trifluoromethyl)phenylsulfonyl)-5,6-dihydro-2*H*-pyrazolo[4,3-*c*]pyridin-7(4*H*)-one (146). To a solution of compound 145 (0.37 g, 0.96 mmol) in EtOH (5 mL) was added silver(I) oxide (0.02 g, 0.09 mmol). The reaction mixture was heated to 80 °C for 18 h, and then cooled to room temperature. The reaction mixture was filtered through a pad of Celite and concentrated. The resulting residue was purified by flash chromatography (40% EtOAc in hexanes) to afford 0.19 g of 146 (51%). MS (ES) *m/z:* 386.1 $(M+H)^+$.

1-(*tert*-Butyldimethylsilyl)-7-(*tert*-butyldimethylsilyloxy)-4-cyclopropyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridine (147). To a solution of compound 146 (0.33 g, 0.87 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C was added triethylamine (0.14 mL, 1.04 mmol) followed by *tert*-butyldimethysilyl trifluoromethanesulfonate (0.21 mL, 0.87 mmol). The reaction mixture was stirred at 0 °C for 1.5 h, and then quenched with H_2O (1 mL). The reaction mixture was warmed to room temperature and the layers were separated. The organic layer was dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography (10% EtOAc in hexanes) to afford 0.38 g of 147 (72%). MS (ES) *m/z:* 500.1 $(M-TBS)^+$.

4-Cyclopropyl-7-methyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5,5a,8a-tetrahydro-1*H*-pyrazolo[3,4-*d*]thiazolo[5,4-*b*]pyridin-8a-ol (148). To a solution of compound 147 (0.05 g, 0.08 mmol) in CH_3CN (1 mL) was added xenon difluoride (0.05 g, 0.28 mmol). The reaction mixture was stirred for 3 h at room temperature and then thioacetamide (0.03 g, 0.41 mmol) was added in bulk. The reaction mixture was stirred for 18 h at room temperature and then quenched with saturated aqueous $NaHCO_3$ (1 mL). The reaction mixture was diluted with EtOAc (5 mL) and the layers were separated. The organic layer was dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography (50% EtOAc in hexanes) to afford 0.03 g of 148 (80%). MS (ES) *m/z:* 459.0 $(M+H)^+$.

4-Cyclopropyl-7-methyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]thiazolo[5,4-*b*]pyridine (149). To a solution of compound 148 (0.03 g, 0.06 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added trifluoroacetic anhydride (0.04 mL, 0.32 mmol) followed by pyridine (0.05 mL, 0.65 mmol). The reaction mixture was stirred for 1 h at 0 °C, and then

quenched with saturated aqueous $NaHCO_3$ (1 mL) and diluted with CH_2Cl_2 (5 mL). The layers were separated. The organic layer was washed with H_2O (2 mL), dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography (50% EtOAc in hexanes) to afford 0.03 g of 149 (79%). ^1H NMR (300 MHz, CD_3Cl_3) δ 7.62 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.36 (s, 4H), 5.06 (d, *J* = 7.5 Hz, 1H), 2.78 (s, 3H), 1.24 (m, 2H), 0.46 (m, 3H), 0.22 (m, 1H); ^{13}C NMR (75 MHz, CD_3Cl_3) δ 163.7, 140.9, 137.6, 136.8, 135.0, 134.6, 130.4, 127.4, 126.0, 121.8, 113.4, 61.0, 21.2, 17.6, 3.47, 2.92; MS (ES) *m/z:* 441.1 $(M+H)^+$.

Example 104

5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline-7,8-diol. MS m/z: 391.9 $(M+H)^+$. ^1H NMR (CD_3CN) δ 7.28 (s, 1H), 7.18 (s, 1H), 7.13 (s 4H), 7.00 (s, 1H), 5.54 (q, *J* = 6.8Hz, 1H), 1.24 (d, *J* = 6.8 Hz, 1H)

Example 105

5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinolin-8-ol. Prepared from 8-(benzyloxy)-5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1H-pyrazolo[4,3-c]quinoline as described for compound **119** in Example 21. MS m/z: 375.9 $(M+H)^+$. ^1H NMR (CD_3OD) δ 7.55 (d, *J* = 8.7 Hz, 1H), 7.45 (s, 1H), 7.11 (m, 4H), 6.84 (dd, *J* = 8.7, 2.8 Hz, 1H), 5.60 (q, *J* = 6.9 Hz, 1H), 1.25 (d, *J* = 7.0 Hz, 3H).

Example 106

4-(8-fluoro-4-methyl-1*H*-pyrazolo[4,3-*c*]quinolin-5(4*H*)-ylsulfonyl)-3,5-dimethylisoxazole. Prepared as described in Example 29 using 3,5-dimethylisoxazole-4-sulfonyl chloride. ^1H NMR ($CDCl_3$) δ 11.09 (s, 1H) 7.79-7.74 (dd, J = 8.9, 5.1 Hz, 1H), 7.53-7.49 (dd, J = 8.5, 3.0 Hz, 1H), 7.40 (s, 1H), 7.16-7.09 (dt, J = 8.4, 3.0 Hz, 1H), 5.64-5.57 (q, J = 6.9 Hz, 1H), 2.03 (s, 3H), 1.97 (s, 3H), 1.35-1.33 (d, J = 6.9 Hz, 3H).

Example 107

8-fluoro-4-methyl-5-(1-methyl-1*H*-pyrazol-4-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 29 using 1-methyl-1H-pyrazole-4-sulfonyl chloride. ^1H NMR ($CDCl_3$) δ 7.79-7.74 (dd, J = 8.9, 5.1 Hz, 1H), 7.45-7.41 (dd, J = 8.4, 2.7 Hz, 1H), 7.36 (s, 1H), 7.15-7.07 (m, 2H), 6.98 (m, 1H), 5.70-5.63 (q, J = 6.9 Hz, 1H), 3.67 (s, 3H), 1.33-1.31 (d, J = 6.9 Hz, 3H).

Example 108

8-fluoro-4-methyl-5-(5-(pyridin-2-yl)thiophen-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 29 using 5-pyrid-2-ylthiophene-2-sulfonyl chloride. ^{1}H NMR ($CDCl_3$) δ 10.25 (s, 1H) 8.51-8.49 (d, J = 4.0 Hz, 1H), 7.83-7.79 (dd, J = 8.8, 5.1 Hz, 1H), 7.69-7.65 (m, 1H), 7.49-7.41 (m, 2H), 7.28-7.11 (m, 5H), 6.82-6.80 (d, J = 3.8 Hz, 1H), 5.73-5.68 (q, J = 6.8 Hz, 1H), 1.36-1.34 (d, J = 6.8 Hz, 3H).

Example 109

8-fluoro-4-methyl-5-(1-methyl-1*H*-imidazol-4-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. MS m/z: 348.1 $(M+H)^+$. ^{1}H NMR (DMSO-d6) δ 12.83 (s, 1H), 7.67-7.63 (dd, J = 9.0, 5.4 Hz, 1H), 7.54-7.48 (m, 2H), 7.40-7.36 (dd, J = 9.0, 3.0 Hz, 1H), 7.17-7.10 (td, J = 8.7, 3.0 Hz, 1H), 5.58-5.51 (q, J = 7.2 Hz, 1H), 1.14-1.12 (d, J = 7.2 Hz, 3H).

Example 110

(*R*)-4-ethyl-7,8-difluoro-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline. Prepared as described in Example 13 using 2-bromo-4,5-difluorophenylboronic acid, ethylmagnesium bromide, and sulfonamide **72**. MS m/z: 444.1 $(M+H)^+$. ^{1}H NMR ($CDCl_3$) δ 7.70 (dd, 1H, J=7.5, 11.1 Hz), 7.47 (t, J = 8.4 Hz, 1H), 7.40-7.34 (m, 4H), 7.19 (s, 1H), 5.25 (t, J = 8.4 Hz, 1H), 1.64-1.54(m, 1H), 1.47-1.38 (m, 1H), 0.97(t, J = 7.2Hz, 3H)

Example 111

(R)-4-cyclopropyl-8-fluoro-5-(4-(trifluoromethoxy)phenylsulfonyl)-4,5-dihydro-1H-pyrazolo[4,3-c]quinoline. Prepared as described in Example 13 using 4-(trifluoromethoxy)benzenesulfonyl chloride. MS m/z: 454.0. ^{1}H NMR ($CDCl_3$) δ 7.69 (dd, *J* = 9.5 Hz, 2.2 Hz, 1H), 7.66 (dd, *J* = 8.4, 5.9 Hz, 1H), 7.27 (s, 1H), 7.20 (d, *J* = 8.7, 2H), 7.16-7.10 (m, 1H) 6.94 (d, *J* = 8.4 Hz, 2H), 4.95 (d, *J* = 8.1 Hz, 1H), 1.07-1.0 (m, 1H), 0.58-0.42 (m, 3H), 0.15-0.12 (m, 1H).

Example 112

(R)-4-cyclopropyl-8-fluoro-5-(4-methoxyphenylsulfonyl)-4,5-dihydro-1H-pyrazolo[4,3-c]quinoline. Prepared as described in Example 13 using 4-methoxybenzenesulfonyl chloride. MS m/z: 400.1 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7.69 (dd, *J* = 4.0, 2.6 Hz, 1H), 7.60 (dd, *J* = 8.4, 5.9 Hz, 1H), 7.30 (s, 1H), 7.15-7.12 (m, 2H), 7.12-7.04 (m, 1H), 6.60-6.55 (m, 2H), 5.0 (d, *J* = 7.6 Hz, 1H), 3.71 (s, 3H), 1.20-0.92 (m, 1H), 0.60-0.35 (m, 3H), 0.19-0.14 (m, 1H).

Chiral chromatography was performed with an isocratic 10:90 ethanol:hexanes eluent at 1 mL/min on a CHIRALCEL #ODH0CE-EF074.

BIOLOGICAL EXAMPLES

Gamma-Secretase Assay

The gamma-secretase APP enzyme assay was designed to measure the specific proteolytic cleavage of an APP substrate (MBP-C125 Swe fusion protein) at the Aβ40 site. The assay used a partially purified extract of IMR-32 cell membranes as the gamma-secretase enzyme preparation and a recombinant fusion protein containing the C-terminal 125 amino acids of the Swedish variant of the APP (MBP-C125swe) as the substrate. This assay involved two steps beginning with the enzymatic reaction generating a cleavage product that was captured with an immobilized antibody specific for the neo-epitope Aβ40 site. The captured cleavage product was then detected in a sandwich ELISA assay with a biotinylated reporter antibody that is specific to Aβ (17-28). Streptavidin-linked alkaline phosphatase was then added that would generate a fluorescent signal proportional to the amount of cleavage product. This assay was used to discover small molecule inhibitors of gamma-secretase.

Materials and Methods:

Briefly, a 149 mg/ml solution of BIGCHAP detergent was made with water at 42°C and then rotated for 30 minutes at the same temperature. This warmed solution of BigCHAPS (N,N-Bis(3-D-gluconamidopropyl)cholamide) detergent was used to dissolve Brain Extract Type-V (lipid containing a minimum of 40% phosphatidylethanolamine) from Sigma (St. Louis, Mo.) to a concentration of 8 mg/ml. This solution containing BigCHAPS and lipid at 8mg/ml is then diluted to 0.53 mg/ml lipid with a pre-warmed solution of Hepes and sodium chloride. This final solution containing Hepes buffer, sodium chloride, BigCHAPS detergent

and lipid is used to create working solutions of both gamma-secretase (25 Units) and the MBP-C125 substrate (0.05 mg/ml).

Gamma-secretase was then added to a 96-well micro-titre plate and then incubated with various concentrations of inhibitor for 30 minutes at 37° C. MBPC125 substrate was then added to initiate the reaction that would run for two hours at 37° C. The reaction was quenched with the addition of SDS to a final concentration of 0.1% and then 100µl of the reaction mixture was transferred to a capture ELISA plate and incubated overnight at 4° C. Detection of the cleavage product was performed using a standard sandwich ELISA assay and quantified using a six point standard curve.

Results

The following compounds prepared essentially according to the above methods and schemes, when tested as described above exhibited inhibition in the gamma secretase assay with an IC_{50} as described in the table below, where "A" refers to an IC_{50} of 0.1 to 100 nm; "B" refers to an IC_{50} of 101 to 500 nm, "C" refers to an IC_{50} value of 501 to 1000 nm, and "D" refers to an IC_{50} value of 1000 to 10,000.

TABLE A

Name	IC_{50}
5-[(4-chlorophenyl)sulfonyl]-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline	A
5-[(4-chlorophenyl)sulfonyl]-8-fluoro-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline	A
5-[(4-chlorophenyl)sulfonyl]-7-fluoro-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline	A
5-[(4-chlorophenyl)sulfonyl]-9-fluoro-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline	A
5-[(4-chlorophenyl)sulfonyl]-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline (racemic)	A
5-[(4-chlorophenyl)sulfonyl]-7-methoxy-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline	A
5-[(4-chlorophenyl)sulfonyl]-9-methoxy-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline	D

Name	IC_{50}
5-[(4-chlorophenyl)sulfonyl]-3-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline	D
8-chloro-5-[(4-chlorophenyl)sulfonyl]-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline	C
4-methyl-5-(pyridin-2-ylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline	B
5-[(4-chlorophenyl)sulfonyl]-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinolin-3-ol	D
6-(4-chlorophenylsulfonyl)-5-ethyl-5,6-dihydropyrazolo[1,5-c]quinazoline	B
5-[(4-chlorophenyl)sulfonyl]-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline; (resolved enantiomer, with a retention time of about 9.3 min*.)	A
5-[(4-chlorophenyl)sulfonyl]-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline (resolved enantiomer, with a retention time of about 20.5 min*.)	D
5-[(4-chlorophenyl)sulfonyl]-8-fluoro-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline (racemic)	A
5-[(4-chlorophenyl)sulfonyl]-8-fluoro-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline (resolved enantiomer, with a retention time of about 9.8 min*.)	A
8-fluoro-4-methyl-5-(pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline (racemic)	B
8-fluoro-4-methyl-5-(pyridin-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline	B
4-methyl-5-(pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline	B
8-fluoro-4-methyl-5-(pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline (resolved enantiomer, with a retention time of about 15.2 min*.)	A
8-fluoro-4-methyl-5-(pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline (resolved enantiomer, with a retention time of about 17.2 min*.)	D
5-[(4-chlorophenyl)sulfonyl]-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one	B
5-[(4-chlorophenyl)sulfonyl]-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]-1,5-naphthyridine	A
8-fluoro-4-methyl-5-(pyridin-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline	A
5-(4-chlorophenylsulfonyl)-4-ethyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline	A

Name	IC_{50}
5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinolin-7-ol	A
5-(4-chlorophenylsulfonyl)-8-fluoro-1*H*-pyrazolo[4,3-c]quinolin-4(5H)-one	D
5-(4-chlorophenylsulfonyl)-4-methyl-4,5,5a,6,7,8,9,9a-octahydro-1*H*-pyrazolo[4,3-c]quinoline Racemate Enantiomer A Enantiomer B	 A B A
5-(4-chlorophenylsulfonyl)-9-fluoro-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline	A
5-(4-chlorophenylsulfonyl)-7-fluoro-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline	A
8-fluoro-5-(4-fluorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline	A
4-methyl-5-(pyridin-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline Enantiomer A (retention time of about 9.3 min*.) Enantiomer B	 B D
9-fluoro-6-(4-fluorophenylsulfonyl)-5-methyl-5,6-dihydropyrimido[5,4-c]quinolin-2-amine Enantiomer A Enantiomer B	 D B
5-(4-chlorophenylsulfonyl)-4-cyclopropyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline	A
5-(4-chlorophenylsulfonyl)-4-(trifluoromethyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline	A
5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinolin-7-ol Enantiomer A (retention time of about 13.4 min*.) Enantiomer B (retention time of about 17.0 min*.)	 A A
5-(4-chlorophenylsulfonyl)-4-isopropyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline	A

Name	IC_{50}
1,5-bis(4-chlorophenylsulfonyl)-1*H*-pyrazolo[4,3-c]quinolin-4(5H)-one	D
5-(4-chlorophenylsulfonyl)-4,5-dihydro-1*H*-imidazo[1,2-a]pyrazolo[4,3-e]pyrimidine	B
8-fluoro-5-(4-fluorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline	A
5'-(4-chlorophenylsulfonyl)-2',5'-dihydrospiro[cyclopropane-1,4'-pyrazolo[4,3-c]quinoline]	A
5-(4-chlorophenylsulfonyl)-7,8-difluoro-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline Enantiomer A Enantiomer B	 A A
7,8-difluoro-4-methyl-5-(thiophen-2-ylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline	A
5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-c][1,8]naphthyridine	A
5-(4-chlorophenylsulfonyl)-4-ethyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline	A
5-(5-chlorothiophen-2-ylsulfonyl)-7,8-difluoro-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline	A
5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinolin-7-yl dimethylcarbamate	A
4-cyclopropyl-7,8-difluoro-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline Racemate Enantiomer A (retention time of about 6.0 min*.) Enantiomer B (retention time of about 9.3 min*.)	 A A A
7-chloro-4-methyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[3,4-d]thieno[2,3-b]pyridine	A
5-(4-chlorophenylsulfonyl)-4-cyclopropyl-4,5-dihydro-1*H*-imidazo[1,2-a]pyrazolo[4,3-c]pyrimidine	B
4-ethyl-7,8-difluoro-5-(5-(trifluoromethyl)pyridin-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline	A

Name	IC_{50}
7,8-difluoro-4-methyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline	
Enantiomer A (retention time of about 7.0 min*.)	A
Enantiomer B (retention time of about 9.5 min*.)	B
5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-c][1,7]naphthyridine	A
5'-(4-(trifluoromethyl)phenylsulfonyl)-1',5'-dihydrospiro[cyclopropane-1,4'-pyrazolo[4,3-c]quinoline]	A
4-cyclopropyl-7,8-difluoro-5-(5-(trifluoromethyl)pyridin-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline	A
5-(5-chlorothiophen-2-ylsulfonyl)-4-cyclopropyl-7,8-difluoro-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline	A
4-cyclopropyl-7,8-difluoro-5-(4-fluorophenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline	A
4-cyclopropyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c][1,8]naphthyridine	A
4-cyclopropyl-5-(4-fluorophenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c][1,8]naphthyridine	A
4-cyclopropyl-5-(4-fluorophenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline	A
4-cyclopropyl-7,8-difluoro-5-(thiophen-2-ylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline	A
4-cyclopropyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-imidazo[1,2-a]pyrazolo[4,3-e]pyrimidine	C
4-cyclopropyl-7,8-difluoro-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline	A
5-(4-fluorophenylsulfonyl)-4-(trifluoromethyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c][1,8]naphthyridine	A
7,8-difluoro-4-(pyridin-3-yl)-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline	A

Name	IC_{50}
4-cyclopropyl-8-fluoro-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline	
Racemate	A
Enantiomer A (retention time of about 8.0 min*.)	A
Enantiomer B (retention time of about 12.6 min*.)	B
5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-2*H*-[1,3]dioxolo[4,5-g]pyrazolo[4,3-c]quinoline	A
5-(5-chloropyridin-2-ylsulfonyl)-4-cyclopropyl-7,8-difluoro-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline	A
5-(5-chlorothiophen-2-ylsulfonyl)-4-cyclopropyl-7,8-difluoro-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline	
Enantiomer A (retention time of about 10.3 min*.)	A
Enantiomer B (retention time of about 16.1 min*.)	A
4-cyclopropyl-7,8-difluoro-5-(4-fluorophenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline	
Enantiomer A (retention time of about 16.9 min*.)	A
Enantiomer B (retention time of about 19.7 min*.)	A
4-cyclopropyl-8-fluoro-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline	
Enantiomer A	A
Enantiomer B	A
4-cyclopropyl-7,8-difluoro-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline	
Enantiomer A (retention time of about 17.3 min*.)	A
Enantiomer B (retention time of about 13.0 min*.)	A
7,8-difluoro-4-isopropyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline	A
4-cyclopropyl-7,8-difluoro-5-(4-(trifluoromethoxy)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline	A

Name	IC_{50}
7,8-difluoro-5-(4-(trifluoromethyl) phenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline	A
5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline-7,8-diol	A
5-(5-chloropyridin-2-ylsulfonyl)-4-cyclopropyl-8-fluoro-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline	A
4-cyclopropyl-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline	A
(R)-4-cyclopropyl-7-(trifluoromethoxy)-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline	A
4-cyclopropyl-5-(4-(trifluoromethylphenyl sulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c][1,7]naphthyridine 7-oxide	A
5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinolin-8-ol	A
4-(8-fluoro-4-methyl-1*H*-pyrazolo[4,3-c]quinolin-5(4*H*)-ylsulfonyl)-3,5-dimethylisoxazole	C
8-fluoro-4-methyl-5-(1-methyl-1*H*-pyrazol-4-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline	B
8-fluoro-4-methyl-5-(5-(pyridin-2-yl)thiophen-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline	D
(R)-4-cyclopropyl-7-(trifluoromethyl)-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;	A
(*R*)-4-cyclopropyl-7-(trifluoromethoxy)-5-(4-(trifluoromethoxy)phenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline	A
(*R*)-4-(4-cyclopropyl-7,8-difluoro-1*H*-pyrazolo[4,3-c]quinolin-5(4*H*)-ylsulfonyl)aniline	A
(*R*)-4-cyclopropyl-7,8-difluoro-5-(4-nitrophenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline	A
(*R*)-4-cyclopropyl-8-(trifluoromethyl)-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*- pyrazolo[4,3-c]quinoline	A
5-chloro-2-(4-cyclopropyl-7,8-difluoro-1*H*-pyrazolo[4,3-c]quinolin-5(4*H*)-ylsulfonyl)thiazole	A

Name	IC_{50}
(*R*)-4-cyclopropyl-5-(4-(difluoromethoxy) phenylsulfonyl)-7,8-difluoro-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline	A
4-cyclopropyl-5-(4-(trifluoromethyl) phenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c][1,5]naphthyridine	A
4-cyclopropyl-8-fluoro-5-(5-(trifluoromethyl) pyridin-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline Enantiomer A (retention time of about 13.7 min*.) Enantiomer B (retention time of about 7.6 min*.)	 B A
4-cyclopropyl-5-(4-(difluoromethoxy) phenylsulfonyl)-8-fluoro-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline	A
4-cyclopropyl-7,8-difluoro-5-(5-(trifluoromethyl)pyridin-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline	A
5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline-7,8-diol Enantiomer A Enantiomer B	 A B
8-fluoro-4-methyl-5-(1-methyl-1*H*-imidazol-4-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline	D
(*R*)-4-ethyl-7,8-difluoro-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline	A
(R)-4-cyclopropyl-8-fluoro-5-(4-(trifluoromethoxy)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline	A
4-cyclopropyl-7-methyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[3,4-d]thiazolo[5,4-b]pyridine	A
(R)-4-cyclopropyl-8-fluoro-5-(4-methoxyphenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline	A

Notch signaling assay for selective inhibitors of gamma secretase.

A convergence of evidence indicates that the gamma secretase complex, comprised of the presenilin subunits, mediates the intra-membrane cleavage of Amyloid precursor protein (APP), and the Notch family of proteins (De Strooper, B., P. Saftig, K. Craessaerts, H. Vanderstichele, G. Guhde, W. Annaert, K. Von Figura and F. Van Leuven (1998).

"Deficiency of presenilin-1 inhibits the normal cleavage of amyloid precursor protein." Nature **391** (6665): 387-90; De Strooper, B., W. Annaert, P. Cupers, P. Saftig, K. Craessaerts, J. S. Mumm, E. H. Schroeter, V. Schrijvers, M. S. Wolfe, W. J. Ray et al. (1999). "A presenilin-1-dependent gamma-secretase-like protease mediates release of Notch intracellular domain." Nature **398** (6727): 518-22; Mumm, J. S., E. H. Schroeter, M. T. Saxena, A. Griesemer, X. Tian, D. J. Pan, W. J. Ray and R. Kopan (2000). "A ligand-induced extracellular cleavage regulates gamma-secretase-like proteolytic activation of Notch1." Mol Cell **5**(2): 197-206; Zhang, Z., P. Nadeau, W. Song, D. Donoviel, M. Yuan, A. Bernstein and B. A. Yankner (2000). "Presenilins are required for gamma-secretase cleavage of beta-APP and transmembrane cleavage of Notch-1." Nat Cell Biol **2**(7): 463-5). Cleavage of APP by gamma secretase leads to beta-amyloid synthesis. Cleavage of Notch1 by gamma secretase results in release of the Notch intracellular domain (NICD), which translocates to the nucleus and activates gene expression (Jarriault, S., C. Brou, F. Logeat, E. H. Schroeter, R. Kopan and A. Israel (1995). "Signalling downstream of activated mammalian Notch." Nature **377**(6547): 355-8; Kopan, R., E. H. Schroeter, H. Weintraub and J. S. Nye (1996). "Signal transduction by activated Notch: importance of proteolytic processing and its regulation by the extracellular domain." Proc Natl Acad Sci U S A **93**(4): 1683-8; Schroeter, E. H., J. A. Kisslinger and R. Kopan (1998). "Notch-1 signalling requires ligand-induced proteolytic release of intracellular domain." Nature **393**(6683): 382-6). In particular, Notch signaling activates transcription of the mammalian homolog of the *Drosophila* transcription factor *hairy-enhancer of split* (*Hes*). Transcriptional activation of *Hes1* is mediated by de-repression of CBF1/RBPJk upon binding by NICD in the nucleus. These facts have been exploited to develop a reporter gene assay for Notch Signaling Hsieh, J. J., T. Henkel, P. Salmon, E. Robey, M. G. Peterson and S. D. Hayward (1996). "Truncated mammalian Notch1 activates CBF1/RBPJk-repressed genes by a mechanism resembling that of Epstein-Barr virus EBNA2." Mol Cell Biol **16**(3): 952-9; Lu, F. M. and S. E. Lux (1996). "Constitutively active human Notch1 binds to the transcription factor CBF1 and stimulates transcription through a promoter containing a CBF1-responsive element." Proc Natl Acad Sci U S A **93**(11): 5663-7).

Gamma secretase inhibitors have been observed to block NICD formation, and inhibit Notch signaling (De Strooper, B., W. Annaert, P. Cupers, P. Saftig, K. Craessaerts, J. S. Mumm, E. H. Schroeter, V. Schrijvers, M. S. Wolfe, W. J. Ray et al. (1999). "A presenilin-1-dependent gamma-secretase-like protease mediates release of Notch intracellular domain." Nature **398**(6727): 518-22). Due to the importance of Notch signaling in cell fate

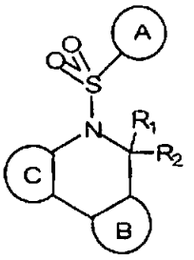
determination, and tissue differentiation during both development and in the adult, inhibition of Notch signaling by gamma secretase inhibitors is postulated to be a limiting factor in their therapeutic utility. In order to identify selective gamma secretase inhibitors, we have employed a reporter gene based Notch signaling assay using a constitutively active rat Notch1 construct (ZEDN1) provided by Dr Gerry Weinmaster, who is at the University of California at Los Angeles (UCLA) as described in Shawber, C., D. Nofziger, J. J. Hsieh, C. Lindsell, O. Bogler, D. Hayward and G. Weinmaster (1996). "Notch signaling inhibits muscle cell differentiation through a CBF1-independent pathway." Development 122(12): 3765-73 in combination with the CBF1 repressible Luciferase reporter gene 4xwtCBF1Luc (Hsieh, J. J., T. Henkel, P. Salmon, E. Robey, M. G. Peterson and S. D. Hayward (1996). "Truncated mammalian Notch1 activates CBF1/RBPJk-repressed genes by a mechanism resembling that of Epstein-Barr virus EBNA2." Mol Cell Biol 16(3): 952-9).

When 4xwtCBF1 Luciferase is co-transfected with NotchδE (ZEDN1), gamma-secretase cleavage of NotchδE releases the Notch intracellular domain (NICD), which translocates to the nucleus and de-represses CBF1mediated transcriptional repression, leading to transcription of the Luciferase reporter gene. Luciferase activity is easily assayed in cell extracts using commercially available kits. The activity of the reporter gene is directly correlated with gamma secretase cleavage of NotchδE, and as such, a reduction in Luciferase activity provides a convenient measure of inhibition of gamma secretase cleavage of NotchδE. A comparison of the IC_{50} values of compounds for inhibition of Notch signaling versus inhibition of beta-amyloid production in 293sw cells is employed to guide in the selection of compounds that have the desired property of potent inhibition of beta-amyloid synthesis with minimal inhibition of Notch Signaling.

The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the invention and that modifications may be made therein without departing from the spirit or scope of the invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

What is claimed is:

1. A compound of the formula:



stereoisomers, tautomers, mixtures of stereoisomers and/or tautomers or pharmaceutically acceptable salts thereof, wherein

the C-ring is cycloalkyl, aryl, heterocycloalkyl, or heteroaryl, each of which is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, aryloxy, aryl-(C_1-C_6alkoxy), C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, hydroxyl, hydroxy-(C_1-C_6 alkyl), -NR'R", -(C_1-C_6 alkyl)-NR'R", -NR'C(O)OR', -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, oxo, aryl-(C_1-C_6alkyl), aryl, heteroaryl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$ aryl or -S(O)$_z$ (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2 or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R";

or where two adjacent substituents form –O-$(CH_2)_{1-3}$-O-;

the A-ring is aryl, cycloalkyl, heteroaryl or heterocycloalkyl, where each ring is optionally substituted at a substitutable position with halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, hydroxyl, hydroxy-(C_1-C_6 alkyl), CN, NO_2, aryloxy, aryl-(C_1-C_6 alkoxy), -SO_2-(C_1-C_6 alkyl), -NR'R", C_1-C_6 alkanoyl, -C(O)OR', -(C_1-C_6 alkyl)-C(O)OR', heteroaryl, aryl, aryl-(C_1-C_6 alkyl), -SO_2-NR'R", -C(O)NR'R", -OC(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", or -NR'C(O)OR';

the B-ring is heteroaryl or heterocycloalkyl ring, each of which is optionally substituted at a substitutable position with a group that is independently C_1-C_6 alkyl, C_1-C_6 alkoxy,

-NR'R", -SO_2-NR'R", -C(O)NR'R", -NR'SO_2R", -NR'SO_2NR'R", -NR'SO_2-(C_1-C_6 alkyl), -NR'SO_2-phenyl, -NR'C(O)R", -NR'C(O)NR'R", -NR'C(O)OR', -(C_1-C_6 alkyl)-NR'R", -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", NO_2, CN, -C(O)OR', hydroxyl, hydroxy-(C_1-C_6 alkyl), -S(O)$_z$ aryl, -S(O)$_z$ (C_1-C_6 alkyl), halogen, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, phenyl, C_1-C_6 alkanoyl, aryl-C_1-C_6 alkanoyl, aryl-(C_1-C_6 alkyl), arylcarbonyl, heteroarylcarbonyl, or heteroaryl-C_1-C_6 alkanoyl, where the aryl or heteroaryl groups are optionally substituted with 1 to 5 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, CN or NO_2; and

where each z is independently 0, 1, or 2;

R_1 is hydrogen or C_1-C_6 alkyl;

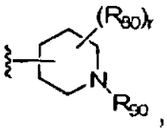
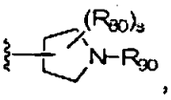
R_2 is hydrogen, C_1-C_6 alkyl, C_1-C_4 haloalkyl, hydroxyl, hydroxy-(C_1-C_4 alkyl), -NO_2, -CN, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkanoyl, -C(O)OR', -NR'R", -X(CO)Y, -$(C(R_{30})_2)_{1-4}$X(CO)Y, unsubstituted C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl substituted with one to four R_{50} groups, unsubstituted aryl, aryl substituted with one to four R_{50} groups, unsubstituted heteroaryl; or heteroaryl substituted with one to four R_{50} groups, unsubstituted heterocycloalkyl; or heterocycloalkyl substituted with one to four R_{50} groups; where

each R_{30} is independently hydrogen or C_1-C_6 alkyl;

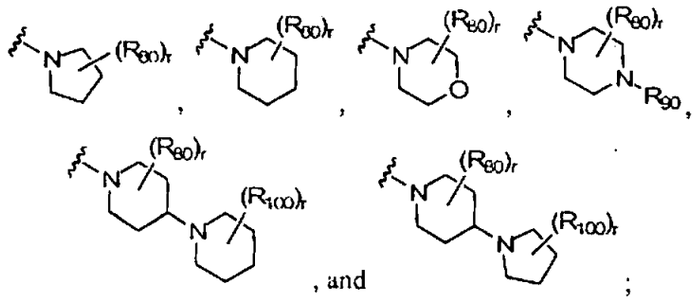
each R_{50} is independently selected from: halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -OH, -O-(C_1-C_6 alkyl), -OCF_3, -CN, -$NR_{60}R_{70}$, -C(O)O-C_1-C_6 alkyl, -$CONR_{60}R_{70}$, -(C_1-C_6 alkyl)-$NR_{60}R_{70}$, -NR_{60}COalkyl, -NR_{60}COaryl, -NR_{60}COheteroaryl, -$NR_{60}CONR_{60}R_{70}$,

X is: -O-, -NH-, or -N(alkyl)-;

Y is selected from –O-(C_1-C_6 alkyl), –O- phenyl, -$NR_{60}R_{70}$, or -$N(R_{30})(CH_2)_{2-6}NR_{60}R_{70}$;

R_{60} and R_{70} are independently selected from: hydrogen, C_1-C_6 alkyl, cycloalkyl, arylalkyl; heteroarylalkyl;  , and  , or

R_{60} and R_{70} taken together with the nitrogen atom to which they are bound form a heterocycloalkyl group selected from:



where

each R_{80} is independently unsubstituted C_1-C_6 alkyl or C_1-C_6 alkyl substituted with hydroxyl or halogen;

each R_{90} is independently H; unsubstituted C_1-C_6 alkyl; C_1-C_6 alkyl substituted with hydroxyl or halogen; unsubstituted cycloalkyl; cycloalkyl substituted with one to four R_{50} groups; aryl-(C_1-C_6alkyl); heteroarylalkyl; -C(O)O-(C_1-C_6alkyl); -C(O)O-aryl; -SO_2-(C_1-C_6alkyl); -SO_2-aryl; unsubstituted aryl; aryl substituted with one to four R_{50} groups; heteroaryl; or heteroaryl substituted with one to four R_{50} groups;

each R_{100} is independently hydrogen or C_1-C_6 alkyl;

each r is 0 to 4;

each s is 0 to 3;

or R_1 and R_2 combined are oxo or =N-OR where R is hydrogen, C_1-C_6 alkyl, aryl or arylalkyl;

or R_1 and R_2 together with the carbon to which they are attached form a C_3-C_6 cycloalkyl group wherein one of the carbons might be replaced with a heteroatom selected from N, O or S and wherein said C_3-C_6 cycloalkyl ring may be optionally substituted with C_1-C_6 alkyl; and

R' and R" are independently hydrogen, C_1-C_6 alkyl, or phenyl, where the phenyl is optionally substituted with 1 to 5 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, CN or NO_2, or

R' and R" taken together with the nitrogen atom to which they are bound form a 3 to 7 membered heterocycloalkyl group that may have an additional heteroatom selected from N, O or S and that may be optionally substituted with 1 to 3 R_{80} or R_{90} groups;

provided that 5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline, 2-phenyl-5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline, 7-methoxy-2-phenyl-5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline, 8-methoxy-5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline, 8-methoxy-2-phenyl-5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline, 3-(methylthio)-5-tosyl-

4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline, 7-methoxy-5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline, 5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline, ethyl 1-(4-sulfamoylphenyl)-5-tosyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline-3-carboxylate, 1-(4-sulfamoylphenyl)-5-tosyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline-3-carboxamide and ethyl 1-methyl-5-tosyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline-3-carboxylate, are not encompassed by formula I.

2. Compounds or salts according to claim 1, wherein

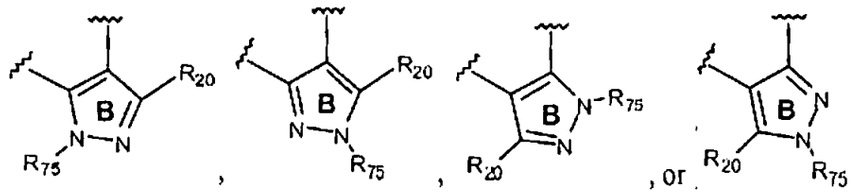
the B-ring is pyrazolyl, imidazolyl, pyrrolyl, triazolyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, pyridyl, pyrimidyl, or isoxazolyl, each of which is optionally substituted at a substitutable position with a group that is independently C_1-C_6 alkyl, C_1-C_6 alkoxy, -NR'R", -SO_2-NR'R", -C(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, NO_2, CN, -C(O)OR', hydroxyl, hydroxy-(C_1-C_6 alkyl), halogen, -S(O)z (C_1-C_6 alkyl), -S(O)z aryl, halogen, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, benzyl, or phenyl.

3. Compounds or salts according to claim 1, wherein

the C-ring is cyclohexyl, cyclopentyl, phenyl, naphthyl, thienyl, imidazolyl, pyrimidyl, pyrazinyl, furanyl, thiazolyl, or pyridyl, each of which is optionally substituted at each substitutable position with groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, aryloxy, aryl-(C_1-C_4alkoxy), C_1-C_6 haloalkyl, (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), -NR'R", -(C_1-C_4 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R", -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, oxo, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -S(O)z (C_1-C_6 alkyl), or -S(O)z aryl, where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2 or 3 groups that are independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R"; or

where two adjacent substituents of the C-ring C –O-$(CH_2)_{1,3}$-O-.

4. Compounds or salts according to claim 3, wherein the B-ring has the formula:

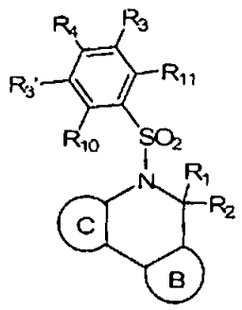


wherein

R_{20} is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, -NR'R", -(C_1-C_4 alkyl)-NR'R", -S(O)$_Z$ (C_1-C_6 alkyl), hydroxyl, halogen, CN, NO_2, CH_2F, CHF_2, CF_3, -C(O)OR', -C(O)NR'R", -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", or phenyl, and

R_{75} is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkanoyl, phenyl-(C_1-C_6 alkanoyl)-, -C(O)NR'R", -S(O)$_Z$ (C_1-C_6 alkyl), -S(O)$_Z$ -aryl, -SO_2NR'R", phenyl, phenyl-(C_1-C_6alkyl) (preferably phenethyl or benzyl, more preferably, benzyl), phenylcarbonyl, benzylcarbonyl, or heteroarylcarbonyl, where the heteroaryl group is pyridyl, pyrimidyl, thienyl or furanyl.

5. Compounds or salts according to claim 4, having the following formula:

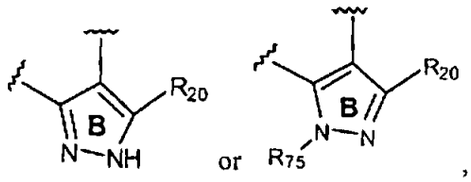


wherein

R_3, $R_{3'}$, R_4, R_{10} or R_{11} are independently hydrogen, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, hydroxyl, hydroxy-(C_1-C_4 alkyl), CN, NO_2, aryloxy (such as phenyloxy), aryl-(C_1-C_4alkoxy) such as benzyloxy, -SO_2-(C_1-C_6 alkyl), -NR'R", C_1-C_6 alkanoyl, -C(O)OR', -(C_1-C_4 alkyl)-C(O)OR', pyridyl, phenyl, phenyl-(C_1-C_4 alkyl)-, -SO_2-NR'R", -C(O)NR'R", -OC(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", or -NR'C(O)O-R', where each R' and R" is independently hydrogen, C_1-C_6 alkyl, or phenyl, where the phenyl is optionally substituted with 1 to 5 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, CN or NO_2; or

R_4 and $R_{3'}$, or R_{10} and $R_{3'}$ and the carbons to which they are attached form a benzo ring.

6. Compounds or salts according to claim 5, wherein the B-ring has the formula:



wherein R_{20} and R_{75} are both hydrogen.

7. Compounds or salts according to claim 6, wherein the C-ring is phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryloxy, aryl-(C_1-C_4 alkoxy), C_1-C_4 haloalkyl (in another aspect, CF_3), C_1-C_4 haloalkoxy (in another aspect, OCF_3), hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", -(C_1-C_4 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, oxo, benzyl, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -S(O)z phenyl, or -S(O)z (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1, 2 or 3 groups that are independently halogen, hydroxy, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl (such as CF_3), C_1-C_6 haloalkoxy (such as OCF_3), hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R" or
where two adjacent substituents from the C-ring form $-O-(CH_2)_{1-3}-O-$.

8. Compounds or salts according to claim 7, wherein R_4 is Cl, F, CH_2F, CHF_2, CF_3, OCH_2F, $OCHF_2$, or OCF_3; R_3, $R_{3'}$, R_{10} and R_{11} are independently Cl, F, methyl or hydrogen; R_2 is independently hydrogen, methyl, ethyl, propyl, isopropyl, or cyclopropyl; and R_1 is H or methyl.

9. Compounds or salts according to claim 8, wherein the C-ring is phenyl substituted with 1 or 2 groups that are Cl, F, methyl, ethyl, isopropyl, methoxy, CF_3, OCF_3, OH, $-OC(O)N(CH_3)_2$ or with two adjacent substituents forming $-O-(CH_2)_{1-3}-O-$, where the C-ring is substituted at least at the 8-position.

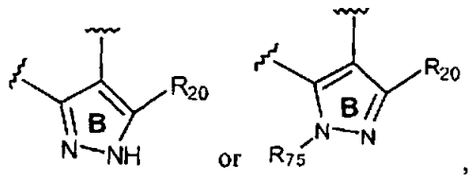
10. Compounds or salts according to claim 6, wherein

R_4 is halogen or C_1-C_4 alkyl; R_1 is H; R_2 is H, C_1-C_4 alkyl, or C_3-C_6 cycloalkyl; and the C-ring is phenyl substituted with one or two halogens.

11. Compounds or salts according to claim 6, wherein
R_4 is F, Cl, or CF_3; R_2 is H, methyl, ethyl, isopropyl, or cyclopropyl; and the C-ring is phenyl substituted with one or two halogens.

12. Compounds or salts according to claim 4, wherein
the A-ring is heteroaryl, which is pyridyl, pyrimidyl, quinolinyl, isoquinolinyl, thienyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, or oxazolyl, each of which is optionally substituted at a substitutable position with halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, hydroxyl, hydroxy-(C_1-C_4 alkyl), CN, NO_2, aryloxy, aryl-(C_1-C_4 alkoxy) (such as benzyloxy),-SO_2-(C_1-C_6 alkyl), -NR'R", C_1-C_6 alkanoyl, -C(O)OR', -(C_1-C_4 alkyl)-C(O)OR', heteroaryl, aryl, aryl-(C_1-C_4 alkyl), -SO_2-NR'R", -C(O)NR'R", -OC(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", -NR'C(O)O-(C_1-C_6 alkyl) or -NR'C(O)O-phenyl, where each R' and R" is independently hydrogen or C_1-C_6 alkyl.

13. Compounds or salts according to claim 12, wherein the B-ring has the formula:



wherein R_{20} and R_{75} are both hydrogen.

14. Compounds or salts according to claim 13, wherein C-ring is phenyl, which is optionally substituted with 1, 2, 3, or 4 groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, aryloxy, aryl-(C_1-C_4 alkoxy), C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, hydroxyl, hydroxy-(C_1-C_4 alkyl), -NR'R", -(C_1-C_4 alkyl)-NR'R", -NR'C(O)O-(C_1-C_6 alkyl), -NR'C(O)O-phenyl, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(C_1-C_6 alkyl)-C(O)OR', -(C_1-C_6 alkyl)-C(O)NR'R", -NR'C(O)R", NO_2, CN, phenyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -NR'SO_2R", -SO_2-NR'R", -S(O)z phenyl, or -S(O)z (C_1-C_6 alkyl), where the alkyl, alkenyl and alkynyl portions of the above are unsubstituted or substituted with 1 or 2 groups that are

independently halogen, hydroxyl, -NR'R" or C_1-C_6 alkoxy, and where the aryl or heteroaryl portions of the above are optionally substituted with 1, 2, 3, or 4 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, hydroxyl, hydroxy-(C_1-C_6 alkyl), or -NR'R".

15. Compounds or salts according to claim 14, wherein R_2 is independently hydrogen, methyl, ethyl, propyl, isopropyl, or cyclopropyl; and R_1 is H or methyl.

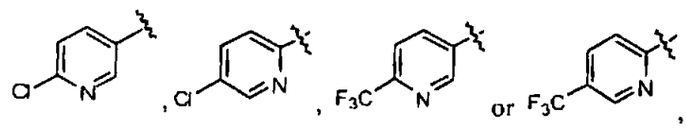
16. Compounds or salts according to claim 15, wherein the C-ring is phenyl substituted with 1 or 2 groups that are Cl, F, methyl, ethyl, isopropyl, methoxy, CF_3, OCF_3, OH, or $-OC(O)N(CH_3)_2$, where the C-ring is substituted at least at the 8-position.

17. Compounds or salts according to claim 13, wherein
R_4 is halogen or C_1-C_4 alkyl; R_1 is H; R_2 is H, C_1-C_4 alkyl, or C_3-C_6 cycloalkyl; and the C-ring is phenyl substituted with one or two halogens.

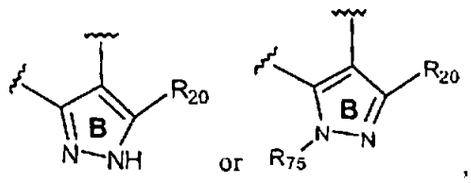
18. Compounds or salts according to claim 13, wherein
R_4 is F, Cl, or CF_3; R_2 is H, methyl, ethyl, isopropyl, or cyclopropyl; and the C-ring is phenyl substituted with one or two halogens.

19. Compounds or salts according to claim 13, wherein
the A-ring is heteroaryl, which is pyridyl, or thienyl, each of which is optionally substituted with 1 or 2 groups that are independently halo, methyl, methoxy, CF_3, or OCF_3.

20. Compounds or salts according to claim 12, wherein
the A-ring is a heteroaryl group, which has the following structures:



R_1 is hydrogen or methyl; R_2 is H, C_1-C_4 alkyl, or C_3-C_6 cycloalkyl; the C-ring is phenyl substituted with 1 or 2 groups that are independently Cl, F, methyl, ethyl, isopropyl, methoxy, ethoxy, CF_3, OCF_3, OH, CH_2OH, NH_2, $NH(CH_3)$, or $N(CH_3)_2$; and the B-ring has the formula:



where R_{20} and R_{75} are both hydrogen.

21. Compounds, stereoisomers, tautomers, mixtures of stereoisomers and/or tautomers or pharmaceutically acceptable salts thereof, of claim 1 that are

5-[(4-chlorophenyl)sulfonyl]-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline;

5-[(4-chlorophenyl)sulfonyl]-8-fluoro-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline;

5-[(4-chlorophenyl)sulfonyl]-7-fluoro-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline;

5-[(4-chlorophenyl)sulfonyl]-9-fluoro-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline;

5-[(4-chlorophenyl)sulfonyl]-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline (racemic);

5-[(4-chlorophenyl)sulfonyl]-7-methoxy-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline;

5-[(4-chlorophenyl)sulfonyl]-9-methoxy-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline ;

5-[(4-chlorophenyl)sulfonyl]-3-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline;

8-chloro-5-[(4-chlorophenyl)sulfonyl]-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline;

4-methyl-5-(pyridin-2-ylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline;

5-[(4-chlorophenyl)sulfonyl]-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinolin-3-ol;

5-[(4-chlorophenyl)sulfonyl]-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline; (resolved enantiomer, with a retention time of about 9.3 min.*

5-[(4-chlorophenyl)sulfonyl]-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline (resolved enantiomer, with a retention time of about 20.5 min.*);

5-[(4-chlorophenyl)sulfonyl]-8-fluoro-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline (racemic);

5-[(4-chlorophenyl)sulfonyl]-8-fluoro-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinoline resolved enantiomer, with a retention time of about 9.8 min.*);

8-fluoro-4-methyl-5-(pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline (racemic);

8-fluoro-4-methyl-5-(pyridin-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline;

4-(4-cyclopropyl-1*H*-pyrazolo[4,3-c]quinolin-5(4*H*)-ylsulfonyl)benzonitrile;

4-methyl-5-(pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline;

8-fluoro-4-methyl-5-(pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline (resolved enantiomer, with a retention time of about 15.2 min.*);

8-fluoro-4-methyl-5-(pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline (resolved enantiomer, with a retention time of about 17.2 min.*);

5-[(4-chlorophenyl)sulfonyl]-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-one;

5-[(4-chlorophenyl)sulfonyl]-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]-1,5-naphthyridine;

8-fluoro-4-methyl-5-(pyridin-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

5-(4-chlorophenylsulfonyl)-4-ethyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinolin-7-ol;

5-(4-chlorophenylsulfonyl)-8-fluoro-1*H*-pyrazolo[4,3-c]quinolin-4(5*H*)-one;

5-(4-chlorophenylsulfonyl)-4-methyl-4,5,5a,6,7,8,9,9a-octahydro-1*H*-pyrazolo[4,3-c]quinoline;

5-(4-chlorophenylsulfonyl)-9-fluoro-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

5-(4-chlorophenylsulfonyl)-7-fluoro-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

8-fluoro-5-(4-fluorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

4-methyl-5-(pyridin-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

5-(4-chlorophenylsulfonyl)-4-cyclopropyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

5-(4-chlorophenylsulfonyl)-4-(trifluoromethyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinolin-7-ol;

5-(4-chlorophenylsulfonyl)-4-isopropyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

1,5-bis(4-chlorophenylsulfonyl)-1*H*-pyrazolo[4,3-c]quinolin-4(5*H*)-one;

8-fluoro-5-(4-fluorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

5'-(4-chlorophenylsulfonyl)-2',5'-dihydrospiro[cyclopropane-1,4'-pyrazolo[4,3-c]quinoline];

5-(4-chlorophenylsulfonyl)-7,8-difluoro-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

7,8-difluoro-4-methyl-5-(thiophen-2-ylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-c][1,8]naphthyridine;

5-(4-chlorophenylsulfonyl)-4-ethyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

5-(5-chlorothiophen-2-ylsulfonyl)-7,8-difluoro-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinolin-7-yl dimethylcarbamate;

4-cyclopropyl-7,8-difluoro-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

7-chloro-4-methyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[3,4-d]thieno[2,3-b]pyridine;

4-ethyl-7,8-difluoro-5-(5-(trifluoromethyl)pyridin-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

7,8-difluoro-4-methyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-c][1,7]naphthyridine;

5'-(4-(trifluoromethyl)phenylsulfonyl)-1',5'-dihydrospiro[cyclopropane-1,4'-pyrazolo[4,3-c]quinoline];

5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-imidazo[1,2-a]pyrazolo[4,3-e]pyrimidine;

4-cyclopropyl-7,8-difluoro-5-(5-(trifluoromethyl)pyridin-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

5-(5-chlorothiophen-2-ylsulfonyl)-4-cyclopropyl-7,8-difluoro-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-7,8-difluoro-5-(4-fluorophenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c][1,8]naphthyridine;

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4-cyclopropyl-5-(4-fluorophenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c][1,8]naphthyridine;

4-cyclopropyl-5-(4-fluorophenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-7,8-difluoro-1-(methoxymethyl)-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-7,8-difluoro-5-(thiophen-2-ylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-imidazo[1,2-a]pyrazolo[4,3-e]pyrimidine;

4-cyclopropyl-7,8-difluoro-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

5-(4-fluorophenylsulfonyl)-4-(trifluoromethyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c][1,8]naphthyridine;

7,8-difluoro-4-(pyridin-3-yl)-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-8-fluoro-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-2*H*-[1,3]dioxolo[4,5-g]pyrazolo[4,3-c]quinoline;

5-(5-chloropyridin-2-ylsulfonyl)-4-cyclopropyl-7,8-difluoro-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

5-(5-chlorothiophen-2-ylsulfonyl)-4-cyclopropyl-7,8-difluoro-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-7,8-difluoro-5-(4-fluorophenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-8-fluoro-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-7,8-difluoro-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

7,8-difluoro-4-isopropyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-7,8-difluoro-5-(4-(trifluoromethoxy)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

7,8-difluoro-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline-7,8-diol;

5-(5-chloropyridin-2-ylsulfonyl)-4-cyclopropyl-8-fluoro-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-7-(trifluoromethoxy)-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c][1,7]naphthyridine 7-oxide;

5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinolin-8-ol;

4-(8-fluoro-4-methyl-1*H*-pyrazolo[4,3-c]quinolin-5(4*H*)-ylsulfonyl)-3,5-dimethylisoxazole;

8-fluoro-4-methyl-5-(1-methyl-1*H*-pyrazol-4-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

8-fluoro-4-methyl-5-(5-(pyridin-2-yl)thiophen-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-7-(trifluoromethyl)-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-7-(trifluoromethoxy)-5-(4-(trifluoromethoxy)phenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline;

4-(4-cyclopropyl-7,8-difluoro-1*H*-pyrazolo[4,3-c]quinolin-5(4*H*)-ylsulfonyl)aniline;

4-cyclopropyl-7,8-difluoro-5-(4-nitrophenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-8-(trifluoromethyl)-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-1*H*- pyrazolo[4,3-c]quinoline;

5-chloro-2-(4-cyclopropyl-7,8-difluoro-1H-pyrazolo[4,3-c]quinolin-5(4H)-ylsulfonyl)thiazole;

4-cyclopropyl-5-(4-(difluoromethoxy)phenylsulfonyl)-7,8-difluoro-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-2*H*-pyrazolo[4,3-c][1,5]naphthyridine;

4-cyclopropyl-8-fluoro-5-(5-(trifluoromethyl)pyridin-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-8-fluoro-5-(5-(trifluoromethyl)pyridin-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-5-(4-(difluoromethoxy)phenylsulfonyl)-8-fluoro-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-7,8-difluoro-5-(5-(trifluoromethyl)pyridin-2-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

5-(4-chlorophenylsulfonyl)-4-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline-7,8-diol;

8-fluoro-4-methyl-5-(1-methyl-1H-imidazol-4-ylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

(*R*)-4-ethyl-7,8-difluoro-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline;

(R)-4-cyclopropyl-8-fluoro-5-(4-(trifluoromethoxy)phenylsulfonyl)-4,5-dihydro-1H-pyrazolo[4,3-c]quinoline;

4-cyclopropyl-7-methyl-5-(4-(trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1H-pyrazolo[3,4-d]thiazolo[5,4-b]pyridine; or

(R)-4-cyclopropyl-8-fluoro-5-(4-methoxyphenylsulfonyl)-4,5-dihydro-1H-pyrazolo[4,3-c]quinoline.

22. A pharmaceutical composition comprising a compound of claim 1, a pharmaceutically acceptable salt of claim 1, or a combination of a compound and a pharmaceutically acceptable salt of claim 1, further comprising at least one solvent, excipient, adjuvant, or a mixture thereof.

23. A method of treating an A beta-related disease comprising administering a therapeutically effective amount of a compound or salt of claim 1 to a patient in need of such treatment.

24. A method of treating Alzheimer's disease, mild cognitive impairment, dementia, or Down's syndrome, comprising administering a therapeutically effective amount of a compound or salt of claim 1 to a patient in need of such treatment.

25. A method of treating Alzheimer's disease, mild cognitive impairment, dementia, or Down's syndrome, comprising administering a therapeutically effective amount of a compound or salt of claim 1, where claim 1 further comprises 5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline, 2-phenyl-5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline, 7-methoxy-2-phenyl-5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline, 8-methoxy-5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline, 8-methoxy-2-phenyl-5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline, 3-(methylthio)-5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline, 7-methoxy-5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline, 5-tosyl-4,5-dihydro-2*H*-pyrazolo[4,3-c]quinoline, ethyl 1-(4-sulfamoylphenyl)-5-tosyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline-3-carboxylate, 1-(4-sulfamoylphenyl)-5-tosyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline-3-carboxamide ethyl 1-methyl-5-tosyl-4,5-dihydro-1*H*-pyrazolo[4,3-c]quinoline-3-carboxylate, and pharmaceutically acceptable salts thereof, or a combination of a compound and a pharmaceutically acceptable salt, to a patient in need of such treatment

Inhibidores de Sulfonamida Triciclica Fusionada de Gama-secretasa

Esta solicitud reivindica la prioridad de la Solicitud Provisional Estadounidense No. 60/810.431, presentada el 2 de junio de 2006; Solicitud Provisional Estadounidense No. 60/876.932, presentada el 22 de diciembre de 2006; y la Solicitud Provisional Estadounidense No. 60/922.771, presentada el 10 de abril de 2007. Cada referencia se incorpora como referencia en su totalidad.

Antecedentes de la invención

Campo de la invención

La invención se relaciona con compuestos sulfonamina triciclica fusionada, que inhiben la liberación de péptido ß-amiloide, gama-secretasa, y/o su síntesis. Por lo tanto, los compuestos Sulfonamida triciclica fusionada son útiles en la prevención de trastornos cognitivos, tal como enfermedad de Alzheimer, en pacientes suceptibles a trastornos cognitivos y/o en el tratamiento de pacientes con trastornos cognitivos con en fin de inhibir el deterioro progresivo de su afección. Los compuestos de la invención son útiles también para iniciar o incrementar la angiogenia.

Estado de la técnica

La enfermedad de Alzheimer (AD) es un trastorno cerebral degenerativo caracterizado clínicamente por una pérdida progresiva de la memoria, cognición, razonamiento, juicio y estabilidad emocional que conduce en forma gradual a un deterioro mental profundo y en última instancia a la muerte.

El AD es una causa muy común de falla mental progresiva (demencia) en personas de edad y se cree que representa la cuarta causa médica más común de muerte en Estados Unidos. Se ha observado AD en razas y grupos étnicos a nivel mundial y plantea un problema de gran importancia en materia de salud pública tanto presente como futuro. Se estima actualmente que la enfermedad afecta a alrededor de dos a tres millones de personas en Estados Unidos solamente. En el momento, el AD es incurable. No se conoce en la actualidad ningún tratamiento que prevenga en forma efectiva el AD o que revierta sus síntomas y curso.

Los cerebros de los individuos con AD exhiben lesiones características calificadas como placas seniles (o amiloides), angiopatía amiloide (depósitos amiloide en vasos sanguíneos) y ovillos neurofibrilares. Grandes cantidades de estas lesiones, en particular placas amiloide y ovillos neurofibrilares, se encuentran generalmente en varias áreas del cerebro humano importantes para la memoria y la función cognitiva en los pacientes con AD. Cantidades menores de estas lesiones en una distribución anatómica más restrictiva se encuentran también en los cerebros de la mayoría de los humanos de mayor edad quienes no tienen un diagnóstico de AD a nivel clínico. Las placas amiloide y angiopatía amiloide caracterizan también los cerebros de individuos con Trisomía 21 (síndrome de Down) y Hemorragia Cerebral Hereditaria con Amiloidosis de Tipo Holandés (HCHWA-D). En el momento, un diagnóstic definitivo de AD normalmente requiere la observación de las lesiones

mencionadas anteriormente en el tejido cerebral de pacientes que han muerto a causa con la enfermedad o, más raramente, en pequeñas muestras biopsadas del tejido cerebral tomadas durante un procedimiento neuroquirúrgico invasivo.

El principal componente químico de las placas amiloide y depósitos amiloides vasculares (angiopatía amiloide) característicos de AD y los otros trastornos mencionados anteriormente es una proteína de aproximadamente 4,2 kilodaltones (kD) de alrededor de 39-43 aminoácidos designados como péptido ß-amiloide (ßAP) o algunas veces Aß, AßP o ß/A4. El péptido ß-amiloide se purifica primero y se proporciona una secuencia parcial de aminoácidos en Glenner et al., Biochem. Biophys. Res. Commun., 120:885-890 (1984). El procedimiento de aislamiento y los datos de la secuencia para los primeros 28 aminoácidos se describen en la Patente Estadounidense No. 4.666.829.

Los análisis químicos de proteínas y biológicos moleculares han mostrado que el péptido ß-amiloide es un pequeño fragmento de una proteína precursora más grande calificada como proteína precursora de amiloide (APP), que normalmente se produce a nivel de las células en varios tejidos de varios animales, incluyendo humanos. El conocimiento de la estructura del gen que codifica APP ha demostrado que el péptido ß-amiloide surge como un fragmento de péptido que se divide de APP mediante enzima(s) proteasa(s). El procesamiento secuencial de la proteína precursora mediante las enzimas a las que se hace referencia generalmente como secretasas beta y gama, da origen

al fragmento de péptido ß-amiloide. Ambas enzimas se han clonado ahora a nivel molecular y se caracterizaron a niveles muy diferentes.

Varias líneas de prueba indican que la deposición cerebral progresiva de péptido ß-amiloide desempeña un papel seminal en la patogénesis de AD y puede anteceder síntomas cognitivos en años o décadas. Ver, por ejemplo, Selkoe, Neuron, 6:487-498 (1991). La línea de prueba más importante es el descubrimiento de que pueden encontrarse mutaciones de ADN sin sentido en el aminoácido 717 del isoformo de 770 aminoácidos de APP en miembros afectados pero no en miembros no afectados de varias familias con una forma genéticamente determinada (familiar) de AD (Goate y col., Nature, 349:704-706 (1990); Chartier Harlan y col., Nature, 353:844-846 (1989); y Murrell y col., Science, 254:97-99 (1991.). Otra de tales mutaciones, conocida como la variante sueca, que comprende una doble mutación que cambia lisina^{595}-metionina^{596} por asparagina^{595}-leucina^{596} (con referencia a la isoforma 695 se encontró en una familia sueca) se reporta en 1992 (Mullan y col., Nature Genet., 1:345-347 (1992). Análisis de enlace genético han demostrado que estas mutaciones, así como otras mutaciones en el gen APP, son la causa molecular específica de AD en los miembros afectados de tales familias. Además, se ha identificado una mutación en el aminoácido 693 de la isoforma de 770 aminoácidos de APP como la causa de la enfermedad de deposición de péptido ß-amiloide, HCHWA-D, y un cambio de alanina a glicina en el aminoácido 692 parece causar un fenotipo que se asemeja a AD en algunos

pacientes y HCHWA-D en otros. El descubrimiento de éstas y otras mutaciones en APP en casos de AD con base genética demuestran que la alteración del metabolismo de APP y la deposición posterior de su fragmento de péptido ß-amiloide pueden causar AD.

A pesar del progreso que se ha hecho en la comprensión de los mecanismos subyacentes de AD y otras enfermedades relacionadas con el péptido ß-amiloide, aún subsiste la necesidad de desarrollar métodos y composiciones para el tratamiento de la(s) enfermedad(es). En forma ideal, los métodos de tratamiento deberían basarse ventajosamente en fármacos, capaces de inhibir la liberación del péptido ß-amiloide y/o su síntesis *in vivo*.

Un enfoque hacia la inhibición de la síntesis *in vivo* del péptido amiloide se realiza mediante la inhibición de gama-secretasa, la enzima responsable de la división del terminal carboxi resulta en la producción de fragmentos de péptido ß-amiloide de 40 ó 42 residuos de largo. Los sustratos inmediatos para gama-secretasa son fragmentos β-divididos, así como también fragmentos del terminal carboxi (CTF) α-divididos de APP. El sitio de división de gama-secretasa en fragmentos α- y β-CTF se produce en el dominio transmembrana predicho de APP. Se ha demostrado que los inhibidores de gama-secretasa afectan la patología amiloide en modelos de ratones transgénicos (Dovey, H. F., V. John, J. P. Anderson, L. Z. Chen, P. de Saint Andrieu, L. Y. Fang, S. B. Freedman, B. Folmer, E. Goldbach, E. J. Holsztynska y col. (2001).

"Functional gamma-secretase inhibitors reduce beta-amyloid peptide levels in brain". J Neurochem 76(1): 173-81.)

Se reconoce que la gama-secretasa es un complejo de subunidades múltiples compuesto por presenilinas (PS1 o PS2), Nicastrina, Af-1, y Pen 2 (De Strooper, B. (2003). "Aph-1, Pen-2, and Nicastrin with Presenilin generate an active gamma-secretase complex". Neuron 38(1): 9-12; Edbauer, D., E. Winkler, J. T. Regula, B. Pesold, H. Steiner y C. Haass (2003). "Reconstitution of gama-secretasa activity." Nat Cell Biol 5(5): 486-8; Kimberly, W. T., M. J. LaVoie, B. L. Ostaszewski, W. Ye, M. S. Wolfe y D. J. Selkoe (2003). "Gamma-secretase is a membrana protein complex comprised of presenilin, nicastrin, Aph-1, and Pen-2". Proc Natl Acad Sci U S A 100(11): 6382-7). Mayor evidencia indica que PS comprende el grupo funcional catalítico del complejo, mientras que las otras subunidades identificadas son necesarias para la debida saturación y ubicación subcelular del complejo enzimático activo (reseñado en De Strooper, B. (2003). "Aph-1, Pen-2, and Nicastrin with Presenilin generate an active gamma-secretase complex". Neuron 38(1): 9-12.). Consistente con esta hipótesis, ratones con genes inactivados PS exhiben reducciones significativas en la producción de β-amiloide (De Strooper, B., P. Saftig, K. Craessaerts, H. Vanderstichele, G. Guhde, W. Annaert, K. Von Figura y F. Van Leuven (1998). "Deficiency of presenilin-1 inhibits the normal cleavage of amyloid precursor protein". Nature 391(6665): 387-90; Haass, C. y D. J. Selkoe (1998). "Alzheimer's disease. A technical KO

of amiloyd-beta peptide." Nature 391(6665): 339-40; Herreman, A., L. Serneels, W. Annaert, D. Collen, L. Schoonjans y B. De Strooper (2000). "Total inactivation of gama-secretasa activity in presenilin-deficient embryonic stem cells." Nat Cell Biol 2(7): 461-2); mutaciones puntuales de residuos de aspartato en sitios activos putativos en dominios de transmembrana PS inhiben la producción β-amiloide en células de una forma dominante negativa (Wolfe, M. S., W. Xia, B. L. Ostaszewski, T. S. Diehl, W. T. Kimberly y D. J. Selkoe (1999). "Two transmembrane aspartates in presenilin-1 required for presenilin endoproteolysis and gamma-secretase activity". Nature 398(6727): 513-7; Kimberly, W. T., W. Xia, T. Rahmati, M. S. Wolfe y D. J. Selkoe (2000). "The transmembrane aspartates in presenilin 1 and 2 are obligatory for gamma-secretase activity and amyloid beta-protein generation". J Biol Chem 275(5): 3173-8); isosteros de estado de transición con base al sustrato dirigido del sitio activo diseñado para inhibir gama-secretasa se conjuga directamente en PS (Esler, W. P., W. T. Kimberly, B. L. Ostaszewski, T. S. Diehl, C. L. Moore, J. Y. Tsai, T. Rahmati, W. Xia, D. J. Selkoe y M. S. Wolfe (2000). "Transition-state analogue inhibitors of gamma-secretase bind directly to presenilin-1". Nat Cell Biol 2(7): 428-34; Li, Y. M., M. Xu, M. T. Lai, Q. Huang, J. L. Castro, J. DiMuzio-Mower, T. Harrison, C. Lellis, A. Nadin, J. G. Neduvelil y col. (2000). "Photoactivated gamma-secretase inhibibators directed to the active site covalently label presenilin 1". Nature 405(6787): 689-94); finalmente, se ha

demostrado que inhibidores alostéricos de gama-secretasa se unen directamente a PS (Seiffert, D., J. D. Bradley, C. M. Rominger, D. H. Rominger, F. Yang, J. E. Meredith, Jr., Q. Wang, A. H. Roach, L. A. Thompson, S. M. Spitz y col. (2000). "Presenilin-1 and -2 are molecular targets for gamma-secretase inhibitors". J Biol Chem 275(44): 34086-91.)

La evidencia actual indica que además del tratamiento de APP que conduce a la síntesis de β-amiloide, la gama-secretasa también emedia la división intra-membrana de otras proteínas de transmembrana tipo I (reseñado en Fortini, M. E. (2002). "Gama-secretasa-mediated proteolysis in cell-surface-receptor signaling." Nat Rev Mol Cell Biol 3(9): 673-84, ver también Struhl, G. y A. Adachi (2000). "Requirements for presenilin-dependent cleavage of notch and other transmembrane proteins." Mol Cell 6(3): 625-36.). Entre otros sustratos conocidos dignos de mención de gama-secretasa se encuentra el Notch 1 de mamífero. La proteína Notch 1 es importante para la determinación del destino celular durante desarrollo y homeostasis de tejido en el adulto. Tras el entrecruzamiento del ligando vía el dominio ecto Notch, el Notch experimenta procesamiento de membrana extra e intracelular secuencial análogo al de APP. El procesamiento intramembrana de Notch mediado por gama-secretasa conduce a la liberación del dominio intracelular de Notch (NICD). El fragmento de NICD media la señalización de Notch vía la translocación al núcleo, donde regula la expresión de genes que median la diferenciación

celular en muchos tejidos durante desarrollo, así como también en el adulto.

La interrupción de la señalización de Notch vía los resultados genéticos de genes inactivados (KO) resulta en fenotipo letal embrico en los ratones (Swiatek, P. J., C. E. Lindsell, F. F. del Amo, G. Weinmaster y T. Gridley (1994). "Notch1 is essential for postimplantation development in mice". Genes Dev 8(6): 707-19; Conlon, R. A., A. G. Reaume y J. Rossant (1995). " Notch1 is required for the coordinate segmentation of somites". Development 121(5): 1533-45.) El fenotipo KO Notch es muy similar al fenotipo observado en ratones KO con PS1, y reproducido en forma precisa mediante ratones KO con PS1/PS2 doble (De Strooper y col. (1998). " Deficiency of presenilin-1 inhibits the normal cleavage of amyloid precursor protein". Nature 391(6665): 387-90; Donoviel, D. B., A. K. Hadjantonakis, M. Ikeda, H. Zheng, P. S. Hyslop y A. Bernstein (1999). " Mice lacking both presenilin genes exhibit early embryonic patterning defects". Genes Dev 13(21): 2801-10; Herreman, A., L. Serneels, W. Annaert, D. Collen, L. Schoonjans y B. De Strooper (2000). " Total inactivation of gamma-secretase activity in presenilin-deficient embryonic stem cells". Nat Cell Biol 2(7): 461-2.). Esta convergencia de fenotipos observada en ratones con genes inactivos del sustrato (Notch) o la enzima (PS) sugiere que los inhibidores de gama-secretasa que inhiben también la función de Notch pueden limitarse como agentes terapéuticos debido a la importancia de la función de Notch en tejidos adultos

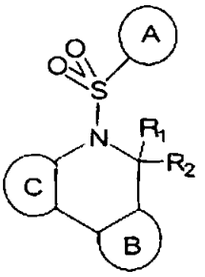
(Fortini, M. E. (2002). "Gamma-secretase-mediated proteolysis in cell-surface-receptor signaling." Nat Rev Mol Cell Biol 3(9): 673-84.) Dado que los ratones con genes inactivos para APP desarrollan normalmente y sin un fenotipo manifiesto Zheng, H., M. Jiang, M. E. Trumbauer, R. Hopkins, D. J. Sirinathsinghji, K. A. Stevens, M. W. Conner, H. H. Slunt, S. S. Sisodia, H. Y. Chen y col. (1996). "Mice deficient for the amiloyd precursor protein gene." Ann N Y Acad Sci 777: 421-6; Zheng, H., M. Jiang, M. E. Trumbauer, D. J. Sirinathsinghji, R. Hopkins, D. W. Smith, R. P. Heavens, G. R. Dawson, S. Boyce, M. W. Conner y col. (1995). "beta- Amyloid precursor protein-deficient mice show reactive gliosis and decreased locomotor activity". Cell 81(4): 525-31, la evidencia acumulada, por lo tanto, sugiere que los inhibidores de gama-secretasa preferidos presentarían selectividad para inhibir el procesamiento de la gama-secretasa de APP sobre el procesamiento de gama-secretasa de Notch.

La inhibición aguda de gama-secretasa mediante DAPT in-vivo demostró conducir a la reducción de Aβ en el cerebro de ratones PDAPP. Dovey, H. F., John, V., y col. (2001). "Functional gamma-secretase inhibitors reduce beta-amyloid peptide levels in brain". J Neurochem **76**(1): 173-81.

Los inhibidores de gama-secretasa han mostrado también incrementar la angiogenia. Ver US 2006/0264380. Como tal, los inhibidores de gama-secretasa de la invención son útiles en la promoción de angiogenia.

Resumen de la Invención

En un amplio aspecto, la invención proporciona compuestos de la Fórmula I:



estereoisómeros, tautómeros, hidratos, mezclas de estereoisómeros y/o tautómeros, o sus sales farmacéuticamente aceptables, en donde

el anillo C es cicloalquilo, arilo, heterocicloalquilo, o heteroarilo, cada uno de los cuales se sustituye opcionalmente con 1, 2, 3 ó 4 grupos que son independientemente halógeno, alquilo C_1-C_6, alcoxi C_1-C_6, ariloxi, aril-(alcoxi C_1-C_6), haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), NR'R", (alquilo C_1-C_6)-NR'R", -NR'C(O)OR', -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, oxo, aril-(alquilo C_1-C_6), arilo, heteroarilo, alquenilo C_2-C_6, alquinilo C_2-C_6, NR'SO_2R", -SO_2-NR'R", -S(O)$_z$ arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo), o -S(O)$_z$ (alquilo C_1-C_6), en donde las porciones de alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1, 2 ó 3 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_6,

y en donde las porciones de arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, 2, 3 ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R"; o

en donde dos sustituyentes adyacentes forman $-O-(CH_2)_{1-3}-O-$;

el anillo A es arilo, cicloalquilo, heteroarilo o heterocicloalquilo, en donde cada anillo se sustituye opcionalmente en una posición sustituible con halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, alcoxi C_1-C_6, haloalquilo C_1-C_6, haloalcoxi C_1-C_6, hidroxilo, hidroxi-(alquilo C_1-C_6), CN, NO_2, ariloxi, aril-(alcoxi C_1-C_6), $-SO_2$-(alquilo C_1-C_6), -NR'R", alcanoilo C_1-C_6, C(O)OR', (alquilo C_1-C_6)-C(O)OR', heteroarilo, arilo, aril-(alquilo C_1-C_6), $-SO_2$-NR'R", C(O)NR'R", OC(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", o -NR'C(O)OR';

el anillo B es un anillo heteroarilo o heterocicloalquilo, cada uno de los cuales se sustituye opcionalmente en una posición sustituible con un grupo que es independientemente alquilo C_1-C_6, alcoxi C_1-C_6, NR'R", SO_2-NR'R", -C(O)NR'R", -NR'SO_2R", -NR'SO_2NR'R", -NR'SO_2-(alquilo C_1-C_6), NR'SO_2-fenilo, -NR'C(O)R", -NR'C(O)NR'R", -NR'C(O)OR', -(alquilo C_1-C_6)-NR'R", -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", NO_2, CN, C(O)OR', hidroxilo, hidroxi-(alquilo C_1-C_6), S(O)$_z$(alquilo C_1-C_6), -S(O)$_z$ arilo, halógeno, haloalquilo C_1-C_6, haloalcoxi C_1-C_6, fenilo, alcanoilo C_1-C_6, aril-(alcanoilo C_1-C_6) (en donde el

grupo arilo es preferiblemente naftilo o fenilo, más preferiblemente fenilo), aril-(alquilo C_1-C_6) (preferiblemente fenetilo o bencilo, más preferiblemente, bencilo), arilcarbonilo, heteroarilcarbonilo, o heteroaril-(alcanoilo C_1-C_6), en donde el grupo heteroarilo es preferiblemente piridilo, pirimidilo, tienilo o furanilo; en donde los grupos arilo o heteroarilo se sustituyen opcionalmente con 1 a 5 grupos que son independientemente halógeno, hidroxilo, alquilo C_1-C_6, alcoxi C_1-C_6, alcanoilo C_1-C_6, haloalquilo C_1-C_6, haloalcoxi C_1-C_6, CN o NO_2; y

en donde cada z es independientemente 0, 1, ó 2;

R_1 es hidrógeno o alquilo C_1-C_6;

R_2 es hidrógeno, alquilo C_1-C_6, haloalquilo C_1-C_4, hidroxilo, hidroxi-(alquilo C_1-C_4), $-NO_2$, -CN, alquenilo C_2-C_6, alquinilo C_2-C_6, alcanoilo C_1-C_6, C(O)OR', -NR'R", -X(CO)Y, $(C(R_{30})_2)_{1-4}X(CO)Y$, cicloalquilo C_3-C_6 no sustituido, cicloalquilo C_3-C_6 sustituido con uno o más grupos (por ejemplo, 1-4) R_{50}, arilo no sustituido, arilo sustituido con uno o más grupos (por ejemplo, 1-4) R_{50}, heteroarilo no sustituido; o heteroarilo sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}, heterocicloalquilo no sustituido; o heterocicloalquilo sustituido con uno o más grupos (por ejemplo, 1-4) R_{50}; en donde

cada R_{30} es independientemente hidrógeno o alquilo C_1-C_6;

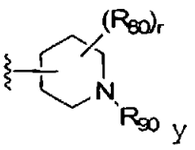
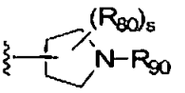
cada R_{50} se selecciona independientemente de: halógeno, alquilo C_1-C_6, haloalquilo C_1-C_6, -OH, O-(alquilo C_1-C_6), $-OCF_3$, -CN, -

$NR_{60}R_{70}$, $C(O)O$-(alquilo C_1-C_6), $CONR_{60}R_{70}$, alquilo (C_1-C_6)-$NR_{60}R_{70}$, $-NR_{60}C$Oalquilo, $NR_{60}C$Oarilo, $NR_{60}C$Oheteroarilo, $NR_{60}CONR_{60}R_{70}$,

X es: -O-, -NH-, o -N(alquilo)-;

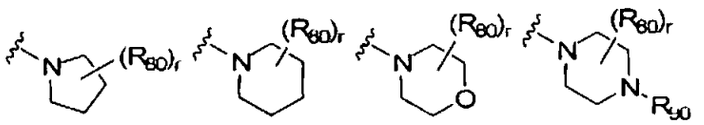
Y se selecciona de -O-(alquilo C_1-C_6), -O-fenilo, $-NR_{60}R_{70}$, o $-N(R_{30})(CH_2)_{2-6}NR_{60}R_{70}$;

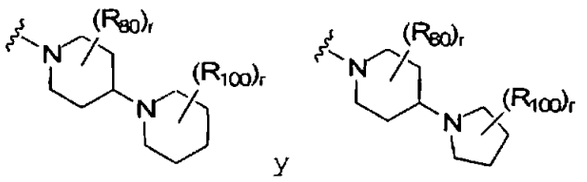
R_{60} y R_{70} se seleccionan independientemente de: hidrógeno, alquilo C_1-C_6, cicloalquilo

arilaquilo; heteroarilalquilo  y 

cicloalquilo, arilalquilo; heteroarilalquilo;, y, o

R_{60} y R_{70} tomados junto con el átomo de nitrógeno al que están unidos forman un grupo heterocicloalquilo seleccionado de:





y

en donde

cada R_{30} es independientemente alquilo C_1-C_6 no sustituido o alquilo C_1-C_6 sustituido con hidroxilo o halógeno;

cada R_{90} es independientemente H; alquilo C_1-C_6 no sustituido; alquilo C_1-C_6 sustituido con hidroxilo o halógeno, cicloalquilo no sustituido; cicloalquilo sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}; aril-(alquilo C_1-C_6); heteroarilalquilo; $-C(O)O$-(alquilo C_1-C_6), $-C(O)O$-arilo; $-SO_2$-(alquilo C_1-C_6); $-SO_2$-arilo; arilo no sustituido; arilo

sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}; heteroarilo; o heteroarilo sustituido con uno o más (por ejemplo, 1-4) grupos R_{50};

cada R_{100} es independientemente hidrógeno o alquilo C_1-C_6 ;

cada r es 0 a 4;

cada s es 0 a 3; o

R_1 y R_2 combinados son oxo o =N-OR donde R es hidrógeno, alquilo C_1-C_6, arilo o arilalquilo; o

R_1 y R_2 junto con el carbono al que están unidos forman un grupo cicloalquilo C_{3-6} en donde uno de los carbonos puede remplazarse con un heteroátomo seleccionado de N, O o S y en donde dicho anillo cicloalquilo C_{3-6} puede sustituirse opcionalmente con alquilo C_1-C_6 o halógeno; y

R' y R" son independientemente hidrógeno, alquilo C_1-C_6, o fenilo, en donde el fenilo se sustituye opcionalmente con 1 a 5 grupos que son independientemente halógeno, hidroxilo, alquilo C_1-C_6, alcoxi C_1-C_6, alcanoilo C_1-C_6, haloalquilo C_1-C_4, haloalcoxi C_1-C_4, CN o NO_2, o

R' y R" tomados junto con el átomo de nitrógeno al que están unidos forman un grupo heterocicloalquilo de 3 a 7 miembros que puede tener un heteroátomo adicional seleccionado de N, O o S y que puede sustituirse opcionalmente con 1 a 3 grupos R_{80} o R_{90} ;

dado que 5-tosil-4,5-dihidro-2H-pirazol[4,3-c]quinolina, 2-fenil-5-tosil-4,5-dihidro-2H-pirazol[4,3-c]quinolina, 7-metoxi-2-fenil-5-tosil-4,5-dihidro-2H-pirazol[4,3-c]quinolina, 8-metoxi-5-tosil-4,5-dihidro-2H-pirazol[4,3-c]quinolina, 8-

metoxi-2-fenil-5-tosil-4,5-dihidro-2H-pirazol[4,3-c]quinolina, 3-(metiltio)-5-tosil-4,5-dihidro-2H-pirazol[4,3-c]quinolina, 7-metoxi-5-tosil-4,5-dihidro-2H-pirazol[4,3-c]quinolina, 5-tosil-4,5-dihidro-2H-pirazol[4,3-c]quinolina, 1-(4-sulfamoilfenil)-5-tosil-4,5-dihidro-1H-pirazol[4,3-c]quinolina-3-carboxilato de etilo, 1-(4-sulfamoilfenil)-5-tosil-4,5-dihidro-1H-pirazol[4,3-c]quinolin-3-carboxamida; y 1-metil-5-tosil-4,5-dihidro-1H-pirazol[4,3-c]quinolina-3-carboxilato de etilo, no se abarcan en la Fórmula I.

Los compuestos de la Fórmula I inhiben la liberación de péptido β-amiloide y/o su síntesis y, por lo tanto, son útiles en la prevención de la enfermedad de Alzheimer (AD) en pacientes susceptibles de padecer AD y/o en el tratamiento de pacientes con AD de modo de inhibir el deterioro progresivo de su afección. La invención abarca también composiciones farmacéuticas que contienen los compuestos de la Fórmula I, y métodos que emplean Estos compuestos o composiciones en el tratamiento de enfermedades cognitivas, incluyendo enfermedad de Alzheimer.

La invención también proporciona un método para tratar a un paciente que tiene, o para prevenir que un paciente contraiga, una enfermedad o afección seleccionada del grupo que consiste de enfermedad de Alzheimer para ayudar a prevenir o retardar el comienzo de la enfermedad de Alzheimer, para tratar pacientes con daño cognitivo leve (MCI) y para prevenir o retardar el inicio de la enfermedad de Alzheimer en aquéllos quienes progresarían de MCI a AD, para tratar síndrome de

Down, para tratar humanos que tienen Hemorragia Cerebral Hereditaria con Amiloidosis de Tipo Holandés, para tratar angiopatía cerebral amiloide y prevenir sus potenciales consecuencias, es decir, hemorragias lobulares simples y recurrentes, para tratar otras demencias degenerativas, incluyendo demencias de origen mixto vascular y degenerativo, demencia asociada con enfermedad de Parkinson, demencia asociada con parálisis supranuclear progresiva, demencia asociada con degeneración corticobasal, degeneración macular relacionada con la edad o enfermedad de Alzheimer de tipo cuerpo de Lewy difuso y que necesita dicho tratamiento que comprende la administración de una cantidad terapéuticamente efectiva de un compuesto de la Fórmula I.

La invención proporciona adicionalmente un método para influenciar un estado de enfermedad en una célula, un grupo de células u organismos, que comprende: administrar al menos un inhibidor de gama-secretasa o un inhibidor de la ruta de gama-secretasa de la Fórmula I, o su sal farmacéuticamente aceptable, a la célula, grupo de células, u organismo, en donde la enfermedad se selecciona del grupo que consiste de aterosclerosis, hemangioma, hemangioendotelioma, malformaciones vasculares, verrugas, granulomas piogénicos, crecimiento de cabello, sarcoma de Kaposi, queloides en cicatrices, edema alérgico, neoplasmas, soriasis, úlceras por estasis o del decubitus, úlceras gastrointestinales, sangrado uterino disfuncional, quistes foliculares, hiperestimulación del ovario, endometriosis, neoplasmas, preeclampsia,

insuficiencia de la placenta, molestia respiratoria, ascitis, esclerosis peritoneal, formación por adhesión, propagación metastásica, enfermedad arterial coronaria, enfermedad isquémica cardiaca, enfermedad de miembro isquémico, obesidad, artritis reumatoide, sinovitis, destrucción ósea, destrucción de cartílagos, osteomielitis, crecimiento de panus, formación osteofítica, cáncer, necrosis aséptica, curación deficiente de fracturas, hepatitis, neumonía, glomerulonefritis, asma, pólipos nasales, regeneración del hígado, hipertensión pulmonar, hipertensión sistémica, diabetes, retinopatía de la premadurez, retinopatía diabética, trastornos coroidales, trastornos intraoculares (por ejemplo, degeneración macular relacionada a la edad), leucomalacia, apoplejía, demencia vascular, enfermedad, tiroiditis, ampliación de la tiroides, seudoquiste de tiroides, metástasis tumoral, trastornos linfoproliferativos, linfoedema, SIDA, y malignidades hematológicas.

Más aun, la invención proporciona un método para incrementar el proceso angiogénico en una célula, un grupo de células, o un organismo, que comprende administrar una composición farmacéutica que comprende una cantidad farmacéuticamente efectiva de al menos un inhibidor de gama-secretasa o inhibidor de la ruta de gama-secretasa de la Fórmula I, o su sal farmacéuticamente aceptable, a la célula, grupo de células, u organismo.

Más aun, la invención proporciona un método para incrementar el proceso angiogénico en una célula, un grupo de células, o

un organismo, que comprende administrar una composición farmacéutica que comprende una cantidad farmacéuticamente efectiva de al menos un inhibidor de gama-secretasa o inhibidor de la ruta de gama-secretasa de la Fórmula I, o su sal farmacéuticamente aceptable, a la célula, grupo de células, u organismo, en donde la composición farmacéutica se administra para prevenir, tratar o curar una afección seleccionada del grupo que consiste de aterosclerosis, hemangioma, hemangioendotelioma, malformaciones vasculares, verrugas, granulomas piogénicos, crecimiento de cabello, sarcoma de Kaposi, queloides en cicatrices, edema alérgico, neoplasmas, soriasis, úlceras por estasis o decúbito, úlceras gastrointestinales, sangrado uterino disfuncional, quistes foliculares, hiperestimulación de ovarios, endometriosis, neoplasmas, preeclampsia, insuficiencia de placenta, molestia respiratoria, ascitis, esclerosis peritoneal, formación por adhesiones, propagación metastásica, enfermedad coronaria arterial, enfermedad coronaria isquémica, enfermedad del miembro isquémico, obesidad, artritis reumatoide, sinovitis, destrucción ósea, destrucción de cartílagos, osteomielitis, crecimiento de panus, formación osteofita, cáncer, necrosis aséptica, curación deficiente de fracturas, hepatitis, neumonia, glomerulonefritis, asma, pólipos nasales, regeneración del hígado, hipertensión pulmonar, hipertensión sistémica, diabetes, retinopatía por prematurez, retinopatía diabética, trastornos coroidales, trastornos intraoculares (por ejemplo, degeneración macular relacionada a la edad),

leucomalacia, apoplejía, demencia vascular, enfermedad, tiroiditis, expansión de la tiroides, seudoquiste de tiroides, metástasis tumoral, trastornos linfoproliferativos, linfoedema, SIDA y malignidades hematológicas.

La invención proporciona adicionalmente un método para buscar una sustancia que inicie o aumente la angiogenia, que comprende: medir una actividad de una ruta de gama-secretasa en presencia de un compuesto candidato en un modelo adecuado; medir la actividad de la ruta de gama-secretasa en ausencia de un compuesto candidato; y comparar dicha actividad en presencia de un compuesto candidato con dicha actividad en ausencia del compuesto candidato, en donde un cambio en la actividad indica que dicho candidato inicia o aumenta la angiogenia.

En otro aspecto, la invención proporciona métodos para preparar los compuestos de interés, así como también intermedios útiles para preparar los compuestos de interés.

La invención proporciona adicionalmente un método para tratar una enfermedad relacionada con A beta que comprende administrar una cantidad terapéuticamente efectiva de un compuesto o sal de la Fórmula I a un paciente necesitado de tal tratamiento.

Descripción detallada de la invención

Como se describe anteriormente, la invención proporciona compuestos de acuerdo con la Fórmula I.

En otro aspecto, la invención proporciona compuestos de la Fórmula 2, es decir, compuestos de la Fórmula I donde el

anillo A es fenilo o naftilo, cada uno de los cuales se sustituye opcionalmente en una posición sustituible con halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, alcoxi C_1-C_6, haloalquilo C_1-C_6, haloalcoxi C_1-C_6, hidroxilo, hidroxi-(alquilo C_1-C_4), CN, ariloxi, aril-(alcoxi C_1-C_4), $-SO_2$-(alquilo C_1-C_6), -NR'R", alcanoilo C_1-C_6, -C(O)OR', -(alquilo C_1-C_4)-C(O)OR', piridilo, fenilo, fenil-(alquilo C_1-C_4), $-SO_2$-NR'R", -C(O)NR'R", -OC(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", o -NR'C(O)OR', en donde cada R' y R" son independientemente hidrógeno, alquilo C_1-C_6 o fenilo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 3, es decir, compuestos de la Fórmula I en donde el anillo B es pirazolilo, imidazolilo, pirrolilo, triazolilo, pirrolidinilo, pirazolidinilo, imidazolidinilo, piridilo, pirimidilo, o isoxazolilo, cada uno de los cuales se sustituye opcionalmente en una posición sustituible con un grupo que es independientemente alquilo C_1-C_6, alcoxi C_1-C_6, -NR'R", -C(O)OR', $-SO_2$NR'R", -C(O)NR'R", -NR'SO_2R", -NR'SO_2NR'R", -NR'SO_2-(alquilo C_1-C_6), -NR'SO_2-fenilo, -NR'C(O)R", -NR'C(O)NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -(alquilo C_1-C_4)-NR'R", -(alquilo C_1-C_4)-C(O)OR', -(alquilo C_1-C_4)-C(O)NR'R", NO_2, CN, hidroxilo, hidroxi-(alquilo C_1-C_6), -$S(O)_z$(alquilo C_1-C_6), $S(O)_2$ fenilo, halógeno, haloalquilo C_1-C_4, haloalcoxi C_1-C_4, fenilo, alcanoilo C_1-C_6, fenil-(alcanoilo C_1-C_4), fenetilo, bencilo, fenilcarbonilo, heteroarilcarbonilo, o heteroaril-(alcanoilo C_1-C_4), en donde el grupo heteroarilo es piridilo, pirimidilo, tienilo o furanilo; en donde los grupos

fenilo o heteroarilo se sustituyen opcionalmente con 1 a 5 grupos que son independientemente halógeno, hidroxilo, alquilo C_1-C_6, alcoxi C_1-C_6, alcanoilo C_1-C_6, haloalquilo C_1-C_4, haloalcoxi C_1-C_4, CN o NO_2.

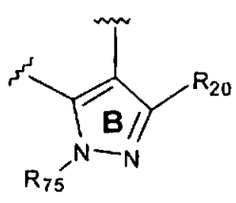
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 4, es decir, compuestos de la Fórmula I donde el anillo A es fenilo o naftilo, cada uno de los cuales se sustituye opcionalmente en una posición sustituible con halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, alcoxi C_1-C_6, haloalquilo C_1-C_4, haloalcoxi C_1-C_4, hidroxilo, hidroxi-(alquilo C_1-C_4), CN, feniloxi, benciloxi, -SO_2-(alquilo C_1-C_6), -NR'R", alcanoilo C_1-C_6, -C(O)OR', -(alquilo C_1-C_4)-C(O)OR', piridilo, fenilo, fenil-(alquilo C_1-C_4), -SO_2-NR'R", -C(O)NR'R", -OC(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", o -NR'C(O)OR', en donde cada R' y R" es independientemente H, alquilo C_1-C_6 o fenilo; y el anillo B es pirazolilo, imidazolilo, pirrolilo, triazolilo, pirrolidinilo, pirazolidinilo, imidazolidinilo, piridilo, pirimidilo, o isoxazolilo, cada uno de los cuales se sustituye opcionalmente en una posición sustituible con un grupo que es independientemente alquilo C_1-C_6, alcoxi C_1-C_6, -NR'R", -SO_2-NR'R", -C(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, NO_2, CN, -C(O)OR', hidroxilo, hidroxi-(alquilo C_1-C_6), halógeno, -S(O)$_z$(alquilo C_1-C_6), -S(O)$_z$arilo, halógeno, haloalquilo C1-2, haloalcoxi C1-2, bencilo, o fenilo.

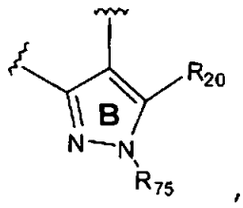
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 4-1, es decir, compuestos de la Fórmula I donde el anillo C es ciclohexilo, ciclopentilo, fenilo, naftilo, tienilo, imidazolilo, pirimidilo, pirazinilo, furanilo, o piridilo, cada uno de los cuales se sustituye opcionalmente en cada posición sustituible con grupos que son independientemente halógeno, alquilo C_1-C_6, alcoxi C_1-C_6, ariloxi, aril-(alcoxi C_1-C_4), haloalquilo C_1-C_6, (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), -NR'R", -(alquilo C_1-C_4)-NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R", -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, oxo, bencilo, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo, furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$(alquilo C_1-C_6), o -S(O)$_z$arilo, en donde las porciones de alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1, 2 ó 3 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_6, y en donde las porciones de arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R"; o

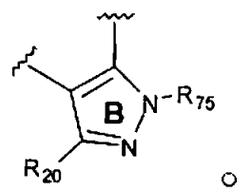
en donde dos sustituyentes adyacentes del anillo C C -O-$(CH_2)_{2-3}$-O-.

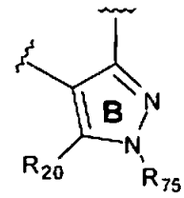
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 4-2, es decir, compuestos de la Fórmula I, 4, ó 4-1, en donde el anillo B es pirazolilo, imidazolilo, pirrolilo, triazolilo, pirrolidinilo, pirazolidinilo, imidazolidinilo, piridilo, pirimidilo, o isoxazolilo, cada uno de los cuales se sustituye opcionalmente en una posición sustituible con un grupo que es independientemente alquilo C_1-C_6, alcoxi C_1-C_6, -NR'R", $-SO_2$-NR'R", -C(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, NO_2, CN, -C(O)OR', hidroxilo, hidroxi-(alquilo C_1-C_6), halógeno, -$S(O)_z$(alquilo C_1-C_6), -$S(O)_z$arilo, halógeno, haloalquilo Cl-2, haloalcoxi C_1-C_2, bencilo, o fenilo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 4-3, es decir, compuestos de la Fórmula I, 4, ó 4-1, en donde el anillo B tiene la Fórmula:



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o


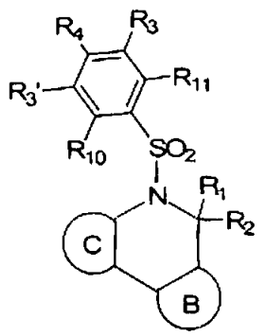
en donde

R_{20} es hidrógeno, alquilo C_1-C_6, alcoxi C_1-C_6, -NR'R", -(alquilo C_1-C_4)-NR'R", -$S(O)_z$(alquilo C_1-C_6), hidroxilo, halógeno, CN, NO_2, CH_2F, CHF_2, CF_3, -C(O)OR', -C(O)NR'R", -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", o fenilo, y

R_{75} es hidrógeno, alquilo C_1-C_6, alcanoilo C_1-C_6, fenil-(alcanoilo C_1-C_6)-, -C(O)NR'R", -$S(O)_z$(alquilo C_1-C_6), -$S(O)_z$-arilo, $-SO_2$NR'R", fenilo, fenil-(alquilo C_1-C_6) (preferiblemente

fenetilo o bencilo, más preferiblemente, bencilo), fenilcarbonilo, bencilcarbonilo, o heteroarilcarbonilo, en donde el grupo heteroarilo es piridilo, pirimidilo, tienilo o furanilo; en donde z es 0, 1, ó 2.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 5, es decir, compuestos de acuerdo con cualquiera de las Fórmulas I, 4, 4-1, ó 4-2, que tienen la Fórmula:



Fórmula 5

estereoisómeros, tautómeros, mezclas de estereoisómeros y/o tautómeros o sus sales farmacéuticamente aceptables, en donde el anillo C es un ciclohexilo, fenilo, tienilo, imidazolilo, tiazolilo, isotiazolilo, oxazolilo, isoxazolilo, pirrolilo, pirazolilo, pirimidilo, pirazinilo o piridilo opcionalmente sustituido;

R_3, $R_{3'}$, R_4, R_{10} o R_{11} son independientemente hidrógeno, halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, alcoxi C_1-C_6, haloalquilo C_1-C_6, haloalcoxi C_1-C_6, hidroxilo, hidroxi-(alquilo C_1-C_4), CN, NO_2, ariloxi (tal como feniloxi), aril-(alcoxi C_1-C_4) tal como benciloxi, -SO_2-(alquilo C_1-C_6), -NR'R", alcanoilo C_1-C_6, -C(O)OR', -(alquilo C_1-C_4)-C(O)OR', piridilo, fenilo,

fenil-(alquilo C_1-C_4)-, $-SO_2-NR'R''$, $-C(O)NR'R''$, $-OC(O)NR'R''$, $-NR'C(O)R''$, $-NR'C(O)NR'R''$, o $-NR'C(O)O-R'$, en donde cada R' y R" son independientemente hidrógeno, alquilo C_1-C_6, o fenilo, en donde el fenilo se sustituye opcionalmente con 1 a 5 grupos que son independientemente halógeno, hidroxilo, alquilo C_1-C_6, alcoxi C_1-C_6, alcanoilo C_1-C_6, haloalquilo C_1-C_4, haloalcoxi C_1-C_4, CN o NO_2; o

R_4 y $R_{3'}$, o R_{10} y $R_{3'}$ y los carbonos a los que están unidos forman un anillo benzo.

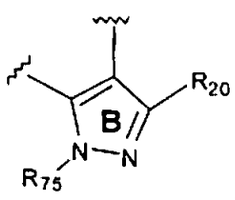
En otro aspecto, la invención proporciona compuestos de la Fórmula 6, es decir, compuestos de la Fórmula 5, en donde el anillo C es ciclohexilo, fenilo, tienilo, imidazolilo, pirimidilo, pirazinilo, o piridilo, cada uno de los cuales se sustituye opcionalmente en cada posición sustituible con grupos que son independientemente halógeno, alquilo C_1-C_6, alcoxi C_1-C_6, ariloxi, aril-(alcoxi C_1-C_4), haloalquilo C_1-C_6, (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), $-NR'R''$, -(alquilo C_1-C_4)-$NR'R''$, $-NR'C(O)O$-(alquilo C_1-C_6), $-NR'C(O)O$-fenilo, $-COR'$, $-C(O)OR'$, $-C(O)NR'R''$, $-OC(O)NR'R''$, $-NR'C(O)NR'R''$, -(alquilo C_1-C_6)-$C(O)OR'$, -(alquilo C_1-C_6)-$C(O)NR'R''$, $-NR'C(O)R''$, NO_2, CN, oxo, bencilo, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo, furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, $-NR'SO_2R''$, $-SO_2-NR'R''$, $-S(O)_z$(alquilo C_1-C_6), o $-S(O)_z$arilo, en donde las porciones de alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1, 2 ó 3 grupos que son independientemente halógeno, hidroxilo, $-NR'R''$ o alcoxi C_1-C_6,

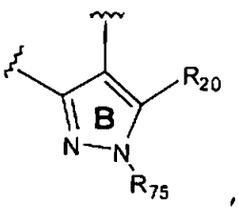
y en donde las porciones de arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R"; o

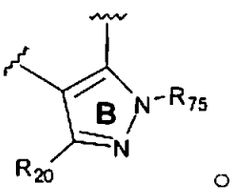
en donde dos sustituyentes adyacentes del anillo CC-O-$(CH_2)_{1-3}$-O-.

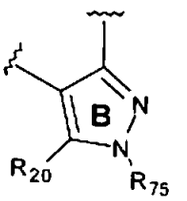
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 6-1, es decir, compuestos de la Fórmula 6 donde el anillo B es pirazolilo, imidazolilo, pirrolilo, triazolilo, pirrolidinilo, pirazolidinilo, imidazolidinilo, o isoxazolilo, cada uno de los cuales no se sustituye.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 6-2, es decir, compuestos de la Fórmula 6 donde el anillo B tiene la Fórmula:



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o


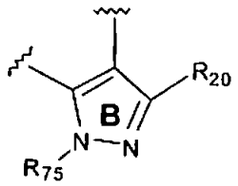
en donde

R_{20} es hidrógeno, alquilo C_1-C_6, alcoxi C_1-C_6, -NR'R", -(alquilo C_1-C_4)-NR'R", -S(O)$_z$(alquilo C_1-C_6), hidroxilo, halógeno, CN, NO_2, CH_2F, CHF_2, CF_3, -C(O)OR', -C(O)NR'R", -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", o fenilo, y

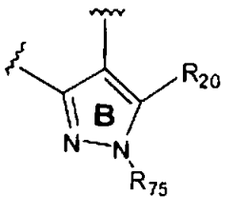
R_{75} es hidrógeno, alquilo C_1-C_6, alcanoilo C_1-C_6, fenil-(alcanoilo C_1-C_6)-, -C(O)NR'R", -S(O)$_z$(alquilo C_1-C_6), -S(O)$_z$-

arilo, $-SO_2NR'R''$, fenilo, fenil-(alquilo C_1-C_6) (preferiblemente fenetilo o bencilo, más preferiblemente, bencilo), fenilcarbonilo, bencilcarbonilo, o heteroarilcarbonilo, en donde el grupo heteroarilo es piridilo, pirimidilo, tienilo o furanilo.

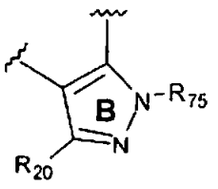
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 6-3, es decir, compuestos de la Fórmula 6-2 en donde el anillo B tiene la Fórmula:



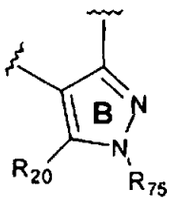
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 6-4, es decir, compuestos de la Fórmula 6-2 donde el anillo B tiene la Fórmula:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 6-5, es decir, compuestos de la Fórmula 6-2 donde el anillo B tiene la Fórmula:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 6-6, es decir, compuestos de la Fórmula 6-2 en donde el anillo B tiene la Fórmula:



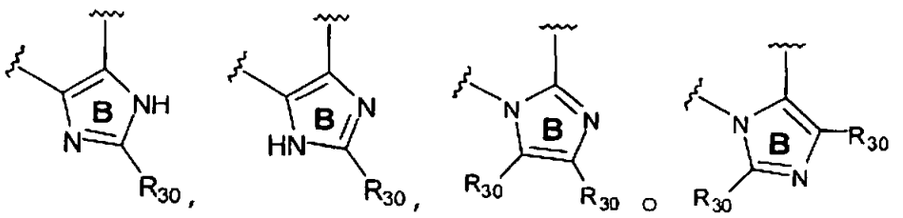
En un aspecto adicional, la invención proporciona compuestos de la Fórmula 6-6a, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 6-2, 6-3, 6-4, 6-5, o 6-6, en donde R_{20} es hidrógeno, alquilo C_1-C_4, CH_2F, CHF_2, CF_3, -C(O)OR', -S(O)$_2$ (alquilo C_1-C_4), o hidroxilo; y R_{75} es hidrógeno, alquilo C_1-C_4, o -S(O)$_2$-fenilo.

En otro aspecto, la invención proporciona compuestos de la Fórmula 6-6b, es decir, compuestos de la Fórmula 6-6a, en donde R_{20} es hidrógeno o metilo, y R_{75} es hidrógeno o metilo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 6-6c, es decir, compuestos de la Fórmula 6-6a, en donde R_{20} es hidrógeno o metilo, y R_{75} es hidrógeno.

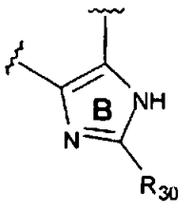
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 6-6d, es decir, compuestos de la Fórmula 6-6a, en donde R_{20} es hidrógeno y R_{75} es hidrógeno.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 6-7, es decir, compuestos de la Fórmula 6 donde el anillo B tiene la Fórmula:

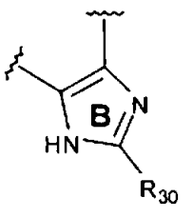


en donde cada R_{30} es independientemente hidrógeno, alquilo C_1-C_4, alcoxi C_1-C_4, -NR'R", alquiltio C_1-C_4, hidroxilo, halógeno, CH_2F, CHF_2, CF_3, o fenilo.

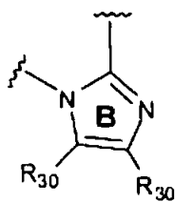
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 6-8, es decir, compuestos de la Fórmula 6-7 donde el anillo B tiene la Fórmula:



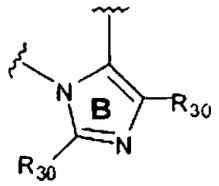
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 6-9, es decir, compuestos de la Fórmula 6-7 donde el anillo B tiene la Fórmula:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 6-10, es decir, compuestos de la Fórmula 6-7 donde el anillo B tiene la Fórmula:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 6-11, es decir, compuestos de la Fórmula 6-7 donde el anillo B tiene la Fórmula:

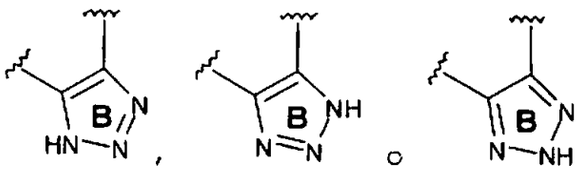


En un aspecto adicional, la invención proporciona compuestos de la Fórmula 6-11a, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 6-8, 6-9, 6-10, o 6-11, en donde cada R_{30} es independientemente hidrógeno, alquilo C_1-C_4, CH_2F, CHF_2, o CF_3.

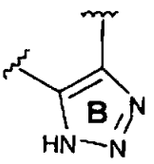
En otro aspecto, la invención proporciona compuestos de la Fórmula 6-11b, es decir, compuestos de la Fórmula 6-11a, en donde cada R_{30} es independientemente hidrógeno o metilo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 6-11c, es decir, compuestos de la Fórmula 6-11a, en donde cada R_{30} es hidrógeno.

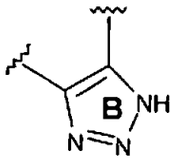
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 6-12, es decir, compuestos de la Fórmula 6 donde el anillo B tiene la Fórmula:



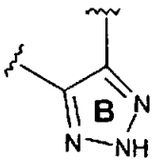
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 6-13, es decir, compuestos de la Fórmula 6-12 donde el anillo B tiene la Fórmula:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 6-14, es decir, compuestos de la Fórmula 6-12 en donde el anillo B tiene la Fórmula:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 6-15, es decir, compuestos de la Fórmula 6-12 en donde el anillo B tiene la Fórmula:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7, es decir, compuestos de las Fórmulas 4, 4-1, 4-2, 4-3, 5, o una cualquiera de las Fórmulas 6, 6-1, 6-2, 6-3, 6-4, 6-5, 6-6, 6-6a, 6-6b, 6-6c, 6-6d, 6-7, 6-8, 6-9, 6-10, 6-11, 6-11a, 6-11b, 6-11c, 6-12, 6-13, 6-14, o 6-15 en donde el anillo C es fenilo o ciclohexilo, que se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, ariloxi, aril-(alcoxi C_1-C_4), haloalquilo C_1-C_4 (en otro aspecto, CF_3), haloalcoxi C_1-C_4 (en otro aspecto, OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_4), -NR'R", -(alquilo C_1-C_4)-NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, oxo, bencilo, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo,

furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -$S(O)_z$ fenilo, o -$S(O)_z$ (alquilo C_1-C_6), en donde las porciones de alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1, 2 ó 3 grupos que son independientemente halógeno, hidroxi, -NR'R" o alcoxi C_1-C_6, y en donde las porciones de arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R" o en donde dos sustituyentes adyacentes del anillo C forman -O-$(CH_2)_{1-3}$-O-. En una modalidad, el anillo C es un fenilo opcionalmente sustituido.

En otro aspecto, la invención proporciona compuestos de la Fórmula 7-1, es decir, compuestos de la Fórmula 7 donde el anillo C es fenilo no sustituido.

En otro aspecto, la invención proporciona compuestos de la Fórmula 7-1a, es decir, compuestos de la Fórmula 7 donde el anillo C es ciclohexilo no sustituido.

En otro aspecto, la invención proporciona compuestos de la Fórmula 7-2, es decir, compuestos de la Fórmula 7, en donde el anillo C es fenilo sustituido con 1 ó 2 grupos que son independientemente Cl, F, metilo, etilo, isopropilo, metoxi, etoxi, CF_3, OCF_3, OH, CH_2OH, NH_2, $NH(CH_3)$, $N(CH_3)_2$, o -$OC(O)N(CH_3)_2$. En una modalidad, el anillo C está bis-sustituido con al menos un halógeno. En otra modalidad, el halógeno es F. En todavía otra modalidad, el halógeno es Cl. En otra

modalidad, el anillo C está bis-sustituido con dos halógenos, que son idénticos o diferentes. En todavía otra modalidad, el anillo C está sustituido al menos en la posición 7. En otra modalidad, el anillo C está sustituido en las posiciones 7 y 8. En otra modalidad, el anillo C está monosustituido con un halógeno. En otra modalidad, el halógeno es F. En todavía otra modalidad, el halógeno es Cl. En todavía otra modalidad, el anillo C está sustituido en la posición 7. En todavía otra modalidad, el anillo C está sustituido en la posición 8.

En otro aspecto, la invención proporciona compuestos de la Fórmula 7-2a, es decir, compuestos de la Fórmula 7, en donde el anillo C es ciclohexilo sustituido con 1 ó 2 grupos que son independientemente Cl, F, metilo, etilo, isopropilo, metoxi, etoxi, CF_3, OCF_3, OH, CH_2OH, NH_2, $NH(CH_3)$, $N(CH_3)_2$, u $-OC(O)N(CH_3)_2$.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-3, es decir, compuestos de la Fórmula 7, en donde el anillo C es fenilo sustituido con 1 ó 2 grupos que son Cl, F, metil, etilo, isopropilo, metoxi, CF_3, OCF_3, OH, $-OC(O)N(CH_3)_2$ o con dos sustituyentes adyacentes que forman $-O-(CH_2)_{1-3}-O-$. En una modalidad, el anillo C está monosustituido con un halógeno. En otra modalidad, el halógeno es Cl. En todavía otra modalidad, el halógeno es F. En otra modalidad, el anillo C está sustituido en la posición 7. En todavía otra modalidad, el anillo C está sustituido en la posición 8. En otra modalidad, el anillo C está bis-sustituido en las posiciones 7 y 8. En todavía otra modalidad, el anillo C está

sustituido en las posiciones 7 y 8, con un grupo que es halógeno, metilo, o metoxi. En todavía otra modalidad, los dos grupos son idénticos. En una modalidad adicional, los dos grupos son idénticos, y son un halógeno (tal como F o Cl).

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-3a, es decir, compuestos de la Fórmula 7, en donde el anillo C es ciclohexilo sustituido con 1 ó 2 grupos que son Cl, F, metilo, etilo, isopropilo, metoxi, CF_3, OCF_3, OH, o $-OC(O)N(CH_3)_2$.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-3b, es decir, compuestos de la Fórmula 7, en donde el anillo C es fenilo sustituido con 1 ó 2 grupos que son independientemente $-NR'C(O)O-$(alquilo C_1-C_6), $-NR'C(O)O-$fenilo, $-C(O)OR'$, $-C(O)NR'R''$, -(alquilo C_1-C_6)$-C(O)OR'$, -(alquilo C_1-C_6)$-C(O)NR'R''$, $-NR'C(O)R''$, $-OC(O)NR'R''$, $-NR'C(O)NR'R''$; NO_2, CN, fenilo, $-S(O)_z$fenilo, o $-S(O)_z$(alquilo C_1-C_6), en donde las porciones fenilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6) o, $-NR'R''$. En una modalidad, el anillo C está sustituido al menos en la posición 7. En otra modalidad, el anillo C está sustituido al menos en la posición 8.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-3c, es decir, compuestos de la Fórmula 7, en donde el anillo C es ciclohexilo sustituido con 1 ó 2 grupos

que son independientemente -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -C(O)OR', -C(O)NR'R", -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_4)-C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R"; NO_2, CN, fenilo, -S(O)$_z$fenilo, o -S(O)$_z$(alquilo C_1-C_6), en donde las porciones fenilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R".

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-3d, es decir, compuestos de la Fórmula 7, en donde el anillo C es fenilo sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alquenilo C_2-C_6, alquinilo C_2-C_6, en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1 ó 2 grupos que son independientemente halógeno, hidroxi, -NR'R" o alcoxi C_1-C_4. En una modalidad, el anillo C está sustituido al menos en la posición 7. En otra modalidad, el anillo C está sustituido al menos en la posición 8.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-3e, es decir, compuestos de la Fórmula 7, en donde el anillo C es ciclohexilo sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alquenilo C_2-C_6, alquinilo C_2-C_6, en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1 ó 2 grupos que son independientemente halógeno, hidroxi, -NR'R" o alcoxi C_1-C_4.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-3f, es decir, compuestos de la Fórmula 7, en donde el anillo C es fenilo sustituido con 1 ó 2 grupos que son independientemente -C(O)OH, -C(O)O-(alquilo C_1-C_6), NO_2, CN, o fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una modalidad, el anillo C está sustituido al menos en la posición 7. En otra modalidad, el anillo C está sustituido al menos en la posición 8.

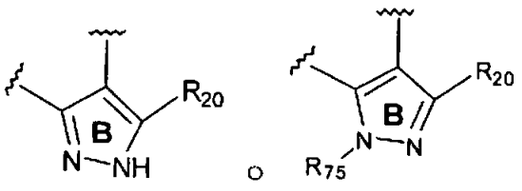
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-3g, es decir, compuestos de la Fórmula 7, en donde el anillo C es ciclohexilo sustituido con 1 ó 2 grupos que son independientemente -C(O)OH, -C(O)O-(alquilo C_1-C_6), NO_2, CN, o fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R".

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-3h, es decir, compuestos de la Fórmula 7, en donde el anillo C es fenilo sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alcoxi C_1-C_4, halógeno, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R", -NR'C(O)O-(alquilo C_1-C_6), o -NR'C(O)O-fenilo, en donde el grupo fenilo

se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una modalidad, el anillo C está sustituido al menos en la posición 7. En otra modalidad, el anillo C está sustituido al menos en la posición 8.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-3i, es decir, compuestos de la Fórmula 7, en donde el anillo C es ciclohexilo sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alcoxi C_1-C_4, halógeno, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R", -NR'C(O)O-(alquilo C_1-C_6) o -NR'C(O)O-fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R".

En otro aspecto, la invención proporciona compuestos de la Fórmula 7-4, es decir, compuestos de cualquiera de las Fórmulas 7, 7-1, 7-1a, 7-2, 7-2a, 7-3, 7-3a, 7-3b, 7-3c, 7-3d, 7-3e, 7-3f, 7-3g, 7-3h, 7-3i, en donde el anillo B tiene la Fórmula:



en donde R_{20} es hidrógeno, alquilo C_1-C_6, alcoxi C_1-C_6, -NR'R", -(alquilo C_1-C_4)-NR'R", $-S(O)_z$(alquilo C_1-C_6), hidroxilo, halógeno, CN, NO_2, CH_2F, CHF_2, CF_3, -C(O)OR', -C(O)NR'R", -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", o fenilo; y R_{75} es H o alquilo C_1-C_4 (tal como metilo o etilo). En una modalidad, R_{20} es hidrógeno o metilo. En otra modalidad, R_{20} es hidrógeno. En todavía otra modalidad, R_{20} y R_{75} son ambos H.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-4a, es decir, compuestos de la Fórmula 7-4, en donde R_4 es halógeno, haloalquilo C_1-C_6, o haloalcoxi C_1-C_6; R_3, $R_{3'}$, R_{10} y R_{11} son independientemente halógeno, metilo o hidrógeno; y R_2 es hidrógeno, alquilo C_1-C_3, o cicloalquilo C_3-C_6. En una modalidad, R_4 es Cl, mientras que R_3, $R_{3'}$, R_{10} y R_{11} son H.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-4aa, es decir, compuestos de la Fórmula 7-4a, en donde R_4 es Cl, F, CH_2F, CHF_2, CF_3, OCH_2F, $OCHF_2$, o OCF_3; R_3, $R_{3'}$, R_{10} y R_{11} son independientemente Cl, F, metilo o hidrógeno; y R_2 es independientemente hidrógeno, metilo, etilo, propilo, isopropilo, o ciclopropilo. En una modalidad, R_1 es hidrógeno o metilo. En otra modalidad, R_1 es hidrógeno.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-4al, es decir, compuestos de la Fórmula 7-4, en donde R_4 es halógeno (en un aspecto, cloro o flúor, haloalquilo C_1-C_6 o haloalcoxi C_1-C_6; R_3, $R_{3'}$, R_{10} y R_{11} son independientemente halógeno, metilo o hidrógeno; y R_2 es NO_2 o CN.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-4a2, es decir, compuestos de la Fórmula 7-4, en donde R_4 es halógeno (en un aspecto, cloro o flúor haloalquilo C_1-C_6 o haloalcoxi C_1-C_6; R_3, $R_{3'}$, R_{10} y R_{11} son independientemente halógeno, metilo o hidrógeno; y R_2 es alquenilo C_2-C_6 o alquinilo C_2-C_6.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-4a3, es decir, compuestos de la Fórmula 7-4, en donde R_4 es halógeno (en un aspecto, cloro o flúor haloalquilo C_1-C_6 o haloalcoxi C_1-C_6; R_3, $R_{3'}$, R_{10} y R_{11} son independientemente halógeno, metilo o hidrógeno; y R_2 es haloalquilo C_1-C_4. En una modalidad, R_4 es Cl, mientras que R_3, $R_{3'}$, R_{10} y R_{11} son H.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-4a4, es decir, compuestos de la Fórmula 7-4, 7-4a, 7-4a1, 7-4a2, o 7-4a3 donde R_1 es hidrógeno.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-4a5, es decir, compuestos de la Fórmula 7-4, en donde R_1 y R_2 combinados son oxo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-4a6, es decir, compuestos de la Fórmula 7-4, en donde R_1 y R_2 combinados son =N-OR donde R es hidrógeno, alquilo C_1-C_6, arilo (tal como fenilo) o arilalquilo (tal como bencilo o fenetilo).

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-4a7, es decir, compuestos de la Fórmula 7-4,

en donde R_1 y R_2 junto con el carbono al que están unidos forman un grupo cicloalquilo C_{3-6}.

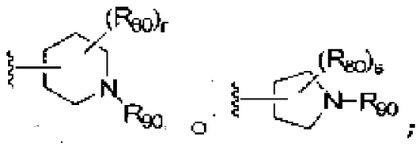
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-4a8, es decir, compuestos de la Fórmula 7-4, en donde R_1 y R_2 junto con el carbono al que están unidos forman un grupo ciclopropilo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-4a9, es decir, compuestos de la Fórmula 7-4 o 7-4a, en donde R_1 es hidrógeno y R_2 es ciclopropilo. En una modalidad, el compuesto es racémico. En otra modalidad, el compuesto está enantioméricamente enriquecido.

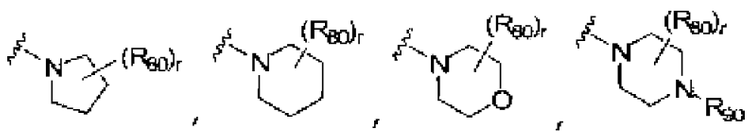
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-4a10, es decir, compuestos de la Fórmula 7-4 o 7-4a, en donde R_4 es CF_3; R_1 es H; R_2 es H, o cicloalquilo C_{3-6}; R_{20} es H o metilo; R_{75} es H o metilo; y el anillo C es fenilo sustituido con dos halógenos.

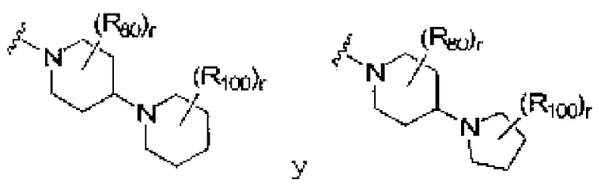
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-4b, es decir, compuestos de acuerdo con una cualquiera de las Fórmulas 7, 7-1, 7-1a, 7-2, 7-2a, 7-3, 7-3a, 7-3b, 7-3c, 7-3d, 7-3e, 7-3f, 7-3g, 7-3h, 7-3i, 7-4, en donde R_2 es $-X(CO)Y$ o $-(C(R_3)_2)_{1-6}X(CO)Y$.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-4c, es decir, compuestos de la Fórmula 7-4b, en donde X es O; e Y es $-NR_{60}R_{70}$ o $-N(R_{30})(CH_2)_{2-6}NR_{60}R_{70}$; en donde R_{60} y R_{70} se seleccionan independientemente de: hidrógeno, metilo, etilo, cicloalquilo C_3-C_8, aril-(alquilo C_1-C_6) (tal como bencilo o fenetilo), 4-piridilmetilo,



R_{60} y R_{70} tomados junto con el átomo de nitrógeno al que están unidos forman un grupo heterocicloalquilo seleccionado de:





en donde

cada R_{89} es alquilo C_1-C_4 independientemente no sustituido o alquilo C_1-C_4 sustituido con hidroxilo o halógeno;

cada R_{90} es independientemente hidrógeno, alquilo C_1-C_4 no sustituido, alquilo C_1-C_4 sustituido con hidroxilo o halógeno, cicloalquilo C_3-C_8 no sustituido, cicloalquilo C_3-C_8 sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}, fenil-(alquilo C_1-C_4)-, piridil-(alquilo C_1-C_4)-, tienil-(alquilo C_1-C_4), -C(O)O-(alquilo C_1-C_4), -C(O)O-fenilo, $-SO_2$-(alquilo C_1-C_6), $-SO_2$-fenilo, fenilo no sustituido, fenilo sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}, piridilo, tienilo, piridilo sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}, tienilo sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}, en donde

cada R_{50} se selecciona independientemente de: halógeno, alquilo C_1-C_6, haloalquilo C_1-C_6, -OH, -O-(alquilo C_1-C_4), OCF_3, -CN, -

$NR_{60}R_{70}$, $-C(O)O-$(alquilo C_1-C_4), $-CONR_{60}R_{70}$, -(alquilo C_1-C_6)-$NR_{60}R_{70}$, $-NR_{60}CO-$(alquilo C_1-C_4), $-NR_{60}CO-$fenilo, $-NR_{60}CO-$piridilo, $-NR_{60}CO-$tienilo, y $-NR_{60}CONR_{60}R_{70}$;

cada R_{100} es independientemente hidrógeno o alquilo C_1-C_4;

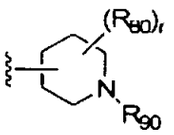
cada r es de 0 a 4; y

cada s es de 0 a 3.

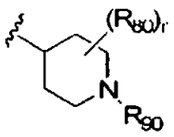
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-4c1, es decir, compuestos de la Fórmula 7-4b, en donde Y es $-O-$(alquilo C_1-C_6). En una modalidad, Y es $-O-$(alquilo C_1-C_4).

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-4c2, es decir, compuestos de la Fórmula 7-4b, en donde Y es -O-fenilo.

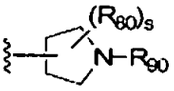
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-4d, es decir, compuestos de la Fórmula 7-4c, en donde dicho grupo



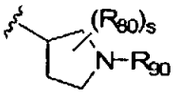
es un grupo de la Fórmula:



y dicho grupo

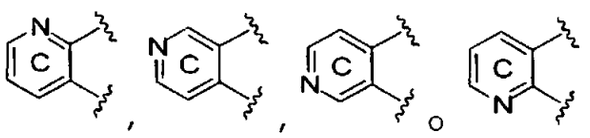


es un grupo de Fórmula:



En un aspecto adicional, la invención proporciona compuestos de la Fórmula 7-4d1, es decir, compuestos de acuerdo con cualquiera de las Fórmulas, 7-4b, 7-4c, 7-4c1, 7-4c2, o 7-4d, en donde R_1 es H o alquilo C_1-C_4. En una modalidad, R_1 es H o metilo. En otra modalidad, R_1 es H.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-5, es decir, compuestos de la Fórmulas 4, 4-1, 4-2, 4-3, 5, o una cualquiera de las Fórmulas 6, 6-1, 6-2, 6-3, 6-4, 6-5, 6-6, 6-6a, 6-6b, 6-6c, 6-6d, 6-7, 6-8, 6-9, 6-10, 6-11, 6-11a, 6-11b, 6-11c, 6-12, 6-13, 6-14, o 6-15 en donde el anillo C es



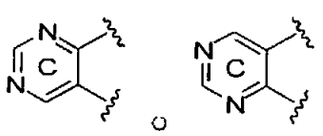
o sus derivados de N-óxido,

cada uno de los cuales se sustituye opcionalmente con 1, 2, ó 3 grupos que son independientemente halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, ariloxi, aril-(alcoxi C_1-C_4), haloalquilo C_1-C_4 (en otro aspecto, CF_3), haloalcoxi C_1-C_4 (en otro aspecto, OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_4), -NR'R", -(alquilo C_1-C_6)-NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, bencilo, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo, furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$ arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente,

fenilo), o -S(O)$_z$(alquilo C_1-C_6), en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1, 2, ó 3 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_6, y en donde las porciones arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una modalidad, la invención proporciona compuestos donde el anillo C es piridilo o N-óxido de piridilo sustituido con 1 ó 2 grupos que son independientemente -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -C(O)OR', -C(O)NR'R", -(alquilo C_1-C_6)-C(O)OR', alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R"; NO_2, CN, fenilo, -S(O)$_z$ arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo) o -S(O)$_z$ (alquilo C_1-C_6) donde las porciones de arilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una modalidad alternativa, el anillo C es piridilo o N-óxido de piridilo sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alquenilo C_2-C_6, alquinilo C_2-C_6, en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1 ó 2

grupos que son independientemente halógeno, hidroxi, -NR'R" o alcoxi C_1-C_4. En otra modalidad alternativa, el anillo C es piridilo o N-óxido de piridilo sustituido con 1 ó 2 grupos que son independientemente -C(O)OH, -C(O)O-(alquilo C_1-C_4), NO_2, CN, o fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En todavía otra modalidad alternativa, el anillo C es piridilo o N-óxido de piridilo sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alcoxi C_1-C_4, halógeno, -C(O)NR'R", -NR'C(O)R", -OC(O)N-(alquilo C_1-C_6)$_2$, -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF3), haloalcoxi C_1-C_6 (tal como OCF3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R".

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-5a, es decir, compuestos de las Fórmulas 4, 4-1, 4-2, 4-3, 5, o una cualquiera de las Fórmulas 6, 6-1, 6-2, 6-3, 6-4, 6-5, 6-6, 6-6a, 6-6b, 6-6c, 6-6d, 6-7, 6-8, 6-9, 6-10, 6-11, 6-11a, 6-11b, 6-11c, 6-12, 6-13, 6-14, o 6-15 donde el anillo C es

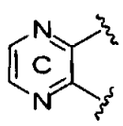


cada uno de los cuales se sustituye opcionalmente con 1 ó 2, grupos que son independientemente halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, ariloxi, aril-(alcoxi C_1-C_4), haloalquilo C_1-C_4 (en otro aspecto, CF_3), haloalcoxi C_1-C_4 (en otro aspecto, OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_4), -NR'R", -(alquilo C_1-C_4)-NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, bencilo, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo, furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$ arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo) , o -S(O)$_z$ (alquilo C_1-C_6), en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1, 2 ó 3 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_6, y en donde las porciones arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una modalidad, la invención proporciona compuestos donde el anillo C es pirimidinilo sustituido con 1 ó 2 grupos que son independientemente -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -C(O)OR', -C(O)NR'R", -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", NO_2, CN, fenilo, -

$S(O)_z$arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo) o $-S(O)_z$ (alquilo C_1-C_6) donde las porciones de arilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una alternativa, el anillo C es pirimidinilo sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alquenilo C_2-C_6, alquinilo C_2-C_6, en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1 ó 2 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_4. En una modalidad alternativa adicional, el anillo C es pirimidinilo sustituido con 1 ó 2 grupos que son independientemente -COOH, -(O)O-(alquilo C_1-C_4), NO_2, CN, o fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En todavía otra modalidad alternativa, el anillo C es pirimidinilo sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alcoxi C_1-C_4, halógeno, -C(O)NR'R", -NR'C(O)R", -OC(O)N-(alquilo C_1-C_6)$_2$, -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), halcalcoxi

C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R".

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-5b, es decir, compuestos de las Fórmulas 4, 4-1, 4-2, 4-3, 5, o una cualquiera de las Fórmulas 6, 6-1, 6-2, 6-3, 6-4, 6-5, 6-6, 6-6a, 6-6b, 6-6c, 6-6d, 6-7, 6-8, 6-9, 6-10, 6-11, 6-11a, 6-11b, 6-11c, 6-12, 6-13, 6-14, o 6-15, en donde el anillo C es

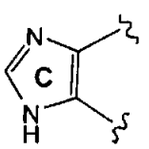
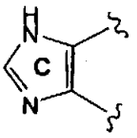


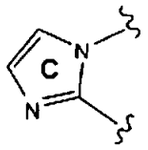
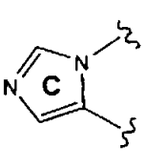
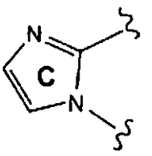
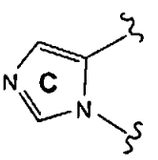
que se sustituye opcionalmente con 1 ó 2 grupos que son independientemente halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, ariloxi, aril-(alcoxi C_1-C_4), haloalquilo C_1-C_4 (en otro aspecto, CF_3), haloalcoxi C_1-C_4 (en otro aspecto, OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_4), -NR'R", -(alquilo C_1-C_4)-NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)Ofenilo, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, bencilo, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo, furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo), o -S(O)$_z$(alquilo C_1-C_6), en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1, 2, ó 3 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_6,

y en donde las porciones arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una modalidad, la invención proporciona compuestos donde el anillo C es pirazina sustituida con 1 ó 2 grupos que son independientemente -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -C(O)OR', -C(O)NR'R", -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", -OC(O)N(alquilo C_1-C_6)$_2$, NO_2, CN, fenilo, -S(O)$_z$ arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo) o -S(O)$_z$(alquilo C_1-C_6) donde las porciones de arilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una modalidad alternativa, el anillo C es pirazina sustituida con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alquenilo C_2-C_6, alquinilo C_2-C_6, en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1 ó 2 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_4. En otro aspecto alternativo, el anillo C es pirazina sustituida con 1 ó 2 grupos que son independientemente -C(O)OH, -C(O)O-(alquilo C_1-C_4), NO_2, CN, o fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son

independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En todavía otra modalidad alternativa, el anillo C es pirazina sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alcoxi C_1-C_4, halógeno, -C(O)NR'R", -NR'C(O)R", -OC(O)N(alquilo C_1-C_6)$_2$, -NR'C(O)O-(alquilo C_1-C_6) o -NR'C(O)O-fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R".

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-5c, es decir, compuestos de la Fórmulas 4, 4-1, 4-2, 4-3, 5, o una cualquiera de las Fórmulas 6, 6-1, 6-2, 6-3, 6-4, 6-5, 6-6, 6-6a, 6-6b, 6-6c, 6-6d, 6-7, 6-8, 6-9, 6-10, 6-11, 6-11a, 6-11b, 6-11c, 6-12, 6-13, 6-14, o 6-15 en donde el anillo C es:

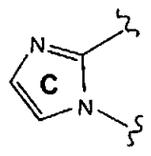






o


cada uno de los cuales se sustituye opcionalmente con 1 ó 2 grupos que son independientemente halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, ariloxi, aril-(alcoxi C_1-C_4), haloalquilo C_1-C_4 (en otro aspecto, CF_3), haloalcoxi C_1-C_4 (en otro aspecto,

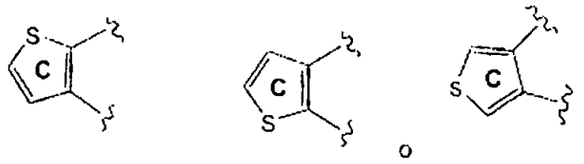
OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_4), -NR'R", -(alquilo C_1-C_6)-NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, bencilo, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo, furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$ arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo), o -S(O)$_z$(alquilo C_1-C_6), en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1, 2, ó 3 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_6, y en donde las porciones arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R".

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-5c1, es decir, compuestos de la Fórmula 7-5c en donde el anillo C es:



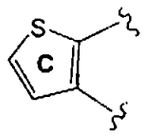
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-5d, es decir, compuestos de la Fórmula 4, 4-1, 4-2, 4-3, 5, o una cualquiera de las Fórmulas 6, 6-1, 6-2, 6-3, 6-4, 6-5, 6-6, 6-6a, 6-6b, 6-6c, 6-6d, 6-7, 6-8, 6-9, 6-10,

6-11, 6-11a, 6-11b, 6-11c, 6-12, 6-13, 6-14, o 6-15, en donde el anillo C es:

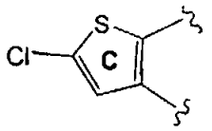


cada uno de los cuales se sustituye opcionalmente con 1 ó 2 grupos que son independientemente halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, ariloxi, aril-(alcoxi C_1-C_4), haloalquilo C_1-C_4 (en otro aspecto, CF_3), haloalcoxi C_1-C_4 (en otro aspecto, OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_4), -NR'R", -(alquilo C_1-C_6)-NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, bencilo, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo, furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$ arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo), o -S(O)$_z$(alquilo C_1-C_6), en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1, 2, ó 3 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_6, y en donde las porciones arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R".

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-5d1, es decir, compuestos de la Fórmula 7-5d en donde el anillo C es:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-5d2, es decir, compuestos de la Fórmula 7-5d en donde el anillo C es:

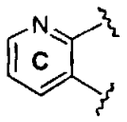


En otro aspecto, la invención proporciona compuestos de la Fórmula 7-6, es decir, compuestos de la Fórmula 7-5, 7-5a, 7-5b, 7-5c o 7-5d, en donde el anillo C no está sustituido.

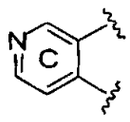
En otro aspecto, la invención proporciona compuestos de la Fórmula 7-7, es decir, compuestos de la Fórmula 7-5, 7-5a, 7-5b, 7-5c o 7-5d, en donde el anillo C se sustituye con 1 ó 2 grupos que son independientemente Cl, F, metilo, etilo, isopropilo, metoxi, etoxi, CF_3, OCF_3, OH, o $C(O)CH_3$.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-8, es decir, compuestos de la Fórmula 7-5, 7-5a, 7-5b, 7-5c o 7-5d, en donde el anillo C se sustituye con 1 ó 2 grupos que son Cl, F, o metilo.

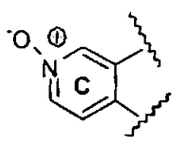
En todavía otro aspecto, la invención proporciona compuestos de las Fórmulas 7-9, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 7-5, 7-6, 7-7, o 7-8, en donde el anillo C presenta la siguiente estructura:



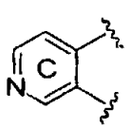
En todavía otro aspecto, la invención proporciona compuestos de las Fórmulas 7-10, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 7-5, 7-6, 7-7, o 7-8, en donde el anillo C presenta la siguiente estructura:



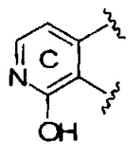
En todavía otro aspecto, la invención proporciona compuestos de las Fórmulas 7-10a, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 7-5, 7-6, 7-7, o 7-8, en donde el anillo C presenta la siguiente estructura:



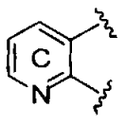
En todavía otro aspecto, la invención proporciona compuestos de las Fórmulas 7-11, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 7-5, 7-6, 7-7, o 7-8, en donde el anillo C presenta la siguiente estructura:



En todavía otro aspecto, la invención proporciona compuestos de las Fórmulas 7-11a, es decir, compuestos de acuerdo con la Fórmula 7-5, en donde el anillo C presenta la siguiente estructura:



En todavía otro aspecto, la invención proporciona compuestos de las Fórmulas 7-12, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 7-5, 7-6, 7-7, o 7-8, en donde el anillo C presenta la siguiente estructura:



En todavía otro aspecto, la invención proporciona compuestos de las Fórmulas 7-13, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 7-5, 7-5a, 7-5b, 7-5c 7-5d, 7-5d1, 7-5d2, 7-6, 7-7, 7-8, 7-9, 7-10, 7-10a, 7-11, 7-11a, o 7-12, en donde R_2 es $-X(CO)Y$ o $-(C(R_3)_2)_{1-4}X(CO)Y$.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-13a, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 7-5, 7-5a, 7-5b, 7-5c 7-5d, 7-5d1, 7-5d2, 7-6, 7-7, 7-8, 7-9, 7-10, 7-10a, 7-11, 7-11a, o 7-12, en donde R_2 es hidrógeno, alquilo C_1-C_3 o cicloalquilo C_3-C_6.

En todavía otro aspecto, la invención proporciona compuestos de las Fórmulas 7-13b, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 7-5, 7-5a, 7-5b, 7-5c 7-5d, 7-5d1, 7-5d2, 7-6, 7-7, 7-8, 7-9, 7-10, 7-10a, 7-11, 7-11a, o 7-12, en donde R_2 es NO_2 o CN.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-13c, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 7-5, 7-5a, 7-5b, 7-5c 7-5d, 7-5d1,

7-5d2, 7-6, 7-7, 7-8, 7-9, 7-10, 7-10a, 7-11, 7-11a, o 7-12, en donde R_2 es alquenilo C_2-C_6 o alquinilo C_2-C_6.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-13d, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 7-5, 7-5a, 7-5b, 7-5c 7-5d, 7-5d1, 7-5d2, 7-6, 7-7, 7-8, 7-9, 7-10, 7-10a, 7-11, 7-11a, o 7-12, en donde R_2 es haloalquilo C_1-C_4.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-13e, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 7-5, 7-5a, 7-5b, 7-5c 7-5d, 7-5d1, 7-5d2, 7-6, 7-7, 7-8, 7-9, 7-10, 7-10a, 7-11, 7-11a, 7-12, 7-13, 7-13a, 7-13b, 7-13c, o 7-13d, en donde R_1 es hidrógeno.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-13f, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 7-5, 7-5a, 7-5b, 7-5c 7-5d, 7-5d1, 7-5d2, 7-6, 7-7, 7-8, 7-9, 7-10, 7-10a, 7-11, 7-11a, o 7-12, en donde R_1 y R_2 combinados son oxo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-13g, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 7-5, 7-5a, 7-5b, 7-5c 7-5d, 7-5d1, 7-5d2, 7-6, 7-7, 7-8, 7-9, 7-10, 7-10a, 7-11, 7-11a, o 7-12, en donde R_1 y R_2 combinados son =N-OR, en donde R es hidrógeno, alquilo C_1-C_6, arilo (tal como fenilo) o arilalquilo (tal como bencilo o fenetilo).

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-13h, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 7-5, 7-5a, 7-5b, 7-5c 7-5d, 7-5d1,

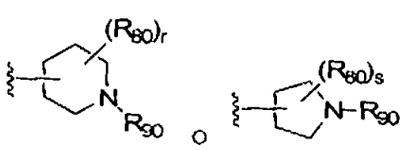
7-5d2, 7-6, 7-7, 7-8, 7-9, 7-10, 7-10a, 7-11, 7-11a, o 7-12, en donde R_1 y R_2 junto con el carbono al que están unidos forman un grupo cicloalquilo C_{3-6}.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-13i, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 7-5, 7-5a, 7-5b, 7-5c 7-5d, 7-5d1, 7-5d2, 7-6, 7-7, 7-8, 7-9, 7-10, 7-10a, 7-11, 7-11a, o 7-12, en donde R_1 y R_2 junto con el carbono al que están unidos forman un grupo ciclopropilo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-13j, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 7-5, 7-5a, 7-5b, 7-5c 7-5d, 7-5d1, 7-5d2, 7-6, 7-7, 7-8, 7-9, 7-10, 7-10a, 7-11, 7-11a, o 7-12, en donde R_1 es hidrógeno y R_2 es ciclopropilo. En una modalidad, el compuesto es racémico. En otra modalidad, el compuesto está enantioméricamente enriquecido.

En todavía otro aspecto, la invención proporciona compuestos de las Fórmulas 7-14, es decir, compuestos de las Fórmulas 7-13, en donde,

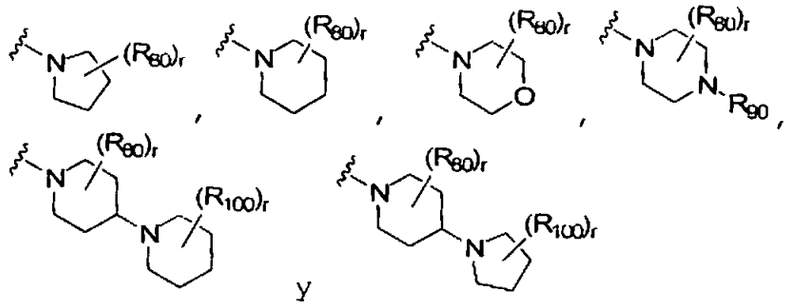
X es O; e Y es $-NR_{60}R_{70}$ o $-N(R_{50})(CH_2)_{2-6}NR_{60}R_{70}$; en donde R_{60} y R_{70} se seleccionan independientemente de: hidrógeno, metilo, etilo, cicloalquilo (C_3-C_8), aril-(alquilo C_1-C_6) (tal como bencilo o fenetilo), 4-piridilmetilo,



o

; o

R_{60} y R_{70} tomados junto con el átomo de nitrógeno al que están unidos forman un grupo heterocicloalquilo seleccionado de



y

en donde

cada R_{80} es alquilo C_1-C_4 independientemente no sustituido o alquilo C_1-C_4 sustituido con hidroxilo o halógeno;

cada R_{90} es independientemente hidrógeno, alquilo C_1-C_4 no sustituido, alquilo C_1-C_4 sustituido con hidroxilo o halógeno, cicloalquilo C_3-C_8 no sustituido, cicloalquilo C_3-C_8 sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}, fenil-(alquilo C_1-C_4), piridil-(alquilo C_1-C_4), tienil-(alquilo C_1-C_4), -C(O)O-(alquilo C_1-C_4), -C(O)O-fenilo, -SO_2-(alquilo C_1-C_6), -SO_2-fenilo, fenilo no sustituido, fenilo sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}, piridilo, tienilo, piridilo sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}, tienilo sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}, en donde

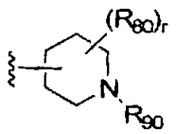
cada R_{50} se selecciona independientemente de: halógeno, alquilo C_1-C_6, haloalquilo C_1-C_6, -OH, -O (alquilo C_1-C_4), OCF_3, -CN, -$NR_{60}R_{70}$, -C(O)O-(alquilo C_1-C_4), -$CONR_{60}R_{70}$, -(alquilo C_1-C_6)-$NR_{60}R_{70}$, -NR_{60}CO-(alquilo C_1-C_4), -NR_{60}CO-fenilo, -NR_{60}CO-piridilo, -NR_{60}CO-tienilo, y -$NR_{60}CONR_{60}R_{70}$,

cada R_{100} es independientemente hidrógeno o alquilo C_1-C_4;

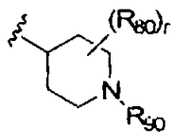
cada r es de 0 a 4; y

cada s es de 0 a 3.

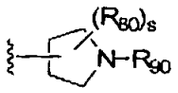
En todavía otro aspecto, la invención proporciona compuestos de las Fórmulas 7-15, es decir, compuestos de las Fórmulas 7-14, en donde dicho grupo



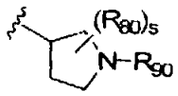
es un grupo de la Fórmula:



y dicho grupo



es un grupo de la Fórmula:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-16, es decir, compuestos de la Fórmula 7-13, en donde Y es -O-(alquilo C_1-C_6). En una modalidad, Y es -O-(alquilo C_1-C_4).

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 7-17, es decir, compuestos de la Fórmula 7-13, en donde Y es -O-fenilo.

En un aspecto adicional, la invención proporciona compuestos de la Fórmula 7-18, es decir, compuestos de acuerdo con cualquiera de las Fórmulas, 7-14, 7-15, 7-16, o 7-17, en donde

R_1 es H o alquilo C_1-C_4. En una modalidad, R_1 es H o metilo. En otra modalidad, R_1 es H.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 8, es decir, compuestos de acuerdo con la Fórmula 6 o cualquiera de las Fórmulas 7, 7-1, 7-1a, 7-2, 7-2a, 7-3, 7-3a, 7-3b, 7-3c, 7-3d, 7-3e, 7-3f, 7-3g, 7-3h, 7-3i, 7-4, 7-4a, 7-4aa, 7-4a1, 7-4a2, 7-4a3, 7-4a4, 7-4a5, 7-4a6, 7-4a7, 7-4a8, 7-4a9, 7-4a10, 7-4b, 7-4c, 7-4c1, 7-4c2, 7-4d, 7-4d1, 7-5, 7-5a, 7-5b, 7-5c, 7-5c1, 7-5d, 7-5d1, 7-5d2, 7-6, 7-7, 7-8, 7-9, 7-10, 7-10a, 7-11, 7-11a, 7-12, 7-13, 7-13a, 7-13b, 7-13c, 7-13d, 7-13e, 7-13f, 7-13g, 7-13h, 7-13i, 7-13j, 7-14, 7-15, 7-16, 7-17, o 7-18 en donde

R_3 y R_3' son hidrógeno, halógeno, alquilo C_1-C_6, alcoxi C_1-C_6, CF_3, CN;

R_4 es hidrógeno, halógeno, alquilo C_1-C_6, alcoxi C_1-C_6, haloalquilo C_1-C_6, haloalcoxi C_1-C_6, CN, $-SO_2$-(alquilo C_1-C_6), o -NR'R",

R_{10} y R_{11} son independientemente hidrógeno, o metilo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 8-1, es decir, compuestos de la Fórmula 8, en donde R_3 y R_3' son independientemente hidrógeno, halógeno, o metilo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 8-2, es decir, compuestos de la Fórmula 8, en donde R_4 es hidrógeno, F, Cl, alcoxi C_1-C_6, CH_2F, CHF_2, CF_3, OCF_3, $OCHF_2$, OCH_2F, o CN.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 8-3, es decir, compuestos de la Fórmula 8 en donde R_4 es, $-SO_2-$(alquilo C_1-C_6), o $-NR'R''$,

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 8-4, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 8, 8-1, 8-2, u 8-3, en donde R_3, $R_{3'}$ R_{10} y R_{11} son hidrógeno.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 8-5, es decir, compuestos de la Fórmula 8, 8-1, 8-2, u 8-4, en donde R_4 es CF_3.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 8-6, es decir, compuestos de las Fórmulas 8, 8-1, 8-2, o 8-4, en donde R_4 es cloro. En una modalidad, R_4 es Cl, mientras que R_3, $R_{3'}$, R_{10} y R_{11} son H.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 8-7, es decir, compuestos de la Fórmula 8, 8-1, 8-2, u 8-4, en donde R_4 es flúor.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 8-8, es decir, compuestos de la Fórmula 8, 8-1, 8-2, u 8-4, en donde R_4 es OCF_3.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 8-9, es decir, compuestos de la Fórmula 8-5, 8-6, 8-7 u 8-8, en donde el anillo B es un anillo de pirazolilo, el anillo C es un anillo de fenilo opcionalmente sustituido con halógeno, alquilo C_1-C_6, alcoxi C_1-C_6, haloalquilo, haloalcoxi, OH o $OC(O)N$(alquilo C_1-C_6)$_2$; R_1 es hidrógeno o alquilo C_1-C_6, y R_2 es hidrógeno, alquilo C_1-C_6, cicloalquilo C_3-

$_6$, o haloalquilo. En una modalidad, el anillo C está sustituido al menos en la posición 7. En otra modalidad, el anillo C está sustituido al menos en la posición 8. En todavía otra modalidad, el anillo C está sustituido en las posiciones 7 y 8.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 8-10, esto es compuestos de la Fórmula 8-5, 8-6, 8-7, o 8-8, en donde el anillo B es un anillo de pirazolilo, el anillo C es un anillo de fenilo opcionalmente sustituido con uno o más grupos que son independientemente halógeno (tal como F o Cl), alquilo C_1-C_6, alcoxi C_1-C_6, haloalquilo (Como CF_3), haloalcoxi (tal como OCF_3), OH o OC(O)N(alquilo C_1-C_6)$_2$; y R_1 y R_2 juntos forman un grupo cicloalquilo, oxo o C=N-OR donde R es hidrógeno, alquilo o fenilo. En una modalidad, el anillo C está sustituido al menos en la posición 7. En otra modalidad, el anillo C está sustituido al menos en la posición 8. En todavía otra modalidad, el anillo C está sustituido en las dos posiciones 7 y 8.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 8-11, esto es compuestos de la Fórmula 8-5. 8-6, 8-7 o 8-8, en donde el anillo B es un anillo de pirazolilo, el anillo C es un anillo de piridilo o un anillo de N-óxido de piridilo opcionalmente sustituido con halógeno, alquilo C_1-C_6, alcoxi C_1-C_6, haloalquilo, haloalcoxi, OH u OC(O)N(alquilo C_1-C_6)$_2$; R_1 es hidrógeno o alquilo C_1-C_6, y R_2 es hidrógeno, alquilo C_1-C_6, cicloalquilo C_{3-6} o haloalquilo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 8-11a, esto es compuestos de la Fórmula 8-11, en donde el anillo B y el anillo C junto con el anillo de piperidina forman una 4,5-dihidro-2H-pirazolo[4,3-c][1,7]naftiridina opcionalmente sustituida.

En todavía otro aspecto, la invención proporciona compuestos de las Fórmulas 8-11b, esto es compuestos de las Fórmulas 8-11, en donde el anillo B y el anillo C junto con el anillo de piperidina forman un 7-óxido de 4,5-dihidro-2H-pirazol[4,3-c][1,7]naftiridina opcionalmente sustituido.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 8-11c, esto es compuestos de la Fórmula 8-11, en donde el anillo B y el anillo C junto con el anillo de piperidina forman una 4,5-dihidro-2H-pirazolo[4,3-c][1,8]naftiridina opcionalmente sustituida.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 8-11d, esto es compuestos de la Fórmula 8-11, en donde el anillo B y el anillo C junto con el anillo de piperidina forman un 8-óxido de 4,5-dihidro-2H-pirazol[4,3-c][1,8]naftiridina opcionalmente sustituido.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 8-11e, esto es compuestos de cualquiera de las Fórmulas 8-12, 8-12a, 8-12b, 8-12c, 8-12d, en donde R_1 es H y R_2 es cicloalquilo. En una modalidad, R_2 es ciclopropilo, ciclopentilo, o ciclohexilo. En todavía otra modalidad, R_2 es ciclopropilo. En otra modalidad, el compuesto es racémico. En

todavía otra modalidad, el compuesto está enantioméricamente enriquecido.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 8-12, esto es compuestos de la Fórmula 8-5. 8-6, 8-7 o 8-8, en donde el anillo B es un anillo de pirazolilo, el anillo C es un anillo de piridilo o un anillo de N-óxido de piridilo opcionalmente sustituido con halógeno, alquilo C_1-C_6, alcoxi C_1-C_6, haloalquilo, haloalcoxi, OH u OC(O)N(alquilo C_1-C_6)$_2$; y R_1 y R_2 juntos forman un grupo cicloalquilo, oxo o C=N-OR donde R es hidrógeno, alquilo o fenilo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 8-12a, esto es compuestos de la Fórmula 8-12, en donde el anillo B y el anillo C junto con el anillo de piperidina forman una 4,5-dihidro-2H-pirazol[4,3-c][1,7]naftiridina opcionalmente sustituida.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 8-12b, esto es compuestos de la Fórmula 8-12, en donde el anillo B y el anillo C junto con el anillo de piperidina forman un 7-óxido de 4,5-dihidro-2H-pirazol[4,3-c][1,7]naftiridina.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 8-12c, esto es compuestos de la Fórmula 8-12, en donde el anillo B y el anillo C junto con el anillo de piperidina forman una 4,5-dihidro-2H-pirazol[4,3-c][1,8]naftiridina opcionalmente sustituida.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 8-12d, esto es compuestos de la Fórmula 8-12, en

donde el anillo B y el anillo C junto con el anillo de piperidina forman un 8-óxido de 4,5-dihidro-2H-pirazolo[4,3-c][1,8]naftiridina opcionalmente sustituido.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 8-13, esto es compuestos de cualquiera de las Fórmulas 8-12, 8-12a, 8-12b, 8-12c, 8-12d, en donde R^1 y R^2 juntos forman un anillo cicloalquilo C_3-C_6.

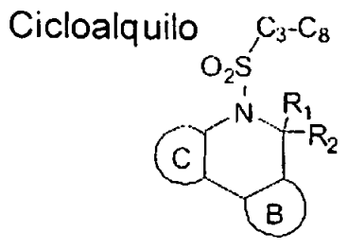
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 8-14, esto es compuestos de cualquiera de las Fórmulas 8-12, 8-12a, 8-12b, 8-12c, 8-12d, en donde R^1 y R^2 juntos son oxo.

En otro aspecto, la invención proporciona compuestos de la Fórmula 9, es decir, compuestos de la Fórmula I, en donde el anillo A es cicloalquilo C_3-C_8, que se sustituye opcionalmente en una posición sustituible con halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, alcoxi C_1-C_6, haloalquilo C_1-C_6, haloalcoxi C_1-C_6, hidroxilo, hidroxi-(alquilo C_1-C_4), CN, NO_2, ariloxi (tal como feniloxi), aril-(alcoxi C_1-C_4) (tal como benciloxi), $-SO_2$-(alquilo C_1-C_6), -NR'R", alcanoilo C_1-C_6, -C(O)OR', -(alquilo C_1-C_4)-C(O)OR', piridilo, fenilo, fenil-(alquilo C_1-C_4), $-SO_2$-NR'R", -C(O)NR'R", -OC(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", -NR'C(O)O-(alquilo C_1-C_6), o NR'C(O)O-fenilo donde cada R' y R" es independientemente hidrógeno o alquilo C_1-C_6 ; y

el anillo B es pirazolilo, imidazolilo, pirrolilo, triazolilo, pirrolidinilo, pirazolidinilo, o imidazolidinilo, cada uno de los cuales se sustituye opcionalmente en una posición

sustituible con un grupo que es independientemente alquilo C_1-C_6, alcoxi C_1-C_6, -NR'R", $-SO_2$-NR'R", -C(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, NO_2, CN, -C(O)OR', hidroxilo, hidroxi-(alquilo C_1-C_6), $-S(O)_z$ (alquilo C_1-C_6), $-S(O)_z$ arilo, halógeno, haloalquilo C_1-C_2, haloalcoxi C1-2, bencilo o fenilo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 10, es decir, compuestos de la Fórmula 9 que tienen la siguiente Fórmula:



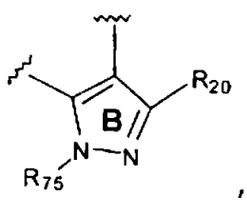
Fórmula 10

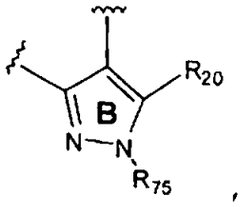
estereoisómeros, tautómeros, mezclas de estereoisómeros y/o tautómeros o sus sales farmacéuticamente aceptables, en donde el grupo cicloalquilo se sustituye opcionalmente en una posición sustituible con halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, alcoxi C_1-C_6, haloalquilo C_1-C_6, haloalcoxi C_1-C_6, hidroxilo, CN, NO_2, ariloxi, aril-(alcoxi C_1-C_4), $-SO_2$-(alquilo C_1-C_6), -NR'R", alcanoilo C_1-C_6, -C(O)OR', -(alquilo C_1-C_4)-C(O)OR', piridilo, fenilo, fenil-(alquilo C_1-C_4), $-SO_2$-NR'R", -C(O)NR'R", -OC(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", o -NR'C(O)OR', en donde cada R' y R" es independientemente hidrógeno o alquilo C_1-C_6 ; y

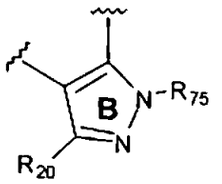
el anillo C es ciclohexilo, fenilo, tienilo, imidazolinilo, tiazolilo, isotiazolilo, oxazolilo, isoxazolilo, pirrolilo,

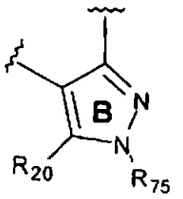
pirazolilo, pirimidilo, pirazinilo o piridilo, cada uno de los cuales se sustituye opcionalmente en cada posición sustituible con grupos que son independientemente halógeno, alquilo C_1-C_6, alcoxi C_1-C_6, ariloxi, aril-(alcoxi C_1-C_6), haloalquilo C_1-C_6, haloalcoxi C_1-C_6, hidroxilo, hidroxi-(alquilo C_1-C_6), -NR'R", -(alquilo C_1-C_4)-NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, oxo, bencilo, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo, furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo), o -S(O)$_z$(alquilo C_1-C_6), en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1, 2 ó 3 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_6, y en donde las porciones arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, ó 2 grupos que son independientemente alquilo C_1-C_4, alcoxi C_1-C_4, halógeno, CF_3, OCF_3, hidroxi, hidroxi-(alquilo C_1-C_4), o -NR'R". En todavía otro aspecto, la invención proporciona compuestos de las Fórmulas 10-1, es decir, compuestos de la Fórmula 10, en donde el anillo B es pirazolilo, imidazolilo, pirrolilo, triazolilo, pirrolidinilo, pirazolidinilo, imidazolidinilo, piridilo, pirimidilo, o isoxazolilo, cada uno de los cuales está no sustituido.

En todavía otro aspecto, la invención proporciona compuestos de las Fórmulas 10-2, es decir, compuestos de la Fórmula 10, en donde el anillo B tiene la Fórmula:



,


,


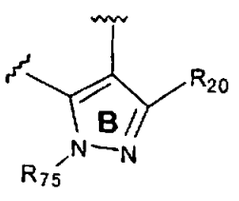
o


en donde

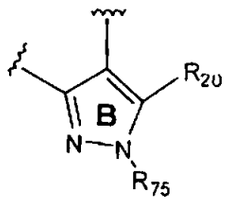
R_{20} es hidrógeno, alquilo C_1-C_6, alcoxi C_1-C_6, -NR'R", -(alquilo C_1-C_4)-NR'R", -S(O)$_2$ (alquilo C_1-C_6), hidroxilo, halógeno, CN, NO_2, CH_2F, CHF_2, CF_3, -C(O)OR', -C(O)NR'R", -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", o fenilo, y

R_{75} es hidrógeno, alquilo C_1-C_6, alcanoilo C_1-C_6, fenil-(alcanoilo C_1-C_6), -C(O)NR'R", -S(O)$_2$(alquilo C_1-C_6), -S(O)$_2$-arilo, -SO_2NR'R", fenilo, fenilalquilo C_1-C_6 (preferiblemente fenetilo o bencilo, más preferiblemente, bencilo), fenilcarbonilo, bencilcarbonilo, o heteroarilcarbonilo, en donde el grupo heteroarilo es piridilo, pirimidilo, tienilo o furanilo.

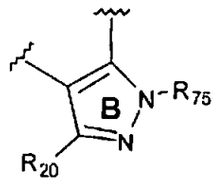
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 10-3, es decir, compuestos de la Fórmula 10-2, en donde el anillo B tiene la Fórmula:



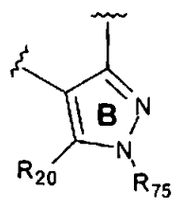
En todavía otro aspecto, la invención proporciona compuestos de las Fórmulas 10-4, es decir, compuestos de la Fórmula 10-2, en donde el anillo B tiene la Fórmula:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 10-5, es decir, compuestos de la Fórmula 10-2, en donde el anillo B tiene la Fórmula:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 10-6, es decir, compuestos de la Fórmula 10-2, en donde el anillo B tiene la Fórmula:



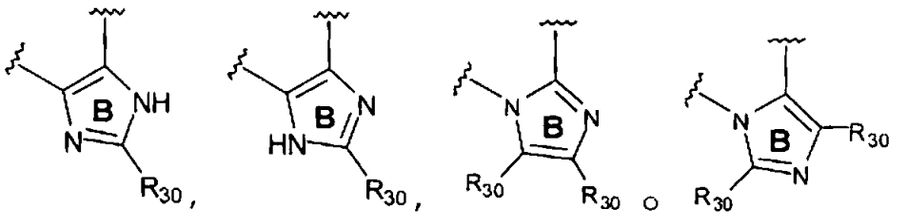
En un aspecto adicional, la invención proporciona compuestos de la Fórmula 10-6a, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 10-2, 10-3, 10-4, 10-5, o 10-6, en donde R_{20} es hidrógeno, alquilo C_1-C_4, CH_2F, CHF_2, CF_3, -C(O)OR', -$S(O)_z$(alquilo C_1-C_4), o hidroxilo; y R_{75} es hidrógeno, alquilo C_1-C_4, o -$S(O)_z$ -fenilo.

En otro aspecto, la invención proporciona compuestos de la Fórmula 10-6b, es decir, compuestos de la Fórmula 10-6a, en donde R_{20} es hidrógeno o metilo, y R_{75} es hidrógeno o metilo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 10-6c, es decir, compuestos de la Fórmula 10-6a, en donde R_{20} es hidrógeno o metilo, y R_{75} es hidrógeno.

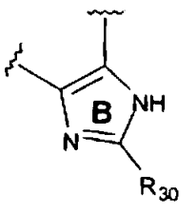
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 10-6d, es decir, compuestos de la Fórmula 10-6a, en donde R_{20} es hidrógeno y R_{75} es hidrógeno.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 10-7, es decir, compuestos de la Fórmula 10, en donde el anillo B tiene la Fórmula:

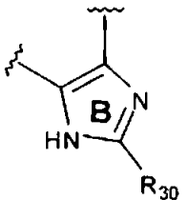


en donde R_{30} es hidrógeno, alquilo C_1-C_4, alcoxi C_1-C_4, -NR'R", alquilo C_1-C_4tio, hidroxilo, halógeno, CH_2F, CHF_2, CF_3, o fenilo.

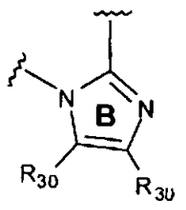
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 10-8, es decir, compuestos de la Fórmula 10-7, en donde el anillo B tiene la Fórmula:



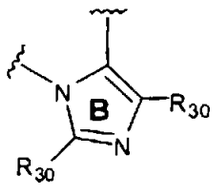
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 10-9, es decir, compuestos de la Fórmula 10-7, en donde el anillo B tiene la Fórmula:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 10-10, es decir, compuestos de la Fórmula 10-7, en donde el anillo B tiene la Fórmula:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 10-11, es decir, compuestos de la Fórmula 10-7, en donde el anillo B tiene la Fórmula:

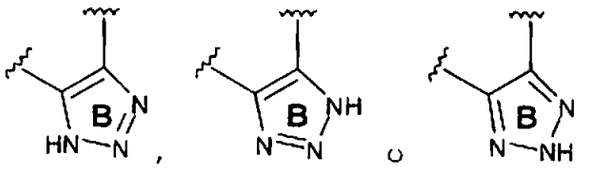


En un aspecto adicional, la invención proporciona compuestos de la Fórmula 10-11a, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 10-8, 10-9, 10-10, o 10-11, en donde cada R_{30} es independientemente hidrógeno, alquilo C_1-C_4, CH_2F, CHF_2, o CF_3.

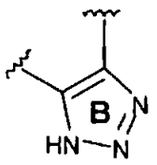
En otro aspecto, la invención proporciona compuestos de la Fórmula 10-11b, es decir, compuestos de la Fórmula 10-11a, en donde cada R_{30} es independientemente hidrógeno o metilo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 10-11c, es decir, compuestos de la Fórmula 10-11a, en donde cada R_{30} es hidrógeno.

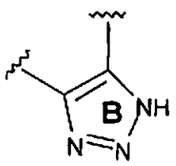
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 10-12, es decir, compuestos de la Fórmula 10, en donde el anillo B tiene la Fórmula:



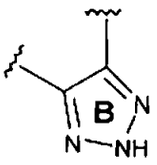
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 10-13, es decir, compuestos de la Fórmula 10-12, en donde el anillo B tiene la Fórmula:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 10-14, es decir, compuestos de la Fórmula 10-12, en donde el anillo B tiene la Fórmula:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 10-15, es decir, compuestos de la Fórmula 10-12, en donde el anillo B tiene la Fórmula:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11, es decir, compuestos de la Fórmula 9 o cualquiera de las Fórmulas 10, 10-1, 10-2, 10-3, 10-4, 10-5, 10-6, 10-6a, 10-6b, 10-6c, 10-6d, 10-7, 10-8, 10-9, 10-10, 10-

11, 10-11a, 10-11b, 10-11c, 10-12, 10-13, 10-14, o 10-15 en donde el anillo C es fenilo o ciclohexilo, que se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, ariloxi, aril-(alcoxi C_1-C_6), haloalquilo C_1-C_4 (en otro aspecto, CF_3), haloalcoxi C_1-C_4 (en otro aspecto, OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_4), -NR'R", -(alquilo C_1-C_4)-NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, oxo, bencilo, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo, furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$ arilo, o -S(O)$_z$(alquilo C_1-C_6), en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1 ó 2 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_6, y en donde las porciones arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una modalidad, el anillo C es un fenilo opcionalmente sustituido.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-1, es decir, compuestos de la Fórmula 11 en donde el anillo C es fenilo no sustituido.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-1a, es decir, compuestos de la Fórmula 11 en donde el anillo C es ciclohexilo no sustituido.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-2, es decir, compuestos de la Fórmula 11, en donde el anillo C es fenilo sustituido con 1 ó 2 grupos que son independientemente Cl, F, metilo, etilo, isopropilo, metoxi, etoxi, CF_3, OCF_3, OH, CH_2OH, NH_2, $NH(CH_3)$, $N(CH_3)_2$ o $-OC(O)N(CH_3)_2$. En una modalidad, el anillo C está bis-sustituido con al menos un halógeno. En otra modalidad, el halógeno es F. En todavía otra modalidad, el halógeno es Cl. En otra modalidad, el anillo C está bis-sustituido con dos halógenos, que son idénticos o diferentes. En todavía otra modalidad, el anillo C está sustituido al menos en la posición 7. En otra modalidad, el anillo C está sustituido en las posiciones 7 y 8. En otra modalidad, el anillo C está monosustituido con un halógeno. En otra modalidad, el halógeno es F. En todavía otra modalidad, el halógeno es Cl. En todavía otra modalidad, el anillo C está sustituido en la posición 7. En todavía otra modalidad, el anillo C está sustituido en la posición 8.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-2a, es decir, compuestos de la Fórmula 11, en donde el anillo C es fenilo sustituido con 1 ó 2 grupos que son independientemente $-NR'C(O)O-$(alquilo C_1-C_6), $-NR'C(O)O-$fenilo, $-C(O)OR'$, $-C(O)NR'R''$, $-OC(O)NR'R''$, $-NR'C(O)NR'R''$; $-$(alquilo C_1-C_6)$-C(O)OR'$, $-$(alquilo C_1-C_6)$-C(O)NR'R''$, $-NR'C(O)R''$, NO_2, CN, fenilo, $-S(O)_z$ fenilo, o $-S(O)_z$(alquilo C_1-C_6), en

donde las porciones fenilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una modalidad, el anillo C está sustituido al menos en la posición 7. En otra modalidad, el anillo C está sustituido al menos en la posición 8.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-2b, es decir, compuestos de la Fórmula 11, en donde el anillo C es fenilo sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alquenilo C_2-C_6, alquinilo C_2-C_6, en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1 ó 2 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_4. En una modalidad, el anillo C está sustituido al menos en la posición 7. En otra modalidad, el anillo C está sustituido al menos en la posición 8.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-2c, es decir, compuestos de la Fórmula 11, en donde el anillo C es fenilo sustituido con 1 ó 2 grupos que son independientemente -C(O)OH, -C(O)O-(alquilo C_1-C_4), NO_2, CN, o fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una

modalidad, el anillo C está sustituido al menos en la posición 7. En otra modalidad, el anillo C está sustituido al menos en la posición 8.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-2d, es decir, compuestos de la Fórmula 11, en donde el anillo C es fenilo sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R", -NR'C(O)O-(alquilo C_1-C_6), o -NR'C(O)O-fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una modalidad, el anillo C está sustituido al menos en la posición 7. En otra modalidad, el anillo C está sustituido al menos en la posición 8.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-2e, es decir, compuestos de la Fórmula 11, en donde el anillo C es ciclohexilo sustituido con 1 ó 2 grupos que son independientemente Cl, F, metilo, etilo, isopropilo, metoxi, etoxi, CF_3, OCF_3, OH, CH_2OH, NH_2, $NH(CH_3)$, $N(CH_3)_2$, o -$OC(O)N(CH_3)_2$.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-2f, es decir, compuestos de la Fórmula 11, en donde el anillo C es ciclohexilo sustituido con 1 ó 2 grupos que son independientemente -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -

$NR'C(O)NR'R''$; -(alquilo C_1-C_4)-$C(O)OR'$, -(alquilo C_1-C_4)-$C(O)NR'R''$, $-NR'C(O)R''$, NO_2, CN, fenilo, $-S(O)_z$ fenilo, o $-S(O)_z$ (alquilo C_1-C_6), en donde las porciones fenilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o $-NR'R''$.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-2g, es decir, compuestos de la Fórmula 11, en donde el anillo C es ciclohexilo sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alquenilo C_2-C_6, alquinilo C_2-C_6, en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1 ó 2 grupos que son independientemente halógeno, hidroxilo, $-NR'R''$ o alcoxi C_1-C_4.

En todavia otro aspecto, la invención proporciona compuestos de la Fórmula 11-2h, es decir, compuestos de la Fórmula 11, en donde el anillo C es ciclohexilo sustituido con 1 ó 2 grupos que son independientemente $-C(O)OH$, -$C(O)O$-(alquilo C_1-C_4), NO_2, CN, o fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o $-NR'R''$.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-2i, es decir, compuestos de la Fórmula 11, en donde el anillo C es ciclohexilo sustituido con 1 ó 2 grupos

que son independientemente alquilo C_1-C_4, alcoxi C_1-C_4, halógeno, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R", -NR'C(O)O-(alquilo C_1-C_6) o -NR'C(O)O-fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R".

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-3, es decir, compuestos de la Fórmula 11, en donde el anillo C es fenilo o ciclohexilo sustituido con 1 ó 2 grupos que son Cl, F, metilo, etilo, isopropilo, metoxi, CF_3, OCF_3, OH, NH_2, $NH(CH_3)$, $N(CH_3)_2$ o $-OC(O)N(CH_3)_2$.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-3a, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 11, 11-1, 11-2, o 11-3, en donde R_2 es -X(CO)Y o $-(C(R_3)_2)_{1-4}X(CO)Y$.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-3a1, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-2e, 11-2f, 11-2g, 11-2h, 11-2i, o 11-3, en donde R_2 es hidrógeno, alquilo C_1-C_3 o cicloalquilo C_{3-6}.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-3a2, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-2e, 11-2f, 11-2g, 11-2h, 11-2i, o 11-3, en donde R_2 es NO_2 o CN.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-3a3, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-2e, 11-2f, 11-2g, 11-2h, 11-2i, o 11-3, en donde R_2 es alquenilo C_2-C_6 o alquinilo C_2-C_6.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-3a4, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-2e, 11-2f, 11-2g, 11-2h, 11-2i, o 11-3, en donde R_2 es haloalquilo C_1-C_4.

En todavía otro aspecto, la invención proporciona compuestos de las Fórmulas 11-3a5, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-2e, 11-2f, 11-2g, 11-2h, 11-2i, 11-3, 11-3a, 11-3a1, 11-3a2, 11-3a3, o 11-3a4, en donde R_1 es hidrógeno.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-3a6, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-2e, 11-2f, 11-2g, 11-2h, 11-2i, o 11-3, en donde R_1 y R_2 combinados son oxo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-3a7, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-2e, 11-2f, 11-2g, 11-2h, 11-2i u 11-3, en donde R_1 y R_2 combinados son =N-OR, en donde R es hidrógeno, alquilo C_1-C_6, arilo (tal como fenilo) o arilalquilo (Como bencilo o fenetilo).

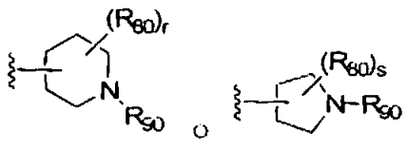
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-3a8, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-2e, 11-2f, 11-2g, 11-2h, 11-2i, o 11-3, en donde R_1 y R_2 junto con el carbono al que están unidos forman un grupo cicloalquilo C_{3-6}.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-3a9, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-2e, 11-2f, 11-2g, 11-2h, 11-2i, o 11-3, en donde R_1 y R_2 junto con el carbono al que están unidos forman un grupo ciclopropilo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-3a10, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-2e, 11-2f, 11-2g, 11-2h, 11-2i, o 11-3, en donde R_1 es hidrógeno y R_2 es ciclopropilo. En una modalidad, el compuesto es racémico. En otra modalidad, el compuesto está enantioméricamente enriquecido.

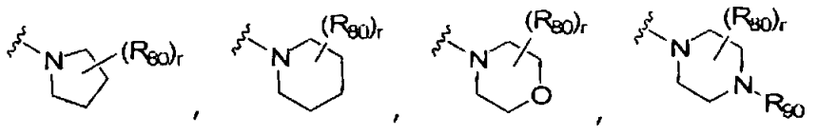
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-3b, es decir, compuestos de la Fórmula 11-3a, donde,

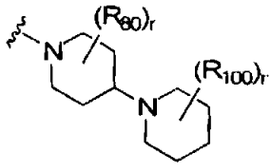
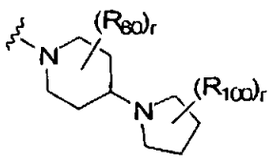
X es O; e Y es $-NR_{60}R_{70}$ o $-N(R_{30})(CH_2)_{2-6}NR_{60}R_{70}$; en donde R_{60} y R_{70} se seleccionan independientemente de: hidrógeno, metilo, etilo, cicloalquilo C_3-C_8, aril-(alquilo C_1-C_6) (tal como bencilo o fenetilo), 4-piridilmetilo,



; o

R_{60} y R_{70} tomados junto con el átomo de nitrógeno al que están unidos forman un grupo heterocicloalquilo seleccionado de




y

;

en donde

cada R_{80} es alquilo C_1-C_4 independientemente no sustituido o alquilo C_1-C_4 sustituido con hidroxi o halógeno;

cada R_{90} es independientemente hidrógeno, alquilo C_1-C_4 no sustituido, alquilo C_1-C_4 sustituido con hidroxi o halógeno, cicloalquilo C_3-C_8 no sustituido, cicloalquilo C_3-C_8 sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}, fenil-(alquilo C_1-C_4), piridil-(alquilo C_1-C_4), tienil-(alquilo C_1-C_4), -C(O)O-(alquilo C_1-C_4), -C(O)O-fenilo, -SO_2-(alquilo C_1-C_6), -SO_2-fenilo, fenilo no sustituido, fenilo sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}, piridilo, tienilo, piridilo sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}, tienilo sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}, en donde

cada R_{50} se selecciona independientemente de: halógeno, alquilo C_1-C_6, -haloalquilo C_1-C_6, -OH, -O(alquilo C_1-C_4), -OCF_3, -CN, -

$NR_{60}R_{70}$, $-C(O)O-$(alquilo C_1-C_4), $-CONR_{60}R_{70}$, -(alquilo C_1-C_6)-$NR_{60}R_{70}$, $-NR_{60}CO-$(alquilo C_1-C_4), $-NR_{60}CO-$fenilo, $-NR_{60}CO-$piridilo, $-NR_{60}CO-$tienilo, y $-NR_{60}CONR_{60}R_{70}$,

cada R_{100} es independientemente hidrógeno o alquilo C_1-C_4;

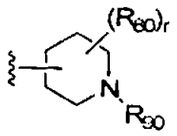
cada r es de 0 a 4; y

cada s es de 0 a 3.

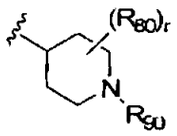
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-3b1, es decir, compuestos de la Fórmula 11-3a, en donde Y es $-O-$(alquilo C_1-C_6). En una modalidad, Y es $-O-$(alquilo C_1-C_4).

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-3b2, es decir, compuestos de la Fórmula 11-3a, en donde Y es -O-fenilo.

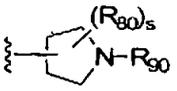
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-3c, es decir, compuestos de la Fórmula 11-3b, en donde dicho grupo



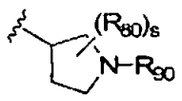
es un grupo de la Fórmula:



y, dicho grupo

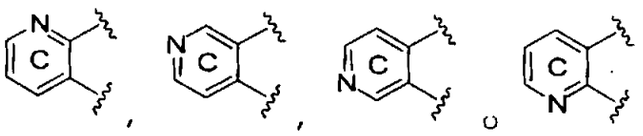


es un grupo de la Fórmula:



En un aspecto adicional, la invención proporciona compuestos de la Fórmula 11-3d, es decir, compuestos de acuerdo con cualquiera de las Fórmulas, 11-3b, 11-3b1, 11-3b2, o 11-3c, en donde R_1 es H o alquilo C_1-C_4. En una modalidad, R_1 es H o metilo. En otra modalidad, R_1 es H.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-4, es decir, compuestos de acuerdo con la Fórmula 9 o cualquiera de las Fórmulas 10, 10-1, 10-2, 10-3, 10-4, 10-5, 10-6, 10-6a, 10-6b, 10-6c, 10-6d, 10-7, 10-8, 10-9, 10-10, 10-11, 10-11a, 10-11b, 10-11c, 10-12, 10-13, 10-14, o 10-15 en donde el anillo C es



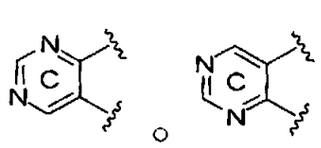
o sus derivados de N-óxido,

cada uno de los cuales se sustituye opcionalmente con 1, 2, ó 3 grupos que son independientemente halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, ariloxi, aril-(alcoxi C_1-C_6), haloalquilo C_1-C_4 (en otro aspecto, CF_3), haloalcoxi C_1-C_4 (en otro aspecto, OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_4), -NR'R", -(alquilo C_1-C_4)-NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, bencilo, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo, furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$ arilo (en donde el grupo arilo es

preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo), o $-S(O)_z$(alquilo C_1-C_6), en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1, 2 ó 3 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_6, y en donde las porciones arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En otra modalidad, la invención proporciona compuestos de la Fórmula 11-4 donde el anillo C es piridilo o N-óxido de piridilo sustituido con 1 ó 2 grupos que son independientemente -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, fenilo, $-S(O)_z$ arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo) o $-S(O)_z$(alquilo C_1-C_6) donde las porciones de arilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una modalidad alternativa, el anillo C es piridilo o N-óxido de piridilo sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alquenilo C_2-C_6, alquinilo C_2-C_6, en donde las porciones alquilo, alquenilo y alquinilo de

los anteriores se sustituyen o no se sustituyen con 1 ó 2 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_4. En otra modalidad alternativa, el anillo C es piridilo o N-óxido de piridilo sustituido con 1 ó 2 grupos que son independientemente -C(O)OH, -C(O)O-(alquilo C_1-C_4), NO_2, CN, o fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En todavía otra modalidad alternativa, el anillo C es piridilo o N-óxido de piridilo sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alcoxi C_1-C_4, halógeno, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R"; -NR'C(O)O-(alquilo C_1-C_6), o -NR'C(O)O-fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R".

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-4a, es decir, compuestos de la Fórmula 9 o cualquiera de las Fórmulas 10, 10-1, 10-2, 10-3, 10-4, 10-5, 10-6, 10-7, 10-8, 10-9, 10-10, 10-11, 10-12, 10-13, 10-14, o 10-15 en donde el anillo C es

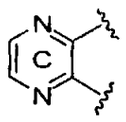


cada uno de los cuales se sustituye opcionalmente con 1 ó 2 grupos que son independientemente halógeno, alquilo C_1-C_4, alcoxi C_1-C_6, ariloxi, aril-(alcoxi C_1-C_4), haloalquilo C_1-C_4 (en otro aspecto, CF_3), haloalcoxi C_1-C_4 (en otro aspecto, OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_4), -NR'R", -(alquilo C_1-C_4)-NR'R",-NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -COR', -C(O)OR', -C(O)NR'R", -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -NR'C(O)R", NO_2, CN, bencilo, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo, furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$ arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo), o -S(O)$_z$ (alquilo C_1-C_6), en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1, 2 ó 3 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_6, y en donde las porciones arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una modalidad, la invención proporciona compuestos de la Fórmula 11-4a donde el anillo C es pirimidinilo sustituido con 1 ó 2 grupos que son independientemente -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, fenilo, -S(O)$_z$ arilo (en donde

el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo) o $-S(O)_2$ (alquilo C_1-C_6) donde las porciones de arilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una modalidad alternativa, el anillo C es pirimidinilo sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alquenilo C_2-C_6, alquinilo C_2-C_6, en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1 ó 2 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_4. En otra modalidad alternativa, el anillo C es pirimidinilo sustituido con 1 ó 2 grupos que son independientemente -C(O)OH, -C(O)O-(alquilo C_1-C_4), NO_2, CN, o fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En todavía otra modalidad alternativa, el anillo C es pirimidinilo sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alcoxi C_1-C_4, halógeno, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R"; o -NR'C(O)O-(alquilo C_1-C_6) o -NR'C(O)O-fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno,

haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R".

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-4b, es decir, compuestos de la Fórmula 9 o cualquiera de las Fórmulas 10, 10-1, 10-2, 10-3, 10-4, 10-5, 10-6, 10-6a, 10-6b, 10-6c, 10-6d, 10-7, 10-8, 10-9, 10-10, 10-11, 10-11a, 10-11b, 10-11c, 10-12, 10-13, 10-14, o 10-15 en donde el anillo C es

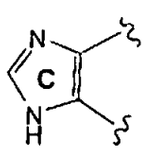
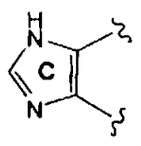


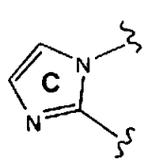
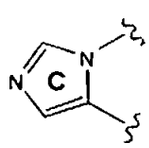
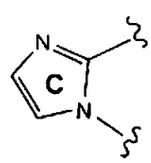
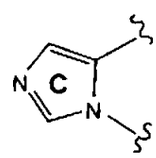
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que se sustituye opcionalmente con 1 ó 2 grupos que son independientemente halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, ariloxi, aril-(alcoxi C_1-C_4), haloalquilo C_1-C_4 (en otro aspecto, CF_3), haloalcoxi C_1-C_4 (en otro aspecto, OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_4), -NR'R", -(alquilo C_1-C_6)-NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, bencilo, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo, furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$ arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo), o -S(O)$_z$(alquilo C_1-C_6), en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1, 2 ó 3 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_6,

y en donde las porciones arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una modalidad, la invención proporciona compuestos de la Fórmula II-4b donde el anillo C es pirazina sustituida con 1 ó 2 grupos que son independientemente -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -C(O)OR', -C(O)NR'R", -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, fenilo, $-S(O)_2$ arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo) o $-S(O)_2$ (alquilo C_1-C_6) donde las porciones de arilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una modalidad alternativa, el anillo C es pirazina sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alquenilo C_2-C_6, alquinilo C_2-C_6, en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1 ó 2 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_4. En otra modalidad alternativa, el anillo C es pirazina sustituido con 1 ó 2 grupos que son independientemente -C(O)OH, -C(O)O-(alquilo C_1-C_4), NO_2, CN, o fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son

independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En todavía otra modalidad alternativa, el anillo C es pirazina sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alcoxi C_1-C_4, halógeno, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R"; -NR'C(O)O-(alquilo C_1-C_6), o -NR'C(O)O-fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-4c, es decir, compuestos de la Fórmula 9 o cualquiera de las Fórmulas 10, 10-1, 10-2, 10-3, 10-4, 10-5, 10-6, 10-6a, 10-6b, 10-6c, 10-6d, 10-7, 10-8, 10-9, 10-10, 10-11, 10-11a, 10-11b, 10-11c, 10-12, 10-13, 10-14, o 10-15 en donde el anillo C es:

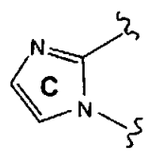

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o


cada uno de los cuales se sustituye opcionalmente con 1 ó 2 grupos que son independientemente halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, ariloxi, aril-(alcoxi C_1-C_4), haloalquilo C_1-C_4 (en otro aspecto, CF_3), haloalcoxi C_1-C_4 (en otro aspecto,

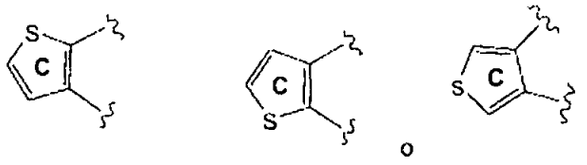
OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_4), -NR'R", -(alquilo C_1-C_6)-NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, bencilo, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo, furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$ arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo), o -S(O)$_z$ (alquilo C_1-C_6), en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1, 2, ó 3 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_6, y en donde las porciones arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R".

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-4c1, es decir, compuestos de la Fórmula 11-4c donde el anillo C es:



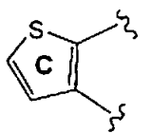
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-4d, es decir, compuestos de la Fórmula 9 o cualquiera de las Fórmulas 10, 10-1, 10-2, 10-3, 10-4, 10-5, 10-6, 10-6a, 10-6b, 10-6c, 10-6d, 10-7, 10-8, 10-9, 10-10, 10-

11, 10-11a, 10-11b, 10-11c, 10-12, 10-13, 10-14, o 10-15 en donde el anillo C es:

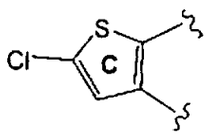


cada uno de los cuales se sustituye opcionalmente con 1 ó 2 grupos que son independientemente halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, ariloxi, aril-(alcoxi C_1-C_4), haloalquilo C_1-C_4 (en otro aspecto, CF_3), haloalcoxi C_1-C_4 (en otro aspecto, OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_4), -NR'R", -(alquilo C_1-C_6)-NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, bencilo, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo, furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$ arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo), o -S(O)$_z$ (alquilo C_1-C_6), en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1, 2, ó 3 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_6, y en donde las porciones arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6) o -NR'R".

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-4d1, es decir, compuestos de la Fórmula 11-4d donde el anillo C es:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-4d2, es decir, compuestos de la Fórmula 11-4d en donde el anillo C es:

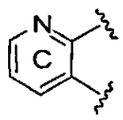


En otro aspecto, la invención proporciona compuestos de la Fórmula 11-5, es decir, compuestos de la Fórmula 11-4, 11-4a, 11-4b, 11-4c o 11-4d, en donde el anillo C está no sustituido.

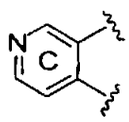
En otro aspecto, la invención proporciona compuestos de la Fórmula 11-5a, es decir, compuestos de la Fórmula 11-4, 11-4a, 11-4b, 11-4c o 11-4d en donde el anillo C se sustituye con 1 ó 2 grupos que son independientemente Cl, F, metilo, etilo, isopropilo, metoxi, etoxi, CF_3, OCF_3, OH, o $C(O)CH_3$.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-5b, es decir, compuestos de la Fórmula 11-4, 11-4a, 11-4b, 11-4c o 11-4d, en donde el anillo C se sustituye con 1 ó 2 grupos que son Cl, F, o metilo.

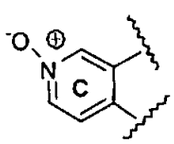
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-5c, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 11-4, 11-5, 11-5a, o 11-5b, en donde el anillo C presenta la siguiente estructura:



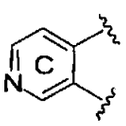
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-5d, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 11-4, 11-5, 11-5a, o 11-5b, en donde el anillo C presenta la siguiente estructura:



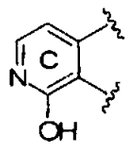
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-5d1, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 11-4, en donde el anillo C presenta la siguiente estructura:



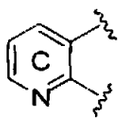
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-5e, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 11-4, 11-5, 11-5a, o 11-5b, en donde el anillo C presenta la siguiente estructura:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-5e1, es decir, compuestos de acuerdo con la Fórmula 11-4, en donde el anillo C presenta la siguiente estructura:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-5f, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 11-4, 11-5, 11-5a, o 11-5b, en donde el anillo C presenta la siguiente estructura:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-5g, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 11-4, 11-4a, 11-4b, 11-4c, 11-4d, 11-5, 11-5a, 11-5b, 11-5c, 11-5d , 11-5d1, 11-5e, 11-5e1, o 11-5f, en donde R_2 es $-X(CO)Y$ o $-(C(R_3)_2)_{1-4}X(CO)Y$.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-5g1, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 11-4, 11-4a, 11-4b, 11-4c, 11-4d, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, o 11-5f, en donde R_2 es H, alquilo C_1-C_3 o ciclopropilo C_3-C_6.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-5g2, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 11-4, 11-4a, 11-4b, 11-4c, 11-4d, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, o 11-5f, en donde R_2 es NO_2 o CN.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-5g3, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 11-4, 11-4a, 11-4b, 11-4c, 11-4d,

11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, o 11-5f, en donde R_2 es alquenilo C_2-C_6 o alquinilo C_2-C_6.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-5g4, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 11-4, 11-4a, 11-4b, 11-4c, 11-4d, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, o 11-5f, en donde R_2 es haloalquilo C_1-C_4.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-5g5, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 11-4, 11-4a, 11-4b, 11-4c, 11-4d, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, o 11-5f, 11-5g, 11-5g1, 11-5g2, 11-5g3, o 11-5g4, en donde R_1 es hidrógeno.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-5g6, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 11-4, 11-4a, 11-4b, 11-4c, 11-4d, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, o 11-5f, en donde R_1 y R_2 combinados son oxo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-5g7, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 11-4, 11-4a, 11-4b, 11-4c, 11-4d, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, o 11-5f, en donde R_1 y R_2 combinados son =N-OR, en donde R es hidrógeno, alquilo C_1-C_6, arilo (tal como fenilo) o arilalquilo(como bencilo o fenetilo).

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-5g8, es decir, compuestos de acuerdo con

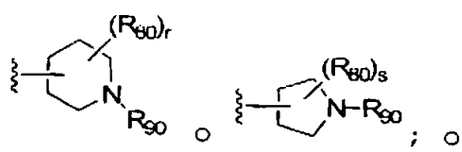
cualquiera de las Fórmulas 11-4, 11-4a, 11-4b, 11-4c, 11-4d, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, o 11-5f, en donde R_1 y R_2 junto con el carbono al que están unidos forman un grupo cicloalquilo C_{3-6}.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-5g9, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 11-4, 11-4a, 11-4b, 11-4c, 11-4d, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, o 11-5f, en donde R_1 y R_2 junto con el carbono al que están unidos forman un grupo ciclopropilo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-5g10, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 11-4, 11-4a, 11-4b, 11-4c, 11-4d, 11-5, 11-5a, 11-5b, 11-5c, 11-5d 11-5e, 11-5e1, o 11-5f, en donde R_1 es hidrógeno y R_2 es ciclopropilo. En una modalidad, el compuesto es racémico. En otra modalidad, el compuesto está enantioméricamente enriquecido.

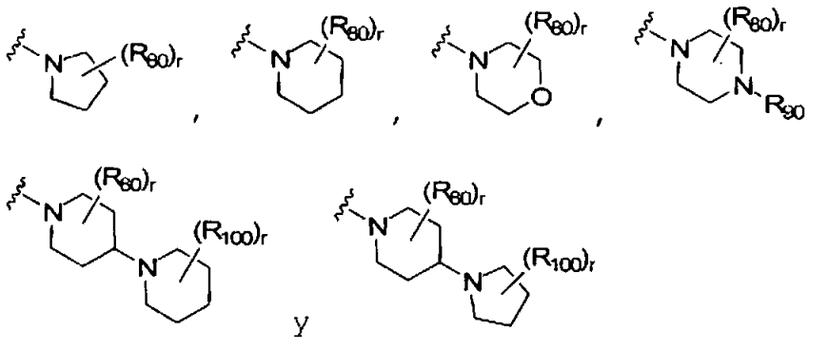
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-5h, es decir, compuestos de la Fórmula 11-5g en donde,

X es O; e Y es $-NR_{60}R_{70}$ o $-N(R_{30})(CH_2)_{2-6}NR_{60}R_{70}$; en donde R_{60} y R_{70} se seleccionan independientemente de: hidrógeno, metilo, etilo, cicloalquilo C_3-C_8, aril-(alquilo C_1-C_6) (tal como bencilo o fenetilo), 4-piridilmetilo,



; o

R_{60} y R_{70} tomados junto con el átomo de nitrógeno al que están unidos forman un grupo heterocicloalquilo seleccionado de



y

en donde

cada R_{80} es alquilo C_1-C_4 independientemente no sustituido o alquilo C_1-C_4 sustituido con hidroxilo o halógeno;

cada R_{90} es independientemente hidrógeno, alquilo C_1-C_4 no sustituido, alquilo C_1-C_4 sustituido con hidroxilo o halógeno, cicloalquilo C_3-C_8 no sustituido, cicloalquilo C_3-C_8 sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}, fenil-(alquilo C_1-C_4)-, piridil-(alquilo C_1-C_4)-, tienil-(alquilo C_1-C_4)-, -C(O)O-(alquilo C_1-C_4), -C(O)O-fenilo, $-SO_2$-(alquilo C_1-C_6) $-SO_2$-fenilo, fenilo no sustituido, fenilo sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}, piridilo, tienilo, piridilo sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}, tienilo sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}, en donde

cada R_{50} se selecciona independientemente de: halógeno, alquilo C_1-C_6, haloalquilo C_1-C_6, -OH, -O-alquilo C_1-C_4, OCF_3, -CN, -$NR_{60}R_{70}$, -C(O)O-(alquilo C_1-C_4), -$CONR_{60}R_{70}$, -(alquilo C_1-C_6)-$NR_{60}R_{70}$, -NR_{60}CO-(alquilo C_1-C_4), -NR_{60}CO-fenilo, -NR_{60}CO-piridilo, -NR_{60}CO-tienilo, y -$NR_{60}CONR_{60}R_{70}$,

cada R_{100} es independientemente hidrógeno o alquilo C_1-C_4;

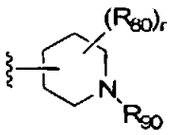
cada r es de 0 a 4; y

cada s es de 0 a 3.

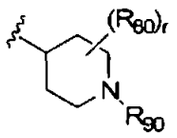
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-5h1, es decir, compuestos de la Fórmula 11-5g, en donde Y es -O-(alquilo C_1-C_6). En una modalidad, Y es -O-(alquilo C_1-C_4).

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-5h2, es decir, compuestos de la Fórmula 11-5g, en donde Y es -O-fenilo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-5i, es decir, compuestos de la Fórmula 11-5h, en donde dicho grupo

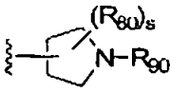


es un grupo de la Fórmula:

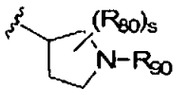


;

y dicho grupo



es un grupo de la Fórmula:



En un aspecto adicional, la invención proporciona compuestos de la Fórmula 11-5j, es decir, compuestos de acuerdo con

cualquiera de las Fórmulas, 11-5h, 11-5h1, 11-5h2, o 11-5i, en donde R_1 es H o alquilo C_1-C_4. En una modalidad, R_1 es H o metilo. En otra modalidad, R_1 es H.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-6, es decir, compuestos de acuerdo con la Fórmula 9 o cualquiera de las Fórmulas 10, 10-1, 10-2, 10-3, 10-4, 10-5, 10-6, 10-6a, 10-6b, 10-6c, 10-6d, 10-7, 10-8, 10-9, 10-10, 10-11, 10-11a, 10-11b, 10-11c, 10-12, 10-13, 10-14, o 10-15 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-2e, 11-2f, 11-2g, 11-2h, 11-2i, 11-3, 11-3a, 11-3a1, 11-3a2, 11-3a3, 11-3a4, 11-3a5, 11-3a6, 11-3a7, 11-3a8, 11-3a9, 11-3a10, 11-3b, 11-3b1, 11-3b2, 11-3c, 11-3d, 11-4, 11-4a, 11-4b, 11-4c, 11-4c1, 11-4d, 11-4d1, 11-4d2, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, 11-5f, 11-5g, 11-5g1, 11-5g2, 11-5g3, 11-5g4, 11-5g5, 11-5g6, 11-5g7, 11-5g8, 11-5g9, 11-5g10, 11-5h, 11-5h1, 11-5h2, 11-5i, o 11-5j, en donde el grupo cicloalquilo C_3-C_8 (el anillo A de la Fórmula I) es ciclopropilo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-7, es decir, compuestos de acuerdo con la Fórmula 9 o cualquiera de las Fórmulas 10, 10-1, 10-2, 10-3, 10-4, 10-5, 10-6, 10-6a, 10-6b, 10-6c, 10-6d, 10-7, 10-8, 10-9, 10-10, 10-11, 10-11a, 10-11b, 10-11c, 10-12, 10-13, 10-14, o 10-15 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-2e, 11-2f, 11-2g, 11-2h, 11-2i, 11-3, 11-3a, 11-3a1, 11-3a2, 11-3a3, 11-3a4, 11-3a5, 11-3a6, 11-3a7, 11-3a8, 11-3a9, 11-3a10, 11-3b, 11-3b1, 11-3b2, 11-3c, 11-3d, 11-4, 11-4a, 11-4b,

11-4c, 11-4c1, 11-4d, 11-4d1, 11-4d2, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, 11-5f, 11-5g, 11-5g1, 11-5g2, 11-5g3, 11-5g4, 11-5g5, 11-5g6, 11-5g7, 11-5g8, 11-5g9, 11-5g10, 11-5h, 11-5h1, 11-5h2, 11-5i, o 11-5j, en donde el grupo cicloalquilo C_3-C_8 (el anillo A de la Fórmula I) es ciclobutilo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-8, es decir, compuestos de acuerdo con la Fórmula 9 o cualquiera de las Fórmulas 10, 10-1, 10-2, 10-3, 10-4, 10-5, 10-6, 10-6a, 10-6b, 10-6c, 10-6d, 10-7, 10-8, 10-9, 10-10, 10-11, 10-11a, 10-11b, 10-11c, 10-12, 10-13, 10-14, o 10-15 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-2e, 11-2f, 11-2g, 11-2h, 11-2i, 11-3, 11-3a, 11-3a1, 11-3a2, 11-3a3, 11-3a4, 11-3a5, 11-3a6, 11-3a7, 11-3a8, 11-3a9, 11-3a10, 11-3b, 11-3b1, 11-3b2, 11-3c, 11-3d, 11-4, 11-4a, 11-4b, 11-4c, 11-4c1, 11-4d, 11-4d1, 11-4d2, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, 11-5f, 11-5g, 11-5g1, 11-5g2, 11-5g3, 11-5g4, 11-5g5, 11-5g6, 11-5g7, 11-5g8, 11-5g9, 11-5g10, 11-5h, 11-5h1, 11-5h2, 11-5i, o 11-5j, en donde el grupo cicloalquilo C_3-C_8 (el anillo A de la Fórmula I) es ciclopentilo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-9, es decir, compuestos de acuerdo con la Fórmula 9 o cualquiera de las Fórmulas 10, 10-1, 10-2, 10-3, 10-4, 10-5, 10-6, 10-6a, 10-6b, 10-6c, 10-6d, 10-7, 10-8, 10-9, 10-10, 10-11, 10-11a, 10-11b, 10-11c, 10-12, 10-13, 10-14, o 10-15 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-

2e, 11-2f, 11-2g, 11-2h, 11-2i, 11-3, 11-3a, 11-3a1, 11-3a2, 11-3a3, 11-3a4, 11-3a5, 11-3a6, 11-3a7, 11-3a8, 11-3a9, 11-3a10, 11-3b, 11-3b1, 11-3b2, 11-3c, 11-3d, 11-4, 11-4a, 11-4b, 11-4c, 11-4c1, 11-4d, 11-4d1, 11-4d2, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, 11-5f, 11-5g, 11-5g1, 11-5g2, 11-5g3, 11-5g4, 11-5g5, 11-5g6, 11-5g7, 11-5g8, 11-5g9, 11-5g10, 11-5h, 11-5h1, 11-5h2, 11-5i, o 11-5j, en donde el grupo cicloalquilo C_3-C_8 (el anillo A de Fórmula I) es ciclohexilo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-10, es decir, compuestos de acuerdo con cualquiera de las Fórmulas la Fórmula 9 o 10, 10-1, 10-2, 10-3, 10-4, 10-5, 10-6, 10-6a, 10-6b, 10-6c, 10-6d, 10-7, 10-8, 10-9, 10-10, 10-11, 10-11a, 10-11b, 10-11c, 10-12, 10-13, 10-14, o 10-15 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-2e, 11-2f, 11-2g, 11-2h, 11-2i, 11-3, 11-3a, 11-3a1, 11-3a2, 11-3a3, 11-3a4, 11-3a5, 11-3a6, 11-3a7, 11-3a8, 11-3a9, 11-3a10, 11-3b, 11-3b1, 11-3b2, 11-3c, 11-3d, 11-4, 11-4a, 11-4b, 11-4c, 11-4c1, 11-4d, 11-4d1, 11-4d2, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, 11-5f, 11-5g, 11-5g1, 11-5g2, 11-5g3, 11-5g4, 11-5g5, 11-5g6, 11-5g7, 11-5g8, 11-5g9, 11-5g10, 11-5h, 11-5h1, 11-5h2, 11-5i, o 11-5j, en donde el grupo cicloalquilo C_3-C_8 (el anillo A de la Fórmula I) es cicloheptilo.

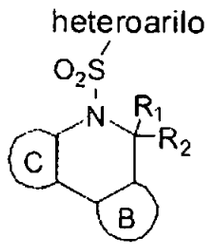
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 11-11, es decir, compuestos de acuerdo con la Fórmula 9 o cualquiera de las Fórmulas 10, 10-1, 10-2, 10-3,

10-4, 10-5, 10-6, 10-6a, 10-6b, 10-6c, 10-6d, 10-7, 10-8, 10-9, 10-10, 10-11, 10-11a, 10-11b, 10-11c, 10-12, 10-13, 10-14, o 10-15 11, 11-1, 11-1a, 11-2, 11-2a, 11-2b, 11-2c, 11-2d, 11-2e, 11-2f, 11-2g, 11-2h, 11-2i, 11-3, 11-3a, 11-3a1, 11-3a2, 11-3a3, 11-3a4, 11-3a5, 11-3a6, 11-3a7, 11-3a8, 11-3a9, 11-3a10, 11-3b, 11-3b1, 11-3b2, 11-3c, 11-3d, 11-4, 11-4a, 11-4b, 11-4c, 11-4c1, 11-4d, 11-4d1, 11-4d2, 11-5, 11-5a, 11-5b, 11-5c, 11-5d, 11-5d1, 11-5e, 11-5e1, 11-5f, 11-5g, 11-5g1, 11-5g2, 11-5g3, 11-5g4, 11-5g5, 11-5g6, 11-5g7, 11-5g8, 11-5g9, 11-5g10, 11-5h, 11-5h1, 11-5h2, 11-5i, o 11-5j, en donde el grupo cicloalquilo C_3-C_8 (el anillo A de la Fórmula I) es ciclooctilo.

En otro aspecto, la invención proporciona compuestos de la Fórmula 12, es decir, compuestos de la Fórmula I, en donde el anillo A es heteroarilo, que es piridilo, pirimidilo, quinolinilo, isoquinolinilo, tienilo, tiazolilo, imidazolilo, pirazolilo, isoxazolilo, o oxazolilo, cada uno de los cuales se sustituye opcionalmente en una posición sustituible con halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, alcoxi C_1-C_6, haloalquilo C_1-C_6, haloalcoxi C_1-C_6, hidroxilo, hidroxi-(alquilo C_1-C_4), CN, NO_2, ariloxi, aril-(alcoxi C_1-C_4) (tal como benciloxi),-SO_2-(alquilo C_1-C_6), -NR'R", alcanoilo C_1-C_6, -C(O)OR', -(alquilo C_1-C_4)-C(O)OR', heteroarilo, arilo, aril-(alquilo C_1-C_4), -SO_2-NR'R", -C(O)NR'R", -OC(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", -NR'C(O)O-(alquilo C_1-C_6) o -NR'C(O)O-fenilo, en donde cada R' y R" es independientemente hidrógeno o alquilo C_1-C_6. En una modalidad, el anillo B es

pirazolilo, imidazolilo, pirrolilo, triazolilo, pirrolidinilo, pirazolidinilo, imidazolidinilo, piridilo, pirimidilo, o isoxazolilo, cada uno de los cuales se sustituye opcionalmente en una posición sustituible con un grupo que es independientemente alquilo C_1-C_6, alcoxi C_1-C_6, -NR'R", -SO_2-NR'R", -C(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, NO_2, CN, -C(O)OR', hidroxilo, hidroxi-(alquilo C_1-C_6), -S(O)$_z$(alquilo C_1-C_6), -S(O)$_z$arilo, halógeno, haloalquilo C_1-C_2, haloalcoxi C_1-C_2, bencilo o fenilo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 13, es decir, compuestos de la Fórmula I o 12 que tienen la siguiente Fórmula:



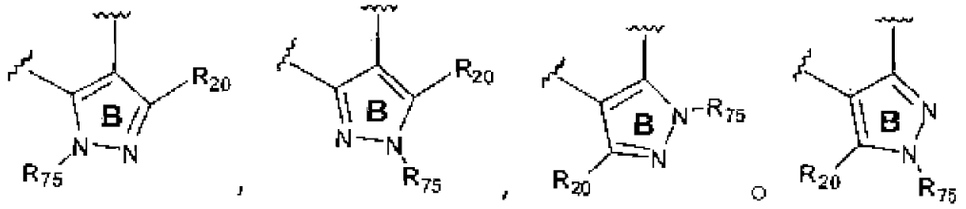
Fórmula 13

estereoisómeros, tautómeros, mezclas de estereoisómeros y/o tautómeros o sus sales farmacéuticamente aceptables. En una modalidad, el grupo heteroarilo se sustituye opcionalmente en una posición sustituible con halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, alcoxi C_1-C_6, haloalquilo C_1-C_6, haloalcoxi C_1-C_6, hidroxilo, hidroxi-(alquilo C_1-C_4), CN, NO_2, ariloxi, aril-(alcoxi C_1-C_4), -SO_2-(alquilo C_1-C_6), -NR'R", alcanoilo C_1-C_6, -C(O)OR', -(alquilo C_1-C_4)-C(O)OR', piridilo, fenilo, fenil-(alquilo C_1-C_4), -SO_2-NR'R", -C(O)NR'R", -

OC(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", o -NR'C(O)OR', en donde cada R' y R" es independientemente hidrógeno o alquilo C_1-C_6 . En otra realización el grupo heteroarilo se sustituye opcionalmente según se describe inmediatamente antes y el anillo C es ciclohexilo, fenilo, tienilo, imidazolinilo, tiazolilo, isotiazolilo, oxazolilo, isoxazolilo, pirrolilo, pirazolilo, pirimidilo, pirazinilo o piridilo, cada uno de los cuales se sustituye opcionalmente en cada posición sustituible con grupos que son independientemente halógeno, alquilo C_1-C_6, alcoxi C_1-C_6, ariloxi, aril-(alcoxi C_1-C_4), haloalquilo C_1-C_6, haloalcoxi C_1-C_6, hidroxilo, hidroxi-(alquilo C_1-C_6), -NR'R", -(alquilo C_1-C_4)-NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, oxo, bencilo, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo, furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$ arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo), o -S(O)$_z$(alquilo C_1-C_6) donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1, 2 ó 3 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_6, y en donde las porciones arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, ó 2 grupos que son independientemente alquilo C_1-C_4, alcoxi C_1-C_4, halógeno, CF_3, OCF_3, hidroxilo, hidroxi-(alquilo C_1-C_4), o -NR'R".

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 13-1, es decir, compuestos de la Fórmula 13, en donde el anillo B es pirazolilo, imidazolilo, pirrolilo, triazolilo, pirrolidinilo, pirazolidinilo, imidazolidinilo, piridilo, pirimidilo, o isoxazolilo, cada uno de los cuales está no sustituido.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 13-2, es decir, compuestos de la Fórmula 13, en donde el anillo B tiene la Fórmula:

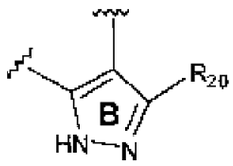


en donde

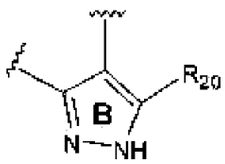
R_{20} es hidrógeno, alquilo C_1-C_6, alcoxi C_1-C_6, $-NR'R''$, -(alquilo C_1-C_4)-$NR'R''$, $-S(O)_2$(alquilo C_1-C_6), halógeno, hidroxilo, CN, NO_2, CH_2F, CHF_2, CF_3, $-C(O)OR'$, $-C(O)NR'R''$, -(alquilo C_1-C_6)-$C(O)OR'$, -(alquilo C_1-C_6)-$C(O)NR'R''$, o fenilo, y

R_{75} es hidrógeno, alquilo C_1-C_6, alcanoilo C_1-C_6, fenil-alcanoilo C_1-C_6, $-C(O)NR'R''$, $-S(O)_2$-(alquilo C_1-C_6), $-S(O)_2$-arilo, $-SO_2NR'R''$, fenilo, fenil-(alquilo C_1-C_6) (preferiblemente fenetilo o bencilo, más preferiblemente, bencilo), fenilcarbonilo, bencilcarbonilo, o heteroarilcarbonilo, en donde el grupo heteroarilo es piridilo, pirimidilo, tienilo o furanilo.

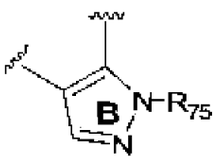
En todavia otro aspecto, la invención proporciona compuestos de la Fórmula 13-3, es decir, compuestos de la Fórmula 13-2, en donde el anillo B tiene la Fórmula:



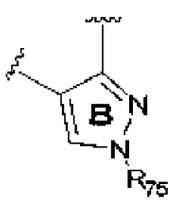
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 13-4, es decir, compuestos de la Fórmula 13-2, en donde el anillo B tiene la Fórmula:



En todavia otro aspecto, la invención proporciona compuestos de la Fórmula 13-5, es decir, compuestos de la Fórmula 13-2, en donde el anillo B tiene la Fórmula:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 13-6, es decir, compuestos de la Fórmula 13-2, en donde el anillo B tiene la Fórmula:



En un aspecto adicional, la invención proporciona compuestos de la Fórmula 13-6a, es decir, compuestos de acuerdo con

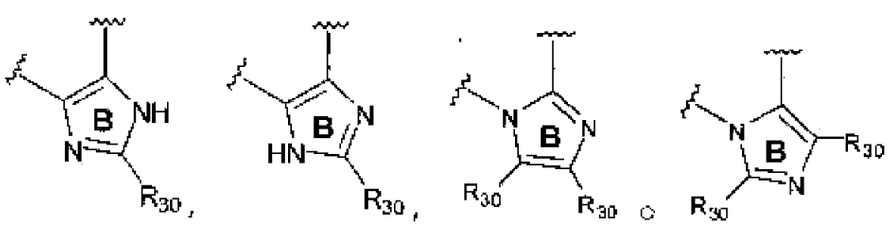
cualquiera de las Fórmulas 13-2, 13-3, o 13-4, en donde R_{20} es hidrógeno, alquilo C_1-C_4, CH_2F, CHF_2, CF_3, -C(O)OR', $-S(O)_2$ (alquilo C_1-C_4), o hidroxilo.

En otro aspecto, la invención proporciona compuestos de la Fórmula 13-6b, es decir, compuestos de la Fórmula 13-6a, en donde R_{20} es hidrógeno o metilo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 13-6c, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 13-2, 13-5 o 13-6, en donde R_{75} es hidrógeno o metilo.

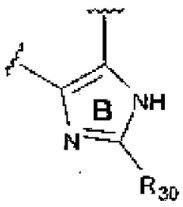
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 13-6d, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 13-2, 13-5 o 13-6, en donde R_{75} es hidrógeno. En una modalidad, R_{20} y R_{75} son ambos hidrógeno.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 13-7, es decir, compuestos de la Fórmula 13-2, en donde el anillo B tiene la Fórmula:

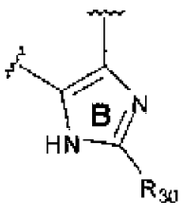


en donde R_{30} es hidrógeno, alquilo C_1-C_4, alcoxi C_1-C_4, -NR'R", alquilo C_1-C_4tio, halógeno, hidroxi, CH_2F, CHF_2, CF_3, o fenilo.

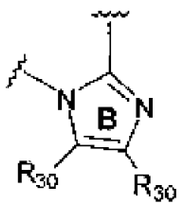
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 13-8, es decir, compuestos de la Fórmula 13-7, en donde el anillo B tiene la Fórmula:



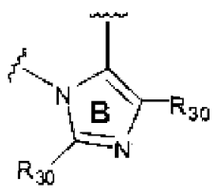
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 13-9, es decir, compuestos de la Fórmula 13-7, en donde el anillo B tiene la Fórmula:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 13-10, es decir, compuestos de la Fórmula 13-7, en donde el anillo B tiene la Fórmula:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 13-11, es decir, compuestos de la Fórmula 13-7, en donde el anillo B tiene la Fórmula:



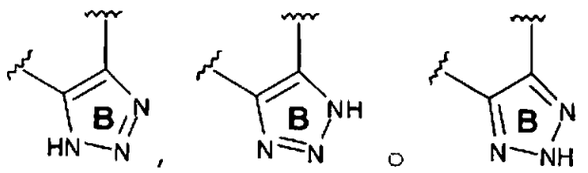
En un aspecto adicional, la invención proporciona compuestos de la Fórmula 13-11a, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 13-8, 13-9, 13-10, o 13-11, en

donde cada R_{30} es independientemente hidrógeno, alquilo C_1-C_4, CH_2F, CHF_2, o CF_3.

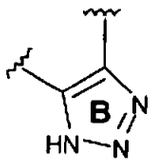
En otro aspecto, la invención proporciona compuestos de la Fórmula 13-11b, es decir, compuestos de la Fórmula 13-11a, en donde cada R_{30} es independientemente hidrógeno o metilo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 13-11c, es decir, compuestos de la Fórmula 13-11a, en donde cada R_{30} es hidrógeno.

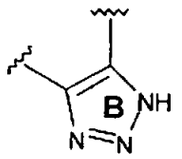
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 13-12, es decir, compuestos de la Fórmula 10, en donde el anillo B tiene la Fórmula:



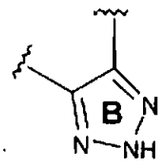
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 13-13, es decir, compuestos de la Fórmula 13-12, en donde el anillo B tiene la Fórmula:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 13-14, es decir, compuestos de la Fórmula 13-12, en donde el anillo B tiene la Fórmula:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 13-15, es decir, compuestos de la Fórmula 13-12, en donde el anillo B tiene la Fórmula:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14, es decir, compuestos de acuerdo con la Fórmula 12 o cualquiera de las Fórmulas 13, 13-1, 13-2, 13-3, 13-4, 13-5, 13-6, 13-6a, 13-6b, 13-6c, 13-6d, 13-7, 13-8, 13-9, 13-10, 13-11, 13-11a, 13-11b, 13-11c, 13-12, 13-13, 13-14, o 13-15, en donde el anillo C es fenilo o ciclohexilo, que se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, ariloxi, aril-(alcoxi C_1-C_4), haloalquilo C_1-C_4 (en otro aspecto, CF_3), haloalcoxi C_1-C_4 (en otro aspecto, OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_4), -NR'R", -(alquilo C_1-C_4)-NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo, furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$ arilo (tal como fenilo), o -S(O)$_z$(alquilo C_1-C_6), en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1 ó 2 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_6, y en donde las porciones arilo o heteroarilo de

los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una modalidad, el anillo C es un fenilo opcionalmente sustituido.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-1, es decir, compuestos de la Fórmula 14 en donde el anillo C es fenilo no sustituido.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-1a, es decir, compuestos de la Fórmula 14 donde el anillo C es ciclohexilo no sustituido.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-2, es decir, compuestos de la Fórmula 14 donde el anillo C es fenilo sustituido con 1 ó 2 grupos que son independientemente Cl, F, metilo, etilo, isopropilo, metoxi, etoxi, CF_3, OCF_3, OH, CH_2OH, NH_2, $NH(CH_3)$, $N(CH_3)_2$, u -$OC(O)N(CH_3)_2$. En una modalidad, el anillo C está bis-sustituido con al menos un halógeno. En otra modalidad, el halógeno es F. En todavía otra modalidad, el halógeno es Cl. En otra modalidad, el anillo C está bis-sustituido con dos halógenos, que son idénticos o diferentes. En todavía otra modalidad, el anillo C está sustituido al menos en la posición 7. En otra modalidad, el anillo C está sustituido en las posiciones 7 y 8. En otra modalidad, el anillo C está monosustituido con un halógeno. En otra modalidad, el halógeno es F. En todavía otra modalidad, el halógeno es Cl. En todavía otra modalidad, el

anillo C está sustituido en la posición 7. En todavía otra modalidad, el anillo C está sustituido en la posición 8.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-2a, es decir, compuestos de la Fórmula 14, en donde el anillo C es fenilo sustituido con 1 ó 2 grupos que son independientemente -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, fenilo, $-S(O)_2$ fenilo, o $-S(O)_2$(alquilo C_1-C_6), en donde las porciones fenilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una modalidad, el anillo C está sustituido al menos en la posición 7. En otra modalidad, el anillo C está sustituido al menos en la posición 8.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-2b, es decir, compuestos de la Fórmula 14, en donde el anillo C es fenilo sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alquenilo C_2-C_6, alquinilo C_2-C_6, en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1 ó 2 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_4. En una modalidad, el anillo C está sustituido al menos en la posición 7. En otra modalidad, el anillo C está sustituido al menos en la posición 8.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-2c, es decir, compuestos de la Fórmula 14, en donde el anillo C es fenilo sustituido con 1 ó 2 grupos que son independientemente -C(O)OH, -C(O)O-(alquilo C_1-C_4), NO_2, CN, o fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una modalidad, el anillo C está sustituido al menos en la posición 7. En otra modalidad, el anillo C está sustituido al menos en la posición 8.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-2d, es decir, compuestos de la Fórmula 14, en donde el anillo C es fenilo sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alcoxi C_1-C_4, halógeno, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R"; o -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una modalidad, el anillo C está sustituido al menos en la posición 7. En otra modalidad, el anillo C está sustituido al menos en la posición 8.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-2e, es decir, compuestos de la Fórmula 14

donde el anillo C es ciclohexilo sustituido con 1 ó 2 grupos que son independientemente Cl, F, metilo, etilo, isopropilo, metoxi, etoxi, CF_3, OCF_3, OH, CH_2OH, NH_2, $NH(CH_3)$, $N(CH_3)_2$, o -$OC(O)N(CH_3)_2$.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-2f, es decir, compuestos de la Fórmula 14, en donde el anillo C es ciclohexilo sustituido con 1 ó 2 grupos que son independientemente -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_4)-C(O)OR', -(alquilo C_1-C_4)-C(O)NR'R", -NR'C(O)R", NO_2, CN, fenilo, -$S(O)_2$ fenilo, o -$S(O)_2$(alquilo C_1-C_6), en donde las porciones fenilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R".

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-2g, es decir, compuestos de la Fórmula 14, en donde el anillo C es ciclohexilo sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alquenilo C_2-C_6, alquinilo C_2-C_6, en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1 ó 2 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_4.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-2h, es decir, compuestos de la Fórmula 14, en donde el anillo C es ciclohexilo sustituido con 1 ó 2 grupos

que son independientemente -C(O)OH, -C(O)O-(alquilo C_1-C_4), NO_2, CN, o fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R".

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-2i, es decir, compuestos de la Fórmula 14, en donde el anillo C es ciclohexilo sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alcoxi C_1-C_4, halógeno, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R"; -NR'C(O)O-(alquilo C_1-C_6) o -NR'C(O)O-fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R".

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-3, es decir, compuestos de la Fórmula 14 donde el anillo C es fenilo o ciclohexilo sustituido con 1 ó 2 grupos que son Cl, F, metilo, isopropilo, metoxi, CF_3, OCF_3, OH, o $-OC(O)N(CH_3)_2$.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-3a, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2e, 14-2f, 14-2g, 14-2h, 14-2i, o 14-3, en donde R_2 es -X(CO)Y o $-(C(R_3)_2)_{1-4}X(CO)Y$.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-3a1, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2e, 14-2f, 14-2g, 14-2h, 14-2i, o 14-3, en donde R_2 es hidrógeno, alquilo C_1-C_3 o ciclopropilo C_3-C_6.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-3a2, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2e, 14-2f, 14-2g, 14-2h, 14-2i, o 14-3, en donde R_2 es NO_2 o CN.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-3a3, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2e, 14-2f, 14-2g, 14-2h, 14-2i, o 14-3, en donde R_2 es alquenilo C_2-C_6 o alquinilo C_2-C_6.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-3a4, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2e, 14-2f, 14-2g, 14-2h, 14-2i, o 14-3, en donde R_2 es haloalquilo C_1-C_4.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-3a5, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2e, 14-2f, 14-2g, 14-2h, 14-2i, 14-3, 14-3a, 14-3a1, 14-3a2, 14-3a3, o 14-3a4, en donde R_1 es hidrógeno.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-3a6, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2e, 14-2f, 14-2g, 14-2h, 14-2i, o 14-3, en donde R_1 y R_2 combinados son oxo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-3a7, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2e, 14-2f, 14-2g, 14-2h, 14-2i, o 14-3, en donde R_1 y R_2 combinados son =N-OR, en donde R es hidrógeno, alquilo C_1-C_6, arilo (tal como fenilo) o arilalquilo(como bencilo o fenetilo).

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-3a8, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2e, 14-2f, 14-2g, 14-2h, 14-2i, o 14-3, en donde R_1 y R_2 junto con el carbono al que están unidos forman un grupo cicloalquilo C_{3-6}.

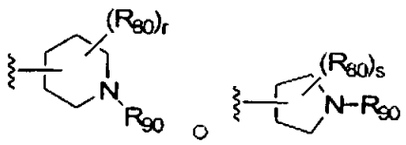
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-3a9, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2e, 14-2f, 14-2g, 14-2h, 14-2i, o 14-3, en donde R_1 y R_2 junto con el carbono al que están unidos forman un grupo ciclopropilo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-3a10, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 14, 14-1, 14-1a, 14-2, 14-2a, 14-

2b, 14-2d, 14-2c, 14-2d, 14-2e, 14-2f, 14-2g, 14-2h, 14-2i, o 14-3, en donde R_1 es hidrógeno y R_2 es ciclopropilo. En una modalidad, el compuesto es racémico. En otra modalidad, el compuesto está enantioméricamente enriquecido.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-3b, es decir, compuestos de la Fórmula 14-3a, en donde

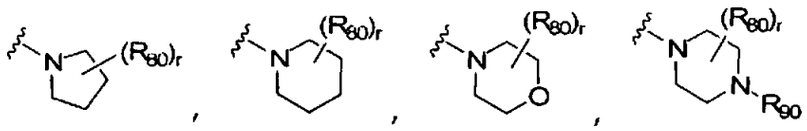
X es O; e Y es $-NR_{60}R_{70}$ o $-N(R_{30})(CH_2)_{2-6}NR_{60}R_{70}$; en donde R_{60} y R_{70} se seleccionan independientemente de: hidrógeno, metilo, etilo, cicloalquilo (C_3-C_8), aril-alquilo (C_1-C_6) (tal como bencilo o fenetilo), 4-piridilmetilo,



o

; o

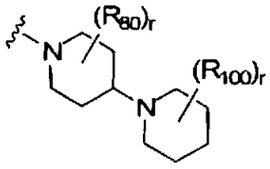
R_{60} y R_{70} tomados junto con el átomo de nitrógeno al que están unidos forman un grupo heterocicloalquilo seleccionado de



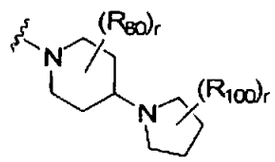
,

,

,



y



donde,

cada R_{80} es alquilo C_1-C_4 independientemente no sustituido o alquilo C_1-C_4 sustituido con hidroxilo o halógeno;

cada R_{90} es independientemente hidrógeno, alquilo C_1-C_4 no sustituido, alquilo C_1-C_4 sustituido con hidroxilo o halógeno,

cicloalquilo C_3-C_8 no sustituido, cicloalquilo C_3-C_8 sustituido con uno o más (por ejemplo, 1-4) R_{50}, fenil-(alquilo C_1-C_4)-, piridil-(alquilo C_1-C_4)-, tienil-(alquilo C_1-C_4)-, -C(O)O-(alquilo C_1-C_4), -C(O)O-fenilo, $-SO_2$-(alquilo C_1-C_6), $-SO_2$-fenilo, fenilo no sustituido, fenilo sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}, piridilo, tienilo, piridilo sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}, tienilo sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}, en donde

cada R_{50} se selecciona independientemente de: halógeno, alquilo C_1-C_6, haloalquilo C_1-C_6, -OH, -O (alquilo C_1-C_4), OCF_3, -CN, -$NR_{60}R_{70}$, -C(O)O-(alquilo C_1-C_4), -$CONR_{60}R_{70}$, -(alquilo C_1-C_6)-$NR_{60}R_{70}$, -NR_{60}CO-(alquilo C_1-C_4), -NR_{60}CO-fenilo, -NR_{60}CO-piridilo, -NR_{60}CO-tienilo, y -$NR_{60}CONR_{60}R_{70}$,

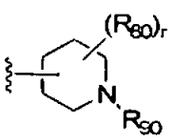
cada R_{100} es independientemente hidrógeno o alquilo C_1-C_4;

cada r es 0 a 4; y

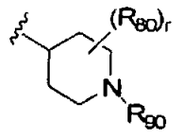
cada s es 0 a 3.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-3b1, es decir, compuestos de la Fórmula 14-3a, en donde Y es -O-(alquilo C_1-C_6). En una modalidad, Y es -O-(alquilo C_1-C_4).

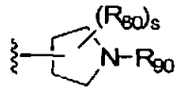
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-3c, es decir, compuestos de la Fórmula 14-3b, en donde dicho grupo



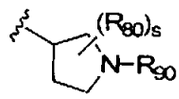
es un grupo de la Fórmula:



y, dicho grupo

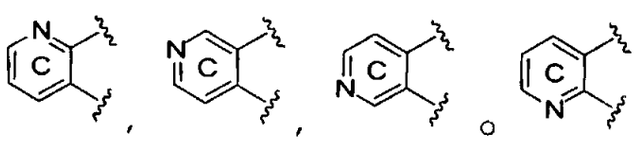


es un grupo de la Fórmula:



En un aspecto adicional, la invención proporciona compuestos de la Fórmula 14-3c1, es decir, compuestos de acuerdo con cualquiera de las Fórmulas, 14-3b, 14-3b1, 14-3b2, o 14-3c, en donde R_1 es H o alquilo C_1-C_4. En una modalidad, R_1 es H o metilo. En otra modalidad, R_1 es H.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-4, es decir, compuestos de acuerdo con la Fórmula 12 o cualquiera de las Fórmulas 13, 13-1, 13-2, 13-3, 13-4, 13-5, 13-6, 13-6a, 13-6b, 13-6c, 13-6d, 13-7, 13-8, 13-9, 13-10, 13-11, 13-11a, 13-11b, 13-11c, 13-12, 13-13, 13-14, o 13-15 el anillo C es



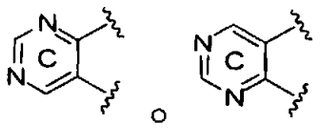
o sus derivados de N-óxido,

cada uno de los cuales se sustituye opcionalmente con 1, 2, ó 3 grupos que son independientemente halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, ariloxi, aril-(alcoxi C_1-C_4), haloalquilo C_1-C_4

(en otro aspecto, CF_3), haloalcoxi C_1-C_4 (en otro aspecto, OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_4), -NR'R", -(alquilo C_1-C_6)-NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -COR', -C(O)OR', -C(O)NR'R", OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, bencilo, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo, furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo), o -S(O)$_z$ (alquilo C_1-C_6), en donde las porciones alquilo, alquenilo y alquinilo de los anteriores están sustituidas o no sustituidos con 1, 2 ó 3 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_6, y en donde las porciones arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una modalidad, la invención proporciona compuestos de la Fórmula 14-4 donde el anillo C es piridilo o N-óxido de piridilo sustituido con 1 ó 2 grupos que son independientemente -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -C(O)OR', -C(O)NR'R", -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R"; NO_2, CN, fenilo, -S(O)$_z$ arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo) o -S(O)$_z$ (alquilo C_1-C_6) donde las porciones de arilo de los anteriores se

sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una modalidad alternativa, el anillo C es piridilo o N-óxido de piridilo sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alquenilo C_2-C_6, alquinilo C_2-C_6, en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1 ó 2 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_4. En otra modalidad alternativa, el anillo C es piridilo o N-óxido de piridilo sustituido con 1 ó 2 grupos que son independientemente -C(O)OH, -C(O)O-(alquilo C_1-C_4), NO_2, CN, o fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En todavía otra modalidad alternativa, el anillo C es piridilo o N-óxido de piridilo sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alcoxi C_1-C_4, halógeno, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R"; o -NR'C(O)O-(alquilo C_1-C_6), o -NR'C(O)O-fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-alquilo C_1-C_6, o -NR'R".

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-4a, es decir, compuestos de la Fórmula 12 o cualquiera de las Fórmulas 13, 13-1, 13-2, 13-3, 13-4, 13-5, 13-6, 13-6a, 13-6b, 13-6c, 13-6d, 13-7, 13-8, 13-9, 13-10, 13-11, 13-11a, 13-11b, 13-11c, 13-12, 13-13, 13-14, o 13-15, en donde el anillo C es

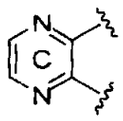


cada uno de los cuales se sustituye opcionalmente con 1 ó 2 grupos que son independientemente halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, alcanoilo C_1-C_6, ariloxi, aril-(alcoxi C_1-C_4), haloalquilo C_1-C_4 (en otro aspecto, CF_3), haloalcoxi C_1-C_4 (en otro aspecto, OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_4), -NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, bencilo, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo, furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$ arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo), o -S(O)$_z$ (alquilo C_1-C_6), en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1, 2 ó 3 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_6, y en donde las porciones de arilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son

independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), halcalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una modalidad, la invención proporciona compuestos de la Fórmula 14-4a, en donde el anillo C es pirimidinilo sustituido con 1 ó 2 grupos que son independientemente -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, fenilo, $-S(O)_z$ arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo) o $-S(O)_z$ (alquilo C_1-C_6) donde las porciones de arilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -R'R". En una modalidad alternativa, el anillo C es pirimidinilo sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alquenilo C_2-C_6, alquinilo C_2-C_6, en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1 ó 2 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_4. En otra modalidad alternativa, el anillo C es pirimidinilo sustituido con 1 ó 2 grupos que son independientemente -C(O)OH, -C(O)O-(alquilo C_1-C_4), NO_2, CN, o fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno,

haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En todavía otra modalidad alternativa, el anillo C es pirimidinilo sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alcoxi C_1-C_4, halógeno, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R"; -NR'C(O)O-(alquilo C_1-C_6), o -NR'C(O)O-fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R".

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-4b, es decir, compuestos de la Fórmula 12 o cualquiera de las Fórmulas 13, 13-1, 13-2, 13-3, 13-4, 13-5, 13-6, 13-6a, 13-6b, 13-6c, 13-6d, 13-7, 13-8, 13-9, 13-10, 13-11, 13-11a, 13-11b, 13-11c, 13-12, 13-13, 13-14, o 13-15, en donde el anillo C es

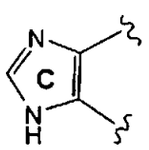
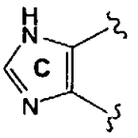
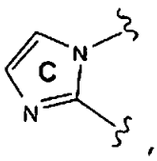
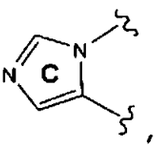
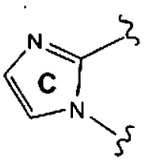
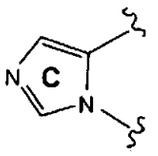


que se sustituye opcionalmente con 1 ó 2 grupos que son independientemente halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, ariloxi, aril-(alcoxi C_1-C_6), haloalquilo C_1-C_4 (en otro aspecto, CF_3), haloalcoxi C_1-C_4 (en otro aspecto, OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_4), -NR'R", -(alquilo C_1-C_4)-NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-

C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, bencilo, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo, furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$ arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo), o -S(O)$_z$(alquilo C_1-C_6), en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1, 2 ó 3 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_6, y en donde las porciones arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una modalidad, la invención proporciona compuestos de la Fórmula 14-4b donde el anillo C es pirazina sustituido con 1 ó 2 grupos que son independientemente -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, fenilo, -S(O)$_z$ arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo) o -S(O)$_z$ (alquilo C_1-C_6) en donde las porciones de arilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una

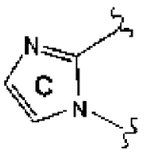
modalidad alternativa, el anillo C es pirazina sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alquenilo C_2-C_6, alquinilo C_2-C_6, en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1 ó 2 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_4. En otra modalidad alternativa, el anillo C es pirazina sustituido con 1 ó 2 grupos que son independientemente -C(O)OH, -C(O)O-(alquilo C_1-C_4), NO_2, CN, o fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En todavía otra modalidad alternativa, el anillo C es pirazina sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alcoxi C_1-C_4, halógeno, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R"; -NR'C(O)O-(alquilo C_1-C_6) o -NR'C(O)O-fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R".

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-4c, es decir, compuestos de la Fórmula 12 o cualquiera de las Fórmulas 13, 13-1, 13-2, 13-3, 13-4, 13-5, 13-6, 13-6a, 13-6b, 13-6c, 13-6d, 13-7, 13-8, 13-9, 13-10, 13-11, 13-11a, 13-11b, 13-11c, 13-12, 13-13, 13-14, o 13-15, en donde el anillo C es:

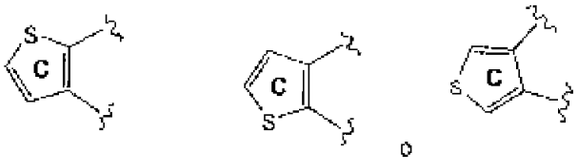







cada uno de los cuales se sustituye opcionalmente con 1 ó 2 grupos que son independientemente halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, ariloxi, aril-(alcoxi C_1-C_4), haloalquilo C_1-C_4 (en otro aspecto, CF_3), haloalcoxi C_1-C_4 (en otro aspecto, OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_4), -NR'R", -(alquilo C_1-C_6)-NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, bencilo, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo, furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -NR'SO_2R", -SO_2-NR'R", -S(O)$_2$arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo), o -S(O)$_2$ (alquilo C_1-C_6), en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1, 2, ó 3 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_6, y en donde las porciones arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R".

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-4c1, es decir, compuestos de la Fórmula 14-4c donde el anillo C es:



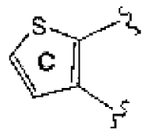
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-4d, es decir, compuestos de la Fórmula 12 o cualquiera de las Fórmulas 13, 13-1, 13-2, 13-3, 13-4, 13-5, 13-6, 13-6a, 13-6b, 13-6c, 13-6d, 13-7, 13-8, 13-9, 13-10, 13-11, 13-11a, 13-11b, 13-11c, 13-12, 13-13, 13-14, o 13-15, en donde el anillo C es:



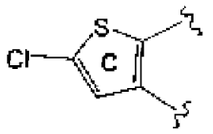
cada uno de los cuales se sustituye opcionalmente con 1 ó 2 grupos que son independientemente halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, ariloxi, aril-(alcoxi C_1-C_4), haloalquilo C_1-C_4 (en otro aspecto, CF_3), haloalcoxi C_1-C_4 (en otro aspecto, OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_4), -NR'R", -(alquilo C_1-C_6)-NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, bencilo, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo, furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -NR'SO_2R", -SO_2-NR'R", -$S(O)_2$ arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente,

fenilo), o $-S(O)_z$ (alquilo C_1-C_6), en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1, 2, ó 3 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_6, y en donde las porciones arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R".

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-4d1, es decir, compuestos de la Fórmula 14-4d en donde el anillo C es:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-4d2, es decir, compuestos de la Fórmula 14-4d donde el anillo C es:



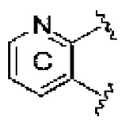
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-5, es decir, compuestos de acuerdo con la Fórmula 14-4, 14-4a, 14-4b, 14-4c, o 14-4d, en donde el anillo C está no sustituido.

En otro aspecto, la invención proporciona compuestos de la Fórmula 14-5a, es decir, compuestos de la Fórmula 14-4, 14-4a, 14-4b, 14-4c, o 14-4d, en donde el anillo C se sustituye con 1

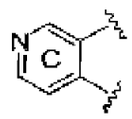
ó 2 grupos que son independientemente Cl, F, metilo, etilo, isopropilo, metoxi, etoxi, CF_3, OCF_3, OH, CH_2OH, o $-C(O)CH_3$.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-5b, es decir, compuestos de la Fórmula 14-4, 14-4a, 14-4b, 14-4c, o 14-4d, en donde el anillo C se sustituye con 1 ó 2 grupos que son independientemente Cl, F, o metilo.

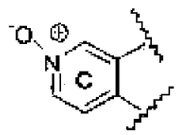
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-5c, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 14-4, 14-5, 14-5a, o 14-4b, en donde el anillo C presenta la siguiente estructura:



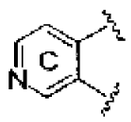
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-5d, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 14-4, 14-5, 14-5a, o 14-5b, en donde el anillo C presenta la siguiente estructura:



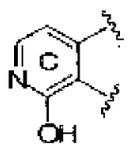
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-5d1, es decir, compuestos de acuerdo con la Fórmula 14-4, en donde el anillo C presenta la siguiente estructura:



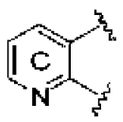
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-5e, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 14-4, 14-5, 14-5a, o 14-5b, en donde el anillo C presenta la siguiente estructura:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-5e1, es decir, compuestos de acuerdo con la Fórmula 14-4, 14-5, 14-5a, o 14-5b, en donde el anillo C presenta la siguiente estructura:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-5f, es decir, compuestos de acuerdo con la Fórmula 14-4, en donde el anillo C presenta la siguiente estructura:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-5g, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 14-4, 14-4a, 14-4b, 14-4c, 14-4d, 14-5, 14-5a, 14-5b, 14-5c, 14-5d 14-5e, 14-5e1, o 14-5f, en donde R_2 es $-X(CO)Y$ o $-(C(R_3)_2)_{1-4}X(CO)Y$.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-5g1, es decir, compuestos de acuerdo con

cualquiera de las Fórmulas 14-4, 14-4a, 14-4b, 14-4c 14-4d, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, o 14-5f, en donde R_2 es hidrógeno, alquilo C_1-C_3 o cicloalquilo C_3-C_6.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-5g2, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 14-4, 14-4a, 14-4b, 14-4c, 14-4d, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, o 14-5f, en donde R_2 es NO_2 o CN.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-5g3, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 14-4, 14-4a, 14-4b, 14-4c, 14-4d, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, o 14-5f, en donde R_2 es alquenilo C_2-C_6 o alquinilo C_2-C_6.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-5g4, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 14-4, 14-4a, 14-4b, 14-4c, 14-4d, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, o 14-5f, en donde R_2 es haloalquilo C_1-C_4.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-5g5, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 14-4, 14-4a, 14-4b, 14-4c, 14-4d, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, 14-5f, 14-5g, 14-5g1, 14-5g2, 14-5g3, o 14-5g4 donde R_1 es hidrógeno.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-5g6, es decir, compuestos de acuerdo con

cualquiera de las Fórmulas 14-4, 14-4a, 14-4b, 14-4c, 14-4d, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, o 14-5f, en donde R_1 y R_2 combinados son oxo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-5g7, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 14-4, 14-4a, 14-4b, 14-4c, 14-4d, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, o 14-5f, en donde R_1 y R_2 combinados son =N-OR, en donde R es hidrógeno, alquilo C_1-C_6, arilo (tal como fenilo) o arilalquilo(como bencilo o fenetilo).

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-5g8, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 14-4, 14-4a, 14-4b, 14-4c, 14-4d, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, o 14-5f, en donde R_1 y R_2 junto con el carbono al que están unidos forman un grupo cicloalquilo C_{3-6}.

En todavia otro aspecto, la invención proporciona compuestos de la Fórmula 14-5g9, es decir, compuestos de acuerdo con cualquiera de la Fórmulas 14-4, 14-4a, 14-4b, 14-4c, 14-4d, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, o 14-5f, en donde R_1 y R_2 junto con el carbono al que están unidos forman un grupo ciclopropilo.

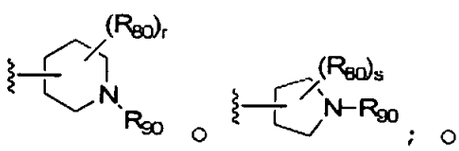
En todavia otro aspecto, la invención proporciona compuestos de la Fórmula 14-5g10, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 14-4, 14-4a, 14-4b, 14-4c, 14-4d, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, o 14-5f, en donde R_1 es hidrógeno y R_2 es ciclopropilo. En una

modalidad, el compuesto es racémico. En otra modalidad, el compuesto está enantioméricamente enriquecido.

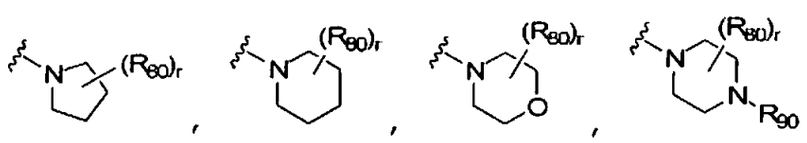
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-5g11, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 14-4, 14-4a, 14-4b, 14-4c, 14-4d, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, o 14-5f, en donde R_2 es independientemente hidrógeno, metilo, etilo, propilo, isopropilo, o ciclopropilo; y R_1 es H o metilo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-5h, es decir, compuestos de la Fórmula 14-5g, en donde

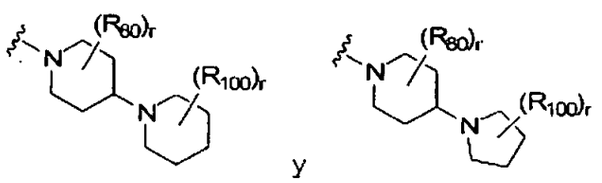
X es O; e Y es $-NR_{60}R_{70}$ o $-N(R_{30})(CH_2)_{2-6}NR_{60}R_{70}$; en donde R_{60} y R_{70} se seleccionan independientemente de: hidrógeno, metilo, etilo, cicloalquilo (C_3-C_8), arilalquilo (C_1-C_6) (tal como bencilo o fenetilo), 4-piridilmetilo,



R_{60} y R_{70} tomados junto con el átomo de nitrógeno al que están unidos forman un grupo heterocicloalquilo seleccionado de



y



en donde

cada R_{80} es alquilo C_1-C_4 independientemente no sustituido o alquilo C_1-C_4 sustituido con hidroxilo o halógeno;

cada R_{90} es independientemente hidrógeno, alquilo C_1-C_4 no sustituido, alquilo C_1-C_4 sustituido con hidroxilo o halógeno, cicloalquilo C_3-C_8 no sustituido, cicloalquilo C_3-C_8 sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}, fenil-(alquilo C_1-C_4), piridil-(alquilo C_1-C_4), tienil-(alquilo C_1-C_4), -C(O)O-(alquilo C_1-C_4), -C(O)O-fenilo, $-SO_2$-(alquilo C_1-C_6), $-SO_2$-fenilo, fenilo no sustituido, fenilo sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}, piridilo, tienilo, piridilo sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}, tienilo sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}, en donde

cada R_{50} se selecciona independientemente de: halógeno, alquilo C_1-C_6, -haloalquilo C_1-C_6, -OH, -O alquilo C_1-C_4, OCF_3, -CN, $-NR_{60}R_{70}$, -C(O)O-(alquilo C_1-C_4), $-CONR_{60}R_{70}$, -(alquilo C_1-C_6)-$NR_{60}R_{70}$, $-NR_{60}CO$-(alquilo C_1-C_4), $-NR_{60}CO$-fenilo, $-NR_{60}CO$-piridilo, $-NR_{60}CO$-tienilo, y $-NR_{60}CONR_{60}R_{70}$,

cada R_{100} es independientemente hidrógeno o alquilo C_1-C_4;

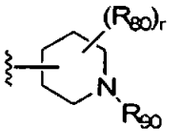
cada r es de 0 a 4; y

cada s es de 0 a 3.

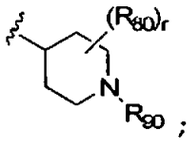
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-5h1, es decir, compuestos de la Fórmula 14-5g, en donde Y es -O-(alquilo C_1-C_6). En una modalidad, Y es -O-(alquilo C_1-C_4).

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-5h2, es decir, compuestos de la Fórmula 14-5g, en donde Y es -O-fenilo.

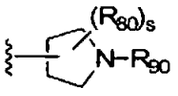
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-5i, es decir, compuestos de la Fórmula 14-5h, en donde dicho grupo



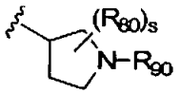
es un grupo de la Fórmula:



y dicho grupo



es un grupo de la Fórmula:



En un aspecto adicional, la invención proporciona compuestos de la Fórmula 14-5j, es decir, compuestos de acuerdo con cualquiera de las Fórmulas, 14-5h, 14-5h1, 14-5h2, o 14-5i, en donde R_1 es H o alquilo C_1-C_4. En una modalidad, R_1 es H o metilo. En otra modalidad, R_1 es H.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-6, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 13, 13-1, 13-2, 13-3, 13-4, 13-5, 13-6, 13-6a, 13-6b, 13-6c, 13-6d, 13-7, 13-8, 13-9, 13-10, 13-

11, 13-11a, 13-11b, 13-11c, 13-12, 13-13, 13-14, o 13-15, 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2e, 14-2f, 14-2g, 14-2h, 14-2i, 14-3, 14-3a, 14-3a1, 14-3a2, 14-3a3, 14-3a4, 14-3a5, 14-3a6, 14-3a7, 14-3a8, 14-3a9, 14-3a10, 14-3b, 14-3c, 14-3c1, 14-4, 14-4a, 14-4b, 14-4c, 14-4d, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, 14-5f, 14-5g, 14-5g1, 14-5g2, 14-5g3, 14-5g4, 14-5g5, 14-5g6, 14-5g7, 14-5g8, 14-5g9, 14-5g10, 14-5h, 14-5h1, 14-5h2, 14-5i, o 14-5j, en donde el grupo heteroarilo (el anillo A de la Fórmula I) es piridilo opcionalmente sustituido con 1 ó 2 grupos que son independientemente halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, haloalquilo C_1-C_4, haloalcoxi C_1-C_4, hidroxi, amino, o mono o di(alquilo C_1-C_4)amino.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-7, es decir, compuestos 14-6, en donde el piridilo se sustituye con un grupo que es halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, haloalquilo C_1-C_4, haloalcoxi C_1-C_4, hidroxi, amino, o mono o di(alquilo C_1-C_4)amino.

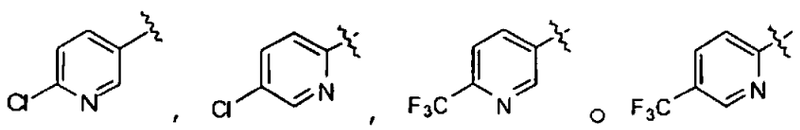
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-8, es decir, compuestos de la Fórmula 14-7, en donde el piridilo está sustituido en la posición 4.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-8a, es decir, compuestos de la Fórmula 14-7, en donde el piridilo está sustituido en la posición 2, es decir, inmediatamente próximo al nitrógeno del anillo de piridilo. En una modalidad, el anillo de piridilo está sustituido en la posición 2, es decir, inmediatamente próximo

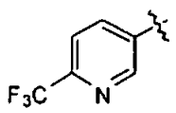
al anillo de piridil nitrógeno y el anillo de piridilo está unido al grupo $-SO_2-$ en la posición 5.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-9, es decir, compuestos de la Fórmula 14-8, en donde el piridilo se sustituye con un grupo que es halógeno (preferiblemente cloro) o haloalquilo C_1-C_4 (preferiblemente CF_3).

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-10, es decir, compuestos de la Fórmula 14-9, en donde el grupo heteroarilo presenta la siguiente estructura:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-10a, es decir, compuestos de la Fórmula 14-9, en donde el grupo heteroarilo presenta la siguiente estructura:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-10b, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 13, 13-1, 13-2, 13-3, 13-4, 13-5, 13-6, 13-6a, 13-6b, 13-6c, 13-6d, 13-7, 13-8, 13-9, 13-10, 13-11, 13-11a, 13-11b, 13-11c, 13-12, 13-13, 13-14, o 13-15, 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2e, 14-2f, 14-2g, 14-2h, 14-2i, 14-3, 14-3a, 14-3a1, 14-3a2, 14-3a3, 14-3a4, 14-3a5, 14-3a6, 14-3a7, 14-3a8, 14-3a9, 14-3a10,

14-3b, 14-3c, 14-3c1, 14-4, 14-4a, 14-4b, 14-4c, 14-4d, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, 14-5f, 14-5g, 14-5g1, 14-5g2, 14-5g3, 14-5g4, 14-5g5, 14-5g6, 14-5g7, 14-5g8, 14-5g9, 14-5g10, 14-5h, 14-5h1, 14-5h2, 14-5i, o 14-5j, en donde el grupo heteroarilo es piridilo, o tienilo, cada uno de los cuales se sustituye opcionalmente con 1 ó 2 grupos que son independientemente halo, metilo, metoxi, CF_3, o OCF_3.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-11, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 13, 13-1, 13-2, 13-3, 13-4, 13-5, 13-6, 13-6a, 13-6b, 13-6c, 13-6d, 13-7, 13-8, 13-9, 13-10, 13-11, 13-11a, 13-11b, 13-11c, 13-12, 13-13, 13-14, o 13-15, 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2e, 14-2f, 14-2g, 14-2h, 14-2i, 14-3, 14-3a, 14-3a1, 14-3a2, 14-3a3, 14-3a4, 14-3a5, 14-3a6, 14-3a7, 14-3a8, 14-3a9, 14-3a10, 14-3b, 14-3c, 14-3c1, 14-4, 14-4a, 14-4b, 14-4c, 14-4d, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, 14-5f, 14-5g, 14-5g1, 14-5g2, 14-5g3, 14-5g4, 14-5g5, 14-5g6, 14-5g7, 14-5g8, 14-5g9, 14-5g10, 14-5h, 14-5h1, 14-5h2, 14-5i, o 14-5j, en donde el grupo heteroarilo es un piridilo no sustituido.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-12, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 13, 13-1, 13-2, 13-3, 13-4, 13-5, 13-6, 13-6a, 13-6b, 13-6c, 13-6d, 13-7, 13-8, 13-9, 13-10, 13-11, 13-11a, 13-11b, 13-11c, 13-12, 13-13, 13-14, o 13-15, 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2e,

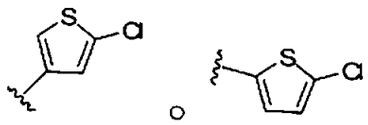
14-2f, 14-2g, 14-2h, 14-2i, 14-3, 14-3a, 14-3a1, 14-3a2, 14-3a3, 14-3a4, 14-3a5, 14-3a6, 14-3a7, 14-3a8, 14-3a9, 14-3a10, 14-3b, 14-3c, 14-3c1, 14-4, 14-4a, 14-4b, 14-4c, 14-4d, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, 14-5f, 14-5g, 14-5g1, 14-5g2, 14-5g3, 14-5g4, 14-5g5, 14-5g6, 14-5g7, 14-5g8, 14-5g9, 14-5g10, 14-5h, 14-5h1, 14-5h2, 14-5i, o 14-5j, en donde el grupo heteroarilo (el anillo A de la Fórmula I) es tienilo opcionalmente sustituido con 1 ó 2 grupos que son independientemente halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, haloalquilo C_1-C_4, haloalcoxi C_1-C_4, hidroxi, amino, o mono o di(alquilo C_1-C_4)amino.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-13, es decir, compuestos de la Fórmula 14-12 donde el grupo tienilo se sustituye con un grupo que es halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, haloalquilo C_1-C_4, haloalcoxi C_1-C_4, hidroxi, amino, o mono o di(alquilo C_1-C_4)amino.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-13a, es decir, compuestos de la Fórmula 14-12 donde el grupo tienilo se sustituye con uno grupo que se sustituye opcionalmente con heteroarilo (por ejemplo piridilo).

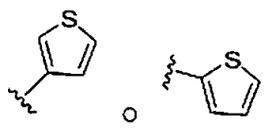
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-14, es decir, compuestos de la Fórmula 14-13, en donde el grupo tienilo se sustituye con un halógeno (preferiblemente Cl).

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-15, es decir, compuestos de la Fórmula 14-14, en donde el grupo tienilo tiene la Fórmula:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-16, es decir, compuestos de la Fórmula 14-12, en donde el grupo tienilo está no sustituido.

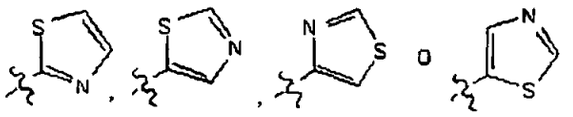
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-17, es decir, compuestos de la Fórmula 14-16, en donde el grupo tienilo tiene la Fórmula:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-18, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 13, 13-1, 13-2, 13-3, 13-4, 13-5, 13-6, 13-6a, 13-6b, 13-6c, 13-6d, 13-7, 13-8, 13-9, 13-10, 13-11, 13-11a, 13-11b, 13-11c, 13-12, 13-13, 13-14, o 13-15, 14, 14-1, 14-1a, 14-2, 14-2a, 14-2b, 14-2d, 14-2c, 14-2d, 14-2e, 14-2f, 14-2g, 14-2h, 14-2i, 14-3, 14-3a, 14-3a1, 14-3a2, 14-3a3, 14-3a4, 14-3a5, 14-3a6, 14-3a7, 14-3a8, 14-3a9, 14-3a10, 14-3b, 14-3c, 14-3c1, 14-4, 14-4a, 14-4b, 14-4c, 14-4d, 14-5, 14-5a, 14-5b, 14-5c, 14-5d, 14-5d1, 14-5e, 14-5e1, 14-5f, 14-5g, 14-5g1, 14-5g2, 14-5g3, 14-5g4, 14-5g5, 14-5g6, 14-5g7, 14-5g8, 14-5g9, 14-5g10, 14-5h, 14-5h1, 14-5h2, 14-5i, o 14-5j, en donde el grupo heteroarilo (el anillo A de la Fórmula

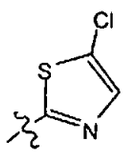
I) comprende tiazolilo, imidazolilo, pirazolilo, isoxazolilo, u oxazolilo opcionalmente sustituido con 1 ó 2 grupos que son independientemente halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, haloalquilo C_1-C_4, haloalcoxi C_1-C_4, hidroxi, amino, o mono o di(alquilo C_1-C_4)amino.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-19, es decir, compuestos de la Fórmula 14-18, en donde el grupo tiazolilo está no sustituido y tiene la Fórmula:

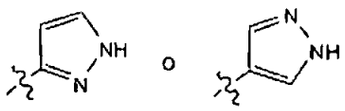


En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-19a, es decir, compuestos de la Fórmula 14-18 donde el grupo heteroarilo (el anillo A de la Fórmula I) es un grupo tiazolilo que se sustituye con uno o dos grupos que son halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, haloalquilo C_1-C_4, haloalcoxi C_1-C_4, hidroxi, amino, o mono o di(alquilo C_1-C_4)amino.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-19b, es decir, compuestos de la Fórmula 14-18, en donde el grupo heteroarilo (el anillo A de la Fórmula I) es un grupo tiazolilo que tiene la Fórmula:

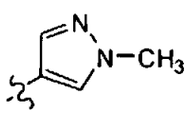


En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-20, es decir, compuestos de la Fórmula 14-18, en donde el grupo heteroarilo (el anillo A de la Fórmula I) es un grupo pirazolilo que está no sustituido y tiene la Fórmula:

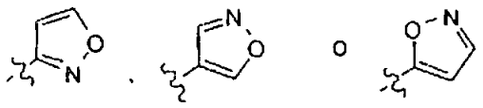


En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-20a, es decir, compuestos de la Fórmula 14-18 donde el grupo heteroarilo (el anillo A de la Fórmula I) es un grupo pirazolilo que se sustituye con uno o dos grupos que son halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, haloalquilo C_1-C_4, haloalcoxi C_1-C_4, hidroxi, amino, o mono o di(alquilo C_1-C_4)amino.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-20b, es decir, compuestos de la Fórmula 14-18, en donde el grupo heteroarilo (el anillo A de la Fórmula I) es un grupo pirazolilo que tiene la Fórmula:

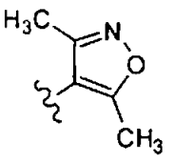


En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-21, es decir, compuestos de la Fórmula 14-18, en donde el grupo heteroarilo (el anillo A de la Fórmula I) es un grupo isoxazolilo que está no sustituido y tiene la Fórmula:

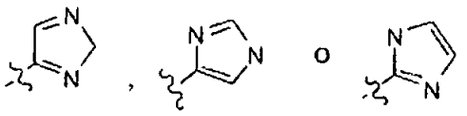


En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-21a, es decir, compuestos de la Fórmula 14-18 donde el grupo heteroarilo (el anillo A de la Fórmula I) es un grupo isoxazolilo que se sustituye con uno o dos grupos que son halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, haloalquilo C_1-C_4, haloalcoxi C_1-C_4, hidroxi, amino, o mono o di(alquilo C_1-C_4)amino.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-21b, es decir, compuestos de la Fórmula 14-18, en donde el grupo heteroarilo (el anillo A de la Fórmula I) es un grupo isoxazolilo que tiene la Fórmula:



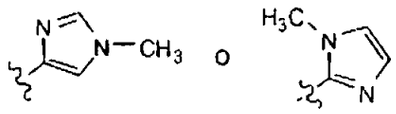
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-22, es decir, compuestos de la Fórmula 14-18, en donde el grupo heteroarilo (el anillo A de la Fórmula I) es un grupo imidazolilo que está no sustituido y tiene la Fórmula:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-22a, es decir, compuestos de la Fórmula 14-18 donde el grupo heteroarilo (el anillo A de la Fórmula I) es un grupo imidazolilo que se sustituye con uno o dos grupos que

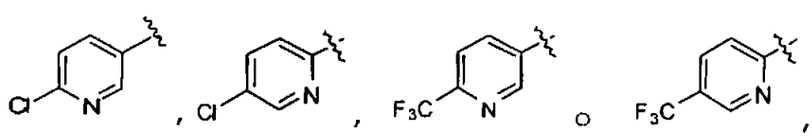
son halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, haloalquilo C_1-C_4, haloalcoxi C_1-C_4, hidroxi, amino, o mono o di(alquilo C_1-C_4)amino.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-22b, es decir, compuestos de la Fórmula 14-18, en donde el grupo heteroarilo (el anillo A de la Fórmula I) es un grupo imidazolilo que tiene la Fórmula:

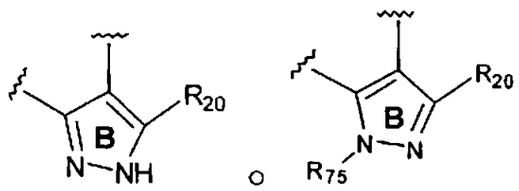


En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 14-23, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 12, 13, 13-1, 13-2, 13-3, 13-4, 13-5, 13-6, 13-6a, 13-6b, 13-6c, 13-6d, 13-7, 13-8, 13-9, 13-10, 13-11, 13-11a, 13-11b, 13-11c, 13-12, 13-13, 13-14, o 13-15, 14, 14-1, 14-2, 14-2a, 14-2b, 14-2c, 14-2d, 14-3, en donde R_1 es H; R_2 es H, o cicloalquilo C_{3-6}; R_{20} es H o metilo; R_{75} es H o metilo; y el anillo C es fenilo sustituido con dos halógenos. En una modalidad, R_{20} y R_{75} son ambos hidrógeno.

En otro aspecto, la invención proporciona compuestos de la Fórmula 14-24, es decir, compuestos de acuerdo con la Fórmula 13, en donde el anillo A es un grupo heteroarilo, que presenta las siguientes estructuras:



R_1 es hidrógeno o metilo; R_2 es H, metilo, o ciclopropilo; el anillo C es fenilo sustituido con 1 ó 2 grupos que son independientemente Cl, F, metilo, etilo, isopropilo, metoxi, etoxi, CF_3, OCF_3, OH, CH_2OH, NH_2, $NH(CH_3)$, o $N(CH_3)_2$; y el anillo B tiene la Fórmula:



en donde R_{20} y R_{75} son independientemente H, metilo o etilo. En una modalidad, el anillo C está bis-sustituido con al menos un halógeno. En otra modalidad, el halógeno es F. En todavía otra modalidad, el halógeno es Cl. En otra modalidad, el anillo C está bis-sustituido con dos halógenos, que son idénticos o diferentes. En todavía otra modalidad, el anillo C está sustituido al menos en la posición 7. En otra modalidad, el anillo C está sustituido en las posiciones 7 y 8. En todavía otra modalidad, el anillo C se sustituye con dos halógenos, que son idénticos, y se unen a las posiciones 7 y 8. En otra modalidad, el anillo C está monosustituido con un halógeno. En otra modalidad, el halógeno es F. En todavía otra modalidad, el halógeno es Cl. En todavía otra modalidad, el anillo C está sustituido en la posición 7. En todavía otra modalidad, el anillo C está sustituido en la posición 8.

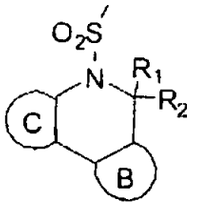
En otro aspecto, la invención proporciona compuestos de la Fórmula 15, es decir, compuestos de la Fórmula I, en donde

el anillo A es heterocicloalquilo, que se sustituye opcionalmente en una posición sustituible con halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, alcoxi C_1-C_6, haloalquilo C_1-C_6, haloalcoxi C_1-C_6, hidroxilo, hidroxi-(alquilo C_1-C_4), CN, ariloxi, aril-(alcoxi C_1-C_4) como benciloxi, $-SO_2$-(alquilo C_1-C_6), -NR'R", alcanoilo C_1-C_6, -C(O)OR', -(alquilo C_1-C_4)-C(O)OR', heteroarilo, arilo, arilo alquilo C_1-C_4, $-SO_2$-NR'R", -C(O)NR'R", -OC(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", -NR'C(O)O-(alquilo C_1-C_6), o -NR'C(O)O-fenilo, en donde cada R' y R" es independientemente hidrógeno o alquilo C_1-C_6; y

el anillo B es pirazolilo, imidazolilo, pirrolilo, triazolilo, pirrolidinilo, pirazolidinilo, imidazolidinilo, piridilo, pirimidilo, o isoxazolilo, cada uno de los cuales se sustituye opcionalmente en una posición sustituible con un grupo que es independientemente alquilo C_1-C_6, alcoxi C_1-C_6, -NR'R", $-SO_2$-NR'R", -C(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, NO_2, CN, -C(O)OR', hidroxilo, hidroxi-(alquilo C_1-C_6), $-S(O)_2$(alquilo C_1-C_6), $-S(O)_2$arilo, halógeno, haloalquilo C_1-C_2, haloalcoxi C_1-C_2, bencilo, o fenilo.

En otro aspecto, la invención proporciona compuestos de la Fórmula 16, es decir, compuestos de la Fórmula I o la Fórmula 15, que tienen la estructura

heterocicloalquilo



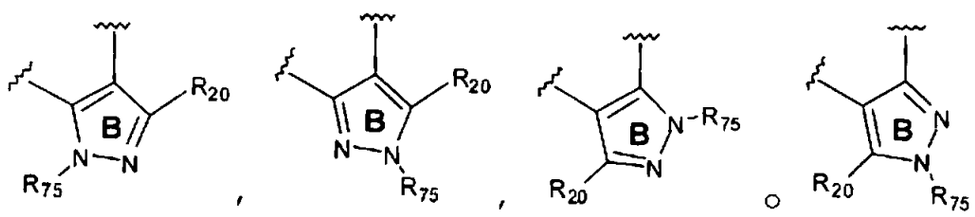
estereoisómeros, tautómeros, mezclas de estereoisómeros y/o tautómeros o sus sales farmacéuticamente aceptables, en donde el grupo heterocicloalquilo se sustituye opcionalmente en cada posición sustituible con halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, alcoxi C_1-C_6, haloalquilo C_1-C_6, haloalcoxi C_1-C_6, hidroxilo, hidroxi-(alquilo C_1-C_4), CN, NO_2, ariloxi, aril-(alcoxi C_1-C_4),-SO_2-(alquilo C_1-C_6), -NR'R", alcanoilo C_1-C_6, -C(O)OR', -(alquilo C_1-C_4)-C(O)OR', piridilo, fenilo, fenil-(alquilo C_1-C_4), -SO_2-NR'R", -C(O)NR'R", -OC(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", o -NR'CO(O)R', en donde cada R' y R" es independientemente hidrógeno o alquilo C_1-C_6; y

en donde el anillo C es ciclohexilo, fenilo, tienilo, imidazolinilo, tiazolilo, isotiazolilo, oxazolilo, isoxazolilo, pirrolilo, pirazolilo, pirimidilo, pirazinilo o piridilo, cada uno de los cuales se sustituye opcionalmente en cada posición sustituible con grupos que son independientemente halógeno, alquilo C_1-C_6, alcoxi C_1-C_6, ariloxi, aril-(alcoxi C_1-C_4), haloalquilo C_1-C_6, haloalcoxi C_1-C_6, hidroxilo, hidroxi-(alquilo C_1-C_6)-, -NR'R", -(alquilo C_1-C_6)-NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, oxo, bencilo, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo, furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -NR'SO_2R", -SO_2-NR'R", -$S(O)_z$ arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente,

fenilo),o $-S(O)_z$ (alquilo C_1-C_6), en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1, 2 ó 3 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_6, y en donde las porciones arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, ó 2 grupos que son independientemente alquilo C_1-C_4, alcoxi C_1-C_4, halógeno, CF_3, OCF_3, hidroxilo, hidroxi-(alquilo C_1-C_4), o -NR'R".

En otro aspecto, la invención proporciona compuestos de la Fórmula 16-1, es decir, compuestos de la Fórmula 16, en donde el anillo B es pirazolilo, imidazolilo, pirrolilo, triazolilo, pirrolidinilo, pirazolidinilo, imidazolidinilo, piridilo, pirimidilo, o isoxazolilo, cada uno de los cuales está no sustituido.

En otro aspecto, la invención proporciona compuestos de la Fórmula 16-2, es decir, compuestos de la Fórmula 16, en donde el anillo B tiene la Fórmula:

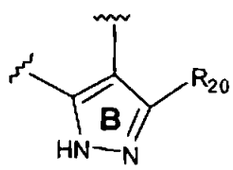


en donde

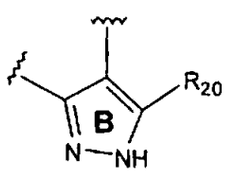
R_{20} es hidrógeno, alquilo C_1-C_6, alcoxi C_1-C_6, -NR'R", -(alquilo C_1-C_4)-NR'R", $-S(O)_z$(alquilo C_1-C_6), hidroxilo, halógeno, CN, NO_2, CH_2F, CHF_2, CF_3, -C(O)OR', -C(O)NR'R", -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", o fenilo, y

R_{75} es hidrógeno, alquilo C_1-C_6, alcanoilo C_1-C_6, fenil-(alcanoilo C_1-C_6), $-C(O)NR'R''$, $-S(O)_2$-alquilo (C_1-C_6), $-S(O)_2$-arilo, $-SO_2NR'R$, fenilo, fenil-(alquilo C_1-C_6) (preferiblemente fenetilo o bencilo, más preferiblemente, bencilo), fenilcarbonilo, bencilcarbonilo, o heteroarilcarbonilo, donde el grupo heteroarilo es piridilo, pirimidilo, tienilo o furanilo.

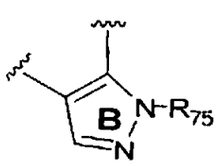
En otro aspecto, la invención proporciona compuestos de la Fórmula 16-3, es decir, compuestos de la Fórmula 16-2, en donde el anillo B tiene la Fórmula:



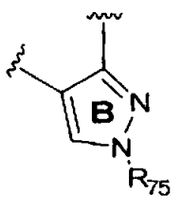
En otro aspecto, la invención proporciona compuestos de la Fórmula 16-4, es decir, compuestos de la Fórmula 16-2, en donde el anillo B tiene la Fórmula:



En otro aspecto, la invención proporciona compuestos de la Fórmula 16-5, es decir, compuestos de la Fórmula 16-2, en donde el anillo B tiene la Fórmula:



En otro aspecto, la invención proporciona compuestos de la Fórmula 16-6, es decir, compuestos de la Fórmula 16-2, en donde el anillo B tiene la Fórmula:



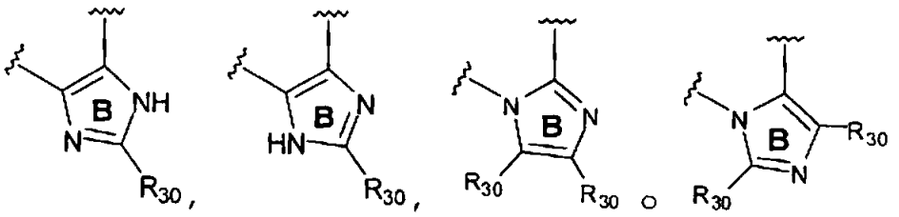
En un aspecto adicional, la invención proporciona compuestos de la Fórmula 16-6a, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 16-2, 16-3, o 16-4, en donde R_{20} es hidrógeno, alquilo C_1-C_4, CH_2F, CHF_2, CF_3, -C(O)OR', $-S(O)_z$ (alquilo C_1-C_4), o hidroxilo.

En otro aspecto, la invención proporciona compuestos de la Fórmula 16-6b, es decir, compuestos de la Fórmula 16-6a, en donde R_{20} es hidrógeno o metilo.

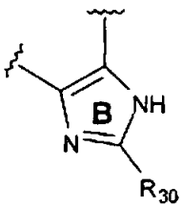
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 16-6c, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 16-2, 16-5 o 16-6, en donde R_{75} es hidrógeno o metilo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 16-6d, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 16-2, 16-5 o 16-6, en donde R_{75} es hidrógeno.

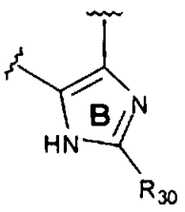
En otro aspecto, la invención proporciona compuestos de la Fórmula 16-7, es decir, compuestos de la Fórmula 16, en donde el anillo B tiene la Fórmula:



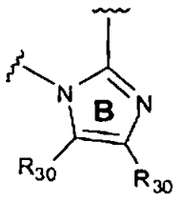
en donde R_{30} es hidrógeno, alquilo C_1-C_4, alcoxi C_1-C_4, -NR'R", alquilo C_1-C_4tio, hidroxilo, halógeno, CH_2F, CHF_2, CF_3, o fenilo. En otro aspecto, la invención proporciona compuestos de la Fórmula 16-8, es decir, compuestos de la Fórmula 16-7, en donde el anillo B tiene la Fórmula:



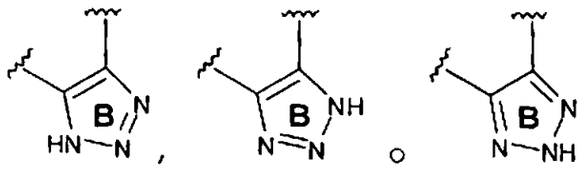
En otro aspecto, la invención proporciona compuestos de la Fórmula 16-9, es decir, compuestos de la Fórmula 16-7, en donde el anillo B tiene la Fórmula:



En otro aspecto, la invención proporciona compuestos de la Fórmula 16-10, es decir, compuestos de la Fórmula 16-7, en donde el anillo B tiene la Fórmula:



En otro aspecto, la invención proporciona compuestos de la Fórmula 16-11, es decir, compuestos de la Fórmula 16-7, en donde el anillo B tiene la Fórmula:

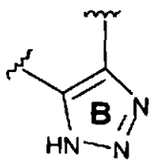


En un aspecto adicional, la invención proporciona compuestos de la Fórmula 16-11a, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 16-8, 16-9, 16-10, o 16-11, en donde cada R_{30} es independientemente hidrógeno, alquilo C_1-C_4, CH_2F, CHF_2, o CF_3.

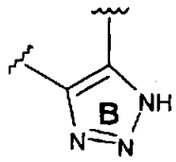
En otro aspecto, la invención proporciona compuestos de la Fórmula 16-11b, es decir, compuestos de la Fórmula 16-11a, en donde cada R_{30} es independientemente hidrógeno o metilo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 16-11c, es decir, compuestos de la Fórmula 16-11a, en donde cada R_{30} es hidrógeno.

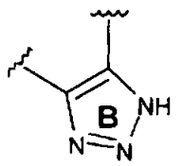
En otro aspecto, la invención proporciona compuestos de la Fórmula 16-12, es decir, compuestos de la Fórmula 16, en donde el anillo B tiene la Fórmula:



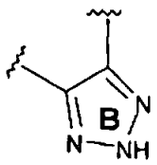
En otro aspecto, la invención proporciona compuestos de la Fórmula 16-13, es decir, compuestos de la Fórmula 16-12, en donde el anillo B tiene la Fórmula:



En otro aspecto, la invención proporciona compuestos de la Fórmula 16-14, es decir, compuestos de la Fórmula 16-12, en donde el anillo B tiene la Fórmula:



En otro aspecto, la invención proporciona compuestos de la Fórmula 16-15, es decir, compuestos de la Fórmula 16-12, en donde el anillo B tiene la Fórmula:



En otro aspecto, la invención proporciona compuestos de la Fórmula 17, es decir, compuestos de las Fórmulas 15, 16, 16-1, 16-2, 16-3, 16-4, 16-5, 16-6, 16-6a, 16-6b, 16-6c, 16-6d, 16-7, 16-8, 16-9, 16-10, 16-11, 16-11a, 16-11b, 16-11c, 16-12, 16-13, 16-14, o 16-15 en donde el anillo C es fenilo o ciclohexilo, que se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, ariloxi, aril-(alcoxi C_1-C_6), haloalquilo C_1-C_4 (en otro aspecto, CF_3), haloalcoxi C_1-C_4 (en otro aspecto, OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_4), -NR'R", -(alquilo C_1-C_4)-NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-

C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, oxo, bencilo, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo, furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -$S(O)_z$arilo, o -$S(O)_z$ (alquilo C_1-C_6), en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1 ó 2 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_6, y en donde las porciones arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una modalidad, el anillo C es un fenilo opcionalmente sustituido.

En otro aspecto, la invención proporciona compuestos de la Fórmula 17-1, es decir, compuestos de la Fórmula 17 donde el anillo C es fenilo no sustituido.

En otro aspecto, la invención proporciona compuestos de la Fórmula 17-1a, es decir, compuestos de la Fórmula 17 donde el anillo C es ciclohexilo no sustituido.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-2, es decir, compuestos de la Fórmula 17 donde el anillo C es fenilo sustituido con 1 ó 2 grupos que son independientemente Cl, F, metilo, etilo, isopropilo, metoxi, etoxi, CF_3, OCF_3, OH, CH_2OH, NH_2, $NH(CH_3)$, o $N(CH_3)_2$, o -$OC(O)N(CH_3)_2$. En una modalidad, el anillo C está bis-sustituido con al menos un halógeno. En otra modalidad, el halógeno es F. En todavía otra modalidad, el halógeno es Cl. En otra

modalidad, el anillo C está bis-sustituido con dos halógenos, que son idénticos o diferentes. En todavía otra modalidad, el anillo C está sustituido al menos en la posición 7. En otra modalidad, el anillo C está sustituido en las posiciones 7 y 8. En otra modalidad, el anillo C está monosustituido con un halógeno. En otra modalidad, el halógeno es F. En todavía otra modalidad, el halógeno es Cl. En todavía otra modalidad, el anillo C está sustituido en la posición 7. En todavía otra modalidad, el anillo C está sustituido en la posición 8.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-2a, es decir, compuestos de la Fórmula 17, en donde el anillo C es fenilo sustituido con 1 ó 2 grupos que son independientemente -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R", -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, fenilo, $-S(O)_z$ fenilo, o $-S(O)_z$(alquilo C_1-C_6), en donde las porciones fenilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-alquilo C_1-C_6, o -NR'R". En una modalidad, el anillo C está sustituido al menos en la posición 7. En otra modalidad, el anillo C está sustituido al menos en la posición 8.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-2b, es decir, compuestos de la Fórmula 17, en donde el anillo C es fenilo sustituido con 1 ó 2 grupos que

son independientemente alquilo C_1-C_4, alquenilo C_2-C_6, alquinilo C_2-C_6, en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1 ó 2 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_4. En una modalidad, el anillo C está sustituido al menos en la posición 7. En otra modalidad, el anillo C está sustituido al menos en la posición 8.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-2c, es decir, compuestos de la Fórmula 17, en donde el anillo C es fenilo sustituido con 1 ó 2 grupos que son independientemente -C(O)OH, -C(O)O-(alquilo C_1-C_4), NO_2, CN, o fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una modalidad, el anillo C está sustituido al menos en la posición 7. En otra modalidad, el anillo C está sustituido al menos en la posición 8.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-2d, es decir, compuestos de la Fórmula 17, en donde el anillo C es fenilo sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alcoxi C_1-C_4, halógeno, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R", -NR'C(O)O-(alquilo C_1-C_6) o -NR'C(O)O-fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno,

haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una modalidad, el anillo C está sustituido al menos en la posición 7. En otra modalidad, el anillo C está sustituido al menos en la posición 8.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-2e, es decir, compuestos de la Fórmula 17 donde el anillo C es ciclohexilo sustituido con 1 ó 2 grupos que son independientemente Cl, F, metilo, etilo, isopropilo, metoxi, etoxi, CF_3, OCF_3, OH, CH_2OH, NH_2, $NH(CH_3)$, $N(CH_3)_2$, o -$OC(O)N(CH_3)_2$.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-2f, es decir, compuestos de la Fórmula 17, en donde el anillo C es ciclohexilo sustituido con 1 ó 2 grupos que son independientemente -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R", -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, fenilo, -S(O)$_2$ arilo, o -S(O)$_2$ (alquilo C_1-C_6), en donde las porciones fenilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R".

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-2g, es decir, compuestos de la Fórmula 17, en donde el anillo C es ciclohexilo sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alquenilo C_2-C_6,

alquinilo C_2-C_6, en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1 ó 2 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_4.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-2h, es decir, compuestos de la Fórmula 17, en donde el anillo C es ciclohexilo sustituido con 1 ó 2 grupos que son independientemente -C(O)OH, -C(O)O-(alquilo C_1-C_4), NO_2, CN, o fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R".

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-2i, es decir, compuestos de la Fórmula 17, en donde el anillo C es ciclohexilo sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alcoxi C_1-C_4, halógeno, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R", -NR'C(O)O-(alquilo C_1-C_6) o -NR'C(O)O-fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R".

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-3, es decir, compuestos de la Fórmula 17 donde el anillo C es fenilo o ciclohexilo sustituido con uno o

dos grupos que son Cl, F, metilo, etilo, isopropilo, metoxi, CF_3, OCF_3, OH, o $-OC(O)N(CH_3)_2$.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-3a, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, o 17-3, en donde R_2 es $-X(CO)Y$ o $-(C(R_3)_2)_{1-4}X(CO)Y$.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-3a1, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, o 17-3, en donde R_2 es hidrógeno, alquilo C_1-C_3 o cicloalquilo C_3-C_6.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-3a2, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, o 17-3, en donde R_2 es NO_2 o CN.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-3a3, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, o 17-3, en donde R_2 es alquenilo C_2-C_6 o alquinilo C_2-C_6.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-3a4, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, o 17-3, en donde R_2 es haloalquilo C_1-C_4.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-3a5, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, 17-3, 17-3a, 17-3a1, 17-3a2, 17-3a3, o 17-3a4, en donde R_1 es hidrógeno.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-3a6, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, o 17-3, en donde R_1 y R_2 combinados son oxo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-3a7, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, o 17-3, en donde R_1 y R_2 combinados son =N-OR, en donde R es hidrógeno, alquilo C_1-C_6, arilo (tal como fenilo) o arilalquilo(como bencilo o fenetilo).

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-3a8, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, o 17-3, en donde R_1 y R_2 junto con el carbono al que están unidos forman un grupo cicloalquilo C_{3-6}.

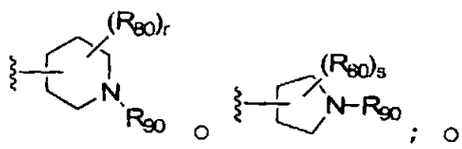
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-3a9, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, o 17-3,

en donde R_1 y R_2 junto con el carbono al que están unidos forman un grupo ciclopropilo.

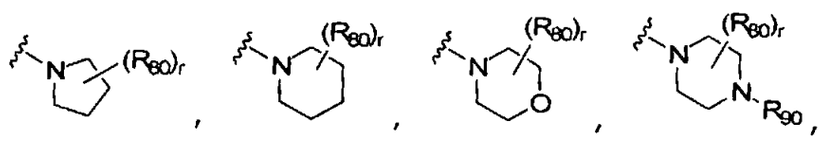
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-3a10, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, o 17-3, en donde R_1 es hidrógeno y R_2 es ciclopropilo. En una modalidad, el compuesto es racémico. En otra modalidad, el compuesto está enantioméricamente enriquecido.

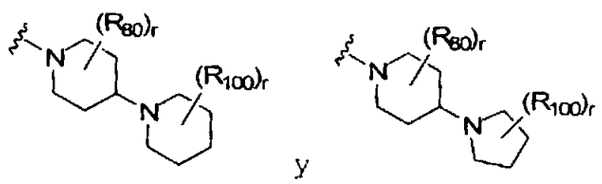
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-3b, es decir, compuestos de la Fórmula 17-3a, en donde

X es O; e Y es $-NR_{60}R_{70}$ o $-N(R_{30})(CH_2)_{2-6}NR_{60}R_{70}$; en donde R_{60} y R_{70} se seleccionan independientemente de: hidrógeno, metilo, etilo, cicloalquilo (C_{3-C8}), aril-(alquilo C_1-C_6) (tal como bencilo o fenetilo), 4-piridilmetilo,


; o

R_{60} y R_{70} tomados junto con el átomo de nitrógeno al que están unidos forman un grupo heterocicloalquilo seleccionado de




y

en donde

cada R_{80} es alquilo C_1-C_4 independientemente no sustituido o alquilo C_1-C_4 sustituido con grupos hidroxilo o halógeno;

cada R_{90} es independientemente hidrógeno, alquilo C_1-C_4 no sustituido, alquilo C_1-C_4 sustituido con hidroxilo o halógeno, cicloalquilo C_3-C_8 no sustituido, cicloalquilo C_3-C_8 sustituido con uno o más (por ejemplo, 1-4) R_{50}, fenil-(alquilo C_1-C_4), piridil-(alquilo C_1-C_4), tienil-(alquilo C_1-C_4), -C(O)O-(alquilo C_1-C_4), -C(O)O-fenilo, -SO_2-(alquilo C_1-C_6), -SO_2-fenilo, fenilo no sustituido, fenilo sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}, piridilo, tienilo, piridilo sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}, tienilo sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}, en donde

cada R_{50} se selecciona independientemente de: halógeno, alquilo C_1-C_6, -haloalquilo C_1-C_6, -OH, -O(alquilo C_1-C_4), OCF_3, -CN, -$NR_{60}R_{70}$, -C(O)O-(alquilo C_1-C_4), -$CONR_{60}R_{70}$, -(alquilo C_1-C_6)-$NR_{60}R_{70}$, -NR_{60}CO-(alquilo C_1-C_4), -NR_{60}CO-fenilo, -NR_{60}CO-piridilo, -NR_{60}CO-tienilo, y -$NR_{60}CONR_{60}R_{70}$,

cada R_{100} es independientemente hidrógeno o alquilo C_1-C_4;

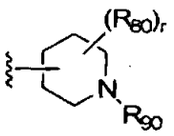
cada r es de 0 a 4; y

cada s es de 0 a 3.

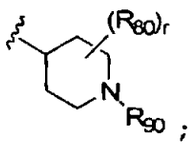
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-3b1, es decir, compuestos de la Fórmula 17-3a, en donde Y es -O-(alquilo C_1-C_6). En una modalidad, Y es -O-(alquilo C_1-C_4).

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-3b2, es decir, compuestos de la Fórmula 17-3a, en donde Y es -O-fenilo.

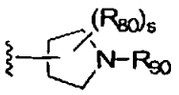
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-3c, es decir, compuestos de la Fórmula 17-3b, en donde dicho grupo



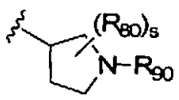
es un grupo de la Fórmula:



y, dicho grupo



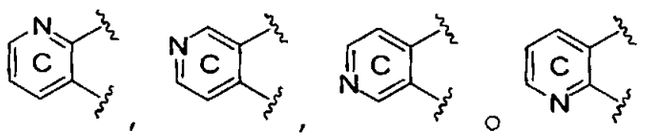
es un grupo de la Fórmula:



En un aspecto adicional, la invención proporciona compuestos de la Fórmula 17-3d, es decir, compuestos de acuerdo con cualquiera de las Fórmulas, 17-3b, 17-3b1, 17-3b2, o 17-3c, en donde R_1 es H o alquilo C_1-C_4. En una modalidad, R_1 es H o metilo. En otra modalidad, R_1 es H.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-4, es decir, compuestos de acuerdo con la Fórmula 15, o una cualquiera de las Fórmulas 16, 16-1, 16-2, 16-3, 16-4, 16-5, 16-6, 16-6a, 16-6b, 16-6c, 16-6d, 16-7, 16-

8, 16-9, 16-10, 16-11, 16-11a, 16-11b, 16-11c, 16-12, 16-13, 16-14, o 16-15, en donde el anillo C es



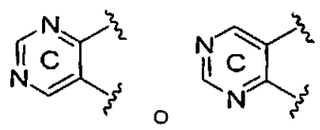
o derivados N-óxido de los mismos

cada uno de los cuales se sustituye opcionalmente con 1, 2, ó 3 grupos que son independientemente halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, ariloxi, aril-(alcoxi C_1-C_4), haloalquilo C_1-C_4 (en otro aspecto, CF_3), haloalcoxi C_1-C_4 (en otro aspecto, OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_4), -NR'R", -(alquilo C_1-C_4)-NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -COR', -C(O)OR', -C(O)NR'R", -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R", NO_2, CN, bencilo, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo, furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo), o -S(O)$_z$ (alquilo C_1-C_6), en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1, 2 ó 3 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_6, y en donde las porciones arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una

modalidad, la invención proporciona compuestos donde el anillo C es piridilo o N-óxido de piridilo sustituido con 1 ó 2 grupos que son independientemente -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -C(O)OR', -C(O)NR'R", -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R", NO_2, CN, fenilo, -S(O)$_2$ arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo) o -S(O)$_2$ (alquilo C_1-C_6) donde las porciones de arilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una modalidad alternativa, el anillo C es piridilo o N-óxido de piridilo sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alquenilo C_2-C_6, alquinilo C_2-C_6, en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1 ó 2 grupos que son independientemente halógeno, hidroxi, -NR'R" o alcoxi C_1-C_4. En otra modalidad alternativa, el anillo C es piridilo o N-óxido de piridilo sustituido con 1 ó 2 grupos que son independientemente -C(O)O-(alquilo C_1-C_4), NO_2, CN, o fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En todavía otra modalidad alternativa, el

anillo C es piridilo o N-óxido de piridilo sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alcoxi C_1-C_4, halógeno, -C(O)NR'R", NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R", -NR'C(O)O-(alquilo C_1-C_6) o -NR'C(O)O-fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R".

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-4a, es decir, compuestos de la Fórmula 15 o cualquiera de las Fórmulas 15, 16, 16-1, 16-2, 16-3, 16-4, 16-5, 16-6, 16-6a, 16-6b, 16-6c, 16-6d, 16-7, 16-8, 16-9, 16-10, 16-11, 16-11a, 16-11b, 16-11c, 16-12, 16-13, 16-14, o 16-15, en donde el anillo C es

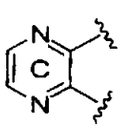


cada uno de los cuales se sustituye opcionalmente con 1, 2, ó 3 grupos que son independientemente halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, ariloxi, aril-(alcoxi C_1-C_4), haloalquilo C_1-C_4 (en otro aspecto, CF_3), haloalcoxi C_1-C_4 (en otro aspecto, OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_4), -NR'R", -(alquilo C_1-C_4)-NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, bencilo, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo, furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -NR'SO_2R",

$-SO_2-NR'R''$, $-S(O)_z$ arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo) , o $-S(O)_z$(alquilo C_1-C_6), en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1, 2 ó 3 grupos que son independientemente halógeno, hidroxilo, $-NR'R''$ o alcoxi C_1-C_6, y en donde las porciones arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o $-NR'R''$. En una modalidad, la invención proporciona compuestos donde el anillo C es pirimidinilo sustituido con 1 ó 2 grupos que son independientemente $-NR'C(O)O-$(alquilo C_1-C_6), $-NR'C(O)O-$fenilo, $-C(O)OR'$, $-C(O)NR'R''$, $-OC(O)NR'R''$, $-NR'C(O)NR'R''$, -(alquilo C_1-C_6)$-C(O)OR'$, -(alquilo C_1-C_6)$-C(O)NR'R''$, $-NR'C(O)R''$, NO_2, CN, fenilo, $-S(O)_z$ arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo) o $-S(O)_z$ (alquilo C_1-C_6) donde las porciones de arilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o $-NR'R''$. En una modalidad alternativa, el anillo C es pirimidinilo sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alquenilo C_2-C_6, alquinilo C_2-C_6, en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen

o no se sustituyen con 1 ó 2 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_4. En otra modalidad alternativa, el anillo C es pirimidinilo sustituido con 1 ó 2 grupos que son independientemente -C(O)OH, -C(O)O-(alquilo C_1-C_4), NO_2, CN, o fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En todavía otra modalidad alternativa, el anillo C es pirimidinilo sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alcoxi C_1-C_4, halógeno, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R", -NR'C(O)O-(alquilo C_1-C_6) o -NR'C(O)O-fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R".

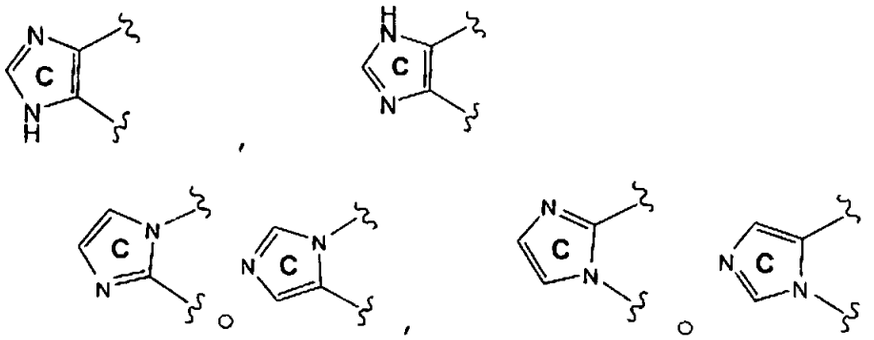
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-4b, es decir, compuestos de la Fórmula 15 o cualquiera de las Fórmulas 15, 16, 16-1, 16-2, 16-3, 16-4, 16-5, 16-6, 16-6a, 16-6b, 16-6c, 16-6d, 16-7, 16-8, 16-9, 16-10, 16-11, 16-11a, 16-11b, 16-11c, 16-12, 16-13, 16-14, o 16-15, en donde el anillo C es



que se sustituye opcionalmente con 1, 2, ó 3 grupos que son independientemente halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, ariloxi, aril-(alcoxi C_1-C_4), haloalquilo C_1-C_4 (en otro aspecto, CF_3), haloalcoxi C_1-C_4 (en otro aspecto, OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_4), -NR'R", -(alquilo C_1-C_4)-NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_4)-C(O)OR', -(alquilo C_1-C_4)-C(O)NR'R", -NR'C(O)R", NO_2, CN, bencilo, fenilo, piridilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$ arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo) , o -S(O)$_z$ (alquilo C_1-C_6), en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1, 2 ó 3 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_6, y en donde las porciones arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una modalidad, la invención proporciona compuestos donde el anillo C es pirazina sustituido con 1 ó 2 grupos que son independientemente -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R", -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, fenilo, -S(O)$_z$ arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente,

fenilo) o -S(O)$_2$(alquilo C_1-C_6) donde las porciones de arilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En una modalidad alternativa, el anillo C es pirazina sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alquenilo C_2-C_6, alquinilo C_2-C_6, en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1 ó 2 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_4. En otra modalidad alternativa, el anillo C es pirazina sustituido con 1 ó 2 grupos que son independientemente -C(O)OH, -C(O)O-(alquilo C_1-C_4), NO_2, CN, o fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R". En otro aspecto alternativo aun, el anillo C es pirazina sustituido con 1 ó 2 grupos que son independientemente alquilo C_1-C_4, alcoxi C_1-C_4, halógeno, -C(O)NR'R", -NR'C(O)R", -OC(O)NR'R", -NR'C(O)NR'R", o NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, en donde el grupo fenilo se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R".

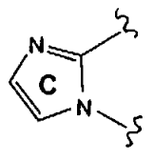
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-4c, es decir, compuestos de la Fórmula 15 o cualquiera de las Fórmulas 15, 16, 16-1, 16-2, 16-3, 16-4, 16-5, 16-6, 16-6a, 16-6b, 16-6c, 16-6d, 16-7, 16-8, 16-9, 16-10, 16-11, 16-11a, 16-11b, 16-11c, 16-12, 16-13, 16-14, o 16-15, donde el anillo C es:



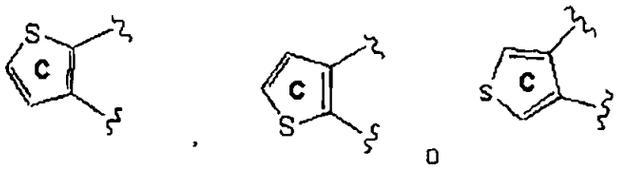
cada uno de los cuales se sustituye opcionalmente con 1 ó 2 grupos que son independientemente halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, ariloxi, aril-(alcoxi C_1-C_4), haloalquilo C_1-C_4 (en otro aspecto, CF_3), haloalcoxi C_1-C_4 (en otro aspecto, OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_4), -NR'R", -(alquilo C_1-C_6)-NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, bencilo, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo, furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo), o -S(O)$_z$ (alquilo C_1-C_6), en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1, 2, ó 3 grupos que son

independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_6, y en donde las porciones arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R".

En todavia otro aspecto, la invención proporciona compuestos de la Fórmula 17-4c1, es decir, compuestos de la Fórmula 17-4c donde el anillo C es:



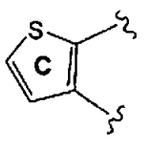
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-4d, es decir, compuestos de la Fórmula 15 o de cualquiera de las Fórmulas 15, 16, 16-1, 16-2, 16-3, 16-4, 16-5, 16-6, 16-6a, 16-6b, 16-6c, 16-6d, 16-7, 16-8, 16-9, 16-10, 16-11, 16-11a, 16-11b, 16-11c, 16-12, 16-13, 16-14, o 16-15, en donde el anillo C es



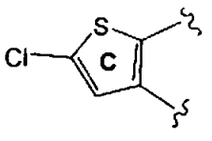
cada uno de los cuales se sustituye opcionalmente con 1 ó 2 grupos que son independientemente halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, ariloxi, aril-(alcoxi C_1-C_4), haloalquilo C_1-C_4 (en otro aspecto, CF_3), haloalcoxi C_1-C_4 (en otro aspecto, OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_4), -NR'R", -(alquilo C_1-

C_6)-NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, bencilo, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo, furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -NR'SO_2R", -SO_2-NR'R", -$S(O)_z$ arilo (en donde el grupo arilo es preferiblemente naftilo o fenilo, aún más preferiblemente, fenilo), o -$S(O)_z$ (alquilo C_1-C_6), en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1, 2, ó 3 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_6, y en donde las porciones arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R".

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-4d1, es decir, compuestos de la Fórmula 17-4d donde el anillo C es:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-4d2, es decir, compuestos de la Fórmula 17-4d donde el anillo C es:

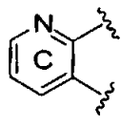


En otro aspecto, la invención proporciona compuestos de la Fórmula 17-5, es decir, compuestos de acuerdo con la Fórmula 17-4, 17-4a, 17-4b, 17-4c, o 17-4d donde el anillo C está no sustituido.

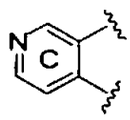
En otro aspecto, la invención proporciona compuestos de la Fórmula 17-5a, es decir, compuestos de la Fórmula 17-4, 17-4a, 17-4b, 17-4c, o 17-4d donde el anillo C se sustituye con 1 ó 2 grupos que son independientemente Cl, F, metilo, etilo, isopropilo, metoxi, etoxi, CF_3, OCF_3, OH, o $-C(O)CH_3$.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-5b, es decir, compuestos de la Fórmula 17-4, 17-4a, 17-4b, 17-4c, o 17-4d donde el anillo C se sustituye con 1 ó 2 grupos que son Cl, F, o metilo.

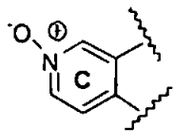
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-5c, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 17-4, 17-5, 17-5a, o 17-5b, en donde el anillo C presenta la siguiente estructura:



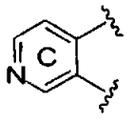
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-5d, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 17-4, 17-5, 17-5a, o 17-5b, en donde el anillo C presenta la siguiente estructura:



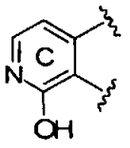
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-5d1, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 17-4, 17-5, 17-5a, o 17-5b, en donde el anillo C presenta la siguiente estructura:



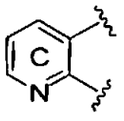
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-5e, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 17-4, 17-5, 17-5a, o 17-5b, en donde el anillo C presenta la siguiente estructura:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-5e1, es decir, compuestos de acuerdo con la Fórmula 17-4, en donde el anillo C presenta la siguiente estructura:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-5f, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 17-4, 17-5, 17-5a, o 17-5b, en donde el anillo C presenta la siguiente estructura:



En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-5g, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 17-4, 17-4a, 17-4b, 17-4c, 17-4d, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, o 17-5f, en donde R_2 es $-X(CO)Y$ o $-(C(R_3)_2)_{1-4}X(CO)Y$.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-5g1, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 17-4, 17-4a, 17-4b, 17-4c, 17-4d, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, o 17-5f, en donde R_2 es hidrógeno, alquilo C_1-C_3 o cicloalquilo C_3-C_6.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-5g2, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 17-4, 17-4a, 17-4b, 17-4c, 17-4d, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, 17-5e1, o 17-5f, en donde R_2 es NO_2 o CN.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-5g3, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 17-4, 17-4a, 17-4b, 17-4c, 17-4d, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, 17-5e1, o 17-5f, en donde R_2 es alquenilo C_2-C_6 o alquinilo C_2-C_6.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-5g4, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 17-4, 17-4a, 17-4b, 17-4c, 17-4d, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, 17-5e1, o 17-5f, en donde R_2 es haloalquilo C_1-C_4.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-5g5, es decir, compuestos de acuerdo con

cualquiera de las Fórmulas 17-4, 17-4a, 17-4b, 17-4c, 17-4d, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, 17-5e1, 17-5f, 17-5g, 17-5g1, 17-5g2, 17-5g3 o 17-5g4 donde R_1 es hidrógeno.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-5g6, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 17-4, 17-4a, 17-4b, 17-4c, 17-4d, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, 17-5e1, o 17-5f, en donde R_1 y R_2 combinados son oxo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-5g7, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 17-4, 17-4a, 17-4b, 17-4c, 17-4d, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, 17-5e1, o 17-5f, en donde R_1 y R_2 combinados son =N-OR, en donde R es hidrógeno, alquilo C_1-C_6, arilo (tal como fenilo) o arilalquilo(como bencilo o fenetilo).

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-5g8, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 17-4, 17-4a, 17-4b, 17-4c, 17-4d, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, 17-5e1, o 17-5f, en donde R_1 y R_2 junto con el carbono al que están unidos forman un grupo cicloalquilo C_{3-6}.

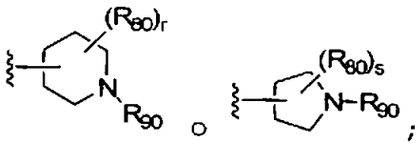
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-5g9, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 17-4, 17-4a, 17-4b, 17-4c, 17-4d, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, 17-5e1, o 17-

5f, en donde R_1 y R_2 junto con el carbono al que están unidos forman un grupo ciclopropilo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-5g10, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 17-4, 17-4a, 17-4b, 17-4c, 17-4d, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, 17-5e1, o 17-5f, en donde R_1 es hidrógeno y R_2 es ciclopropilo. En una modalidad, el compuesto es racémico. En otra modalidad, el compuesto está enantioméricamente enriquecido.

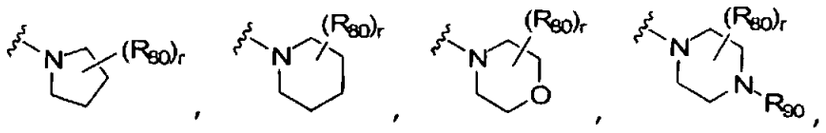
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-5h, es decir, compuestos de la Fórmula 17-5g, en donde

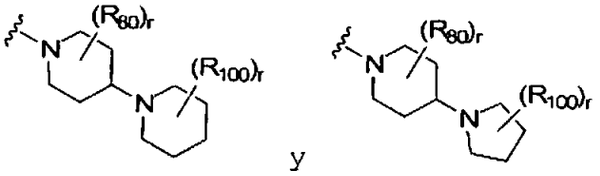
X es O; e Y es $-NR_{60}R_{70}$ o $-N(R_{30})(CH_2)_{2-6}NR_{60}R_{70}$; en donde R_{60} y R_{70} se seleccionan independientemente de: hidrógeno, metilo, etilo, cicloalquilo (C_3-C_8), aril-alquilo (C_1-C_6) (tal como bencilo o fenetilo), 4-piridilmetilo, o



; o

R_{60} y R_{70} tomados junto con el átomo de nitrógeno al que están unidos forman un grupo heterocicloalquilo seleccionado de





y

en donde

cada R_{80} es alquilo C_1-C_4 independientemente no sustituido o alquilo C_1-C_4 sustituido con hidroxilo o halógeno;

cada R_{90} es independientemente hidrógeno, alquilo C_1-C_4 no sustituido, alquilo C_1-C_4 sustituido con hidroxilo o halógeno, cicloalquilo C_3-C_8 no sustituido, cicloalquilo C_3-C_8 sustituido con uno o más (por ejemplo, 1-4) grupos R_5, fenil-(alquilo C_1-C_4), piridil-(alquilo C_1-C_4), tienil-(alquilo C_1-C_4), -C(O)O-(alquilo C_1-C_4), -C(O)O-fenilo, -SO_2-(alquilo C_1-C_6), -SO_2-fenilo, fenilo no sustituido, fenilo sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}, piridilo, tienilo, piridilo sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}, tienilo sustituido con uno o más (por ejemplo, 1-4) grupos R_{50}, en donde

cada R_{50} se selecciona independientemente de: halógeno, alquilo C_1-C_6, -haloalquilo C_1-C_6, -OH, -O- (alquilo C_1-C_4), OCF_3, -CN, -$NR_{60}R_{70}$, -C(O)O-(alquilo C_1-C_4), -$CONR_{60}R_{70}$, -(alquilo C_1-C_6)-$NR_{60}R_{70}$, -NR_{60}CO-(alquilo C_1-C_4), -NR_{60}CO-fenilo, -NR_{60}CO-piridilo, -NR_{60}CO-tienilo, y -$NR_{60}CONR_{60}R_{70}$,

cada R_{100} es independientemente hidrógeno o alquilo C_1-C_4;

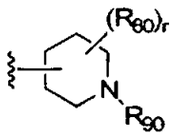
cada r es de 0 a 4; y

cada s es de 0 a 3.

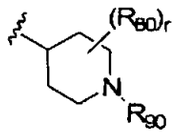
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-5h1, es decir, compuestos de la Fórmula 17-5g, en donde Y es -O-(alquilo C_1-C_6). En una modalidad, Y es -O-(alquilo C_1-C_4).

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-5h2, es decir, compuestos de la Fórmula 17-5g, en donde Y es -O-fenilo.

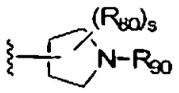
En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-5i, es decir, compuestos de la Fórmula 17-5h, en donde dicho grupo



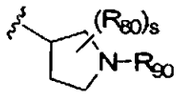
es un grupo de la Fórmula:



y, dicho grupo



es un grupo de la Fórmula:



En un aspecto adicional, la invención proporciona compuestos de la Fórmula 17-5j, es decir, compuestos de acuerdo con cualquiera de las Fórmulas, 17-5h, 17-5h1, 17-5h2, o 17-5i, en donde R_1 es H o alquilo C_1-C_4. En una modalidad, R_1 es H o metilo. En otra modalidad, R_1 es H.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-6, es decir, compuestos de la Fórmulas 15, 16, 16-1, 16-2, 16-3, 16-4, 16-5, 16-6, 16-6a, 16-6b, 16-6c, 16-6d, 16-7, 16-8, 16-9, 16-10, 16-11, 16-11a, 16-11b, 16-11c,

16-12, 16-13, 16-14, o 16-15, 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, 17-3, 17-3a, 17-3a1, 17-3a2, 17-3a3, 17-3a4, 17-3a5, 17-3a6, 17-3a7, 17-3a8, 17-3a9, 17-3a10, 17-3b, 17-3b1, 17-3b2, 17-3c, 17-3d, 17-4, 17-4a, 17-4b, 17-4c, 17-4c1, 17-4d, 17-4d1, 17-4d2, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, 17-5e1, 17-5f, 17-5g, 17-5g1, 17-5g2, 17-5g3, 17-5g4, 17-5g5, 17-5g6, 17-5g7, 17-5g8, 17-5g9, 17-5g10, 17-5h, 17-5h1, 17-5h2, o 17-5i, o 17-5j en donde el grupo heterocicloalquilo (el anillo A de la Fórmula I) es morfolinilo opcionalmente sustituido con uno o más grupos que son independientemente halógeno, alquilo C_1-C_6, alcoxi C_1-C_6, haloalquilo, haloalcoxi, hidroxilo, CN, ariloxi, -SO_2-(alquilo C_1-C_6), -NR'R", alcanoilo C_1-C_6, piridilo, fenilo, o -SO_2-NR'R", en donde cada R' y R" es independientemente hidrógeno o alquilo C_1-C_6 .

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-6a, es decir, compuestos de la Fórmula 17-6 donde el grupo morfolinilo no está unido al azufre del grupo SO_2 vía el anillo de nitrógeno.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-6b, es decir, compuestos de la Fórmula 17-6 donde el grupo morfolinilo está unido al azufre del grupo SO_2 vía el anillo de nitrógeno.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-7, es decir, compuestos de las Fórmulas 15, 16, 16-1, 16-2, 16-3, 16-4, 16-5, 16-6, 16-6a, 16-6b, 16-6c, 16-6d, 16-7, 16-8, 16-9, 16-10, 16-11, 16-11a, 16-11b, 16-11c,

16-12, 16-13, 16-14, o 16-15, 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, 17-3, 17-3a, 17-3a1, 17-3a2, 17-3a3, 17-3a4, 17-3a5, 17-3a6, 17-3a7, 17-3a8, 17-3a9, 17-3a10, 17-3b, 17-3b1, 17-3b2, 17-3c, 17-3d, 17-4, 17-4a, 17-4b, 17-4c, 17-4c1, 17-4d, 17-4d1, 17-4d2, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, 17-5e1, 17-5f, 17-5g, 17-5g1, 17-5g2, 17-5g3, 17-5g4, 17-5g5, 17-5g6, 17-5g7, 17-5g8, 17-5g9, 17-5g10, 17-5h, 17-5h1, 17-5h2, o 17-5i, o 17-5j en donde el grupo heterocicloalquilo(el anillo A de la Fórmula I) es tiomorfolinilo opcionalmente sustituido con uno o más grupos que son independientemente halógeno, alquilo C_1-C_6, alcoxi C_1-C_6, haloalquilo, haloalcoxi, hidroxilo, CN, ariloxi, -SO_2-(alquilo C_1-C_6), -NR'R", alcanoilo C_1-C_6, piridilo, fenilo, o -SO_2-NR'R", en donde cada R' y R" es independientemente hidrógeno o alquilo C_1-C_6 .

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-7a, es decir, compuestos de la Fórmula 17-7 donde el grupo tiomorfolinilo no está unido al azufre del grupo SO_2 vía el anillo de nitrógeno.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-7b, es decir, compuestos de la Fórmula 17-7 donde el grupo tiomorfolinilo está unido al azufre del grupo SO_2 vía el anillo de nitrógeno.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-8, es decir, compuestos de las Fórmulas 15, 16, 16-1, 16-2, 16-3, 16-4, 16-5, 16-6, 16-6a, 16-6b, 16-6c, 16-6d, 16-7, 16-8, 16-9, 16-10, 16-11, 16-11a, 16-11b, 16-11c,

16-12, 16-13, 16-14, o 16-15, 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, 17-3, 17-3a, 17-3a1, 17-3a2, 17-3a3, 17-3a4, 17-3a5, 17-3a6, 17-3a7, 17-3a8, 17-3a9, 17-3a10, 17-3b, 17-3b1, 17-3b2, 17-3c, 17-3d, 17-4, 17-4a, 17-4b, 17-4c, 17-4c1, 17-4d, 17-4d1, 17-4d2, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, 17-5e1, 17-5f, 17-5g, 17-5g1, 17-5g2, 17-5g3, 17-5g4, 17-5g5, 17-5g6, 17-5g7, 17-5g8, 17-5g9, 17-5g10, 17-5h, 17-5h1, 17-5h2, o 17-5i, o 17-5j, en donde el grupo heterocicloalquilo (el anillo A de la Fórmula I) es S,S-dióxido de tiomorfolinilo opcionalmente sustituido con uno o más grupos que son independientemente halógeno, alquilo C_1-C_6, alcoxi C_1-C_6, haloalquilo, haloalcoxi, hidroxilo, CN, ariloxi, -SO_2-(alquilo C_1-C_6), -NR'R", alcanoilo C_1-C_6, piridilo, fenilo, o -SO_2-NR'R", en donde cada R' y R" es independientemente hidrógeno o alquilo C_1-C_6 .

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-8a, es decir, compuestos de la Fórmula 17-8 donde el grupo S,S-dióxido de tiomorfolinilo no está unido al azufre del grupo SO_2 vía el anillo de nitrógeno.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-8b, es decir, compuestos de la Fórmula 17-8 donde el grupo S,S-dióxido de tiomorfolinilo está unido al azufre del grupo SO_2 vía el anillo de nitrógeno.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-9, es decir, compuestos de las Fórmulas 15, 16, 16-1, 16-2, 16-3, 16-4, 16-5, 16-6, 16-6a, 16-6b, 16-6c, 16-6d, 16-7, 16-8, 16-9, 16-10, 16-11, 16-11a, 16-11b, 16-11c,

16-12, 16-13, 16-14, o 16-15, 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, 17-3, 17-3a, 17-3a1, 17-3a2, 17-3a3, 17-3a4, 17-3a5, 17-3a6, 17-3a7, 17-3a8, 17-3a9, 17-3a10, 17-3b, 17-3b1, 17-3b2, 17-3c, 17-3d, 17-4, 17-4a, 17-4b, 17-4c, 17-4c1, 17-4d, 17-4d1, 17-4d2, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, 17-5e1, 17-5f, 17-5g, 17-5g1, 17-5g2, 17-5g3, 17-5g4, 17-5g5, 17-5g6, 17-5g7, 17-5g8, 17-5g9, 17-5g10, 17-5h, 17-5h1, 17-5h2, o 17-5i, o 17-5j, en donde el grupo heterocicloalquilo (el anillo A de la Fórmula I) es piperidinilo opcionalmente sustituido con uno o más grupos que son independientemente halógeno, alquilo C_1-C_6, alcoxi C_1-C_6, haloalquilo, haloalcoxi, hidroxilo, CN, ariloxi, -SO_2-(alquilo C_1-C_6), -NR'R", alcanoilo C_1-C_6, piridilo, fenilo, o -SO_2-NR'R", en donde cada R' y R" es independientemente hidrógeno o alquilo C_1-C_6 .

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-9a, es decir, compuestos de la Fórmula 17-9 donde el grupo piperidinilo no está unido al azufre del grupo SO_2 vía el anillo de nitrógeno.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-9b, es decir, compuestos de la Fórmula 17-9 donde el grupo piperidinilo está unido al azufre del grupo SO_2 vía el anillo de nitrógeno.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-10, es decir, compuestos de las Fórmulas 15, 16, 16-1, 16-2, 16-3, 16-4, 16-5, 16-6, 16-6a, 16-6b, 16-6c, 16-6d, 16-7, 16-8, 16-9, 16-10, 16-11, 16-11a, 16-11b, 16-11c,

16-12, 16-13, 16-14, o 16-15, 17, 17-1, 17-1a, 17-2, 17-2a, 17-2b, 17-2c, 17-2d, 17-2e, 17-2f, 17-2g, 17-2h, 17-2i, 17-3, 17-3a, 17-3a1, 17-3a2, 17-3a3, 17-3a4, 17-3a5, 17-3a6, 17-3a7, 17-3a8, 17-3a9, 17-3a10, 17-3b, 17-3b1, 17-3b2, 17-3c, 17-3d, 17-4, 17-4a, 17-4b, 17-4c, 17-4c1, 17-4d, 17-4d1, 17-4d2, 17-5, 17-5a, 17-5b, 17-5c, 17-5d, 17-5d1, 17-5e, 17-5e1, 17-5f, 17-5g, 17-5g1, 17-5g2, 17-5g3, 17-5g4, 17-5g5, 17-5g6, 17-5g7, 17-5g8, 17-5g9, 17-5g10, 17-5h, 17-5h1, 17-5h2, o 17-5i, o 17-5j en donde el grupo heterocicloalquilo (el anillo A de la Fórmula I) es piperazinilo opcionalmente sustituido con uno o más grupos que son independientemente halógeno, alquilo C_1-C_6, alcoxi C_1-C_6, haloalquilo, haloalcoxi, hidroxilo, CN, ariloxi, -SO_2-(alquilo C_1-C_6), -NR'R", alcanoilo C_1-C_6, piridilo, fenilo, o -SO_2-NR'R", en donde cada R' y R" es independientemente hidrógeno o alquilo C_1-C_6 .

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-10a, es decir, compuestos de la Fórmula 17-10 donde el grupo piperazinilo no está unido al azufre del grupo SO_2 vía el anillo de nitrógeno.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 17-10b, es decir, compuestos de la Fórmula 17-10 donde el grupo piperazinilo está unido al azufre del grupo SO_2 vía el anillo de nitrógeno.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 18, es decir, compuestos de acuerdo con cualquiera de las Fórmulas precedentes donde, cuando R_2 es un grupo cicloalquilo, es un grupo ciclopropilo R_2.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 19, es decir, compuestos de acuerdo con cualquiera de las Fórmulas precedentes donde, cuando R_2 es un grupo cicloalquilo, R_2 es ciclobutilo grupo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 20, es decir, compuestos de acuerdo con cualquiera de las Fórmulas precedentes donde, cuando R_2 es un grupo cicloalquilo, R_2 es un grupo ciclopentilo.

En todavía otro aspecto, la invención proporciona compuestos de la Fórmula 21 esto es, compuestos de acuerdo con cualquiera de las Fórmulas precedentes donde, cuando R_2 es un grupo cicloalquilo, a menos que se identifique específicamente que es diferente de cicloalquilo/sic/. En una modalidad, R_2 un grupo ciclohexilo. En una modalidad adicional, R_2 es ciclopentilo. En una modalidad adicional aun, R_2 es ciclopropilo.

En otro aspecto, la invención proporciona compuestos de la Fórmula 22, es decir, compuestos de acuerdo con cualquiera de las Fórmulas 18, 19, 20, ó 21 donde R_1 es hidrógeno, a menos que se identifique específicamente que es distinto de hidrógeno.

En otro aspecto, la invención proporciona compuestos que son:

5-[(4-clorofenil)sulfonil]-4,5-dihidro-1*H*-pirazol[4,3-*c*]quinolina;

5-[(4-clorofenil)sulfonil]-8-fluoro-4,5-dihidro-2*H*-pirazol[4,3-*c*]quinolina;

5-[(4-clorofenil)sulfonil]-7-fluoro-4,5-dihidro-2*H*-pirazolo[4,3-*c*]quinolina;

5-[(4-clorofenil)sulfonil]-9-fluoro-4,5-dihidro-2*H*-pirazol[4,3-*c*]quinolina;

5-[(4-clorofenil)sulfonil]-4-metil-4,5-dihidro-2*H*-pirazol[4,3-*c*]quinolina;

5-[(4-clorofenil)sulfonil]-7-metoxi-4-metil-4,5-dihidro-1*H*-pirazol[4,3-*c*]quinolina;

5-[(4-clorofenil)sulfonil]-9-metoxi-4-metil-4,5-dihidro-1*H*-pirazol[4,3-*c*]quinolina;

5-[(4-clorofenil)sulfonil]-3-metil-4,5-dihidro-1*H*-pirazol[4,3-*c*]quinolina;

6-(4-clorofenilsulfonil)-4-metoxi-5,6-dihidropirimido[5,4-*c*]quinolin-2-amina;

5-[(4-clorofenil)sulfonil]-3-(difluorometil)-4,5-dihidro-1*H*-pirazol[4,3-*c*]quinolina;

5-(4-cloro-bencenosulfonil)-8-fluoro-4,5-dihidro-isoxazol[4,5-*c*]quinolina;

6-(4-clorofenilsulfonil)-5,6-dihidrobenzo[*f*][1,7]naftiridina;

5-[(4-clorofenil)-sulfonil]-4,5-dihidro-1*H*-pirazol[4,3-*c*]quinolin-3-carboxilato de etilo;

5-[(4-clorofenil)-sulfonil]-8-fluoro-4,5-dihidro-1*H*-pirazol[4,3-*c*]quinolin-3-carboxilato de etilo;

5-[(4-clorofenil)sulfonil]-3-(metiltio)-4,5-dihidro-1*H*-pirazol[4,3-*c*]quinolina;

5-[(4-clorofenil)sulfonil]-3-(metilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-*c*]quinolina;

8-cloro-5-[(4-clorofenil)sulfonil]-4,5-dihidro-2*H*-pirazol[4,3-*c*]quinolina;

4-metil-5-(piridin-2-ilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-*c*]quinolina;

5-[(4-clorofenil)sulfonil]-4,5-dihidro-1*H*-pirazol[4,3-*c*]quinolin-3-ol;

{5-[(4-clorofenil)sulfonil]-8-fluoro-4,5-dihidro-1*H*-pirazol[4,3-*c*]quinolin-3-il}metanol;

5-[(4-clorofenil)sulfonil]-7,9-dimetoxi-4-metil-4,5-dihidro-1*H*-pirazol[4,3-*c*]quinolina;

5-[(4-clorofenil)sulfonil]-8-fluoro-4,5-dihidro-1*H*-pirazol[4,3-*c*]quinolin-3-carboxamida;

ácido 5-[(4-clorofenil)sulfonil]-8-fluoro-4,5-dihidro-1*H*-pirazol[4,3-*c*]quinolin-3-carboxílico;

6-(4-clorofenilsulfonil)-5-etil-5,6-dihidropirazol[1,5-*c*]quinazolina;

5-[(4-clorofenil)sulfonil]-8-fluoro-4,5-dihidro-1*H*-pirazol[4,3-*c*]quinolin-3-carbonitrilo;

5-[(4-clorofenil)sulfonil]-4-metil-4,5-dihidro-2*H*-pirazol[4,3-*c*]quinolina; (enantiómero resuelto, con un tiempo de retención de alrededor de 9.3 min*;)

5-[(4-clorofenil)sulfonil]-4-metil-4,5-dihidro-2*H*-pirazol[4,3-*c*]quinolina (enantiómero resuelto, con un tiempo de retención de aproximadamente 20.5 min*;)

5-[(4-clorofenil)sulfonil]-8-fluoro-4-metil-4,5-dihidro-2*H*-pirazol[4,3-*c*]quinolina (racemato);

5-[(4-clorofenil)sulfonil]-8-fluoro-4-metil-4,5-dihidro-2*H*-pirazol[4,3-*c*]quinolina (enantiómero resuelto, con un tiempo de retención de aproximadamente 9.8 min*;)

5-[(4-clorofenil)sulfonil]-8-fluoro-4-metil-4,5-dihidro-2*H*-pirazol[4,3-*c*]quinolina (enantiómero resuelto, con un tiempo de retención de aproximadamente 27,1 min*;)

5-[(4-Clorofenil)sulfonil]-8-fluoro-4,4-dimetil-4,5-dihidro-2*H*-pirazol[4,3-*c*]quinolina;

8-fluoro-4-metil-5-(piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-*c*]quinolina (racemato);

8-fluoro-4-metil-5-(piridin-2-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-*c*]quinolina;

4-metil-5-(piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-*c*]quinolina;

8-fluoro-4-metil-5-(piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-*c*]quinolina (enantiómero resuelto, con un tiempo de retención de aproximadamente 15.2 min*;)

8-fluoro-4-metil-5-(piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-*c*]quinolina (enantiómero resuelto, con un tiempo de retención de aproximadamente 17.2 min*;)

5-[(4-clorofenil)sulfonil]-1,5-dihidro-4*H*-pirazol[4,3-*c*]quinolin-4-ona;

5-[(4-clorofenil)sulfonil]-4-metil-4,5-dihidro-1*H*-pirazol[4,3-*c*]-1,5-naftiridina;

8-fluoro-4-metil-5-(piridin-2-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina; (enantiómero resuelto, con un tiempo de retención de aproximadamente 16.3 min*;)

5-(4-clorofenilsulfonil)-4-etil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina; (enantiómero resuelto, con un tiempo de retención de aproximadamente 21.4 min*;)

5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolin-7-ol;

5-(4-clorofenilsulfonil)-8-fluoro-1*H*-pirazol[4,3-c]quinolin-4(5*H*)-ona;

5-(4-clorofenilsulfonil)-4-metil-4,5,5a,6,7,8,9,9a-octahidro-1*H*-pirazol[4,3-c]quinolina;

5-(4-clorofenilsulfonil)-9-fluoro-4-metil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

5-(4-clorofenilsulfonil)-7-fluoro-4-metil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

8-fluoro-5-(4-fluorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

4-metil-5-(piridin-2-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina; (racemato y enantiómero resuelto, con un tiempo de retención de aproximadamente 7.9 min*.)

5-(4-clorofenilsulfonil)-8-fluoro-4-deutero-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

9-fluoro-6-(4-fluorofenilsulfonil)-5-metil-5,6-dihidropirimido[5,4-c]quinolin-2-amina;

5-(4-clorofenilsulfonil)-4-ciclopropil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

5-(4-clorofenilsulfonil)-4-(trifluorometil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolin-7-ol; (enantiómero resuelto, con un tiempo de retención de aproximadamente 13.4 min*;)

5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolin-7-ol; (enantiómero resuelto, con un tiempo de retención de aproximadamente 17.0 min*;)

5-(4-clorofenilsulfonil)-4-isopropil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

1,5-bis(4-clorofenilsulfonil)-1*H*-pirazol[4,3-c]quinolin-4(5*H*)-ona;

5-(4-clorofenilsulfonil)-4,5-dihidro-1*H*-imidazo[1,2-a]pirazol[4,3-e]pirimidina;

8-fluoro-5-(4-fluorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina; (enantiómero resuelto, con un tiempo de retención de aproximadamente 7.6 min*;)

8-fluoro-5-(4-fluorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina; (enantiómero resuelto, con un tiempo de retención de aproximadamente 10.1 min*;)

5'-(4-clorofenilsulfonil)-2',5'-dihidrospiro[ciclopropan-1,4'-pirazol[4,3-c]quinolina];

5-(4-clorofenilsulfonil)-7,8-difluoro-4-metil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

7,8-difluoro-4-metil-5-(tiofen-2-ilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-2*H*-pirazol[4,3-c][1,8]naftiridina;

5-(4-clorofenilsulfonil)-4-etil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina; (enantiómero resuelto, con un tiempo de retención de aproximadamente 6.0 min*;)

5-(4-clorofenilsulfonil)-4-etil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina; (enantiómero resuelto, con un tiempo de retención de aproximadamente 9.3 min*;)

5-(5-clorotiofen-2-ilsulfonil)-7,8-difluoro-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

dimetilcarbamato de 5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolin-7-ilo;

4-ciclopropil-7,8-difluoro-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina; (enantiómero resuelto, con un tiempo de retención de aproximadamente 6,0 min*;)

4-ciclopropil-7,8-difluoro-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina; (enantiómero resuelto, con un tiempo de retención de aproximadamente 9.3 min*;)

4-ciclopropil-7,8-difluoro-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina; (racemato;)

7-cloro-4-metil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-pirazolo[3,4-d]tieno[2,3-b]piridina;

5-(4-clorofenilsulfonil)-4-ciclopropil-4,5-dihidro-1*H*-imidazo[1,2-a]pirazol[4,3-e]pirimidina;

4-etil-7,8-difluoro-5-(5-(trifluorometil)piridin-2-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

7,8-difluoro-4-metil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina; (enantiómero resuelto, con un tiempo de retención de aproximadamente 7.0 min*;)

7,8-difluoro-4-metil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina; (enantiómero resuelto, con un tiempo de retención de aproximadamente 9.5 min*;)

4-(4-ciclopropil-1*H*-pirazol[4,3-c]quinolin-5(4*H*)-ilsulfonil)benzonitrilo;

5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-2*H*-pirazol[4,3-c][1,7]naftiridina;

5'-(4-(trifluorometil)fenilsulfonil)-1',5'-dihidrospiro[ciclopropan-1,4'-pirazol[4,3-c]quinolina];

5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-imidazo[1,2-a]pirazol[4,3-e]pirimidina;

4-ciclopropil-7,8-difluoro-5-(5-(trifluorometil)piridin-2-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

5-(5-clorotiofen-2-ilsulfonil)-4-ciclopropil-7,8-difluoro-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-7,8-difluoro-5-(4-fluorofenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c][1,8]naftiridina;

4-ciclopropil-5-(4-fluorofenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c][1,8]naftiridina;

4-ciclopropil-5-(4-fluorofenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-7,8-difluoro-1-(metoximetil)-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-7,8-difluoro-5-(tiofen-2-ilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-imidazo[1,2-a]pirazol[4,3-e]pirimidina;

4-ciclopropil-7,8-difluoro-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

5-(4-fluorofenilsulfonil)-4-(trifluorometil)-4,5-dihidro-2*H*-pirazol[4,3-c][1,8]naftiridina;

7,8-difluoro-4-(piridin-3-il)-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-8-fluoro-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina; (racemato y enantiómero resueltos, con un tiempo de retención de aproximadamente 8.0 min* y 12.6;)

5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-2*H*-[1,3]dioxol[4,5-g]pirazol[4,3-c]quinolina;

5-(5-cloropiridin-2-ilsulfonil)-4-ciclopropil-7,8-difluoro-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

5-(5-clorotiofen-2-ilsulfonil)-4-ciclopropil-7,8-difluoro-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina; (enantiómero resuelto, con un tiempo de retención de aproximadamente 10.3 min*;)

5-(5-clorotiofen-2-ilsulfonil)-4-ciclopropil-7,8-difluoro-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina; (enantiómero resuelto, con un tiempo de retención de aproximadamente 16.1 min*;)

4-ciclopropil-7,8-difluoro-5-(4-fluorofenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina; (enantiómero resuelto, con un tiempo de retención de aproximadamente 16.9 min*;)

4-ciclopropil-7,8-difluoro-5-(4-fluorofenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina; (enantiómero resuelto, con un tiempo de retención de aproximadamente 19.7 min*;)

4-ciclopropil-8-fluoro-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina; (Enantiómero A)

4-ciclopropil-8-fluoro-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina; (Enantiómero B)

4-ciclopropil-7,8-difluoro-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina; (enantiómero resuelto, con un tiempo de retención de aproximadamente 17.3 min*;)

4-ciclopropil-7,8-difluoro-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;(enantiómero resuelto, con un tiempo de retención de aproximadamente 13.0 min*;)

7,8-difluoro-4-isopropil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-7,8-difluoro-5-(4-(trifluorometoxi)fenilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

7,8-difluoro-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolin-7,8-diol;

5-(5-cloropiridin-2-ilsulfonil)-4-ciclopropil-8-fluoro-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

(R)-4-ciclopropil-7-(trifluorometoxi)-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

7-óxido 4-ciclopropil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c][1,7]naftiridina;

5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolin-8-ol;

4-(8-fluoro-4-metil-1*H*-pirazol[4,3-c]quinolin-5(4*H*)-ilsulfonil)-3,5-dimetilisoxazol;

8-fluoro-4-metil-5-(1-metil-1*H*-pirazol-4-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

8-fluoro-4-metil-5-(5-(piridin-2-il)tiofen-2-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

(*R*)-2-terc-butil-4-ciclopropil-7,8-difluoro-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

(*R*)-1-terc-butil-4-ciclopropil-7,8-difluoro-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

(*R*)-4-ciclopropil-7-(trifluorometil)-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

(*R*)-4-ciclopropil-7-(trifluorometoxi)-5-(4-(trifluorometoxi)fenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

(*R*)-4-(4-ciclopropil-7,8-difluoro-1*H*-pirazol[4,3-c]quinolin-5(4*H*)-ilsulfonil)anilina;

(*R*)-4-ciclopropil-7,8-difluoro-5-(4-nitrofenilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

(*R*)-4-ciclopropil-8-(trifluorometil)-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

5-cloro-2-(4-ciclopropil-7,8-difluoro-1*H*-pirazol[4,3-c]quinolin-5(4*H*)-ilsulfonil)tiazol;

(*R*)-4-ciclopropil-5-(4-(difluorometoxi)fenilsulfonil)-7,8-difluoro-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c][1,5]naftiridina;

4-ciclopropil-8-fluoro-5-(5-(trifluorometil)piridin-2-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-8-fluoro-5-(5-(trifluorometil)piridin-2-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-5-(4-(difluorometoxi)fenilsulfonil)-8-fluoro-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-7,8-difluoro-5-(5-(trifluorometil)piridin-2-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolin-7,8-diol;

8-fluoro-4-metil-5-(1-metil-1*H*-imidazol-4-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

(*R*)-1-terc-butil-4-etil-7,8-difluoro-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

(*R*)-4-etil-7,8-difluoro-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

4-(4-(trifluorometil)fenilsulfonil)-4,5,8,8b-tetrahidro-3a*H*-isotiazol[4,5-b]pirazol[3,4-d]piridina; y

7-metil-5-(4-(trifluorometil)fenilsulfonil)-4,5,5a,7-tetrahidro-1*H*-oxazol[5,4-b]pirazol[3,4-d]piridina; y

estereoisómeros, tautómeros, mezclas de estereoisómeros y/o tautómeros, o sus sales farmacéuticamente aceptables.

En otro aspecto, la invención proporciona un método para tratar enfermedad de Alzheimer que comprende administrar una cantidad terapéuticamente efectiva de un compuesto o sal de la Fórmula I, en donde la Fórmula I abarca también:

5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina,

2-fenil-5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina,

7-metoxi-2-fenil-5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina,

8-metoxi-5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina,
8-metoxi-2-fenil-5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina,
3-(metiltio)-5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina,
7-metoxi-5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina,
5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina,
1-(4-sulfamoilfenil)-5-tosil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolin-3-carboxilato de etilo,
1-(4-sulfamoilfenil)-5-tosil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolin-3-carboxamida, y
1-metil-5-tosil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolin-3-carboxilato de etilo;
a un paciente necesitado de dicho tratamiento.

En todavía otro aspecto, la invención proporciona una composición que comprende un compuesto o sal de la Fórmula I, en donde la Fórmula I comprende además 3-(metiltio)-5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina, 7-metoxi-5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina, y 5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina, y al menos un disolvente, adyuvante, excipiente, portador, ligador o desintegrante farmacéuticamente aceptable.

En todavía otro aspecto, la invención proporciona un método para tratar enfermedad de Alzheimer que comprende administrar una cantidad terapéuticamente efectiva de un compuesto o sal de la Fórmula I, en donde la Fórmula I abarca también
5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina,
2-fenil-5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina,

7-metoxi-2-fenil-5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina,

8-metoxi-5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina,

8-metoxi-2-fenil-5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina,

3-(metiltio)-5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina,

7-metoxi-5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina,

5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina,

1-(4-sulfamoilfenil)-5-tosil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolin-3-carboxilato de etilo,

1-(4-sulfamoilfenil)-5-tosil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolin-3-carboxamida; y

1-metil-5-tosil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolin-3-carboxilato de etilo

a un paciente en necesidad de dicho tratamiento.

En otro aspecto, los compuestos de la invención exhiben interacción mínima o preferiblemente, ninguna interacción con Notch.

Definiciones

Las definiciones y explicaciones adelante estblecen los términos que se utilizan a través de este documento completo que incluye la especificación y las reivindicaciones.

Se debe notar que, como se utiliza en esta especificación y las reivindicaciones adjuntas, las formas singulares "un", "una" y "el" incluyen los referentes plurales a menos que el contenido imponga claramente lo contrario. Así, por ejemplo, la referencia para una composición que contiene "un compuesto"

incluye una mezcla de dos o más compuestos. Se debería notar que el término "o" se emplea generalmente en su sentido incluyendo "y/o" a menos que el contenido imponga claramente lo contrario.

Cuando se indican sustituyentes múltiples como unidos a una estructura, se entiende que los sustituyentes pueden ser idénticos o diferentes. Así por ejemplo "R_m opcionalmente sustituido con 1, 2 ó 3 grupos R_q" indica que R_m se sustituye con 1, 2, ó 3 grupos R_q donde los grupos R_q pueden ser idénticos o diferentes. Se entenderá por aquellos expertos en la técnica con respecto a cualquier grupo que contiene uno o más sustituyentes, dichos grupos no están destinados a introducir ninguna sustitución o patrones de sustitución que sean poco viables a nivel estérico y/o no realizables a nivel sintético.

El APP, proteína precursora de amiloide, se define como cualquier polipéptido APP, incluyendo variantes de APP, mutaciones e isoformas, por ejemplo, según se divulga en la patente estadounidense No. 5.766.846.

Un péptido beta, beta amiloide, se define como cualquier péptido que resulta de beta-secretasa mediado por la división de APP incluyendo péptidos de 39, 40, 41, 42, y 43 aminoácidos, y que se extienden del sitio de división de beta-secretasa a los aminoácidos 39, 40, 41, 42, ó 43.

Farmacéuticamente aceptable se refiere a aquellas propiedades y/o sustancias que son aceptables a un paciente desde un punto de vista toxicológico y/o de seguridad.

Una cantidad terapéuticamente efectiva se define como una cantidad efectiva para reducir o disminuir al menos un síntoma de la enfermedad que se está tratando o para reducir o retardar el comienzo de uno o más marcadores clínicos o síntomas de la enfermedad.

Por "una enfermedad relacionada con beta" significa enfermedades o trastornos que se asocian con la acumulación extracelular de A beta (amiloide) en varios órganos y tejidos del cuerpo e incluyen enfermedades, trastornos, afecciones, patologías, y otras anormalidades de la estructura o función del cerebro, incluyendo sus componentes, como el estroma, incluyendo la vasculatura o el parénquima incluyendo regiones anatómicas o funcionales, o las neuronas en sí mismas, en las que el agente causativo es A beta (amiloide). La proteína 4 kDa beta-amiloide (A beta), una proteína de 39-43 aminoácidos, es un componente principal de depósitos cerebrales y cerebro vasculares, tal como placas, que se encuentran en, entre otras, enfermedad de Alzheimer, angiopatía cerebral amiloide, daño cognitivo leve (MCI), y síndrome de Down y se deriva de la división proteolítica de un precursor mayor unido a membrana, la proteína precursora A beta (APP) mediante varias proteasas de aspartilo, una de las cuales es gama-secretasa.

Por "alcanoilo" significa un radical acilo Alk-C(O)-, en donde Alk es un radical alquilo según se define aquí. Ejemplos de alcanoilo incluyen acetilo, propionilo, butirilo, isobutirilo, valerilo, isovalerilo, 2-metil-butirilo, 2,2-dimetilpropionilo, valerilo, hexanoilo, heptanoilo, octanoilo

y similares. Por "alcanoilo C_1-C_6" en la presente invención significa un radical acilo Alk-C(O)-, en donde Alk es un grupo alquilo de cadena lineal o ramificada que tienen 1-6 átomos de carbono.

Por "alquilo" y "alquilo C_1-C_6" en la presente invención significa grupos alquilo de cadena lineal o ramificada que tienen 1-6 átomos de carbono, como, metilo, etilo, propilo, isopropilo, n-butilo, sec-butilo, terc-butilo, pentilo, 2-pentilo, isopentilo, neopentilo, hexilo, 2-hexilo, 3-hexilo, y 3-metilpentilo. Se entiende que en los casos donde una cadena alquilo de un sustituyente (por ejemplo, de un grupo alquilo, alcoxi o alquenilo) es menor o mayor a 6 carbonos, así se lo indicará en el segundo en "C" como, por ejemplo, "C_1-C_{10}" indica un máximo de 10 carbonos. Los grupos alquilo pueden ser mono o di-radicales. El significado será claro para un experto en la técnica. El término también incluye grupos alquilo sustituidos, y se refiere a un grupo alquilo en el que 1 o más átomos de hidrógeno se remplazan con un sustituyente independientemente seleccionado del grupo: acilo, aciloxi, alcoxi, amino (en donde el grupo amino puede ser amina cíclica), arilo, heteroarilo, heterocicloalquilo, carboxilo, oxo, amido, ciano, cicloalquilo, cicloalquenilo, halógeno, hidroxilo, nitro, sulfamoilo, sulfanilo, sulfinilo, sulfonilo, y ácido sulfónico.

Por "alquileno" significa un grupo alquilo diradical, por lo que el alquilo es como se definió anteriormente.

Por "alcoxi" y "alcoxi C_1-C_6" en la presente invención significa grupos alquilo de cadena lineal o ramificada que tienen 1-6 átomos de carbono, unidos a través de al menos un átomo de oxígeno divalente, tal como, por ejemplo, metoxi, etoxi, propoxi, isopropoxi, n-butoxi, sec-butoxi, terc-butoxi, pentoxi, isopentoxi, neopentoxi, hexoxi, y 3-metilpentoxi.

Por el término "halógeno" en la presente invención se entiende flúor, bromo, cloro, y/o yodo.

"alquenilo" y "alquenilo C_2-C_6" significa radicales de hidrocarburo lineales y ramificados que tienen de 2 a 6 átomos de carbono y de uno a tres enlaces dobles e incluyen, por ejemplo, etenilo, propenilo, 1-but-3-enilo, 1-pent-3-enilo, 1-hex-5-enilo y similares. El término incluirá también grupos alquenilo sustituido, y hace referencia a un grupo alquenilo en el que 1 o más átomos de hidrógeno se remplazan con un sustituyente independientemente seleccionado del grupo: acilo, aciloxi, alcoxi, amino (en donde el grupo amino puede ser una amina cíclica), arilo, heteroarilo, heterocicloalquilo, carboxilo, oxo, amido, ciano, cicloalquilo, cicloalquenilo, halógeno, hidroxilo, nitro, sulfamoilo, sulfanilo, sulfinilo, sulfonilo y ácido sulfónico, por ejemplo 1*H*-pirrol-2-ilmetileno.

"alquinilo" y "alquinilo C_2-C_6" significa radicales hidrocarburo lineales y ramificados que tienen de 2 a 6 átomos de carbono y uno o dos enlaces triples e incluyen etinilo, propinilo, butinilo, pentin-2-ilo y similares. El término también incluye grupos alquinilo sustituido, y se refiere a un

grupo alquinilo en el que 1 o más átomos de hidrógeno se remplazan con un sustituyente independientemente seleccionado del grupo: acilo, aciloxi, alcoxi, amino (en donde el grupo amino puede ser una amina cíclica), arilo, heteroarilo, heterociclilo, carboxilo, oxo, amido, ciano, cicloalquilo, cicloalquenilo, halógeno, hidroxilo, nitro, sulfamoilo, sulfanilo, sulfinilo, sulfonilo y ácido sulfónico.

Como se utiliza aquí, el término "cicloalquilo" significa radicales carbocíclicos saturados que tienen de tres a doce átomos de carbono. El cicloalquilo puede ser monocicliclo, un sistema fusionado policíclico, o un sistema puenteado bi o policíclico, tal como adamantilo o biciclo[2.2.1] heptilo. Ejemplos de dichos radicales incluyen ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo. Grupos cicloalquilo preferidos son ciclopentilo, ciclohexilo y cicloheptilo. Los grupos cicloalquilo preferidos aquí se sustituyen o no se sustituyen en una o más posiciones sustituibles con varios grupos. Por ejemplo, dichos grupos cicloalquilo pueden sustituirse opcionalmente con, por ejemplo, alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, hidroxilo, oxo, ciano, nitro, amino, monoalquilo (C_1-C_6)amino, dialquilo (C_1-C_6)amino, alquenilo C_2-C_6, alquinilo C_2-C_6, haloalquilo C_1-C_6, haloalcoxi C_1-C_6, aminoalquilo (C_1-C_6), monoalquilo (C_1-C_6)aminoalquilo (C_1-C_6) o dialquilo (C_1-C_6)aminoalquilo (C_1-C_6).

Por "arilo" significa un grupo carbocíclico aromático que tiene un anillo único (por ejemplo, fenilo) o múltiples anillos condensados en los que al menos uno es aromático, (por

ejemplo, 1,2,3,4-tetrahidronaftilo, naftilo), que se sustituye opcionalmente en una o más posiciones sustituibles. Grupos arilo preferidos de la presente invención son fenilo, 1-naftilo, 2-naftilo, indanilo, indenilo, dihidronaftilo, fluorenilo, tetralinilo o 6,7,8,9-tetrahidro-5H-benzo[a]cicloheptenilo. Grupos arilo más preferidos incluyen fenilo y naftilo. Los grupos arilo aquí están no sustituidos o, sustituidos en una o más posiciones sustituibles con varios grupos. Por ejemplo, dichos grupos arilo pueden sustituirse opcionalmente con, por ejemplo, alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, hidroxilo, ciano, nitro, amino, monoalquilo (C_1-C_6)amino, dialquilo (C_1-C_6)amino, alquenilo C_2-C_6, alquinilo C_2-C_6, haloalquilo C_1-C_6, haloalcoxi C_1-C_6, aminoalquilo (C_1-C_6), monoalquilo (C_1-C_6)aminoalquilo (C_1-C_6) o dialquilo (C_1-C_6)aminoalquilo (C_1-C_6).

Por "arilalquilo" o "aralquilo" se entiende el grupo -alquilen-arilo, o -alquil-arilo, en donde alquileno, alquilo y arilo son como se define aquí.

Por "ariloxi" se entiende el grupo -O-arilo donde el término arilo es según se define aquí.

Por "arilalquiloxi" "arilalquiloxi" o "aralquiloxi" se entiende el grupo -O-alquilen-C_1-C_4-arilo, u -O-alquil-C_1-C_4-arilo, en donde los términos arilo, alquilo, y alquileno son según se define aquí. Un ejemplo de arilalquiloxi es benciloxi (o -O-CH_2-fenilo).

Por el término "halógeno" o "halo" en la presente invención significa flúor, bromo, cloro, y/o yodo.

Por "haloalquilo" significa un radical alquilo que tiene el significado que se definió anteriormente donde uno o más hidrógenos se remplazan con un halógeno. Ejemplos de dichos haloalquilos incluyen clorometilo, 1-bromoetilo, fluorometilo, difluorometilo, trifluorometilo, 1,1,1-trifluoroetilo y similares.

Por "heteroarilo" significa al menos uno o más sistemas de anillos aromáticos de 5, 6, ó 7 miembros que incluyen sistemas de anillos fusionados de 9-11 átomos que contienen al menos uno y hasta cuatro heteroátomos seleccionados de nitrógeno, oxígeno, o azufre. Un anillo de heteroarilo puede ser un mono-radical, o di-radical. Por ejemplo, cuando el anillo B es pirazolilo, el anillo de pirazolilo se fusiona con el anillo de piperidina en el centro y el anillo de pirazolilo es un di-radical. El significado resultará evidente para un experto en la técnica. Grupos de heteroarilo preferidos de la presente invención incluyen piridilo, pirimidinilo, quinolinilo, benzotienilo, indolilo, indolinilo, piridazinilo, pirazinilo, isoindolilo, isoquinolilo, quinazolinilo, quinoxalinilo, ftalazinilo, imidazolilo, isoxazolilo, pirazolilo, oxazolilo, tiazolilo, indolizinilo, indazolilo, benzotiazolilo, benzimidazolilo, benzofuranilo, furanilo, tienilo, pirrolilo, oxadiazolilo, tiadiazolilo, triazolilo, tetrazolilo, isotiazolilo, naftiridinilo, isocromanilo, cromanilo, tetrahidroisoquinolinilo, isoindolinilo, isobenzotetrahidrofuranilo, isobenzotetrahidrotienilo, isobenzotienilo, benzoxazolilo, piridopiridilo,

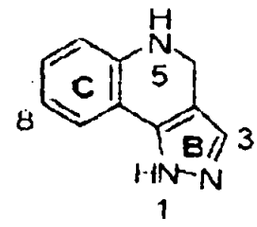
benzotetrahidrofuranilo, benzotetrahidrotienilo, purinilo, benzodioxolilo, triazinilo, pteridinilo, benzotiazolilo, imidazopiridilo, imidazotiazolilo, dihidrobenzisoxazinilo, benzisoxazinilo, benzoxazinilo, dihidrobenzisotiazinilo, benzopiranilo, benzotiopiranilo, cromonilo, cromanonilo, N-óxido de piridilo, tetrahidroquinolinilo, dihidroquinolinilo, dihidroquinolinonilo, dihidroisoquinolinonilo, dihidrocoumarinilo, dihidroisocoumarinilo, isoindolinonilo, benzodioxanilo, benzoxazolinonilo, N-óxido de pirrolilo, N-óxido de pirimidinilo, N-óxido de piridazinilo, N-óxido de pirazinilo, N-óxido de quinolinilo, N-óxido de indolilo, N-óxido de indolinilo, N-óxido de isoquinolilo, N-óxido de quinazolinilo, N-óxido de quinoxalinilo, N-óxido de ftalazinilo, N-óxido de imidazolilo, N-óxido de isoxazolilo, N-óxido de tiazolilo, N-óxido de indolizinilo, N-óxido de indazolilo, N-óxido de benzotiazolilo, N-óxido de benzimidazolilo, N-óxido de pirrolilo, N-óxido de oxadiazolilo, N-óxido de tiadiazolilo, N-óxido de triazolilo, N-óxido de tetrazolilo, S-óxido de benzotiopiranilo, S,S-dióxido de benzotiopiranilo. Los grupos de heteroarilo en la presente se sustituyen o no se sustituyen en una o más posiciones sustituibles con varios grupos. Por ejemplo, dichos grupos de heteroarilo pueden sustituirse opcionalmente con, por ejemplo, alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, hidroxilo, ciano, nitro, amino, monoalquilo (C_1-C_6)amino, dialquilo (C_1-C_6)amino, alquenilo C_2-C_6, alquinilo C_2-C_6, haloalquilo C_1-C_6, haloalcoxi

C_1-C_6, aminoalquilo (C_1-C_6), monoalquilo (C_1-C_6)aminoalquilo (C_1-C_6) o dialquilo (C_1-C_6)aminoalquilo (C_1-C_6).

Por "heterociclo", "heterocicloalquilo" o "heterociclilo" significa uno o más sistemas de anillos carbocíclicos de 4, 5, 6 ó 7 miembros que incluyen sistemas de anillos fusionados de 9-11 átomos que contienen al menos uno y hasta cuatro heteroátomos seleccionados de nitrógeno, oxígeno o azufre. Heterociclos preferidos de la presente invención incluyen morfolinilo, tiomorfolinilo, S-óxido de tiomorfolinilo, S,S-dióxido de tiomorfolinilo, piperazinilo, homopiperazinilo, pirrolidinilo, pirrolinilo, tetrahidropiranilo, piperidinilo, tetrahidrofuranilo, tetrahidrotienilo, homopiperidinilo, homomorfolinilo, homotiomorfolinilo, S,S-dióxido de homotiomorfolinilo, oxazolidinonilo, dihidropirazolilo, dihidropirrolilo, dihidropirazolilo, dihidropiridilo, dihidropirimidinilo, dihidrofurilo, dihidropiranilo, tetrahidrotienilo, S-óxido de tetrahidrotienilo, S,S-dióxido de tetrahidrotienilo y S-óxido de homotiomorfolinilo. Los grupos heterociclo en la presente se sustituyen o no se sustituyen en una o más posiciones sustituibles con varios grupos. Por ejemplo, dichos grupos heterociclo pueden sustituirse opcionalmente con, por ejemplo, alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, hidroxilo, oxo, ciano, nitro, amino, monoalquilo (C_1-C_6)amino, dialquilo (C_1-C_6)amino, alquenilo C_2-C_6, alquinilo C_2-C_6, haloalquilo C_1-C_6, haloalcoxi C_1-C_6, aminoalquilo (C_1-C_6), monoalquilo (C_1-C_6)aminoalquilo (C_1-C_6), dialquilo (C_1-C_6)aminoalquilo (C_1-C_6) u oxo.

Por "hidroxialquilo" significa un alquilo sustituido con un hidroxilo, tal como hidroximetilo, 1-hidroxipropilo, 2-hidroxietilo, 3-hidroxietilo, o 3-hidroxibutilo.

La numeración del núcleo tricíclico cuando el anillo C es un fenilo y el anillo B es pirazolilo:



La mayoría compuestos se nombran utilizando Autonom 2000 4.01.305, el cual se encuentra disponible en Beilstein Information Systems, Inc, Englewood, Colorado, o ChemDraw v.10.0, (disponible en Cambridgesoft, con sede en 100 Cambridge Park Drive, Cambridge, MA 02140). De manera alternativa los nombres se generan con en base a las reglas IUPAC. Los compuestos de la presente invención pueden contener uno o más átomos de carbono asimétricos, por lo cual los compuestos podrán existir en varias formas estereoisoméricas. Estos compuestos podrán ser, por ejemplo, racematos, isómeros quirales no racémicos o diastereómeros. En estas situaciones, los enantiómeros únicos, es decir las formas ópticamente activas, podrán obtenerse mediante síntesis asimétrica o a través de la resolución de racematos. Es posible obtener la resolución de los racematos, por ejemplo, mediante métodos convencionales tales como la cristalización en presencia de un agente de resolución, la cromatografía utilizando por ejemplo

una columna HPLC quiral, o mediante la derivación de la mezcla racémica con un agente de resolución para generar diastereómeros, los cuales se separan mediante cromatografía y quitando luego el agente de resolución para dar el compuesto original en una forma enantioméricamente enriquecida. Cualquiera de los procedimientos mencionados anteriormente podrán repetirse para incrementar la pureza enantiomérica de un compuesto.

Las sales farmacéuticamente aceptables no tóxicas incluyen, pero no se limian a, sales de ácidos inorgánicos tales como clorhídrico, sulfúrico, fosfórico, difosfórico, hidrobrómico y nítrico o sales de ácidos orgánicos tales como ácido fórmico, cítrico, málico, maleico, fumárico, tartárico, succínico, acético, láctico, metansulfónico, p-toluensulfónico, 2-hidroxietilsulfónico, salicílico y esteárico. De manera similar, los cationes farmacéuticamente aceptables incluyen, pero no se limitan a, sodio, potasio, calcio, aluminio, litio y amonio. Aquellos expertos en la técnica serán capaces de reconocer una amplia variedad de sales de adición no tóxicas farmacéuticamente aceptables. La invención también abarca profármacos de los compuestos de Fórmula I.

La invención abarca también los profármacos de los compuestos de Fórmula I. Aquellos expertos en la técnica serán capaces de identificar varias metodologías sintéticas que se pueden emplear para preparar profármacos farmacéuticamente aceptables no tóxicos de los compuestos abarcados dentro de la Fórmula I. Aquellos expertos en la técnica serán capaces de identificar

una amplia variedad de solvatos farmacéuticamente aceptables no tóxicos como agua, etanol, aceite mineral, aceite vegetal y dimetilsulfóxido. La invención abarca además los profármacos acilados de los compuestos de Fórmula I. Aquellos expertos en la técnica serán capaces de reconocer varias metodologías de síntesis que pueden utilizarse para preparar sales de adición y profármacos acilados farmacéuticamente aceptables no tóxicos de los compuestos abarcados por la Fórmula I.

El término "grupo de profármacos ácidos" denota un grupo funcional que se convierte in vivo en un compuesto de ácido carboxílico activo de Fórmula I. Dichos grupos de profármacos son generalmente conocidos en la técnica e incluyen grupos formadores de ésteres para formar un profármaco éster como benziloxi, dialquilaminoetiloxi(C_1-C_6), acetoximetilo, pivaloiloximetilo, ftalidoilo, etoxi Carboniloxietilo, 5-metil-2-oxo-1,3-dioxol-4-il metilo y alcoxi(C_1-C_6) opcionalmente sustituido por N-morfolino y grupos formadores de amidas tales como dialquilamino(C_1-C_6). Los grupos de profármacos preferidos incluyen el alcoxi C_1-C_6 formador de un éster y O^-M^+, en donde M^+ representa un catión para formar una sal del ácido. Los cationes preferidos incluyen sodio, potasio y amonio. Otros cationes incluyen magnesio y calcio. Grupos de profármacos preferidos adicionales incluyen O^-M^{++} donde M^{++} es un catión divalente como magnesio o calcio.

Se entiende que aquellos practicantes de la técnica comprenderán que la definición de compuestos de Fórmula I contienen carbonos asimétricos y abarcan todos los

estereoisómeros posibles, mezclas y regioisómeros de los mismos que poseen la actividad que se analiza a continuación. Tales regioisómeros podrán obtenerse en forma pura mediante métodos de separación estándar conocidos por los expertos en la técnica. La definición abarca cualesquiera isómeros ópticos y diastereómeros así como también los estereoisómeros R y S puros enantioméricamente resueltos y racémicos así como también otras mezclas de los estereoisómeros R y S y sus sales farmacéuticamente aceptables, los cuales poseen la actividad que se analiza a continuación. Será posible obtener isómeros ópticos en su forma pura mediante técnicas de separación estándar o síntesis específica de enantiómeros. Se entiende que esta invención abarca todas las formas cristalinas de los compuestos de Fórmula I.

Cuando los compuestos descritos aquí contienen enlaces dobles olefínicos u otros centros de asimetría geométricos, y a no ser que se indique lo contrario, la intención es que los compuestos incluyan las configuraciones cis, trans, Z- y E-. De igual modo, se busca también que todas las formas tautoméricas estén incluidas.

Los compuestos de Fórmula general I podrán administrarse en forma oral, tópica, parenteral, mediante inhalación o pulverización o por vía rectal mediante formulaciones de dosificación unitaria que contengan portadores, adyuvantes y vehículos farmacéuticamente aceptables no tóxicos convencionales. El término parenteral, como se utiliza aquí, incluye técnicas de inyección o infusión percutánea,

subcutánea, intravascular (por ejemplo intravenosa), intramuscular o intratecal y similares. Además, se proporciona una formulación farmacéutica que comprende un compuesto de Fórmula general I y un portador farmacéuticamente aceptable. Uno o más compuestos de la Fórmula general I pueden estar presentes en asociación con uno o más portadores y/o diluyentes y/o adyuvantes farmacéuticamente aceptables no tóxicos, y si se desea, con otros ingredientes activos. Las composiciones farmacéuticas que contienen compuestos de las Fórmula general I podrán estar bajo formas adecuadas para utilización por vía oral, por ejemplo como comprimidos, píldoras, pastillas, suspensiones acuosas u aceitosas, polvos dispersables o gránulos, emulsiones, cápsulas duras o blandas, jarabes o elixires.

Las composiciones preparadas para uso oral se pueden preparar de acuerdo con cualquier método conocido en la técnica para la fabricación de composiciones farmacéuticas y dichas composiciones pueden contener uno o más agentes seleccionados del grupo que consiste de agentes endulzantes, saborizantes, colorantes y conservantes con el fin de proporcionar preparaciones farmacéuticamente atractivos y con gusto agradable. Los comprimidos contienen el ingrediente activo además de excipientes farmacéuticamente aceptables no tóxicos adecuados para la fabricación de comprimidos. Dichos excipientes podrán ser, por ejemplo, diluyentes inertes tales como carbonato de calcio, carbonato de sodio, lactosa, fosfato de calcio o fosfato de sodio; agentes granulantes y

desintegradores como por ejemplo almidón de maíz o ácido algínico, agentes de unión tales como almidón, gelatina o goma acacia y agentes lubricantes como por ejemplo estearato de magnesio, ácido esteárico o talco. Los comprimidos podrán no estar recubiertos o estar recubiertos mediante técnicas conocidas. En algunos casos dicho recubrimiento podrá prepararse mediante técnicas conocidas para demorar la desintegración y la absorción en el tracto intestinal y por lo tanto proporcionar un efecto sostenido durante un período de tiempo mayor. Por ejemplo, podrá utilizarse un material para lograr dicho retraso como el monoestearato de glicerilo o el diestearato de glicerilo.

Las formulaciones para uso oral también se pueden presentar como cápsulas de gelatina dura en las cuales el ingrediente activo estará mezclado con un diluyente inerte sólido, por ejemplo, carbonato de calcio, fosfato de calcio o caolín, o como cápsulas de gelatina blanda en donde el ingrediente activo se mezcla con agua o un medio aceitoso como aceite de maní, parafina líquida o aceite de oliva.

Las formulaciones para uso oral podrán presentarse también bajo la forma de pastillas.

Las suspensiones acuosas contienen los materiales activos en mezcla con los excipientes adecuados para la fabricación de suspensiones acuosas. Dichos excipientes son agentes de suspensión, por ejemplo carboximetilcelulosa de sodio, metilcelulosa, hidropropil-metilcelulosa, alginato de sodio, polivinilpirrolidona, goma tragacanto y goma acacia; los

agentes dispersantes o humectantes pueden ser fosfátidos de ocurrencia natural como por ejemplo lecitina, o productos de la condensación de un óxido de alquileno con ácidos grasos, por ejemplo estearato de polioxietileno, o productos de la condensación de óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo heptadecaetilenoxi cetanol, o productos de la condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y un hexitol como monooleato de sorbitol polioxietileno, o productos de la condensación del óxido de etileno con ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo monooleato de sorbitan polietileno. Las suspensiones acuosas pueden contener además uno o más conservantes, por ejemplo etilo o p-hidroxibenzoato de n-propilo, uno o más colorantes, uno o más saborizantes y uno o más agentes endulzantes como sacarosa o sacarina.

Se puede formular suspensiones aceitosas al suspender los ingredientes activos en un aceite vegetal, por ejemplo aceite de araquis, de oliva, de sésamo o de coco o en un aceite mineral como parafina líquida. Las suspensiones aceitosas pueden contener un agente espesante como por ejemplo cera de abeja, parafina sólida o cetil alcohol. Se pueden agregar agentes endulzantes y saborizantes para proporcionar preparaciones orales con gusto agradable. Estas composiciones podrán conservarse mediante la adición de un antioxidante como ácido ascórbico.

Los polvos dispersables y los gránulos adecuados para la preparación de una suspensión acuosa mediante la adición de agua proporcionan el ingrediente activo en mezcla con un agente dispersante o humectante, un agente de suspensión y uno o más conservantes. Los agentes dispersantes o humectantes adecuados así como los agentes de suspensión adecuados se ejemplifican en aquellos ya mencionados anteriormente.

También podrán estar presentes excipientes adicionales tales como endulzantes, saborizantes y colorantes.

Las composiciones farmacéuticas de la invención podrán además estar en forma de emulsión de aceite en agua. La fase aceitosa puede estar compuesta de un aceite vegetal o un aceite mineral o de mezclas de los mismos. Serán agentes emulsionantes adecuados, por ejemplo, gomas de ocurrencia natural tales como goma acacia o goma tragacanto, fosfátidas de ocurrencia natural tales como soya, lecitina, ésteres o ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo monooleato de sorbitano, y productos de la condensación de dichos ésteres parciales con óxido de etileno, tal como por ejemplo, monooleato de sorbitan polioxietileno. Las emulsiones podrán además contener endulzantes y saborizantes.

Los jarabes y elixires se pueden formular con agentes endulzantes, por ejemplo glicerol, propilenglicol, sorbitol, glucosa o sacarosa. Dichas formulaciones pueden contener además un emoliente, un conservante y agentes saborizantes y colorantes. Las composiciones farmacéuticas podrán en la forma

de suspensiones estériles inyectables acuosas o aceitosas. Estas suspensiones se pueden formular de acuerdo con la técnica conocida utilizando aquellos agentes dispersantes, humectantes y de suspensión adecuados que fueron mencionados con anterioridad. Una preparación inyectable estéril puede ser también una solución o suspensión inyectable estéril en un diluyente o disolvente no tóxico parenteralmente aceptable, por ejemplo una solución en 1,3-butandiol. Dentro de los vehículos y solventes aceptables que se pueden emplear son el agua, la solución de Ringer y la solución isotónica de cloruro de sodio. Además, convencionalmente se emplean aceites no volátiles, estériles, tal como medio de suspensión o disolvente. Para este propósito se puede emplear cualquier aceite no volátil con poco cuerpo dentro de los cuales se incluyen los mono o diglicéridos sintéticos. Además, ácidos grasos tales como el ácido oleico son útiles en la preparación de soluciones inyectables.

Los compuestos con la Fórmula general I también se pueden administrar en forma de supositorios, por ejemplo para administración rectal del fármaco. Estas composiciones se pueden preparar al mezclar el fármaco con un excipiente adecuado no irritante que sea sólido a temperatura ambiente pero líquido a temperatura rectal y que por lo tanto se derretirá en el recto liberando así el fármaco. Estos materiales incluyen manteca de cacao y polietilenglicol.

Los compuestos de Fórmula general I podrán administrarse parenteralmente en un medio estéril. El fármaco, dependiendo

del vehículo y de la concentración utilizada, podrá estar suspendido o disuelto en el vehículo. De manera ventajosa, los adyuvantes tales como anestésicos locales, conservantes y agentes amortiguantes pueden disolverse en el vehículo.

Para el tratamiento de trastornos de la vista u otros tejidos externos, por ejemplo de la boca y la piel, es preferible que las formulaciones se apliquen como un gel, pulverizadas, tal como ungüento o crema tópicos, o bajo la forma de un supositorio que contenga los ingredientes activos en una cantidad total de, por ejemplo, 0,075 a 30% p/p, preferiblemente 0,2 a 20% p/p y más preferiblemente 0,4 a 15% p/p. Cuando las formulaciones formen parte de un ungüento, los ingredientes activos se pueden emplear con una base de ungüento parafínico o con una base de ungüento miscible en agua.

De manera alternativa, los ingredientes activos se pueden formular en una crema con una base cremosa de aceite en agua. Si se desea, la fase acuosa de la base cremosa podrá incluir, por ejemplo, al menos 30% p/p de un alcohol polihídrico tal como propilenglicol, butan-1,3-diol, manitol, sorbitol, glicerol, polietilenglicol y mezclas de los mismos. Es deseable que la formulación tópica incluya un compuesto que mejore la absorción o penetración del ingrediente activo a través de la piel u otras áreas afectadas. Ejemplos de tales mejoradores de la penetración dérmica se encuentra el dimetilsulfóxido y sustancias análogas relacionadas al mismo. Los compuestos de la presente invención también se pueden

administrar mediante un dispositivo transdérmico. Preferiblemente la administración tópica se obtendrá utilizando un parche que tiene un tipo de membrana porosa y reservorio. En cualquiera de los dos casos, el ingrediente activo se libera de manera continua desde el depósito o las microcápsulas a través de una membrana y hacia el adhesivo permeable por el agente activo, el cual está en contacto con la piel o mucosa de quien recibe la formulación. Si el ingrediente activo es absorbido a través de la piel, se administra un flujo controlado y predeterminado del mismo. En el caso de las microcápsulas, el agente encapsulante puede además funcionar como membrana. El parche transdérmico puede incluir el compuesto dentro de un sistema disolvente adecuado con un sistema adhesivo como una solución acrílica y un parche de poliéster. La fase aceitosa de las emulsiones de esta invención podrá constituirse a partir de ingredientes conocidos y de manera conocida. Mientras que la fase puede comprender solamente un emulsionante, esta puede comprender una mezcla de al menos un emulsionante con una grasa, un aceite o con una grasa y un aceite. Preferiblemente se incluye un emulsionante hidrofílico junto con un emulsionante lipofílico que funciona como estabilizante. También es preferible incluir un aceite y una grasa. Juntos, el o los emulsionantes con o sin estabilizantes generan lo que se conoce con el nombre de cera emulsionante, y la cera junto con el aceite y la grasa generan lo que se conoce con el nombre de base de ungüento emulsionante, que forma la fase aceitosa que

se desvanece de las formulaciones cremosas. Dentro de los emulsionantes y estabilizantes de emulsionantes adecuados para utilizarse en la formulación de la invención se incluye Tween 60, Span 80, alcohol de cetostearilo, alcohol de miristilo, monostearato de glicerilo y lauril sulfato de sodio entre otros. La selección de aceites o grasas adecuados para la formulación está basada en la obtención de las propiedades cosméticas deseadas, dado que la solubilidad del compuesto activo en la mayor parte de los aceites que posiblemente se utilicen en formulaciones para emulsiones farmacéuticas es muy baja. Así, sería preferible que la crema no fuera grasosa, que no manche y que sea un producto lavable, con una consistencia adecuada para evitar derrames hacia fuera de los tubos u otros recipientes. Podrán utilizarse ésteres alquílicos mono o dibásicos de cadena lineal o ramificada tales como di-isoadipato, estearato de isocetilo, propilenglicol, diéster de ácidos grasos de coco, miristato de isopropilo, oleato de decilo, palmitato de isopropilo, estearato de butilo, palmitato de 2-etilhexilo o una mezcla de ésteres de cadena ramificada. Los mismos podrán utilizarse solos o combinados dependiendo de las propiedades que sean necesarias. De manera alternativa, podrán utilizarse lípidos con puntos de fusión altos tal como vaselina y/o parafina líquida u otros aceites minerales.

Las formulaciones adecuadas para la administración tópica en la vista se incluyen además gotas oculares en las cuales los ingredientes activos están disueltos o suspendidos en un

portador adecuado, especialmente un disolvente acuoso de los ingredientes activos. Es preferible que los ingredientes activos con efecto antiinflamatorio están presentes en tales formulaciones en concentraciones de 0,5 a 20%, de manera ventajosa con una concentración de 0,5 a 10% y especialmente con una concentración de aproximadamente 1,5% p/p. Para propósitos terapéuticos, los compuestos activos de la esta invención de combinación se combinan ordinariamente con uno o más adyuvantes apropiados para la ruta de administración indicada. Los compuestos se pueden mezclar con lactosa, sacarosa, almidón en polvo, ésteres celulósicos de ácidos alcanoicos, alquil ésteres de celulosa, talco, ácido esteárico, estearato de magnesio, óxido de magnesio, sales de sodio y calcio de ácidos fosfóricos y sulfúricos, gelatina, goma acacia, alginato de sodio, polivinilpirrolidona y/o alcohol polivinílico y luego conformados en comprimidos o cápsulas para su administración de manera conveniente. Dichas cápsulas o comprimidos pueden contener una formulación de liberación controlada de la manera que puede suministrarse en una dispersión de compuesto activo en hidroxipropilmetil celulosa. Las formulaciones para administración parenteral podrán estar bajo la forma de inyecciones isotónicas estériles de soluciones o suspensiones acuosas o no acuosas. Dichas soluciones o suspensiones se pueden preparar a partir de polvos estériles o gránulos con uno o más de los portadores o diluyentes mencionados para utilizar en las formulaciones para administración oral. Los compuestos se pueden disolver en

agua, polietilenglicol, propilenglicol, etanol, aceite de maíz, aceite de semilla de algodón, aceite de maní, aceite de sésamo, alcohol bencílico, cloruro de sodio y/o varios amortiguantes. Otros adyuvantes y modos de administración son ampliamente conocidos en la técnica farmacéutica.

Los niveles de dosis del orden de aproximadamente 0,1 mg a alrededor de 140 mg por kilogramo de peso corporal por día son útiles en el tratamiento de las afecciones mencionadas anteriormente (alrededor de 0,5 mg a alrededor de 7 g por paciente por día). La cantidad de ingrediente activo que puede combinarse con los materiales que ofician de vehículo para producir una forma de dosificación unitaria variará según el receptor tratado y con la ruta de administración en particular. Las formas de dosificación unitarias contendrán generalmente entre 1 mg y alrededor de 500 mg de ingrediente activo. La dosis diaria podrá administrarse en una a cuatro dosis al día. En el caso de afecciones cutáneas, sería preferible aplicar la preparación tópica de los compuestos de la invención sobre el área afectada de dos a cuatro veces al día.

Sin embargo, se entenderá que el nivel de dosis específica para cualquier paciente en particular dependerá de una variedad de factores dentro de los cuales se incluye la actividad del compuesto específico utilizado, la edad, peso corporal, estado general de salud, y sexo del paciente, la dieta, tiempo de administración, ruta de administración y tasa

de excreción, así como también la combinación de fármacos y la severidad de la enfermedad en particular que se está tratando. En casos de administración a animales no humanos, la composición podrá además agregarse al alimento o el agua del animal. Sería conveniente formular las composiciones en el alimento y agua de los animales de forma tal que el animal consuma una cantidad terapéuticamente adecuada de la composición junto con su dieta. Podría también ser conveniente presentar la composición como una premezcla para que sea agregada al alimento o al agua.

Las divulgaciones en el presente documento de todos los artículos y referencias, incluidas las patentes, se incorporan aquí como referencia en su totalidad.

La invención se ilustra aún más mediante los siguientes ejemplos, que no se construyen como limitantes de la invención en alcance o espíritu para los procedimientos específicos descritos en ellos.

Los materiales de partida y varios intermedios se pueden obtener de fuentes comerciales, preparar a partir de compuestos disponibles comercialmente y/o preparar utilizando métodos sintéticos conocidos.

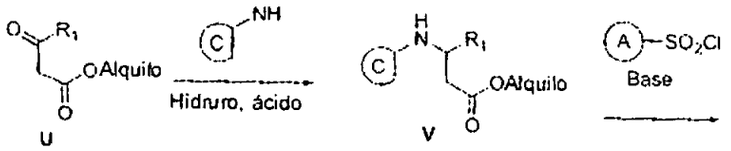
Procedimientos generales sintéticos

Los compuestos de la invención se pueden preparar utilizando métodos conocidos en la técnica de la síntesis orgánica. Por ejemplo, los compuestos de la invención, así como también todos los intermedios, se pueden sintetizar mediante procesos conocidos utilizando ya sea técnicas con fases en solución o

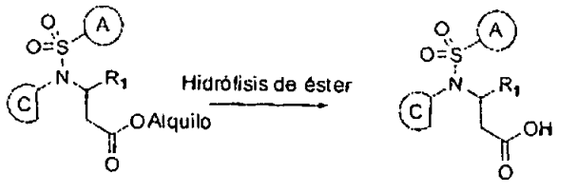
sólidas, tal y como se muestra a continuación. En los siguientes esquemas se describen procedimientos representativos para preparar los compuestos de la invención. De manera adicional, y como será evidente para los expertos en la técnica, podrá ser necesario utilizar grupos protectores para evitar que ciertos grupos funcionales participen en reacciones no deseadas. Los grupos protectores adecuados para varios grupos funcionales, así como también las condiciones adecuadas para proteger y desproteger grupos funcionales en particular son ampliamente conocidos en la técnica. Por ejemplo, en T. W. Greene y G. M. Wuts, Protecting Groups in Organic Synthesis, Segunda Edición, Wiley, Nueva York, 1991 y referencias citadas aquí se describen numerosos grupos protectores.

Esquema 1:

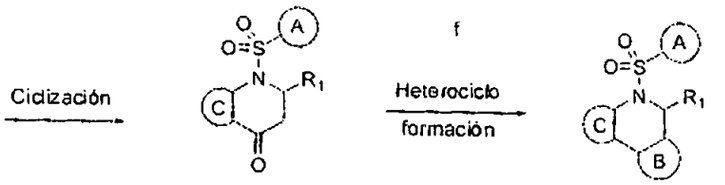
Ejemplo A



U V



W X



Y Z

Los compuestos **V** se pueden preparar mediante aminación reductiva de una anilina adecuada y un β-ceto éster **U** en un disolvente adecuado como diclorometano, 1,2-dicloroetano, benceno, tolueno, tetrahidrofurano o cloroformo, una fuente ácida como ácido acético, ácido propiónico, ácido fórmico, ácido clorhídrico o ácido trifluoroacético y una fuente hidruro como borohidruro de sodio, cianoborohidruro de sodio, triacetoxiborohidruro de sodio, decaborano o complejo cloruro hidruro de dibutilo. Una vez que se completa la reacción se puede apagar el exceso de hidruro con una base como $NaHCO_3$ acuoso saturado, Na_2CO_3 acuoso saturado o K_2CO_3 acuoso saturado. La solución resultante o mezcla bifásica se trata posteriormente mediante procedimientos de extracción estándar para aislar los productos **V**.

Los compuestos **W** se pueden preparar al hacer reaccionar compuestos **V** con un cloruro de sulfonilo en un disolvente

adecuado como diclorometano, 1,2-dicloroetano, benceno, tolueno, tetrahidrofurano, cloroformo o piridina y una base adecuada como trietilamina, diisopropiletilamina, piridina o dimetilaminopiridina. Es posible concentrar la mezcla de reacción y reducir el residuo en un disolvente adecuado para la extracción acuosa como éter dietílico, acetato de etilo, cloroformo o diclorometano y posteriormente tratarla mediante procedimientos de extracción estándar para aislar los productos **W**.

Los compuestos **X** se pueden preparar mediante métodos estándar de hidrólisis de ésteres catalizados con ácidos o bases o utilizando otros métodos como los descritos en "Protective Groups in Organic Synthesis" tercera edición de Greene y Wuts, Wiley interscience, 1999.

Es posible preparar los compuestos **Y** a través de la ciclización de los compuestos **X** calentándolos en anhídrido trifluoroacético y ácido trifluoroacético (mezcla 3:1) seguido por la adición de agua y trabajo acuoso estándar, o por el método de Friedel-Crafts inverso, de la manera descrita en JACS, 71, 1092 (1949).

Se pueden preparar los compuestos Z mediante una variedad de para la construcción del anillo B deseado. Los compuestos Z en los cuales el anillo B es pirazolilo se pueden hacer mediante tratamiento de los compuestos **Y** con agentes acilantes como acetal dimetil dimetilformamida, formato de etilo o acetal dimetil dimetilacetamida seguido de ciclización con hidrazinas

en un disolvente adecuado como ácido acético para obtener los compuestos **Z**.

En el esquema anterior, cada una de las variables contiene independientemente con las definiciones indicadas anteriormente y P es un grupo protector. Un experto en la técnica apreciará que el esquema anterior puede utilizarse para producir de manera selectiva un diastereómero único y/o un enantiómero único.

Los compuestos se pueden desproteger por medios estándar adecuados al tipo de protección utilizado como se describe en Greene, Theodora W.; Wuts, Peter G. M. Protective Groups in Organic Synthesis. 2da Ed. (1991), 473 pp. (tratamiento con yoduro de trimetilsililo, hidrogenación catalítica, alcóxido de sodio, etc.)

Procedimientos experimentales

Ciertos compuestos de la presente invención se preparan a partir de otros compuestos de la presente invención utilizando reacciones y transformaciones de grupos funcionales conocidas. Ejemplos de tales transformaciones incluyen la hidrólisis de ésteres, la formación de amidas y la alquilación reductiva, los cuales se describen en las preparaciones que se mencionan a continuación. Es posible obtener los materiales de partida a través de fuentes comerciales o prepararlos utilizando métodos conocidos de la manera descrita en los ejemplos que figuran a continuación.

Los compuestos incluidos en la presente invención están ejemplificados por los siguientes ejemplos, los cuales no se

deben construir como limitantes del alcance de esta descripción. Estructuras análogas y rutas sintéticas alternativas dentro del alcance de la presente invención serán evidentes para aquellos expertos en la técnica.

Ejemplos

Los siguientes ejemplos sintéticos y biológicos se proporcionan para ilustrar esta invención y no se construyen en cualquier forma como limitantes del alcance de esta invención. A no ser que se indique lo contrario, todas las temperaturas están en grados Celsius.

Los reactivos y disolventes obtenidos de proveedores comerciales se utilizaron sin purificación adicional a no ser que se especifique lo contrario. La cromatografía de capa fina se llevó a cabo en placas precubiertas de 0,25 mm de gel de sílice (E. Merck, gel de sílice 60, F_{254}). La visualización se alcanzó mediante la utilización de iluminación UV o a través de teñido con ácido fosfomolíbdico, ninhidrina u otros reactivos de teñido comunes. La cromatografía flash se realiza utilizando un sistema Biotage Flash 40 y columnas de gel de sílice empacadas previamente o columnas empacadas manualmente. (Gel de sílice 60 E. Merck, malla 230-400). La HPLC preparativa se realiza en un cromatografía líquida de alto desempeño Varian Prepstar. Los espectros de ^{1}HRMN se registraron o en un espectrómetro Varian Gemini de 300 MHz o en un espectrómetro Bruker Avance de 300 MHz. Los desplazamientos químicos están dados en partes por millón (ppm) (δ) y se calibraron utilizando resonancia de disolvente

no deuterado como estándar interno. Los datos de los espectros de masa se registraron en un espectrómetro de masas Agilent serie 1100 conectado a un cromatógrafo de HPLC Agilent serie 1100.

En los ejemplos adelante, las siguientes abreviaturas tienen los siguientes significados. Si una abreviatura no estuviera definida, tendrá el significado aceptado a nivel general.

BSA = albúmina de suero bovino

DBU = 1,8-diazabiciclo[5.4.0]undec-7-eno

DCE = 1,2-dicloroetano

DEAD = azodicarboxilato de dietilo

DMAP = 4-dimetilaminopiridina

DME = 1,2-dimetoxietano

DMF = dimetilformamida

DMF-DMA = *N,N*-dimetilformamida-dimetilacetal

DMSO = dimetilsulfóxido

DPPA = difenilfosforil azida

EDTA = ácido etilendiamin tetraacético

EtOAc = acetato de etilo

EtOH = etanol

Et_3N = trietilamina

HBSS = solución salina balanceada de Hank

HEPES = ácido 4-(2-hidroxietil)-1-piperazinetansulfónico

HOAc = ácido acético

HPLC = cromatografía líquida de alto desempeño

i-PrOH = *iso*-propanol

LC/MS = cromatografía líquida/espectroscopía de masa

MTBE = terc-butiléter de metilo

PBS = solución salina amortiguada con fosfato

PBS++ = PBS con calcio y magnesio

R_f = factor de retención (relación entre la distancia que recorrió una sustancia y la distancia recorrida por el frente del solvente)

R_t = tiempo de retención

SEM = 2-(trimetilsilil)etoximetilo

TFA = ácido trifluoroacético

THF = tetrahidrofurano

TLC = cromatografía de capa fina

Procedimientos de HPLC de ejemplo

La pureza de los compuestos se determinó mediante análisis HPLC/MS utilizando varios métodos de análisis:

Método 1 = [B] al 20%: [A] al 80% a [B] al 70%: [A] al 30% gradiente en 1,75 min, luego se mantuvo en 2 ml/min, en donde [A] = ácido trifluoroacético en agua al 0,1%; [B] = ácido trifluoroacético en acetonitrilo al 0,1% en una columna de 4,6-mm X 30-Cm Phenomenex Luna C18 (2), empaque de 3 micrones, detección a los 210 nm, a 35°C.

Método 2 = [B] al 50%: [A] al 50% a [B] al 95%: [A] al 5% gradiente en 2,5 min, luego se mantuvo en 2 ml/min, en donde [A] = ácido trifluoroacético en agua al 0,1%; [B] = ácido trifluoroacético en acetonitrilo al 0,1% en una columna de 4,6-mm X 30-Cm Phenomenex Luna C18 (2), empaque de 3 micrones, detección a los 210 nm, a 35°C.

Método 3 = [B] al 5%: [A] al 95% a [B] al 20%: [A] al 80% gradiente en 2,5 min, luego se mantuvo en 2 ml/min, en donde [A] = ácido trifluoroacético en agua al 0,1%; [B] = ácido trifluoroacético en acetonitrilo al 0,1% en una columna de 4,6-mm X 30-cm Phenomenex Luna C18 (2), empaque de 3 micrones, detección a los 210 nm, a 35°C.

Método 4 = [B] al 20%: [A] al 80% a [B] al 70%: [A] al 30% gradiente en 2,33 min, luego se mantuvo en 1,5 ml/min, en donde [A] = ácido trifluoroacético en agua al 0,1%; [B] = ácido trifluoroacético en acetonitrilo al 0,1% en una columna de 4,6-mm X 30-cm Phenomenex Luna C18 (2), empaque de 3 micrones, detección a los 210 nm, a 35°C.

Método 5 = [B] al 50%: [A] al 50% a [B] al 95%: [A] al 5% gradiente en 3,33 min, luego se mantuvo en 1,5 ml/min, en donde [A] = ácido trifluoroacético en agua al 0,1%; [B] = ácido trifluoroacético en acetonitrilo al 0,1% en una columna de 4,6-mm X 30-cm Phenomenex Luna C18 (2), empaque de 3 micrones, detección a los 210 nm, a 35°C.

Método 6 = [B] al 5%: [A] al 95% a [B] al 20%: [A] al 80% gradiente en 3,33 min, luego se mantuvo en 1,5 ml/min, en donde [A] = ácido trifluoroacético en agua al 0,1%; [B] = ácido trifluoroacético en acetonitrilo al 0,1% en una columna de 4,6-mm X 30-cm Phenomenex Luna C18 (2), empaque de 3 micrones, detección a los 210 nm, a 35°C.

Método 7 = [B] al 20%: [A] al 80% a [B] al 70%: [A] al 30% gradiente en 10,0 min, luego se mantuvo en 1,5 ml/min, en donde [A] = ácido trifluoroacético en agua al 0,1%; [B] =

ácido trifluoroacético en acetonitrilo al 0,1% en una columna de 4,6-mm X 3-cm Phenomenex Luna C18 (2), empaque de 3 micrones, detección a los 210 nm, a 35°C.

Método 8 = [B] al 10%: [A] al 90% a [B] al 40%: [A] al 60% gradiente en 10,0 min, luego se mantuvo en 1,5 ml/min, en donde [A] = ácido trifluoroacético en agua al 0,1%; [B] = ácido trifluoroacético en acetonitrilo al 0,1% en una columna de 4,6-mm X 3-cm Phenomenex Luna C18 (2), empaque de 3 micrones, detección a los 210 nm, a 35°C.

Método 9 = [B] al 23%: [A] al 77% a [B] al 30%: [A] al 70% gradiente en 15,0 min, luego se mantuvo en 1,0 ml/min, en donde [A] = ácido trifluoroacético en agua al 0,1%; [B] = ácido trifluoroacético en acetonitrilo al 0,1% en una columna de 2,1-mm X 5-cm Zorbex SB-fenilo C18, empaque de 5 micrones, detección a los 210 nm, a 30°C.

Método 10 = [A] al 5%: [B] al 95% isocrático, 1,0 ml/min, en donde [A] = isopropanol; [B] = hexanos; en una columna Chiral Technologies AD (4,6 x 250 mm), empaque de 10 micrones, detección a 220 nm a temperatura ambiente.

Método 11 = [A] al 10%: [B] al 90% isocrático, 1,0 ml/min, en donde [A] = etanol; [B] = hexanos; en una columna Chiral Technologies AD (4,6 x 250 mm), empaque de 10 micrones, detección a 220 nm a temperatura ambiente.

Método 12 = [A] al 10%: [B] al 90% isocrático, 0,8 ml/min, en donde [A] = etanol; [B] = hexanos; en una columna Chiral Technologies IA (4,6 x 250 mm), empaque de 5 micrones, detección a 220 nm a temperatura ambiente.

Método 13 = [A] al 10%: [B] al 90% isocrático, 1,0 ml/min, en donde [A] = isopropanol; [B] = hexanos; en una columna Chiral Technologies IA (4,6 x 250 mm), empaque de 5 micrones, detección a 220 nm a temperatura ambiente.

Método 14 = [A] al 10%: [B] al 90% isocrático, 1,0 ml/min, en donde [A] = isopropanol; [B] = hexanos; en una columna Chiral Technologies IB (4,6 x 250 mm), empaque de 5 micrones, detección a 220 nm a temperatura ambiente.

Método 15 = [A] al 10%: [B] al 90% isocrático, 1,0 ml/min, en donde [A] = etanol; [B] = hexanos; en una columna Chiral Technologies OD (4,6 x 250 mm), empaque de 10 micrones, detección a 220 nm a temperatura ambiente.

Método 16 = [A] al 10%: [B] al 90% isocrático, 1,0 ml/min, en donde [A] = isopropanol; [B] = hexanos; en una columna Chiral Technologies OD (4,6 x 250 mm), empaque de 10 micrones, detección a 220 nm a temperatura ambiente.

Método 17 = [A] al 15%: [B] al 85% isocrático, 1,0 ml/min, en donde [A] = etanol; [B] = hexanos; en una columna Chiral Technologies OD (4,6 x 250 mm), empaque de 10 micrones, detección a 220 nm a temperatura ambiente.

Método 18 = [A] al 5%: [B] al 95% isocrático, 55 ml/min, en donde [A] = isopropanol; [B] = hexanos; en una columna Chiral Technologies AD (5 x 50 cm), empaque de 20 micrones, detección a 220 nm a temperatura ambiente.

Método 19 = [A] al 10%: [B] al 90% isocrático, 0,8 ml/min, en donde [A] = etanol; [B] = hexanos; en una columna Chiral

Technologies IB (4,6 x 250 mm), empaque de 10 micrones, detección a 220 nm a temperatura ambiente.

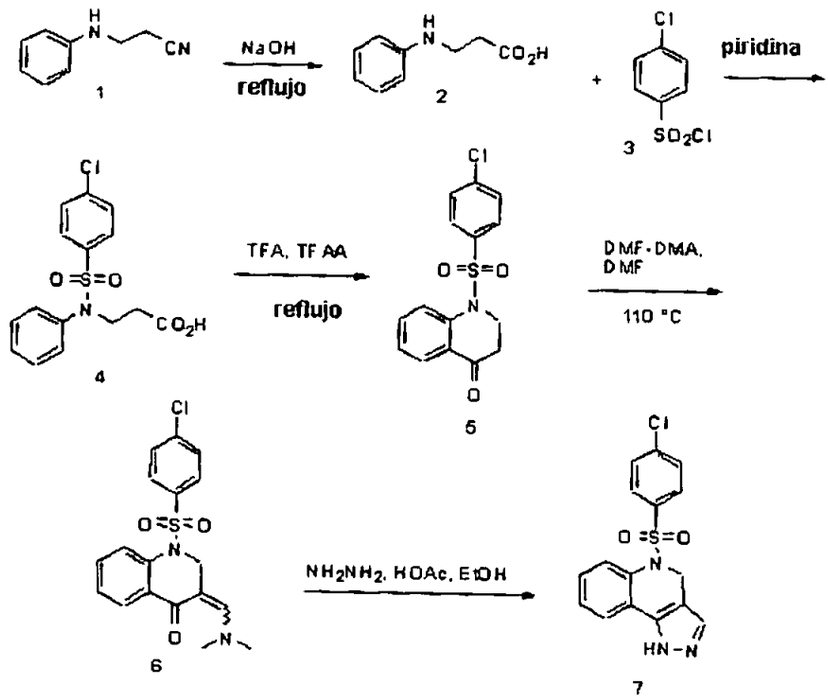
Método 20 = [A] al 10%: [B] al 90% isocrático, 1,0 ml/min, en donde [A] = etanol; [B] = hexanos; en una columna Chiral Technologies OD-H (4,6 x 250 mm), empaque de 5 micrones, detección a 220 nm a temperatura ambiente.

Método 21 = [A] al 20%: [B] al 80% isocrático, 1,0 ml/min, en donde [A] = etanol; [B] = hexanos; en una columna Chiral Technologies OD (4,6 x 250 mm), empaque de 10 micrones, detección a 220 nm a temperatura ambiente.

Método 22 = [A] al 20%: [B] al 80% isocrático, 1,0 ml/min, en donde [A] = isopropanol; [B] = hexanos; en una columna Chiral Technologies OD (4,6 x 250 mm), empaque de 10 micrones, detección a 220 nm a temperatura ambiente.

Ejemplo 1

5-[(4-Clorofenil)sulfonil]-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina (7).



Ácido 3-(fenilamino)propanoico (2).

A una solución acuosa al 10% de NaOH (120 mL) se agrega 3-anilinopropionitrilo (1) (10,3 g, 10,7 mmol). La suspensión se calienta a reflujo durante 6 h y la solución homogénea resultante se enfría a temperatura ambiente y se agita durante la noche. La solución se lava con éter (3 x 50 mL) y el pH de la fase acuosa se ajusta entonces a aproximadamente 3 con HCl conc. La fase acuosa se extrae con EtOAc (4 x 100 mL) y la fase orgánica combinada se lava con agua (1 x 50 mL), solución salina (1 x 50 mL), se seca ($MgSO_4$), se filtra y concentra para dar (2) (11,6 g, 100%) como un sólido marrón. ^1H NMR ($CDCl_3$) δ 7,20 (2 H, t, J = 8,2 Hz), 6,77 (1H, t, J = 8,8 Hz), 6,69 (2H, d, J = 7,7 Hz), 3,46, (2H, t, J = 6,6 Hz), 2,67 (2H, t, J = 6,6 Hz); ^{13}C NMR ($CDCl_3$) δ 178,5, 147,1, 129,4, 118,5, 113,6, 39,4, 33,5; MS *m/z*: 166 $(M+H)^+$.

Ácido 3-(4-Cloro-*N*-fenilfenilsulfonamido)propanoico (4).

A una solución de (2) (2,0 g, 12,3 mmol) en piridina (70 mL) a 0 °C se agrega cloruro de 4-Clorobencenosulfonilo (3) (2,6 g, 12,3 mmol) en forma de porción. La reacción se calienta a temperatura ambiente y se agita durante 3 horas. La mezcla de reacción se concentra entonces y el residuo se toma en EtOAc (100 mL). La fase orgánica se lava con HCl 1N (5 x 100 mL), agua (1 x 100 mL), solución salina (1 x 50 mL), se seca ($MgSO_4$), se filtra y concentra para dar (4) (3,2g, 77%) como un sólido tostado. ^{1}H NMR ($CDCl_3$) δ 7,58-7,54 (2H, m), 7,48-7,45 (2H, m), 7,38-7,36 (3H, m), 7,08-7,06 (2H, m), 3,39 (2H, t, J = 7,5 Hz), 2,64 (2H, t, J = 7,2 Hz); MS *m/z* 340 $(M+H)^+$.

1-(4-Clorofenilsulfonil)-2,3-dihidroquinolin-4(1*H*)-ona (5).

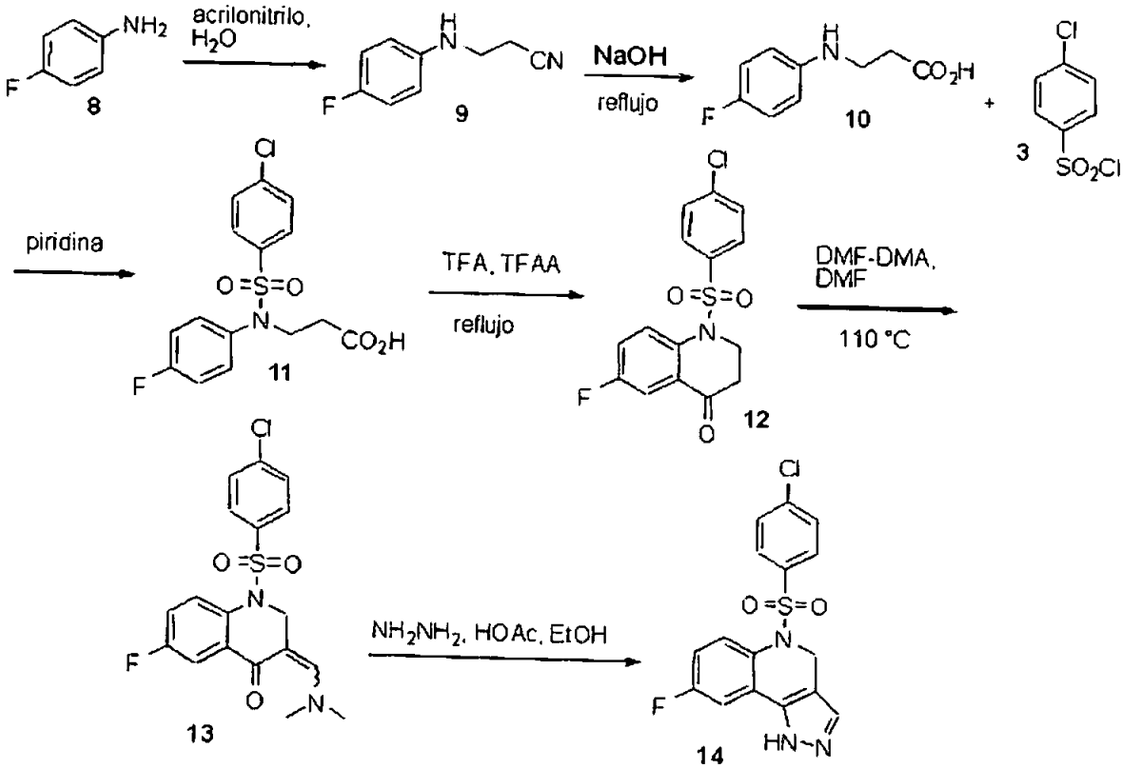
Se agrega ácido trifluoroacético (5 mL) y anhídrido trifluoroacético (2 mL) a (4) (1,64 g, 4,83 mmol). La solución homogénea se calienta a reflujo durante 3,5 horas, se enfría y se vierte en agua helada y el producto se extrae con EtOAc (1 x 50 mL, 2 x 10 mL). La fase orgánica combinada se lava con agua (1 x 20 mL), $NaHCO_3$ acuoso saturado (5 x 50 mL), solución salina (1 x 10 mL), se seca ($MgSO_4$), se filtra y concentra para producir (5) (1,48 g, 95%) como un sólido tostado. TLC: Rf = 0,30 (3:1 hexanos/EtOAc, gel de sílice). ^{1}H NMR ($CDCl_3$) δ 7,98 (1H, dd, J = 7,7, 1,6 Hz), 7,86 (1H, d, J = 8,2 Hz), 7,65-7,61 (3H, m), 7,45-7,42 (2 H, m), 7,31 (1H, d, J = 8,2 Hz), 4,27 (2H, t, J = 6,6 Hz), 2,48 (2H, t, J = 6,6 Hz); MS *m/z* 322 $(M+H)^+$.

5-(4-Clorofenilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina (7).

A una solución de DMF (800 µL) de (5) (151 mg, 0,470 mmol) se agrega dimetilformamida dimetilacetal (62 µL, 0,470 mmol). La reacción se calienta a 110 °C durante 4 horas y luego se enfría a temperatura ambiente y se reserva durante la noche. El análisis por HPLC/MS de la mezcla de reacción determina que el compuesto (6) está presente, (M+H)+ = 377, sin ningún restante de (5). Se remueven los volátiles bajo una corriente de nitrógeno y el producto crudo se utiliza directamente en la reacción siguiente. A una solución de EtOH/HOAc glacial (25:1, 2 mL) de (6) crudo (177 mg, 0,470 mmol) se agrega hidrato de hidrazina (73 µL, 2,34 mmol). La mezcla de reacción se agita durante la noche a temperatura ambiente, se concentra y el residuo se toma en EtOAc (10 mL). La fase orgánica se lava con $NaHCO_3$ ac. sat. (3 x 20 mL), solución salina (1 x 10 mL), se seca sobre $MgSO_4$, se filtra y concentra. El producto crudo se purifica mediante HPLC de fase inversa para dar (7) (26 mg, 12% de (5)) como una sal de TFA amarilla. TLC: Rf = 0,35 (1:1 hexanos/EtOAc, gel de sílice). ^1H NMR (DMSO-d_6) δ 7,68-7,62 (2H, m), 7,46-7,41 (3H, m), 7,32 (2H, d, J = 8,2 Hz), 7,16 (2H, d, J = 8,8 Hz), 4,93 (2H, s); ^{13}C NMR (DMSO-d_6) δ 138,9, 137,1, 135,0, 129,6, 129,5, 129,3, 128,9, 128,6, 123,3, 112,3, 44,2; MS *m/z* 346 $(M+H)^+$

Ejemplo 2

5-[(4-Clorofenil)sulfonil]-8-fluoro-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina (14).



ácido 3-(4-fluorofenilamino)propanoico (10).

Se agrega acrilonitrilo (7,89 mL, 120 mmol) a 4-fluoroanilina (8), (11,1 g, 100 mmol), y H_2O (80 mL). La mezcla bifásica se calienta a reflujo y se agita durante la noche. La mezcla de reacción se enfría a temp. Ambiente. El análisis por HPLC/MS de la mezcla de reacción confirma que el compuesto (9) está presente, $(M+H)^+$ = 165,1. Se agrega NaOH (12 g, 300 mmol) a la mezcla de reacción, y la reacción se calienta a reflujo durante 1,5 horas. El análisis por HPLC/MS de la mezcla de reacción confirma que el compuesto (10), está presente sin

ningún restante de (9). La reacción se enfría a temperatura ambiente y se extrae con dietiléter (3 x 50 mL). El pH se ajusta a aproximadamente 3 con HCl acuoso 3N y luego la capa acuosa se extrae con EtOAc (2 x 50 mL). La capa acuosa se ajusta entonces a pH 5 con NaOH 1 N y se extrae con EtOAc (1 x 100 mL). Los extractos orgánicos combinados se secan sobre $MgSO_4$, se filtran y concentran para producir (10) como un sólido café, (16 g, 87,6 mmol, 87%) MS *m/z* 184,1 $(M+H)^+$.

ácido 3-(4-Cloro-*N*-(4-fluorofenil)fenilsulfonamido)propanoico (11).

A una solución de piridina en agitación rápida a temperatura ambiente (0,5 M, 166 mL) de (10) (15,19 g, 83 mmol) se agrega cloruro de 4-Clorobencenosulfonilo (3), (17,5 g, 83 mmol). Luego de 30 minutos, se remueve la piridina y el residuo se toma entonces en EtOAc, y se lava con agua (5 x 50 mL), solución salina (2 x 50 mL), y HCl 1M (3 x 50 mL). La fase orgánica se seca ($MgSO_4$), se filtra y concentra para producir (11) como un sólido tostado (22,2 g, 62,3 mmol, 75 %). MS *m/z* 357,9 $(M+H)^+$, 379,9 $(M+Na)^+$.

1-(4-Clorofenilsulfonil)-6-fluoro-2,3-dihidroquinolin-4(1*H*)-ona (12).

Se agrega ácido trifluoroacético (10 mL) y anhidrido trifluoroacético (3,2 mL) a (11) (3,3 g, 9,2 mmol). La solución homogénea se calienta a 80 °C durante 6 horas, se enfría y se vierte en agua helada. El producto se extrae con EtOAc. La fase orgánica se lava con $NaHCO_3$ ac. sat. (3 x 25 mL), y se concentra. El residuo se tritura con dietiléter, y

luego se cromatografía con EtOAc para proporcionar (12) (0,8 g, 26%). MS *m/z* 339,9 $(M+H)^+$.

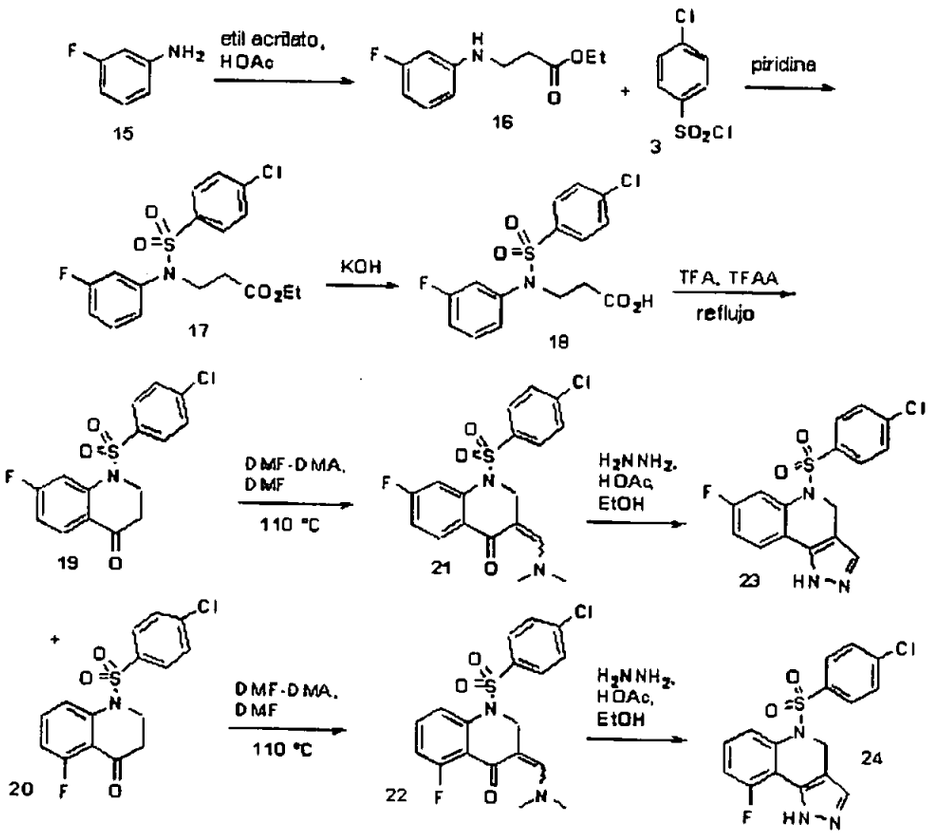
5-(4-Clorofenilsulfonil)-8-fluoro-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina (14).

Se agrega dimetilformamida dimetilacetal (2 mL) a (12) (454 mg, 1,34 mmol). La reacción se calienta a 103 °C durante 20 minutos y luego se enfría a temperatura ambiente. El análisis por HPLC/MS de la mezcla de reacción determina que el compuesto (13) está presente, $(M+H)^+$ = 394,9, sin ningún restante de (12). Se remueven los volátiles y el producto crudo se utiliza directamente en la reacción siguiente. A una solución de HOAc (4 mL) de (13) crudo (1,34 mmol) se agrega hidrato de hidrazina (78 µL, 1,61 mmol). La mezcla de reacción se calienta a 95 °C durante 1 hora. Se remueve el solvente y el residuo se cromatografía con 1:1 hexano/EtOAc para proporcionar (14) (432 mg, 89%). MS *m/z* 364 $(M+H)^+$. ^1H NMR (CD_3OD) δ 7,77-7,74 (dd, J = 8,9, 5,0 Hz, 1H), 7,40(s, 1H), 7,36-7,33 (dd, J = 8,8, 3,0 Hz, 1H), 7,20-7,14 (m, 5H), 4,95 (s, 2H); ^{13}C NMR (CD_3OD) δ 163,6, 160,3, 138,8, 136,0, 130,8, 130,7, 128,6, 128,1, 114,6, 114,3, 112,2, 108,7, 108,4, 43,0.

Ejemplo 3

5-[(4-Clorofenil)sulfonil]-7-fluoro-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina (23) y

5-[(4-Clorofenil)sulfonil]-9-fluoro-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina (24).



3-(3-fluorofenilamino)propanoato de etilo (16).

Se calienta una mezcla de 3-fluoroanilina (15), 10 g, 90 mmol), acrilato de etilo (9,9 g, 10,8 mL, 95 mmol) y HOAc (400 µL) a reflujo durante 17 h. La mezcla se enfría a temperatura ambiente luego se destila (p.e. 120-130 °C a 0,25 Torr) para dar (16), 12,35 g (65%).

3-(4-Cloro-*N*-(3-fluorofenil)fenilsulfonamido)propanoato de etilo (17).

Se disuelve 3-(3'-fluoroanilinilo)propionato de etilo(16), 12,3 g, 58,2 mmol) en piridina (125 mL) y se enfría en un baño de hielo. Se agrega cloruro de 4-Clorobencenosulfonilo (3), 13,5 g, 64 mmol) en porciones sobre 30 min. La mezcla se agita durante 1 h en un baño de hielo y luego se deja calentar a temperatura ambiente durante 1h. Se remueven los volátiles al

vacío y el residuo se diluye con agua (200 mL) y luego se extrae con EtOAc (2 x 200 mL). Los extractos orgánicos combinados se lavan con HCl ac. 1N (2 x 100) luego se secan (Na_2SO_4), se filtran y evaporan al vacío para dar 23,2 g de (17) (cuantitativo).

ácido 3-(4-Cloro-*N*-(3-fluorofenil)fenilsulfonamido)propanoico (18).

El éster etílico (17) (23,2 g, 58 mmol) se absorbe en MeOH (200 mL) y se trata por goteo con una solución de hidróxido de potasio (4,10 g, 73 mmol) en agua (75 mL). La mezcla se agita entonces durante 1 h hasta que el análisis por TLC indica el consumo de material de partida. La mezcla se concentra al vacío, se diluye con agua (200 mL), luego se acidifica con HCl ac. sat. 6N. La mezcla se extrae con EtOAc (2 x 200 mL) y los extractos orgánicos combinados se lavan con agua (2 x 100 mL), luego se secan (Na_2SO_4), se filtran y concentran al vacío para dar un residuo de (18). El residuo se recristaliza a partir de EtOAc/hexanos para dar dos pequeñas cosechas de cristales (2,35g, 1,21 g), pero los líquidos madre restantes se concentran al vacío para dar un residuo (16 g), que se tomó en el paso siguiente.

1-(4-Clorofenilsulfonil)-7-fluoro-2,3-dihidroquinolin-4(1*H*)-ona (19) y

1-(4-Clorofenilsulfonil)-5-fluoro-2,3-dihidroquinolin-4(1*H*)-ona (20).

El ácido carboxílico (18) (16 g) se absorbe en ácido trifluoroacético (75 mL) y se trata con anhídrido

trifluoroacético (30 mL). La mezcla se calienta a reflujo durante 3 horas antes de enfriarse a temperatura ambiente. Se remueven los volátiles al vacío para dar un residuo que se combina con dos reacciones anteriores y se purifica mediante cromatografía de gel de sílice (dos veces, hexanos/EtOAc 4:1 eluidos) para dar (19) (5,5 g) y (20) (1,05 g).

5-(4-Clorofenilsulfonil)-7-fluoro-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina (23).

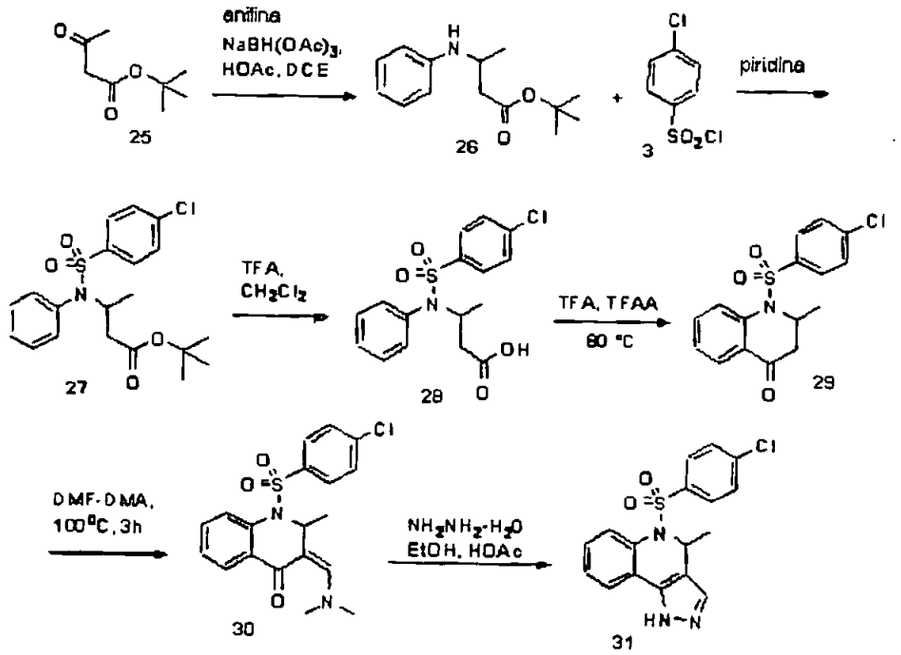
Se agrega dimetilformamida dimetilacetal (2 mL) a (19) (518 mg, 1,53 mmol). La reacción se calienta a 103 °C durante 20 minutos y luego se enfría a temperatura ambiente. El análisis por HPLC/MS de la mezcla de reacción determina que el compuesto (21) está presente, $(M+H)^+$ = 394,9, sin ningún restante de (19). Se removieron los volátiles y el producto crudo se utiliza directamente en la reacción siguiente. A una solución de ácido acético (4 mL) de (21) crudo (1,53 mmol) se agrega hidrato de hidrazina (74 µL, 1,53 mmol). La mezcla de reacción se calienta a 95 °C durante 1 hora. Se remueve el disolvente y el residuo se cromatografía con HPLC para proporcionar (23) (272 mg, 0,75 mmol). MS *m/z* 363,9 $(M+H)^+$. ^1H NMR (CD_3OD) δ 7,68-7,63 (dd, J = 8,6, 6,2 Hz, 1H), 7,53-7,49(dd, J = 10,1, 2,6 Hz, 1H), 7,38 (s, 1H), 7,22-7,14 (m, 5H), 4,96 (s, 2H); ^{13}C NMR (CD_3OD) δ 163,4, 160,2, 139,0, 136,6, 136,4,8, 136,2, 128,5, 128,2, 123,7, 123,6, 115,7, 115,4, 114,8, 114,5, 43,1.

5-(4-Clorofenilsulfonil)-9-fluoro-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina (24).

Se agrega dimetilformamida dimetilacetal (2 mL) a (20) (530 mg, 1,56 mmol). La reacción se calienta a 103 °C durante 20 minutos y luego se enfría a temperatura ambiente. El análisis por HPLC/MS de la mezcla de reacción determina que el compuesto (22) está presente $(M+H)^+$ = 394,9, sin ningún remanente de (20). Se remueven los volátiles y el producto crudo se utiliza directamente en la reacción siguiente. A una solución de ácido acético (4 mL) de (22) crudo (1,56 mmol) se agrega hidrato de hidrazina (76 µL, 1,56 mmol). La mezcla de reacción se calienta a 95 °C durante 1 hora. Se elimina el solvente y el residuo se cromatografía con HPLC para proporcionar (24) (253 mg, 45 %). MS *m/z* 364,0 $(M+H)^+$. ^1H NMR (CD_3OD) δ 7,64-7,61 (d, J = 7,7 Hz, 1H), 7,47-7,39 (m, 2H), 7,24-7,19 (m, 5H), 4,96 (s, 2H); ^{13}C NMR (CD_3OD) δ 159,2, 155,9, 139,0, 136,2, 128,5, 128,3, 128,2, 127,7, 124,5, 124,4, 114,8, 114,5, 112,7, 43,0.

Ejemplo 4

5-(4-Clorofenilsulfonil)-4-metil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina (31).



3-(fenilamino)butanoato de *terc*-butilo (26).

A una solución de 1,2-dicloroetano (100 mL) de anilina (2,52 g, 27,1 mmol) se agrega acetoacetato de *t*-butilo (25), 4,49 mL, 27,1 mmol) y ácido acético glacial (2,0 mL, 35,2 mmol). Se agrega triacetoxiborohidruro de sodio (8,60 g, 40,6 mmol) en forma de porción y la reacción se agita durante la noche a temperatura ambiente. Se agrega lentamente $NaHCO_3$ acuoso saturado (200 mL) y la solución bifásica se agita bien durante 45 min. La solución acuosa se extrae con dicloroetano (1 x 30 mL) y las porciones orgánicas combinadas se lavan con solución salina (1 x 20 mL), se secan ($MgSO_4$), se filtran y concentran para dar (26) (5,2, 81%) como un aceite que se solidifica en reposo. MS *m/z* 236,2 $(M+H)^+$.

3-(4-Cloro-*N*-fenilfenilsulfonamido)butanoato de *terc*-butilo (27).

A una solución de (26) (2,34 g, 9,94 mmol) en piridina (25 mL) a 0 °C se agrega cloruro de 4-Clorobencenosulfonilo (3), (6,29

g, 29,8 mmol) por porciones. La reacción se calienta a temperatura ambiente y luego se calienta a 70 °C durante 5 horas, se enfría y se agita durante la noche a temperatura ambiente. La mezcla de reacción se concentra entonces y el residuo se absorbe en EtOAc (150 mL). La fase orgánica se lava con HCl 1N frío (5 x 100 mL), agua (1 x 50 mL), $NaHCO_3$ ac. sat (3 x 50 mL), solución salina (1 x 20 mL), se seca ($MgSO_4$), se filtra y concentra en un aceite. ^1H NMR revela la presencia de cloruro de 4-Clorobencenosulfonilo sin reaccionar, de modo que se disuelve el producto en piridina (25 mL) y se agrega dimetilaminopropilamina (35 mL) y la solución resultante se agita durante la noche. La mezcla de reacción se concentra y el residuo se absorbe en EtOAc (150 mL) y se lava con HCl 1N frío (6 x 60 mL), agua (1 x 50 mL), $NaHCO_3$ ac. sat. (3 x 60 mL), solución salina (1 x 20 mL), se seca ($MgSO_4$), se filtra y concentra para dar (27) (3,7 g, 91%) como un aceite amarillo pálido. MS *m/z*: 432,1 $(M+Na)^+$.

ácido 3-(4-Cloro-*N*-fenilfenilsulfonamido)butanóico (28).

A una solución de (27) (3,35 g, 8,17 mmol) en CH_2Cl_2 (15 mL) a 0 °C se agrega TFA (45 mL). La mezcla de reacción se deja calentar a temperatura ambiente. Luego de agitar durante 72 horas la mezcla de reacción se concentra para dar (28) (2,63 g, 91%) como un aceite amarillo pálido que se solidifica en reposo. MS *m/z* 354,1 $(M+H)^+$.

5-(4-Clorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina (31).

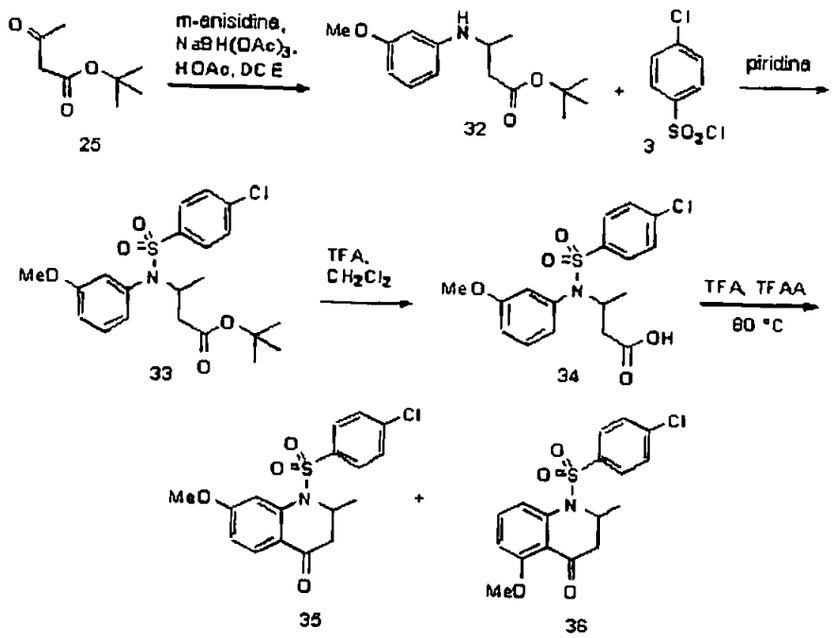
A una solución de (28) (1,02 g, 2,89 mmol) en TFA (3 mL) se agrega anhídrido trifluoroacético (1,2 mL, 8,8 mmol). La mezcla de reacción se calienta a 80 °C durante uno hora, se enfría y se vierte en hielo roto. El producto se extrae con EtOAc (3 x 15 mL) y la porción orgánica combinada se lava con agua (1 x 20 mL), $NaHCO_3$ ac. sat. (3 x 40 mL), solución salina (1 x 20 mL), se seca ($MgSO_4$), se filtra y concentra en un sólido amarillo pegajoso. El producto crudo se purifica mediante cromatografía flash eluyendo con 6:1 hexanos/EtOAc para dar (29) impuro (351 mg) como una espuma de color amarillo pálido. MS *m/z*: 336,1 $(M+H)^+$.

Se calienta una solución de dimetilformamida dimetilacetal (1,5 mL) de (29) (263 mg, 0,782 mmol) a 100 °C durante 3 horas. El análisis por HPLC/MS de la mezcla de reacción determina que no hay ningún restante del material de partida de modo que la reacción se enfría a temperatura ambiente. Luego de concentrar, el producto crudo (30) se utiliza directamente en la reacción siguiente. A una solución de EtOH/ácido acético glacial (25:1 v/v, 2 mL) de (30) (306 mg, 0,782 mmol) se agrega hidrato de hidrazina (189 µL, 3,91 mmol). La mezcla de reacción se agita durante la noche a temperatura ambiente, se concentra, y el residuo se absorbe en EtOAc (10 mL). La fase orgánica se lava con $NaHCO_3$ ac. sat. (3 x 20 mL), solución salina (1 x 10 mL), se seca sobre $MgSO_4$, se filtra y concentra en un semi sólido. El producto crudo se purifica mediante cromatografía flash eluyendo con 10:1 hexanos/EtOAc y luego 2:1 hexanos/EtOAc para dar (31) como un

sólido dorado pálido. MS *m/z* 360,0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7,82 (1H, dd), 7,66 (1H, dd), 7,44-7,33 (2H, m), 7,21 (1H, s), 7,12-7,02 (4H, m), 5,62 (1H, q), 1,30 (3H, d). ^{13}C NMR ($CDCl_3$) 138,9, 136,0, 132,4, 129,8, 128,6, 128,4, 128,3, 127,8, 124,8, 122,4, 118,0, 49,8, 23,1:

Ejemplo 5

1-(4-Clorofenilsulfonil)-7-metoxi-2-metil-2,3-dihidroquinolin-4(1*H*)-ona (35) y 1-(4-Clorofenilsulfonil)-5-metoxi-2-metil-2,3-dihidroquinolin-4(1*H*)-ona (36).



3-(3-metoxifenilamino)butanoato de *terc*-butilo (32).

A una solución de *m*-anisidina (1,00 g, 8,12 mmol) en CH_2Cl_2 (10 mL) se agrega acetoacetato de *terc*-butilo (25), (1,28 g, 8,12 mmol), seguido de HOAc (0,47 mL, 8,12 mmol). La mezcla de reacción se agita durante 45 minutos. Se agrega triacetoxiborohidruro de sodio (2,41 g, 11,3 mmol) y la mezcla

de reacción se agita durante la noche a temperatura ambiente. La mezcla de reacción se inactiva mediante la adición lenta de $NaHCO_3$ acuoso saturado. Las dos capas se separaron. La solución acuosa se extrae con CH_2Cl_2 (10 mL). Las capas orgánicas combinadas se lavan con NaCl acuoso saturado, se secan sobre $MgSO_4$, se filtran y concentran. El residuo resultante se purifica mediante cromatografía flash (EtOAc al 20% en hexanos) para proporcionar (32) (1,09 g, 51%) MS *m/z* 266,1 $(M+H)^+$.

3-(4-Cloro-*N*-(3-metoxifenil)fenilsulfonamido)butanoato *terc*-butilo (33).

A una solución de (32) (1,00 g, 3,76 mmol) en piridina (10 mL) se agrega cloruro de 4-Clorobencenosulfonilo (3), (0,79 g, 3,76 mmol). La mezcla de reacción se agita durante la noche a temperatura ambiente. La mezcla de reacción se concentra, y el residuo resultante se disuelve en CH_2Cl_2 (15 mL). La fase orgánica se lava con agua (10 mL), y NaCl acuoso saturado (10 mL), luego se seca sobre $MgSO_4$, se filtra y concentra. El residuo resultante se purifica mediante cromatografía flash (EtOAc al 20% en hexanos) para proporcionar (33) (1,32 g, 80%) MS *m/z* 462,1 $(M+Na)^+$.

ácido 3-(4-Cloro-*N*-(3-metoxifenil)fenilsulfonamido)butanoico (34).

A una solución de (33) (1,25 g, 2,86 mmol) en CH_2Cl_2 (10 mL) se agrega TFA (10 mL). La mezcla de reacción se agita a temperatura ambiente durante la noche, y luego se concentra. El residuo resultante se disuelve en CH_2Cl_2 (10 mL) y se lava

con agua (5 mL). La capa orgánica se seca con $MgSO_4$, se filtra y concentra para proporcionar (34) (0,93g, 85%), que se solidifica en reposo. MS *m/z* 384,1 $(M+H)^+$.

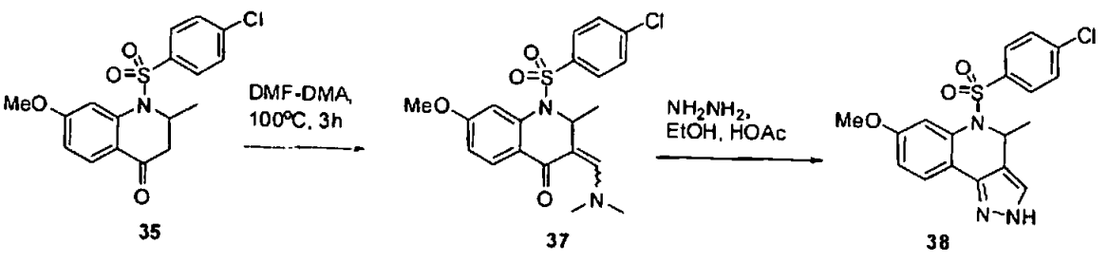
1-(4-Clorofenilsulfonil)-7-metoxi-2-metil-2,3-dihidroquinolin-4(1*H*)-ona (35) y

1-(4-Clorofenilsulfonil)-5-metoxi-2-metil-2,3-dihidroquinolin-4(1*H*)-ona (36).

A una solución de (34) (0,93 g, 2,43 mmol) en ácido trifluoroacético (5 mL) se agrega anhídrido trifluoroacético (2 mL). La mezcla de reacción se calienta a 80 °C durante 3h, y luego se enfría a temperatura ambiente. La mezcla de reacción se vierte en agua y hielo picado. El producto se extrae con EtOAc (3 x 15 mL). Las capas orgánicas combinadas se lavan con acuoso saturado $NaHCO_3$ (3 x 15mL), NaCl acuoso saturado (15 mL), se secan sobre $MgSO_4$, se filtran y concentran. El residuo resultante se purifica mediante cromatografía flash (EtOAc al 20% en hexanos) para dar los dos regioisómeros (35) (0,66 g, 69%) MS *m/z* 366,0 $(M+H)^+$, y (36) (0,06 g, 6%) MS *m/z* 366,0 $(M+H)^+$.

Ejemplo 6

5-(4-Clorofenilsulfonil)-7-metoxi-4-metil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina (38).



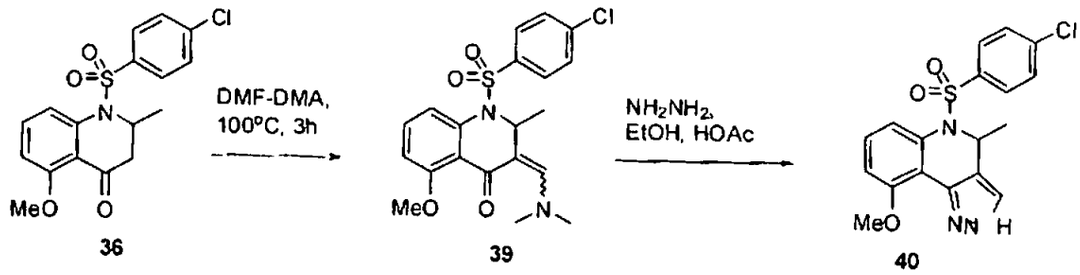
35 37 38

5-(4-Clorofenilsulfonil)-7-metoxi-4-metil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina (38).

A (35) (0,25 g, 0,68 mmol) se agrega dimetilformamida dimetilacetal (5 mL). La mezcla de reacción se calienta a 100 °C durante 3h, luego se enfría a temperatura ambiente y se concentra. El residuo resultante de (37) crudo se utiliza sin purificación en la reacción siguiente. A una solución de (37) en MeOH (5 mL) se agrega HOAc (0,12 mL, 2,05 mmol), seguido de hidrazina anhidra (0,06 g, 2,05 mmol). La mezcla de reacción se agita a temperatura ambiente durante la noche, luego se concentra. El residuo resultante se disuelve en EtOAc (15 mL), se lava con $NaHCO_3$ acuoso saturado (10 mL) y NaCl acuoso saturado (10 mL). La capa orgánica se seca con $MgSO_4$, se filtra y concentra. El residuo resultante se purifica mediante cromatografía flash (EtOAc al 30% en hexanos) para dar (38) (0,16 g, 61%); ^{1}H NMR ($CDCl_3$) δ 7,55 (d, J = 8,3 Hz, 1H), 7,39 (d, J = 2,5 Hz, 1H), 7,16 (m, 3H), 7,03 (d, J = 8,7 Hz, 2H), 6,91 (dd, J = 8,5, 2,5 Hz, 1H), 5,60 (q, J = 6,9 Hz, 1H), 3,91 (s, 3H), 1,32 (d, J = 6,9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 159,7, 139,0, 136,1, 133,9, 128,5, 128,3, 123,3, 117,7, 116,9, 114,6, 114,4, 60,5, 55,7, 50,1, 23,2, 14,2; MS *m/z* 389,0 $(M+H)^+$.

Ejemplo 7

5-(4-Clorofenilsulfonil)-9-metoxi-4-metil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina (40).



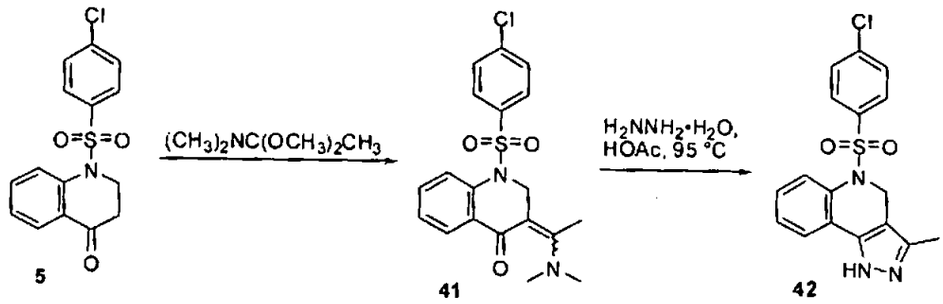
36 39 40

5-(4-Clorofenilsulfonil)-9-metoxi-4-metil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina (40).

A (36) (0,06 g, 0,15 mmol) se agrega dimetilformamida dimetilacetal (2 mL). La mezcla de reacción se calienta a 100 °C durante 3h, luego se enfría a temperatura ambiente y se concentraa. El residuo resultante de (39) crudo se utiliza sin purificación en la reacción siguiente. A una solución de (39) en MeOH (2 mL) se agrega HOAc (0,02 mL, 0,45 mmol), seguido de hidrazina anhidra (0,02 g, 045 mmol). La mezcla de reacción se agita a temperatura ambiente durante la noche, luego se concentra. El residuo resultante se disuelve en EtOAc (15 mL), se lava con $NaHCO_3$ acuoso saturado (10 mL) y NaCl acuoso saturado (10 mL). La capa orgánica se seca con $MgSO_4$, se filtra y concentra. El residuo resultante se purifica mediante cromatografía flash (EtOAc al 30% en hexanos) para dar (40) (0,03 g, 59%); ^1H NMR ($CDCl_3$) δ 7,52 (dd, J, 8,1, 0,8 Hz, 1H), 7,36 (d, J = 8,3 Hz, 1H), 7,28 (s, 1H), 7,17 (m, 4H), 6,92 (dd, J = 8,3, 0,5 Hz, 1H), 5,68 (q, J = 6,9 Hz, 1H), 3,96 (s, 3H), 1,28 (d, J = 6,9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154,4, 139,0, 136,1, 134,0, 132,7, 129,5, 128,7, 122,3, 117,5, 111,3, 109,5, 60,5, 56,1, 50,5, 23,0, 14,3; MS *m/z* 390,0 $(M+H)^+$.

Ejemplo 8

5-[(4-Clorofenil)sulfonil]-3-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina (42).



5-(4-Clorofenilsulfonil)-3-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina (42).

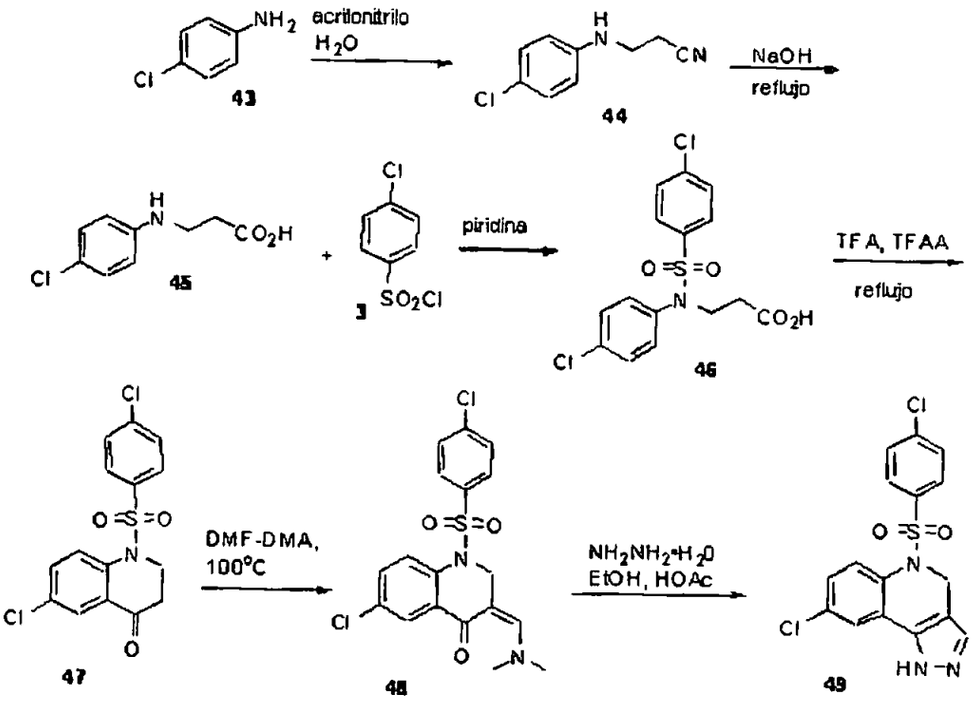
Se calienta cetona (5) (357 mgs, 1,11 mmol) a disolución en *N,N*-dimetilacetamida dimetilacetal puro (1,63 mL, 11,11 mmol) y se agita bajo nitrógeno a 103 °C durante 30 min. La solución de color ámbar se enfría a temperatura ambiente y se seca subsiguientemente mediante evaporación rotatoria para producir el compuesto (41) MS (ES) *m/z* 391,0 $(M+H)^+$.

A una suspensión de (41) intermedio (156 mgs, 0,4 mmol) y HOAc glacial (8 mL) se agrega hidrato de hidrazina (82,4 µL, 1,0 mmol). La solución se agita bajo nitrógeno y se calienta a 95 °C durante 18h. Se agrega luego hidrato de hidrazina adicional (82,4 µL, 1,0 mmol) y la reacción se agita durante 4h adicionales a 95 °C. Luego del consumo completo de (41) (0,3h-22h LC-MS), la mezcla de reacción se enfría a temperatura ambiente y se remueve el solvente mediante evaporación rotatoria. El residuo resultante se disuelve en CH_2Cl_2 (20 mL), se lava con agua (2 x 20 mL) y se seca sobre $MgSO_4$. Luego de filtración y concentración mediante evaporación rotatoria, el

residuo se disuelve en MeOH (6 mL) y se purifica mediante HPLC preparativa de fase inversa, lo que produjo 33 mgs de (42). MS (ES) *m/z* 359,9 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7,81-7,78 (dd, J = 6,2, 1,5 Hz, 1H), 7,66-7,63 (dd, J = 5,4, 1,6 Hz, 1H), 7,43-7,32 (m, 2H), 7,16-7,07 (m, 4H), 4,81 (s, 2H), 2,21 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158,3, 156,2, 143,7, 138,9, 136,5, 135,2, 134,8, 128,7, 128,3, 128,2, 128,1, 127,8, 125,7, 122,4, 109,9, 43,0, 9,6.

Ejemplo 9

5-(4-Clorofenilsulfonil)-9-metoxi-4-metil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina (49).



3-(4-Clorofenilamino)propanonitrilo (44).

Se agrega acrilonitrilo (10,3 mL, 157 mmol) a 4-fluoroanilina (43), (10 g, 78 mmol), y H_2O (62 mL). La mezcla bifásica se calienta a reflujo y se agita durante 4 días. Se añaden 10 mL

de acrilonitrilo adicionales a la mezcla de reacción y el reflujo continua durante la noche. La reacción enfriada se extrae con CH_2Cl_2 (100 mL) y la fase orgánica se lava con 0,1 M de ácido cítrico acuoso (25 mL) y se seca sobre $MgSO_4$ para obtener el compuesto (44) (12,7 g, 90%) MS *m/z* 181 $(M+H)^+$.

ácido 3-(4-Clorofenilamino)propanoico (45).

A (44) (12,7 g, 70,8 mmol) se agrega NaOH acuoso 1M (71 mL), y la reacción se calienta a reflujo durante 4 horas. El análisis por HPLC/MS de la mezcla de reacción confirma que el compuesto (45), está presente sin ningún restante de (44). La reacción se enfría a temperatura ambiente y se filtra el precipitado. El pH se ajusta a aproximadamente 5 con HCl al 37% y el producto se filtra produciendo (45) como un sólido blanco, (10,0 g, 72%) MS *m/z* 200 $(M+H)^+$.

ácido 3-(4-Cloro-*N*-(4-Clorofenil)fenilsulfonamido)propanoico (46).

A una solución de piridina a 0 °C en agitación rápida (0,5 M, 166 mL) de (45) (15,19 g, 83 mmol) se agrega cloruro de 4-Clorobencenosulfonilo (3), 17,5 g, 83 mmol). Luego de 1 h se remueve la piridina y el residuo se pone en EtOAc, se lava con agua (2 x 50 mL) y se seca ($MgSO_4$), se filtra y concentra. La muestra se cristaliza con 1:1 hexano:EtOAc y se obtiene (46) (1,6 g, 46 %) MS *m/z* 395,9 $(M+Na)^+$.

6-Cloro-1-(4-Clorofenilsulfonil)-2,3-dihidroquinolin-4(1*H*)-ona (47).

Se agrega ácido trifluoroacético (10 mL) y anhídrido trifluoroacético (3,2 mL) a (46) (0,8 g, 2,14 mmol). La

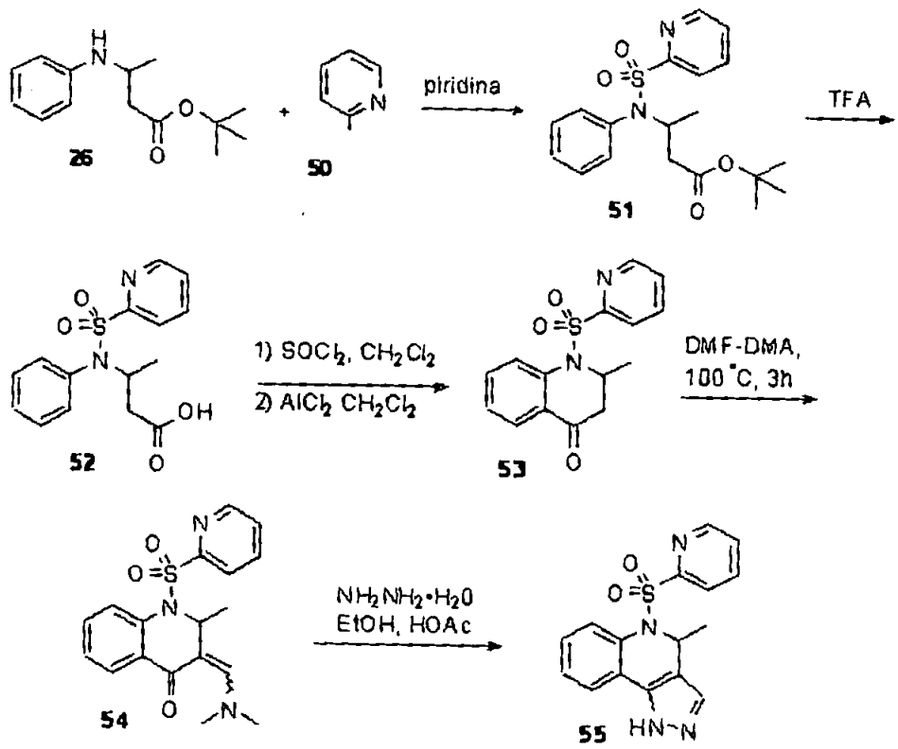
solución homogénea se calienta a reflujo durante 7 horas, se enfría y se vierte en agua helada. El producto se extrae con EtOAc. La fase orgánica se lava con $NaHCO_3$ acuoso saturado (3 x 25 mL), se seca sobre $MgSO_4$, y se concentra. El residuo se cromatografía con HPLC para proporcionar (47) (0,192 g, 25%). MS *m/z* 355,9 $(M+H)^+$.

8-Cloro-5-(4-Clorofenilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina (49).

Se agrega dimetilformamida dimetilacetal (1 mL) a (47) (192 mg, 0,54 mmol). La reacción se calienta a 103 °C durante 20 minutos y luego se enfría a temperatura ambiente. El análisis por HPLC/MS de la mezcla de reacción determina que el compuesto (48) está presente $(M+H)^+$ = 394,9, sin ningún remanente de (47). Se remueven los volátiles y el producto crudo se utiliza directamente en la reacción siguiente. A una solución de ácido acético (1,35 mL) de (48) crudo se agrega hidrato de hidrazina (26 µL, 0,54 mmol). La mezcla de reacción se calienta a 95 °C durante 1 hora. Se remueve el disolvente y el residuo se cromatografía en HPLC para proporcionar (49) (153 mg, 75 %). MS *m/z* 379,9 $(M+H)^+$. ^1H NMR (CD_3OD) δ 7,75-7,72 (d, J = 8,6 Hz, 1H), 7,64-7,63(d, J = 2,4 Hz, 1H) 7,44-7,40(m 2H), 7,19-7,18 (m, 4H), 4,95 (s, 2H); ^{13}C NMR (CD_3OD) δ 138,9, 136,1, 133,5, 133,4, 130,1, 128,5, 128,2, 127,6, 121,9, 112,3, 43,0.

Ejemplo 10

4-metil-5-(piridin-3-ilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina (55).



3-(*N*-fenilpiridin-2-sulfonamido)butanoato de *terc*-butilo (51).

A una solución de (26) (2,74 g, 11,6 mmol) en piridina (46 mL) a 0 °C se agrega cloruro de 2-piridilsulfonilo (50), (5 g, 23,4 mmol). La reacción se calienta a temperatura ambiente y se agita durante la noche. La mezcla de reacción se concentra entonces y el residuo se absorbe en dietiléter (150 mL). La fase orgánica se lava con agua (1 x 200 mL), 3N HCl (1 x 50 mL), $NaHCO_3$ ac. sat. (1 x 50 mL), agua (1 x 50 mL), solución salina (1 x 20 mL), se seca ($MgSO_4$), se filtra y concentra para

dar (51) (4,192 g, 96%) como un aceite amarillo pálido. MS *m/z* 377,1 $(M+H)^+$.

ácido 3-(*N*-fenilpiridin-2-sulfonamido)butanoico (52).

A (51) (4,19 g, 11,1 mmol) se agrega TFA (8,5 mL) a temperatura ambiente y la mezcla se sonica para formar una solución homogénea. Luego de agitar durante 1,5 horas la mezcla de reacción se concentra, luego se disuelve en CH_2Cl_2 (200 mL) y se extrae con $NaHCO_3$ ac. sat. (4 x 100 mL). Los extractos acuosos recogidos se extraen con CH_2Cl_2 y luego se ajusta el pH a 1. La capa acuosa se extrae luego con EtOAc (4 x 100 mL). Los extractos orgánicos recogidos se secan sobre $MgSO_4$, se filtran y concentran para proporcionar (52) (3,26 g, 92%). MS *m/z* 321,0 $(M+H)^+$.

2-metil-1-(piridin-2-ilsulfonil)-2,3-dihidroquinolin-4(1*H*)-ona (53).

A una solución de (52) (1,32 g, 4,11 mmol) en CH_2Cl_2 (30 mL) se agrega cloruro de tionilo (0,45 mL, 6,16 mmol). Luego de 20 min a temperatura ambiente, la mezcla de reacción se transfiere en un espacio de 15 min a CH_2Cl_2 a una solución de $AlCl_3$ a 0 °C (40 mL) (1,36 g, 10,27 mmol). La mezcla de reacción se deja calentar entonces a temperatura ambiente y se agita durante la noche. En la mañana, se agrega lentamente HCl 6N (30 mL) a la mezcla de reacción a 0 °C. La mezcla bifásica resultante se agita rápidamente durante 1,5 horas, y luego se separan las capas. La fase orgánica se lava con agua (1 x 50 mL), $NaHCO_3$ ac. sat. (1 x 50 mL), agua (1 x 50 mL), solución

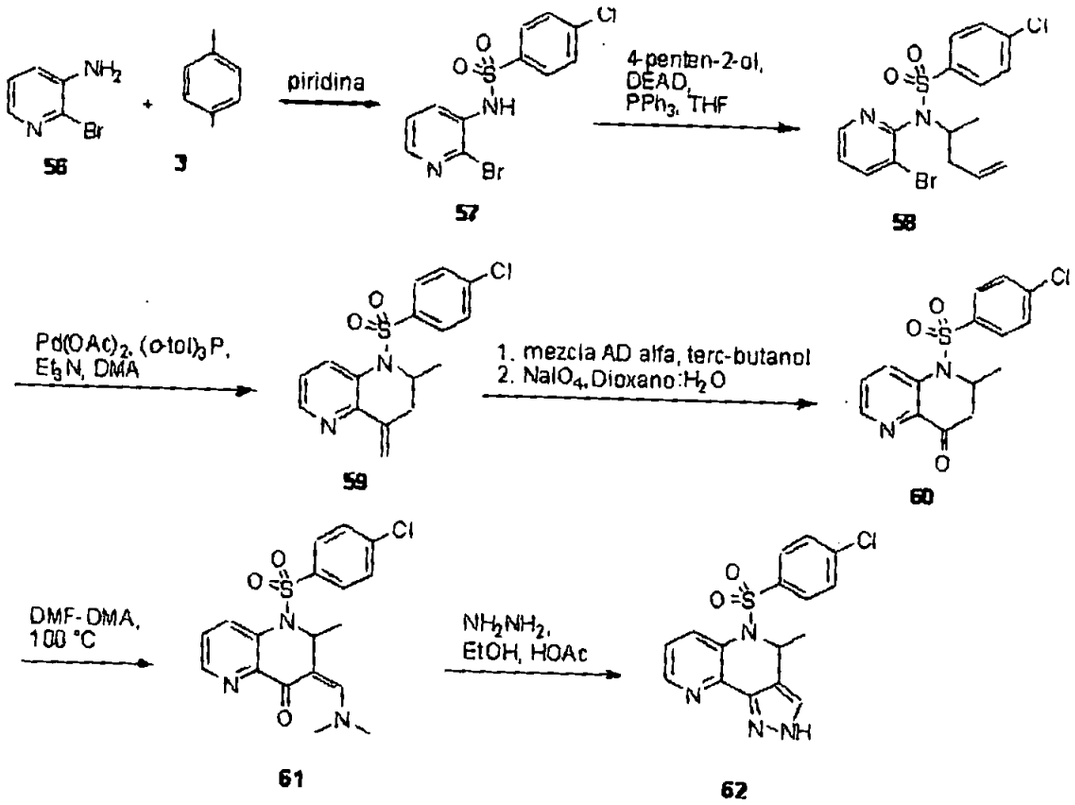
salina (1 x 50 mL), se seca ($MgSO_4$), se filtra y concentra para obtener (53) (1,22 g, 98%) MS *m/z* 303,0 $(M+H)^+$.

4-Metil-5-(piridin-2-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina (55).

Se calienta una solución de dimetilformamida dimetilacetal (6,5 mL) de (53) (1,46 g, 4,83 mmol) a 100 °C durante 2,5 horas. El análisis por HPLC/MS de la mezcla de reacción determina que no hay ningún restante del material de partida de modo que la reacción se enfría a temperatura ambiente y se concentra para obtener el producto crudo (54), que se utiliza directamente en la reacción siguiente. A una solución de ácido acético glacial (12 mL) de (54) se agrega hidrato de hidrazina (257 µL, 5,31 mmol). La mezcla de reacción se calienta a 80 °C durante 45 min, se concentra, y el residuo se absorbe en dietiléter (100 mL). La fase orgánica se lava con agua (1 x 25 mL), $NaHCO_3$ ac. sat. (1 x 20 mL), solución salina (1 x 25 mL), se seca sobre $MgSO_4$, se filtra y concentra. El producto crudo se purifica mediante cromatografía HPLC preparativa para obtener (55) como un sólido amarillo pálido. MS *m/z* 327,0: $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8,45-8,43 (m, 2H), 7,86-7,83 (dd, J = 7,8, 1,3 Hz, 1H), 7,66-7,63 (dd, J = 7,4, 1,6 Hz, 1H), 7,47-7,28 (m, 4H), 7,03-6,99 (m, 1H), 5,75-5,68 (q, J = 6,9 Hz, 1H), 1,35-1,33 (d, J = 6,9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 155,7, 149,3, 137,0, 132,5, 129,3, 128,4, 127,3, 126,4, 124,6, 122,6, 122,1, 118,7, 50,2, 23,1.

Ejemplo 11

5-(4-Clorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c][1,5]naftiridina (62).



56 3 57 58 59 60 61 62

N-(2-Bromopiridin-3-il)-4-Clorobencenosulfonamida (57).

A una solución de 3-amino-2-bromopiridina (56), (2,00 g, 11,6 mmol) en piridina (10 mL) se agrega cloruro de *p*-Clorobencenosulfonilo (3), 2,44 g, 11,6 mmol). La mezcla de reacción se agita a temperatura ambiente durante 24h, y luego se filtra y concentra. El residuo resultante se disuelve en CH_3CN (10 mL) y se purifica mediante HPLC de fase inversa. El residuo resultante se disuelve en CH_2Cl_2 (20 mL) y se lava con $NaHCO_3$ acuoso saturado (2 x 30 mL). La capa orgánica se seca con $MgSO_4$, se filtra y concentra para proporcionar (57) (0,59 g, 25%). MS (ES) *m/z* 348,8 $(M+H)^+$.

N-(3-bromopiridin-2-il)-4-Cloro-*N*-(pent-4-en-2-il)bencenosulfonamida (58).

A una solución de (57) (1,71 g, 4,93 mmol) en THF (10 mL) se agrega 4-penten-2-ol (0,51 mL, 4,93 mmol), seguido de trifenilfosfina (1,55 g, 5,92 mmol). Se agrega dietilazodicarboxilato (1,08 mL, 5,92 mmol) por goteo a la mezcla de reacción. La mezcla de reacción se agita a temperatura ambiente durante 24h, y luego se concentra. El residuo resultante se disuelve en CH_3CN (10 mL) y se purifica mediante HPLC de fase inversa. El residuo resultante se disuelve en CH_2Cl_2 (20 mL) y se lava con $NaHCO_3$ acuoso saturado (2 x 30 mL). La capa orgánica se seca sobre $MgSO_4$, se filtra y concentra para proporcionar (58) (0,68 g, 33%). MS (ES) *m/z* 416,9 $(M+H)^+$.

1-(4-Clorofenilsulfonil)-2-metil-4-metilen-1,2,3,4-tetrahidro-1,5-naftiridina (59).

A una solución de (58) (0,68 g, 1,64 mmol) en DMA (5 mL) se agrega acetato de paladio (0,03 g, 0,16 mmol), tri(*o*-tolil)fosfina (0,16 g, 0,54 mmol), y trietilamina (0,41 mL, 2,95 mmol). La mezcla de reacción se calienta a 150 °C durante 8h. La mezcla de reacción se enfría luego a temperatura ambiente, se diluye con CH_2Cl_2 (10 mL), y se lava con H_2O (15 mL) y solución salina (15 mL). La capa orgánica se seca sobre $MgSO_4$, se filtra y concentra. El residuo resultante se purifica mediante cromatografía flash (EtOAc al 20% en hexanos) para proporcionar (59) (0,31 g, 57%). MS (ES) *m/z* 335,0 $(M+H)^+$.

1-(4-Clorofenilsulfonil)-2-metil-2,3-dihidro-1,5-naftiridin-4(1*H*)-ona (60).

A una solución de (59) (0,21 g, 0,63 mmol) en una mezcla de *terc*-butanol (3 mL) y H_2O (3 mL) 1:1 a 0 °C se agrega AD-mix-α (0,88 g, 1,4 g/mmol). La mezcla de reacción se agita durante 24h mientras se calienta lentamente a temperatura ambiente. La temperatura se reduce luego a 0 °C y se agrega sulfito de sodio (1,51 g, 1,5 g/mmol). Luego de 10 minutos a 0 °C, el baño de hielo se removió y la mezcla de reacción se agita a temperatura ambiente durante 45 minutos. La mezcla de reacción se diluye con CH_2Cl_2 (10 mL) y H_2O (10 mL) y las dos capas se separan. La capa orgánica se lava con solución salina (15 mL), se seca sobre $MgSO_4$, se filtra y concentra. El residuo resultante se disuelve en una mezcla 1:1 de dioxano (2 mL) y H_2O (2 mL), y se agrega periodato de sodio (0,13 g, 0,63 mmol). La mezcla de reacción se agita a temperatura ambiente durante 30 minutos. La mezcla de reacción se diluye con CH_2Cl_2 (10 mL) y H_2O (10 mL) y las dos capas se separan. La capa orgánica se seca sobre $MgSO_4$, se filtra y concentra. El residuo resultante se purifica mediante cromatografía flash (EtOAc al 70% en hexanos) para proporcionar (60) (0,13 g, 61%). MS (ES) *m/z* 337,0 $(M+H)^+$.

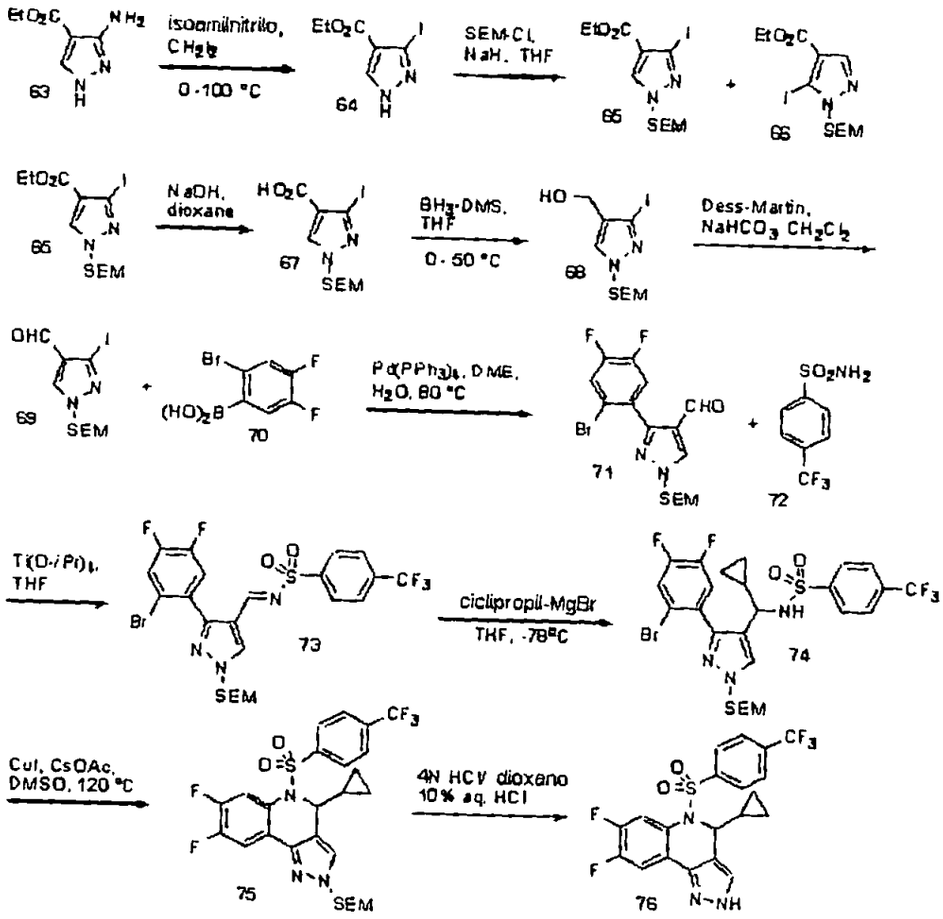
5-(4-Clorofenilsulfonil)-4-metil-4,5-dihidro-2*H*-pirazol[4,3-c][1,5]naftiridina (62).

Se combinaron dimetilformamida dimetilacetal (1 mL) y (60) (0,09 g, 0,28 mmol) y se calientan a 100 °C durante 2h. La mezcla de reacción se enfría luego a temperatura ambiente y se

concentra. El residuo resultante se disuelve en CH_2Cl_2 (15 mL) y se lava con H_2O (10 mL) y solución salina (15 mL). La capa orgánica se seca con $MgSO_4$, se filtra y concentra. El residuo resultante (61) se disuelve en MeOH (1 mL) y la temperatura se reduce a 0 °C. Se agrega hidrazina anhidra (0,02 mL, 0,55 mmol) a la mezcla de reacción, seguido de HOAc (0,03 mL, 0,55 mmol). La mezcla de reacción se agita durante 18h mientras se calienta a temperatura ambiente. La mezcla de reacción se concentra. El residuo resultante se disuelve en CH_2Cl_2 (15 mL) y se lava con H_2O (15 mL), $NaHCO_3$ acuoso saturado (15 mL), y solución salina (15 mL). La capa orgánica se seca sobre $MgSO_4$, se filtra y concentra. El residuo resultante se purifica mediante cromatografía flash sobre alúmina (MeOH al 5% en CH_2Cl_2) para proporcionar (62) (0,03 g, 32%); ^1H NMR ($CDCl_3$) δ 8,64 (dd, J = 4,8, 1,5 Hz, 1H), 8,21 (dd, J = 8,2, 1,5 Hz, 1H), 7,38 (dd, J = 8,2, 4,8 Hz, 1H), 7,36 (s, 1H), 7,17 (m, 2H), 7,09 (m, 2H), 5,67 (q, J = 7,0 Hz, 1H), 1,37 (d, J = 6,8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 147,7, 141,6, 139,6, 137,0, 136,0, 135,3, 129,2, 128,8, 128,3, 123,2, 121,0, 50,7, 23,8. MS (ES) m/z 361,0 $(M+H)^+$.

Ejemplo 12

4-ciclopropil-7,8-difluoro-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina (76).



3-yodo-1*H*-pirazol-4-carboxilato de etilo (64).

Se agrega isoamil nitrito (400 mL, 2,98 mol) a una mezcla heterogénea de 3-amino-1*H*-pirazol-4-carboxilato de etilo (63), 47,69 g, 307 mmol) en diyodometano (800 mL) a -10 °C en un periodo de 30 minutos. La mezcla heterogénea se coloca en un baño de aceite precalentado a 100 °C durante 2 horas. La solución se enfría a temperatura ambiente, se diluye con sulfito de sodio acuoso saturado, y se extrae con EtOAc. Los extractos orgánicos combinados se secan sobre $MgSO_4$, se filtran y concentran bajo presión reducida. El residuo se cromatografía flash sobre sílice utilizando 9:1, 4:1, 7:3, 3:2, y 1:1 hexanos:EtOAc como eluyente para producir 53,85 g (66%) de (64) como un sólido amarillo pálido.

Método 1: Tiempo de retención 1,26 min mediante HPLC. MS *m/z* 267 $(M+H)^+$.

3-yodo-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-carboxilato de etilo(65) y

5-yodo-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-carboxilato de etilo (66).

Se agrega hidruro de sodio (6,00 g, 150 mmol) como una dispersión al 60% en aceite mineral a una solución de 3-yodo-1*H*-pirazol-4-carboxilato de etilo (64), (28,21 g, 106 mmol) en tetrahidrofurano (400 mL). Luego de agitar durante 1 hora, se agrega (2-(clorometoxi)etil)trimetilsilano (25,0 mL, 142 mmol). Luego de agitar durante 18 horas, la mezcla heterogénea se diluye con $NaHCO_3$ acuoso saturado y se extrae con dietiléter. Los extractos orgánicos combinados se secan sobre $MgSO_4$, se filtran y concentran bajo presión reducida. El residuo se cromatografía flash con 49:1, 24:1, 23:2, 22:3, 21:4 y 4:1 hexanos:EtOAc como eluyente para producir 22,50 g (54%) de (65) como un líquido amarillo pálido y 18,00 g (43%) de (66) como un líquido amarillo pálido.

^1H NMR ($CDCl_3$) δ 8,02 (s, 1H), 5,58 (s, 2H), 4,33 (q, J=7,2 Hz, 2H), 3,60 (t, J=8,1 Hz, 2H), 1,37 (t, J=7,2 Hz, 3H), 0,91 (t, J=8,1 Hz, 2H), -0,03 (s, 9H).

^1H NMR ($CDCl_3$) δ 7,97 (s, 1H), 5,40 (s, 2H), 4,31 (q, J=7,2 Hz, 2H), 3,58 (t, J=8,4 Hz, 2H), 1,35 (t, J=7,2 Hz, 3H), 0,90 (t, J=8,4 Hz, 2H), -0,03 (s, 9H).

ácido 3-yodo-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-carboxílico (67).

Se agitaron 3-yodo-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-carboxilato de etilo (65), (22,50 g, 56,8 mmol) y hidróxido de sodio acuoso 3N (50,0 mL, 150 mmol) en dioxano (200 mL) durante cuatro días. La solución se lleva a pH=3 y se extrae con CH_2Cl_2. Los extractos orgánicos combinados se secan sobre $MgSO_4$, se filtran y concentran bajo presión reducida para dar 20,91 g (100%) de (67) como un sólido amarillo pálido.

Método 7: Tiempo de retención 6,22 min mediante HPLC. MS *m/z* 369 $(M+H)^+$, 391 $(M+Na)^+$.

3-yodo-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-il)metanol (68).

Se agrega dimetilsulfuro de borano límpido *ca.* 10M (25 mL, 250 mmol) lentamente a ácido 3-yodo-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-carboxílico (67), (20,91 g, 56,8 mmol) en THF (250 mL) a 0 °C. Luego de agitar durante 30 minutos, la solución se coloca en un baño de aceite precalentado a 50 °C. Luego de agitar durante 18 horas, la solución se enfría a 0 °C y se agrega hielo. Luego de agitar durante 30 minutos, se agrega NH_4Cl acuoso saturado y se agita durante 30 minutos adicionales. La solución se extrae con CH_2Cl_2 y los extractos orgánicos combinados se secan sobre $MgSO_4$, se filtran y concentran bajo presión reducida para dar 19,50 g (97%) de (68) como un líquido amarillo pálido.

Método 7: Tiempo de retención 5,72 min mediante HPLC MS *m/z* 355 $(M+H)^+$.

3-yodo-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-carbaldehído (69).

Se agrega periodinano Dess-Martin (13,80 g, 32,5 mmol) a una mezcla heterogénea de (3-yodo-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-il)metanol (68), 7,19 g, 20,3 mmol) y $NaHCO_3$ (17,44 g, 208 mmol) en CH_2Cl_2 (200 mL). Luego de agitar durante 24 horas, la mezcla heterogénea se diluye con sulfito de sodio acuoso saturado y agua, y luego se extrae con dietiléter. Los extractos orgánicos combinados se secan sobre $MgSO_4$, se filtran y concentran. El residuo se cromatografía flash sobre sílice utilizando 99:1 49:1, 24:1, 23:2, 22:3, 21:4, y 4:1 hexanos:EtOAc como eluyente para producir 7,15 g (100%) de (69) como un sólido blanco.

Método 1: Tiempo de retención 2,43 min mediante HPLC. MS *m/z* 353, 375$(M+Na)^+$.

^1H NMR ($CDCl_3$) δ 9,71 (s, 1H), 8,00 (s, 1H), 5,44 (s, 2H), 3,58 (m, 2H), 1,35 0,90 (m, 2H), -0,03 (s, 9H).

3-(2-bromo-4,5-difluorofenil)-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-carbaldehído (71).

Se colocó tetrakis(trifenilfosfina)paladio(0) (1,29 g, 1,12 mmol), 3-yodo-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-carbaldehído (69), 3,53 g, 10,0 mmol), ácido 2-bromo-4,5-difluorofenilborónico (70), 10,17 g, 42,9 mmol), y K_2CO_3 (15,91 g, 115 mmol) en un frasco que luego se vacía y rellena con nitrógeno tres veces. Se agrega agua (40 mL) y 1,2-dimetoxietano (40 mL) y la solución se coloca en un baño de aceite precalentado a 80 °C. Luego de agitar durante 18 horas,

la solución se extrae con dietiléter. Los extractos orgánicos combinados se secan sobre $MgSO_4$, se filtran y concentran. El residuo se cromatografía flash sobre sílice utilizando 49:1, 24:1, 23:2, 22:3, 21:4, y 4:1 hexanos:EtOAc como eluyente para producir 2,10 g puros (50%) y 1,00 g ligeramente impuro (<24%) de (71) como un aceite de color anaranjado.

Método 2: Tiempo de retención 2,04 min mediante HPLC MS *m/z* 359 y 361 $(M+H)^+$.

N-((3-(2-Bromo-4,5-difluorofenil)-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-il)(ciclopropil)metil)-4-(trifluorometil)bencenosulfonamida (74).

Se agrega isopropóxido de titanio (IV) (3,0 mL, 10,2 mmol) a una solución de 3-(2-bromo-4,5-difluorofenil)-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-carbaldehído (71), (1,00 g, 2,40 mmol) y 4-(trifluorometil)bencenosulfonamida (72), (970 mg, 4,31 mmol) en THF (10 mL). Luego de agitar durante 18 horas, la solución se diluye con CH_2Cl_2, luego agua, y la solución heterogénea se filtra a través de Celite. El filtrado se extrae con CH_2Cl_2, los extractos orgánicos combinados se secan sobre $MgSO_4$, se filtran y concentran. El residuo se cromatografía flash sobre sílice utilizando 9:1, 4:1, 7:3, y 3:2 hexanos:EtOAc como eluyente para proporcionar una mezcla de productos que contiene (73), que se utiliza sin purificación adicional.

Método 2: Tiempo de retención 2,58 min mediante HPLC (M^+=624 y 626).

Se agrega lentamente una solución de bromuro de ciclopropil magnesio 1,0M en THF (20,0 mL, 20,0 mmol) por las paredes del frasco a una solución de (73) en THF (20 mL) a -78 °C. Luego de agitar durante 30 minutos, el baño de hielo seco/acetona se remueve y se agrega NH_4Cl acuoso saturado seguido de agua hasta que la mezcla heterogénea se vuelva homogénea. La solución bifásica se extrae con CH_2Cl_2. Los extractos orgánicos combinados se secan sobre $MgSO_4$, se filtran y concentran. El residuo se cromatografía flash sobre sílice utilizando 9:1, 4:1, 7:3, y 3:2 hexanos:EtOAc como eluyente para producir 1,13 g (>60%, dos pasos) de (74) como un aceite amarillo.

Método 2: Tiempo de retención de 2,55 min mediante HPLC. MS *m/z* 666 y 668 $(M+H)^+$

4-ciclopropil-7,8-difluoro-5-(4-(trifluorometil)fenilsulfonil)-2-((2-(trimetilsilil)etoxi)-metil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina (75).

Se colocan acetato de cesio (2,71g, 14,1 mmol), yoduro cuproso (797 mg, 4,19 mmol), y *N*-((3-(2-bromo-4,5-difluorofenil)-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-il)(ciclopropil)metil)-4-(trifluorometil)bencenosulfonamida (74), 1,13 g, 1,69 mmol) en un frasco que luego se vacía y rellena con nitrógeno. Se agrega DMSO desgasificado (1,7 mL) y la mezcla heterogénea se coloca en un baño de aceite precalentado a 120 °C. Luego de agitar durante 2 horas, la solución se enfría a temperatura ambiente. El sólido que se forma se lava con CH_2Cl_2, y se filtra. El filtrado se concentra y el residuo se cromatografía flash sobre sílice utilizando

19:1, 9:1, 17:3, y 4:1 hexanos:EtOAc como eluyente para producir 645 mg (65%) de (75) como un aceite amarillo.

Método 2: Tiempo de retención 2,82 min mediante HPLC MS *m/z* 586 $(M+H)^+$ 608, $(M+Na)^+$.

4-ciclopropil-7,8-difluoro-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina (76).

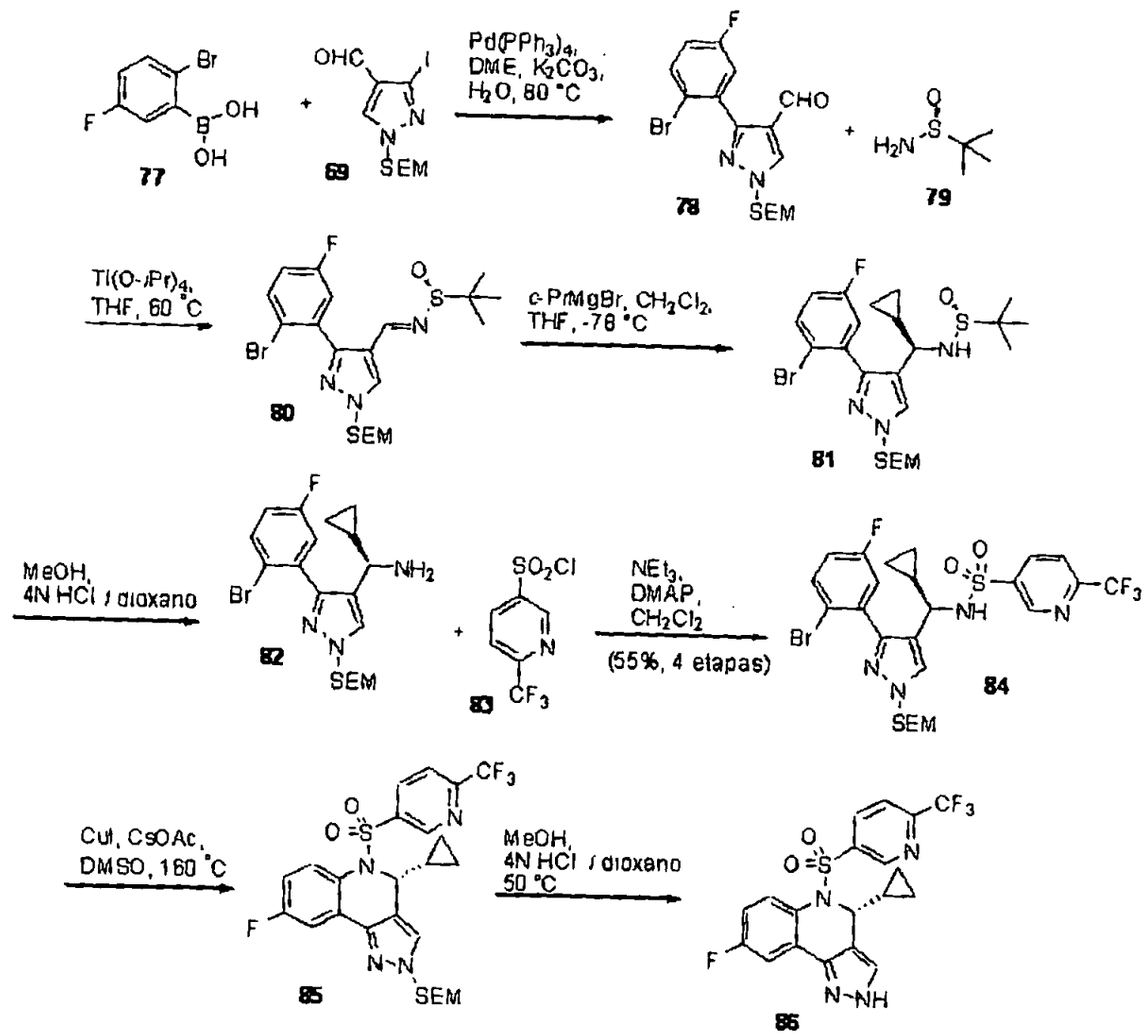
Se agita 4-ciclopropil-7,8-difluoro-5-(4-(trifluorometil)fenilsulfonil)-2-((2-(trimetilsilil)etoxi)metil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina (75), 645 mg, 1,10 mmol) en HCl 4N en dioxano (10 mL) y HCl acuoso al 10% (2 mL) durante 18 horas. La solución se concentra para producir (76) como un sólido amarillo pálido.

Método 7: Tiempo de retención 8,34 min mediante HPLC. MS *m/z* 456,0 $(M+H)^+$, 478 $(M+Na)^+$.

^1H NMR ($CDCl_3$) δ 8,64 (dd, J = 4,8, 1,5 Hz, 1H), 8,21 (dd, J = 8,2, 1,5 Hz, 1H), 7,38 (dd, J = 8,2, 4,8 Hz, 1H), 7,36 (s, 1H), 7,17 (m, 2H), 7,09 (m, 2H), 5,67 (q, J = 7,0 Hz, 1H), 1,37 (d, J = 6,8 Hz, 3H).

Ejemplo 13

(*R*)-4-ciclopropil-8-fluoro-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina (86).



3-(2-bromo-5-fluorofenil)-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-carbaldehído (78).

Se colocan tetrakis(trifenilfosfina)paladio(0) (224 mg, 194 mmol), 3-yodo-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-carbaldehído (69), (1,71 g, 10,0 mmol), ácido 2-bromo-5-fluorofenilborónico (77), 1,36 g, 6,23 mmol), y K_2CO_3 (2,86 g, 20,7 mmol) en un frasco se vacía y rellena con nitrógeno tres veces. Se añade agua (5 mL) y 1,2-dimetoxietano (5 mL) y la solución se coloca en un baño de aceite precalentado a 80 °C. Luego de agitar durante 18 horas, la solución se extrae con dietiléter. Los extractos orgánicos combinados se secan sobre

$MgSO_4$, se filtran y concentran. El residuo se cromatografía flash sobre sílice utilizando 49:1, 24:1, 23:2, 22:3, 21:4, y 4:1 hexanos:EtOAc como eluyente para producir 590 mg (73%) de (78) como un aceite café.

Método 2: Tiempo de retención 1,92 min mediante HPLC MS *m/z* 399 y 401 $(M+H)^+$.

(S)-(E)-N-((3-(2-bromo-5-fluorofenil)-1-((2-(trimetilsilil)etoxi)metil)-1H-pirazol-4-il)metilen)-2-metilpropan-2-sulfinamida (80).

Se agrega isopropóxido de titanio (IV) (1,1 mL, 3,75 mmol) a una solución de 3-(2-bromo-5-fluorofenil)-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-carbaldehido (78), 590 mg, 1,48 mmol) y (*S*)-(-)-terc-butanosulfinamida (79), 254 mg, 2,10 mmol) en THF (10 mL). Luego de agitar durante 18 horas, la solución se coloca en un baño de aceite precalentado a 60 °C. Luego de agitar durante 2 horas, la solución se enfría a temperatura ambiente, se diluye con CH_2Cl_2, luego agua, y la solución heterogénea se filtra a través de Celite. El filtrado se extrae con CH_2Cl_2, los extractos orgánicos combinados se secan sobre $MgSO_4$, se filtran y concentran para dar (80) como un aceite que se utiliza sin purificación adicional.

Método 2: Tiempo de retención 2,28 min mediante HPLC. MS *m/z* 502 y 504 $(M+H)^+$.

(S)-N-((R)-(3-(2-bromo-5-fluorofenil)-1-((2-(trimetilsilil)etoxi)metil)-1H-pirazol-4-il)(ciclopropil)metil)-2-metilpropan-2-sulfinamida (81).

Se agrega lentamente una solución de bromuro de ciclopropilmagnesio 1,0M en THF (15,0 mL, 15,0 mmol) por goteo a una solución de (*S*)-(*E*)-*N*-((3-(2-bromo-5-fluorofenil)-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-il)metilen)-2-metilpropan-2-sulfinamida (80) en CH_2Cl_2 (15 mL) a -78 °C. Luego de agitar durante 30 minutos, el baño de hielo seco/acetona se remueve y $NaHCO_3$ acuoso saturado se agrega seguido de agua hasta que la mezcla heterogénea se vuelve homogénea. La solución bifásica se extrae con CH_2Cl_2, los extractos orgánicos combinados se secan sobre $MgSO_4$, se filtran y concentran para producir (81) como un aceite café que se utiliza sin purificación adicional.

Método 7: Tiempo de retención 9,63 min mediante HPLC, MS *m/z* 544 y 546 $(M+H)^+$. Para el diastereómero mayor y 10,03 min mediante HPLC, MS *m/z* 544 y 546$(M+H)^+$. Para el diastereómero menor.

(*R*)-(3-(2-bromo-5-fluorofenil)-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-il)(ciclopropil)metanamina (82).

Se agrega HCl 4 N en dioxano (1 mL) a una solución de (*S*)-*N*-((*R*)-(3-(2-bromo-5-fluorofenil)-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-il)(ciclopropil)metil)-2-metilpropan-2-sulfinamida (81) en MeOH (20 mL). Luego de agitar durante 1 hora, la solución se concentra. El residuo se diluye con NaOH acuoso 1N, se extrae con CH_2Cl_2, los extractos orgánicos combinados se secan sobre $MgSO_4$, se filtran y concentran para dar (82) como un aceite

marrón que se utiliza sin purificación adicional.

Método 7: Tiempo de retención 5,57 min mediante HPLC MS *m/z* 423 y 425 $(M-NH_2)^+$ y MS *m/z* 440 y 442 $(M+H)^+$.

(R)-*N*-((3-(2-bromo-5-fluorofenil)-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-il)(ciclopropil)metil)-6-(trifluorometil)piridin-3-sulfonamida (84).

Se agrega cloruro de 4-(trifluorometil)benceno-1-sulfonilo (83), (835 mg, 3,40 mmol) a una solución de (*R*)-(3-(2-bromo-5-fluorofenil)-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-il)(ciclopropil)metanamina (82) y DMAP (120 mg, 982 µmol) en CH_2Cl_2 (5 mL) y trietilamina (1 mL). Luego de agitar durante 18 horas, la solución se concentra, y el residuo se cromatografía flash sobre sílice utilizando 9:1, 4:1, 7:3, y 3:2 hexanos:EtOAc como eluyente para producir 525 mg (55%, 4 pasos) de (84) como un aceite.

Método 7: Tiempo de retención 11,00 min mediante HPLC MS *m/z* 649 y 651 $(M+H)^+$.

(R)-4-ciclopropil-8-fluoro-5-(6-(trifluorometil)piridin-3-ilsulfonil)-2-((2-(trimetilsilil)etoxi)metil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina (85).

Se colocan acetato de cesio (1,46 g, 7,61 mmol), yoduro cuproso (446 mg, 2,34 mmol), y (*R*)-*N*-((3-(2-bromo-5-fluorofenil)-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-il)(ciclopropil)metil)-6-(trifluorometil)piridin-3-sulfonamida (84), 613 mg, 944 µmol) en un frasco que se vacía y rellena con nitrógeno. Se agrega DMSO desgasificado (1,0 mL) y la

mezcla heterogénea se coloca en un baño de aceite precalentado a 160 °C. Luego de agitar durante 30 minutos, la solución se enfría a temperatura ambiente; el sólido que se forma se lava con CH_2Cl_2, y se filtra a través de Celite. El filtrado se concentra y el residuo se cromatografía flash sobre sílice utilizando 19:1, 9:1, 17:3, 4:1, y 3:1 hexanos: EtOAc como eluyente para producir 405 mg (75%) de (85) como un aceite amarillo.

Método 2: Tiempo de retención 2,66 min mediante HPLC MS *m/z* 569 $(M+H)^+$, 591$(M+Na)^+$.

(*R*)-4-ciclopropil-8-fluoro-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina (86).

Se agrega HCl 4 N en dioxano (10 mL) a una solución de (*R*)-4-ciclopropil-8-fluoro-5-(6-(trifluorometil)piridin-3-ilsulfonil)-2-((2-(trimetilsilil)etoxi)metil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina (85), (1,30 g, 2,29 mmol) en MeOH (20 mL) que se colocó en un baño de aceite precalentado a 50 °C. Luego de agitar durante 1,5 horas, la solución se concentra. El residuo se diluye con $NaHCO_3$ acuoso saturado, se extrae con CH_2Cl_2, los extractos orgánicos combinados se secan sobre $MgSO_4$, se filtran y concentran. El residuo se cromatografía flash sobre sílice utilizando 9:1, 4:1, 7:3, y 3:2 hexanos:EtOAc como eluyente para producir 1,00 g de (86) como un aceite amarillo pálido.

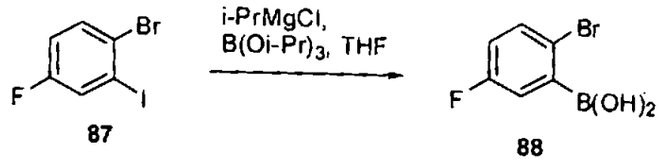
Método 7: Tiempo de retención 7,04 min mediante HPLC MS *m/z* 439 $(M+H)^+$; 461$(M+Na)^+$.

^{1}H NMR ($CDCl_3$) δ 10,13 (ancho s, 1H), 8,51 (s, 1H), 7,85 (dd, J=12,0 y 6,4 Hz, 1H), 7,40 (m, 2H), 7,36 (d, J=3,0 Hz, 1H), 7,28 (s, 1H), 7,14 (dt, J=3,0 y 8,7 Hz, 1H), 4,99 (d, J=7,8 Hz, 1H), 1,01 (m, 1H), 0,54 (m, 1H), 0,39 (m, 2H), 0,09 (m, 1H).

La separación de los enantiómeros mayor y menor se logró utilizando HPLC-Método 18.

Ejemplo 14

ácido 2-bromo-5-fluorofenilborónico (88).



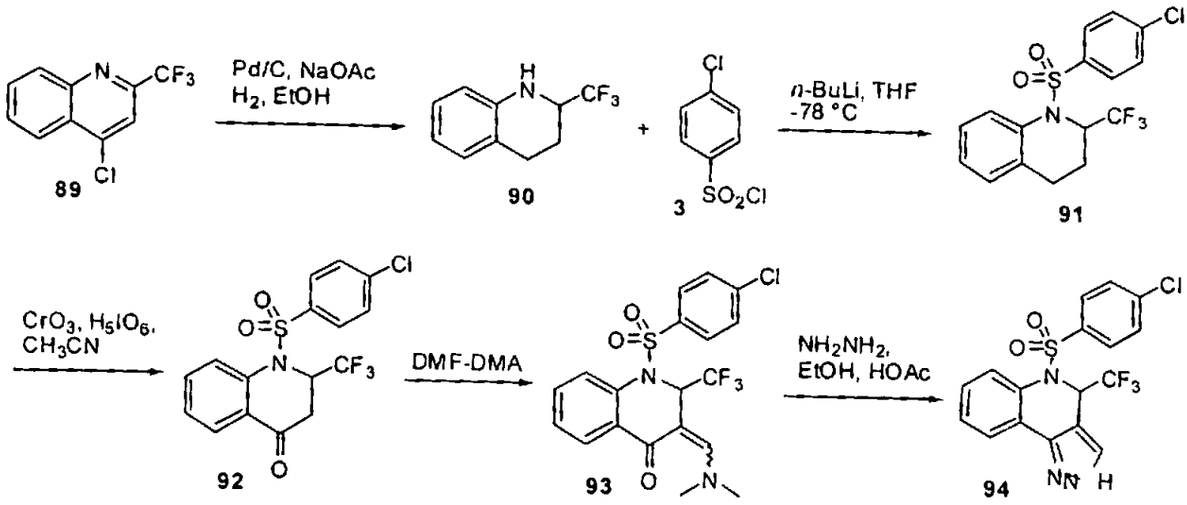
87 88

ácido 2-bromo-5-fluorofenilborónico (88).

Se agrega lentamente cloruro de isopropilmagnesio (36,5 mmol, 2,0 M en THF) a una solución de THF a -42 °C (2,0 M) de 1-bromo-4-fluoro-2-yodobenceno (87) (10 g, 33,2 mmol) bajo N_2, y se agita a -42 °C durante 2 h. Se agrega triisopropilborato (11,4 mL, 49,8 mmol) y la reacción se calienta a temperatura ambiente y se agita durante la noche. Se agrega NaOH 1N (20 mL) y la mezcla se agita durante 1h. El pH se ajustó a 3 con HCl 3N, y la muestra se extrae (2 x 20 mL) con EtOAc. Los productos orgánicos combinados se secan sobre $MgSO_4$, se filtran a través de Celite, y se remueve el solvente para obtener (5,75 g, 26,39 mmol) de ácido 2-bromo-5-fluorofenilborónico (88) como un sólido blanco. ^{1}H NMR ($CDCl_3$) δ 7,68-7,64 (1H, dd, *J* = 9,1, 3,2 Hz), 7,54-7,49 (1H, dd, *J* = 8,8, 4,8 Hz), 7,08-7,01 (1H, m), 5,76 (2H, s).

Ejemplo 15

5-(4-Clorofenilsulfonil)-4-(trifluorometil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina (94).



2-(trifluorometil)-1,2,3,4-tetrahidroquinolina (90).

Se colocó una solución de etanol (70 mL) de 4-Cloro-2-(trifluorometil)quinolina (89) (5,48 g, 23,66 mmol), NaOAc (3,88 g, 47,32 mmol) y Pd/C al 10% (500 mg) bajo 45 psi de H_2 durante un día. La mezcla de reacción se filtra luego a través de una almohadilla de Celite y el filtrado se concentra. El residuo se absorbe en EtOAc y se lava con agua (3 x 50 ml), solución salina (1 x 10 ml), se seca sobre $MgSO_4$, se filtra y concentra para dar (90) (4,43 g, 93%) como un aceite límpido que se solidifica en reposo y se utiliza sin purificación adicional. ^1H NMR ($CDCl_3$) δ 7,07-7,02 (m, 2H), 6,75-6,70 (m, 1H), 6,60 (d, J = 8,0Hz, 1H), 4,09 (br s, 1H), 3,92-3,84 (m, 1H), 2,85-2,81 (m, 2H), 2,15-2,08 (m, 2H); MS *m/z* 202,1 $(M+H)^+$.

1-(4-Clorofenilsulfonil)-2-(trifluorometil)-1,2,3,4-tetrahidroquinolina (91).

A una solución de THF (5,5 mL) de (90) (271 mg, 1,34 mmol) a -78 °C se agrega *n*-BuLi (2,5M en hexanos, 566 µL, 1,41 mmol). Luego de 10 minutos se agrega una solución de THF (2mL) de cloruro de 4-Clorobencenosulfonilo (341 mg, 1,62 mmol) durante un período de 5 minutos para dar una solución negra. La mezcla de reacción se mantiene a -78 °C por una hora y luego se calienta a -30 °C. Luego de 30 minutos la mezcla se enfría a -78 °C, se inactiva con la adición de NH_4Cl saturado, se calienta a temperatura ambiente y se diluye con EtOAc y agua. La porción orgánica se lava con ácido cítrico 0,2 N (3 x 15 mL), agua (1 x 15 mL), $NaHCO_3$ sat. (3 x 15 mL), solución salina (1 x 10 mL), se seca sobre $MgSO_4$, se filtra y concentra para dar el producto crudo que se purifica mediante cromatografía flash eluyendo con hexanos/EtOAc 25:1 para dar (91) (178mg, 35%).

^1H NMR ($CDCl_3$) δ 7,59 (d, J = 7,7 Hz, 1H), 7,42-7,27 (m, 5H), 7,22-7,18 (m, 1H), 7,00, (d, J = 7,1 Hz, 1H), 4,91-4,84 (m, 1H), 2,40-2,27 (m, 2H), 1,81-1,67 (m, 1H), 1,51-1,42 (m, 1H); MS *m/z* 376,0 $(M+H)^+$.

1-(4-Clorofenilsulfonil)-2-(trifluorometil)-2,3-dihidroquinolin-4(1*H*)-ona (92).

A una solución de H_5IO_6 (594 mg, 2,61mmol) en CH_3CN (3 mL) se agrega CrO_3 (7 mg, 70,1 µmol). Luego de agitar durante algunos minutos (91) (178 mg, 0,47 mmol) se agrega a una solución rojiza para dar una solución de mezcla de reacción heterogénea. El análisis por TLC (hexano/EtOAc 10:1) luego de 6 horas determina que no hay ningún restante del material de

partida de modo que la mezcla de reacción se diluye con EtOAc (10 mL) y se lava con agua (2 x 10 mL), $NaHSO_3$ al 5% (2 x 10 mL), solución salina (1 x 20 mL), se seca sobre $MgSO_4$, se filtra y concentra para dar el producto crudo. La purificación mediante TLC preparativa (hexanos/EtOAc 2:1) dio 92 (37,6 mg, 20%). ^1H NMR ($CDCl_3$) δ 7,95-7,92 (m, 1H), 7,86-7,83 (m, 1H), 7,66-7,56 (m, 3H), 7,45-7,32 (m, 3H), 5,28-5,23 (m, 1H), 2,84 (dd, J = 19,9, 1,6 Hz, 1H), 2,64 (dd, J = 18,7, 7,70 Hz, 1H); MS *m/z* 390,0 $(M+H)^+$.

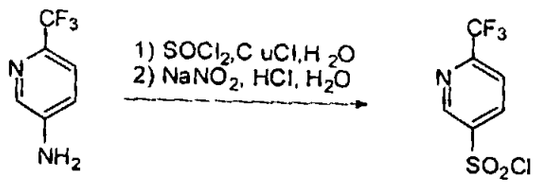
5-(4-Clorofenilsulfonil)-4-(trifluorometil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina (94).

Una solución de dimetilformamida dimetilacetal (173 µL) de (92) (34 mg, 87 µmol) se calienta a 100 °C durante 1 hora. El análisis por HPLC/MS de la mezcla de reacción determina que no hay ningún restante del material de partida de modo que la reacción se enfría a temperatura ambiente y se diluye con EtOAc (5 mL). La fase orgánica se lava con agua (3 x 10 mL), solución salina (1 x 20 mL), se seca sobre $MgSO_4$, se filtra y concentra para dar (93) que se utiliza directamente en la reacción siguiente. A una solución de EtOH/HOAc glacial (25:1 v/v, 400 µL) de (93) (39 mg, 90 µmol) se agrega hidrato de hidrazina (21 µL, 0,45 mmol). La mezcla de reacción se agita 5 días a temperatura ambiente, se transfiere a un tubo sellado y se calienta a 75 °C durante 5 días. La mezcla de reacción se enfría luego a temperatura ambiente, se concentra y el residuo se absorbe en EtOAc (10 mL). La fase orgánica se lava con $NaHCO_3$ sat. (3 x 20 mL), solución salina (1 x 10 mL), se seca

sobre $MgSO_4$, se filtra y concentra. El producto crudo se purifica mediante HPLC preparativa para dar (94) (6,7 mg, 19% en dos pasos) como un polvo blanco. ^1H NMR ($CDCl_3$) δ 7,88 (dd, J = 7,70, 1,1 Hz, 1H), 7,67 (dd, J = 8,5, 1,6 Hz, 1H), 7,53 (s, 1H), 7,43-7,36 (m, 2H), 7,25-7,17 (m, 4H), 6,03 (q, J = 7,1 Hz, 1H); MS *m/z* 414,0 $(M+H)^+$.

Ejemplo 16

Cloruro de 6-(trifluorometil)piridina-3-sulfonilo (83).



95 **83**

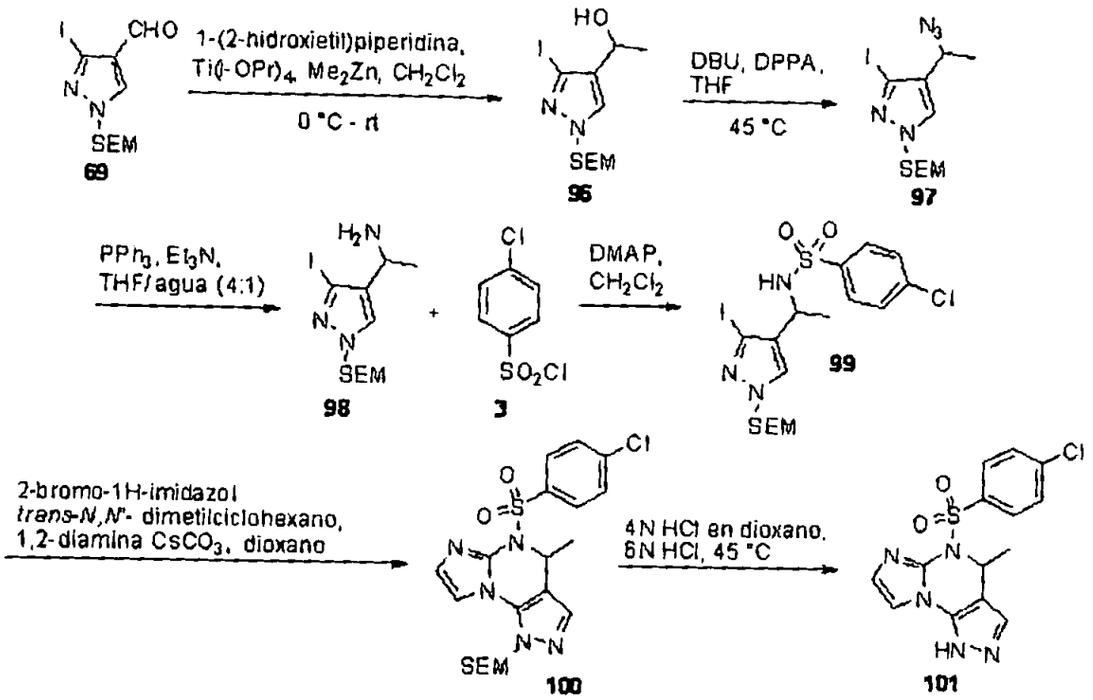
Cloruro de 6-(trifluorometil)piridin-3-sulfonilo (83).

Se agrega lentamente cloruro de tionilo (31 mL, 0,43 mol) a 175 mL de agua a 0 °C. Durante la adición, la temperatura se mantiene entre 0-5 °C. Luego de la adición, la solución se calienta a 15 °C y se agrega 0,47 g (4,8 mmol) de CuCl. La solución se diluye con 100 mL de agua y se enfría a 0 °C. Se agrega lentamente una solución de 7,21 g (0,10 mol) de $NaNO_2$ en 100 mL de agua a una solución de 15,39 g (0,10 mol) de 5-amino-2-(trifluorometil)piridina (95) en 125 mL de HCl conc. a 0 °C. Durante la adición, la temperatura se mantiene entre 0-5 °C. Esta mezcla se agrega luego lentamente a la solución preparada anteriormente de modo de mantener una temperatura entre 0-5 °C. Se forma un precipitado voluminoso. La mezcla se agita durante 30 min adicionales luego de la adición y el sólido se recogió mediante filtración. El sólido se lava con

agua y se disuelve en $CHCl_3$. La solución se seca sobre $MgSO_4$, se filtra y se remueve el solvente para proporcionar 18,03 g (77%) de cloruro de sulfonilo (83) como un sólido tostado. ^1H NMR ($CDCl_3$) δ 9,34 (d, J = 2,2 Hz, 1H), 8,53 (dd, J = 8,4, 2,2 Hz, 1H), 7,98 (d, J = 8,4 Hz, 1H).

Ejemplo 17

5-(4-Clorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-imidazo[1,2-a]pirazol[4,3-e]pirimidina (104).



1-(3-yodo-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-il)etanol (96).

A una mezcla en agitación de 1-(2-hidroxietil)piperidina (149 mg, 1,09 mmol) en CH_2Cl_2 seco (25 mL) bajo N_2 a temperatura ambiente se agrega $Ti(iOPr)_4$. Luego de 1 h de agitación, la mezcla de reacción se enfría a 0 °C y se agrega una solución 2,0 M de dimetilo de zinc en tolueno (17 mL, 33 mmol). Luego

de 30 min, se agrega una solución de aldehído (69) (1,45 g, 5,45 mmol) en CH_2Cl_2 (2 mL) y la reacción se agita durante la noche. La mezcla de reacción se inactiva con HCl 1N y las capas se separan. La capa acuosa se extrae con CH_2Cl_2 (3 x 10 mL). Las capas orgánicas combinadas se secan sobre $MgSO_4$, se filtran y concentran bajo presión reducida. El residuo se cromatografía flash con 9:1, 4:1, y 3:1 hexanos:EtOAc como eluyente para producir 1,3 g (85%) de (96) como un aceite incoloro. El producto se analiza mediante HPLC/MS utiliza el Método 1. Tiempo de retención = 2,199 min. MS *m/z* 369,0 $(M+H)^+$. ^1H NMR (300 MHz, $CDCl_3$) δ 7,45 (s, 1H), 5,38 (s, 2H), 4,79 (q, *J* = 6,1 Hz, 1H), 3,58 (t, *J* = 7,7 Hz, 2H), 1,53 (d, *J* = 6,1 Hz, 3H), 0,91 (t, *J* = 8,2 Hz, 2H), -0,03 (s, 9H).

4-(1-azidoetil)-3-yodo-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol (97).

A una mezcla en agitación del alcohol (96) (1,2 g, 3,26 mmol) en THF (0,5 M, 6,5 mL) a temperatura ambiente se agrega DBU (843 mg, 5,54 mmol), seguido de DPPA (1,5 g, 5,54 mmol). La mezcla resultante se vuelve lentamente café oscuro, y se calienta lentamente a 45 °C. La mezcla de reacción se enfría a temperatura ambiente y luego se diluye con CH_2Cl_2 y se inactiva con solución salina. Las capas se separan. La capa acuosa se extrae con CH_2Cl_2 (3 x 25 mL). Los extractos orgánicos combinados se secan sobre $MgSO_4$, se filtran y concentran bajo presión reducida. El residuo se cromatografía flash con hexanos:EtOAc 10:1 y 9:1 como eluyente para producir 1,1 g de (97) como un aceite incoloro. El producto se analiza mediante

HPLC/MS utilizando el Método 1. Tiempo de retención = 2,076 min. MS *m/z* 394,0 $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 7,47 (s, 1H), 5,41 (s, 2H), 4,47 (q, *J* = 7,0 Hz, 1H), 3,58 (t, *J* = 8,1 Hz, 2H), 1,53 (d, *J* = 6,6 Hz, 3H), 0,91 (t, *J* = 8,2 Hz, 2H), -2,0 (s, 9H).

1-(3-yodo-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-il)etanamina (98).

A una mezcla en agitación de la azida (97) (270 mg, 0,7 mmol) en THF/agua se agrega PPh_3 (545 mg, 2,08 mmol) y Et_3N (0,58 mL, 4,15 mmol). La mezcla de reacción se calienta a 50 °C y se agita durante la noche. La mezcla de reacción se inactiva con agua y se extrae con EtOAc. Las capas orgánicas combinadas se secan sobre $MgSO_4$, se filtran y concentran bajo presión reducida. El residuo se cromatografía flash con 2:1, 1:1 hexanos/EtOAc y 10:1:0,1 EtOAc/MeOH/NH_4OH para dar 240 mg del compuesto (98) como un aceite incoloro. El producto se analiza mediante HPLC/MS utilizando el Método 1. Tiempo de retención = 1,576 min. MS *m/z* 368,1 $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 7,66 (s, 1H), 5,37 (s, 2H), 4,17 (q, *J* = 6,9 Hz, 1H), 3,59 (t, *J* = 7,8 Hz, 2H), 1,56 (d, *J* = 6,5 Hz, 3H), 0,91 (d, *J* = 8,2 Hz, 2H), -1,3 (s, 9H).

4-Cloro-N-(1-(3-yodo-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-il)etil)bencenosulfonamida (99).

A una mezcla en agitación de amina (98) (100 mg, 0,27 mmol) en CH_2Cl_2 (1,0 mL) a temperatura ambiente se agrega cloruro de 4-Clorobencenosulfonilo (3), (111 mg, 0,55 mmol), Et_3N, y DMAP (4 mg). Se hizo reaccionar la mezcla de reacción durante 4 h o

hasta que se consumió todo el material de partida. La mezcla resultante se diluye con $NaHCO_3$ y se extrae con EtOAc. El residuo se cromatografía flash con 2:1, 1:1 y 1:2 hexanos/EtOAc para dar 70 mg de (99) como un aceite incoloro. El producto se analiza mediante HPLC/MS utilizando el Método 1. Tiempo de retención = 2,906 min. MS *m/z* 564,0 $(M+Na)^+$.

5-(4-Clorofenilsulfonil)-4-metil-1-((2-(trimetilsilil)etoxi)metil)-4,5-dihidro-1*H*-imidazo[1,2-a]pirazol[4,3-e]pirimidina (100).

A una mezcla en agitación de sulfonamida (99) (110 mg, 0,2 mmol) en dioxano desoxigenado (0,5 M) se agrega *trans*-*N*,*N*'-dimetilciclohexano-1,2-diamina (114 mg, 0,812 mmol), CuI (38 mg, 0,2 mmol), $CsCO_3$ (263 mg, 0,81 mmol), y 2-bromo-1*H*-imidazol (38 mg, 0,24 mmol). La mezcla de reacción se calienta rápidamente a 110 °C y se agita durante 1 h. La mezcla bruta se cargó directamente en una columna de gel de sílice y se cromatografía para dar 78 mg (80%) de (100) como un aceite incoloro. El producto se analiza mediante HPLC/MS utilizando el Método 2. Tiempo de retención = 1,429 min. MS *m/z* 480,1 $(M+H)^+$.

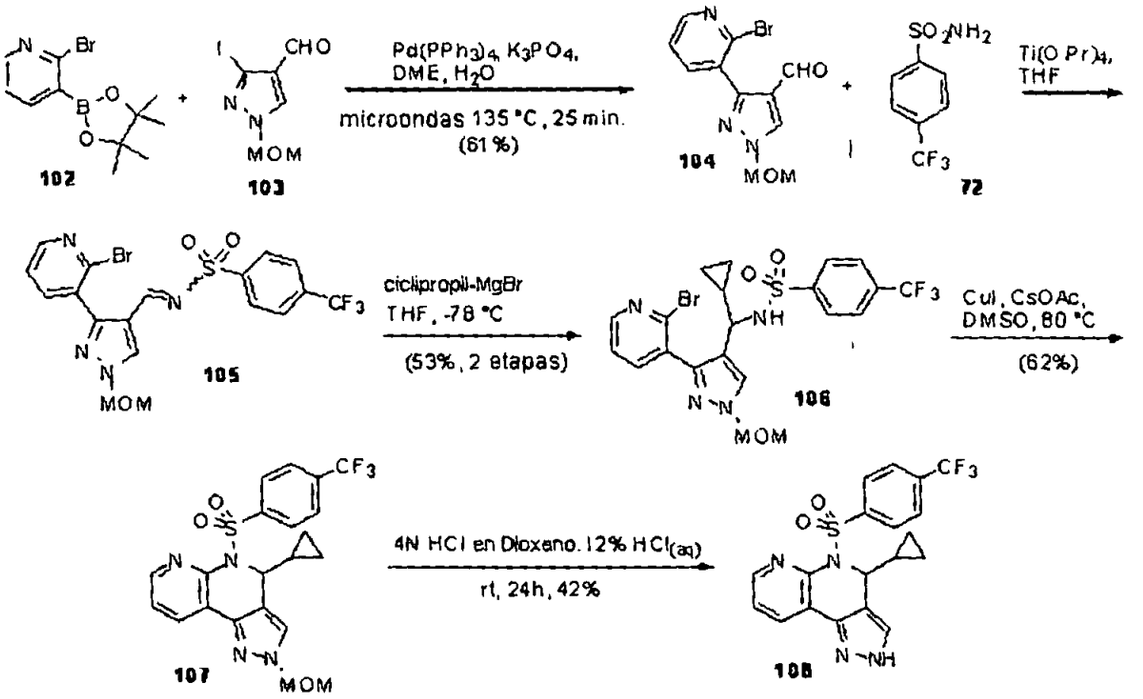
5-(4-Clorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-imidazo[1,2-a]pirazol[4,3-e]pirimidina (101).

Se agita pirimidina (100) en 4N HCl en dioxano (10 mL) y HCl acuoso 6 N (2 mL) durante 18 horas. La solución se concentra para dar el compuesto (101) como un sólido amarillo. El producto deseado se purifica adicionalmente mediante HPLC preparativa utilizando el tipo de columna especificado y se

analiza utilizando el Método 1 para dar un sólido blanco. MS(ESI) *m/z* 350,0 $(M+H)^+$. Tiempo de retención = 1,139 min. ^1H NMR (300 MHz, $CDCl_3$) δ 7,74-7,72 (m, 2H), 7,37-7,35 (m, 2H), 7,32 (s, 2H), 7,08-7,07 (m, 1H), 5,78 (q, *J* = 5,7 Hz, 1H), 1,36 (d, *J* = 6,6 Hz, 3H).

Ejemplo 18

4-ciclopropil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c][1,8]naftiridina (108).



3-(2-bromopiridin-3-il)-1-(metoximetil)-1*H*-pirazol-4-carbaldehído (104).

A una solución de fosfato de potasio (4,78 g, 22,5 mmol) en una mezcla de dimetiléter de etilenglicol (10 mL) y H_2O (10 mL), se agrega pinacol éster del ácido 2-bromopiridin-3-borónico (102) (2,13 g, 7,52 mmol). La mezcla de reacción se agita a temperatura ambiente durante 10 minutos antes de la adición de aldehído (103) (1,00 g, 3,75 mmol) y

tetrakistrifenilfosfinpaladio (0,43 g, 0,37 mmol). La mezcla de reacción se calienta en microondas a 125 °C durante 25 minutos. La mezcla de reacción se diluye luego con EtOAc (25 mL) y las dos capas se separan. La capa orgánica se lava con NaCl acuoso saturado (15 mL), se seca sobre $MgSO_4$, se filtra y concentra. El residuo resultante se purifica mediante cromatografía flash (EtOAc al 50% en hexanos) para proporcionar (104) (0,68 g, 61%). MS (ES) *m/z* 295,9, 297,9 $(M+H)^+$.

N-((3-(2-Bromopiridin-3-il)-1-(metoximetil)-1*H*-pirazol-4-il)(ciclopropil)metil)-4-(trifluorometil)bencenosulfonamida (106).

A una solución de (104) (0,68 g, 2,30 mmol) en THF (10 mL) se agrega sulfonamida (72) (0,77 g, 3,45 mmol), seguido de isopropóxido de titanio (IV) (1,30 g, 4,6 mmol). La mezcla de reacción se agita a temperatura ambiente durante 18 h. La mezcla de reacción se diluye luego con EtOAc (15 mL), y luego se inactiva con NaCl acuoso saturado (3 mL). La mezcla se agita durante 10 minutos, y luego se filtra a través de una almohadilla de Celite. Las dos capas se separan. La capa orgánica se seca sobre $MgSO_4$, se filtra y concentra. La imina resultante (105), se utiliza en la reacción siguiente sin purificación. A una solución de (105) en THF a -78 °C se agrega lentamente bromuro de ciclopropilmagnesio (0,5M en THF, 9,20 mL, 4,60 mmol). La mezcla de reacción se agita durante 2 h a -78 °C, luego se diluye con EtOAc (20 mL) y se inactiva con NH_4Cl acuoso saturado (10 mL). La mezcla se calienta a

temperatura ambiente y las dos capas se separan. La capa orgánica se lava con NaCl acuoso saturado (15mL), se seca sobre $MgSO_4$, se filtra y concentra. El residuo resultante se purifica mediante cromatografía flash (EtOAc al 50% en hexanos) para proporcionar (106) (0,66 g, 53% sobre dos pasos). MS (ES) *m/z* 544,8 y 546,8 $(M+H)^+$.

4-ciclopropil-2-(metoximetil)-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c][1,8]naftiridina (107).

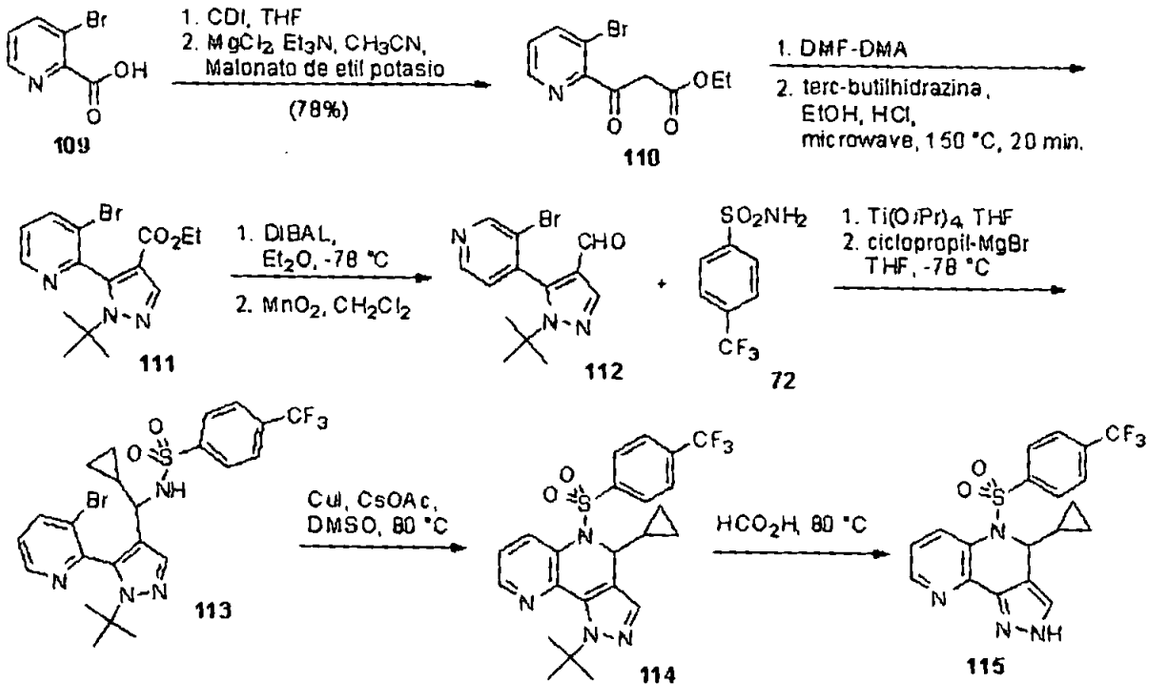
Se disuelve sulfonamida (106) (0,30 g, 0,55 mmol) en DMSO (1 mL) y el nitrógeno burbujea en la solución durante 1 h. En un frasco secado a llama individual, se combinan yoduro de cobre (0,42 g, 2,20 mmol) y acetato de cesio (1,05 g, 5,50 mmol). Se vació el frasco de reacción, luego se rellena con nitrógeno. Este proceso de bombeo/purga se repite tres veces. La solución de DMSO de sulfonamida (106) se agrega al frasco de reacción y el frasco se sumerge en un baño de aceite precalentado a 80 °C. La mezcla de reacción se agita durante 2 h a 80 °C, y luego se enfría a temperatura ambiente. La mezcla se diluye con Et_2O (15 mL) y se lava con H_2O (10 mL). La capa orgánica se seca sobre $MgSO_4$, se filtra y concentra. El residuo resultante se purifica mediante cromatografía flash (EtOAc al 50% en hexanos) para proporcionar (107) (0,16 g, 62%). MS (ES) *m/z* 464,9 $(M+H)^+$.

4-ciclopropil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c][1,8]naftiridina (108).

A una solución de pirazolnaftiridina (107) (0,21 g, 0,45 mmol) en 4N HCl en dioxano (5 mL) se agrega HCl al 12% (0,15 mL). La mezcla de reacción se agita durante 18 h a temperatura ambiente. La mezcla de reacción se diluye con EtOAc (15 mL), y se disminuye la temperatura a 0 °C. La mezcla de reacción se inactiva con la adición de NaOH 1M hasta pH 7. Los dos capas se separaron. La capa acuosa se lava con EtOAc (20 mL, 3x). Las capas orgánicas combinadas se secan sobre $MgSO_4$, se filtran y concentran. El residuo resultante se purifica mediante cromatografía flash (EtOAc al 50% en hexanos) para proporcionar (108) (0,14 g, 42%). ^{1}H NMR ($CDCl_3$) δ 8,32 (dd, *J* = 4,8, 1,6 Hz, 1H), 8,19 (d, *J* = 8,3 Hz, 2H), 8,07 (dd, *J* = 7,6, 1,5 Hz, 1H), 7,72 (d, *J* = 8,3 Hz, 2H), 7,52 (s, 1H), 7,16 (dd, *J* = 7,6, 4,9 Hz, 1H), 5,45 (d, *J* = 8,1 Hz, 1H), 1,15 (m, 1H), 0,51 (m, 2H), 0,38 (m, 1H), 0,21 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159,9, 148,5, 148,1, 144,7, 141,2, 134,6, 134,2, 131,4, 128,9, 126,3, 125,8, 125,7, 121,5, 120,9, 116,0, 57,7, 18,0, 5,07, 2,67. MS (ES) *m/z* 420,9 $(M+H)^+$.

Ejemplo 19

4-ciclopropil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c][1,5]naftiridina (115).



3-(3-bromopiridin-2-il)-3-oxopropanoato de etilo (110).

A una suspensión de ácido 3-bromo-2-piridin-carboxílico (109) (2,00 g, 9,90 mmol) en THF (10 mL) se agrega carbonildiimidazol (1,61 g, 9,90 mmol). La mezcla de reacción se agita durante 18 h a temperatura ambiente. En un frasco individual secado mediante llama, se suspende etil malonato de potasio (3,37 g, 19,8 mmol) en CH_3CN (40 mL) y se agrega Et_3N (3,00 g, 29,7 mmol). La temperatura se reduce a 0 °C. Se agrega cloruro de magnesio (2,35 g, 24,7 mmol) en dos porciones y la mezcla de reacción se agita a temperatura ambiente durante 5 h. Se reduce luego la temperatura a 0 °C y se agrega lentamente una solución de THF (109). La mezcla de reacción se agita a 0 °C durante 10 minutos, luego se calienta a temperatura ambiente y se agita durante 18 h. La mezcla de reacción se concentra, y el residuo resultante se suspende en tolueno (70 mL). La temperatura se reduce a 0 °C y la mezcla

de reacción se inactivo mediante la adición lenta de HCl al 12% (50 mL). La mezcla de reacción se calienta a temperatura ambiente y se agita durante 30 minutos. Las dos capas se separan, y la capa acuosa se lava con EtOAc (50 mL, 3x). Las capas orgánicas combinadas se lavan con $NaHCO_3$ acuoso saturado (50 mL), se secan sobre $MgSO_4$, se filtran y concentran. El residuo resultante se purifica mediante cromatografía flash (EtOAc al 30% en hexanos) para proporcionar (110) (2,09 g, 78%). MS (ES) *m/z* 271,9, 273,9 $(M+H)^+$.

5-(3-bromopiridin-2-il)-1-terc-butil-1*H*-pirazol-4-carboxilato de etilo (111).

El β-keto éter (110) (0,90 g, 3,31 mmol) se disuelve en dimetilformamida dimetilacetal (3 mL), y se calienta a 50 °C durante 15 min. La mezcla de reacción se enfría a temperatura ambiente y se concentra. El residuo resultante se disuelve en EtOH (15 mL) y se agrega clorhidrato de *terc*-butilhidrazina (0,49 g, 4,97 mmol) seguido de tres gotas de HCl concentrado. La mezcla de reacción se agita a temperatura ambiente durante 10 minutos, y luego se calienta en microondas a 150 °C durante 25 min. La mezcla de reacción se concentra. El residuo resultante se disuelve en EtOAc (25 mL) y se lava con H_2O (10 mL) y $NaHCO_3$ acuoso saturado (10 mL). La capa orgánica se seca con $MgSO_4$, se filtra y concentra. El residuo resultante se purifica mediante cromatografía flash (EtOAc al 20% en hexanos) para proporcionar (111) (1,47 g, 60%). MS (ES) *m/z* 351,9, 353,9 $(M+H)^+$.

5-(3-bromopiridin-4-il)-1-terc-butil-1*H*-pirazol-4-carbaldehído (112).

A una solución de (111) (1,00 g, 2,83 mmol) en Et_2O (10 mL) a -78 °C se agrega hidruro de diisobutilaluminio (1M en tolueno, 7,09 mmol). La mezcla de reacción se agita a -78 °C durante 1,5 h, y luego se inactiva con una mezcla 1:1 de Celite y $Na_2S_2O_3 \cdot 5H_2O$ (2,5 g). La mezcla de reacción se agita mientras se calienta a temperatura ambiente y luego se filtra y concentra. El residuo resultante se disuelve en CH_2Cl_2 (20 mL) y se agrega MnO_2 (2,46 g, 28,3 mmol). La mezcla de reacción se agita a temperatura ambiente durante 48 h. La mezcla de reacción se filtra a través de una almohadilla de Celite y se concentra. El residuo resultante se purifica mediante cromatografía flash (EtOAc al 50% en hexanos) para proporcionar (112) (0,27 g, 32%). MS (ES) *m/z* 307,9, 309,9 $(M+H)^+$.

N-((5-(3-bromopiridin-2-il)-1-terc-butil-1*H*-pirazol-4-il)(ciclopropil)metil)-4-(trifluorometil)bencenosulfonamida (113).

A una solución de (112) (0,25 g, 0,81 mmol) en THF (5 mL) se agrega sulfonamida (72) (0,27 g, 1,21 mmol), seguido de isopropóxido de titanio (IV) (0,46 g, 1,62 mmol). La mezcla de reacción se agita a temperatura ambiente durante 18 h. La mezcla de reacción se diluye con EtOAc (10 mL), y luego se inactiva con NaCl acuoso saturado (3 mL). La mezcla de reacción se agita durante 10 minutos, y luego se filtra a través de una almohadilla de Celite. Las dos capas se separan. La capa orgánica se seca con $MgSO_4$, se filtra y concentra. A

una solución del residuo resultante de THF (5 mL) a -78 °C, se agrega lentamente bromuro de ciclopropilmagnesio (0,5M en THF, 16,2 mL, 8,11 mmol). La mezcla de reacción se agita durante 2 h a -78 °C, luego se diluye con EtOAc (20 mL) y se inactiva con $NH_4Cl_{(ac)}$ saturado (10 mL). La mezcla de reacción se calienta a temperatura ambiente y las dos capas se separan. La capa orgánica se lava con NaCl acuoso saturado (15 mL), se seca sobre $MgSO_4$, se filtra y concentra. El residuo resultante se purifica mediante cromatografía flash (EtOAc al 30% en hexanos) para proporcionar (113) (0,17 g, 45% sobre dos pasos). MS (ES) *m/z* 556,9 y 558,9 $(M+H)^+$.

1-terc-butil-4-ciclopropil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c][1,5]naftiridina (114).

Se disuelve sulfonamida (113) (0,82 g, 0,15 mmol) en DMSO (1 mL) y el nitrógeno burbujea durante 1 h. En un frasco individual secado con llama, se combinan yoduro de cobre (0,11 g, 0,59 mmol) y acetato de cesio (0,28 g, 1,48 mmol). El frasco de reacción se vacía, y luego se rellenó con nitrógeno. El proceso de bomba/purga se repite tres veces. Una solución de DMSO de sulfonamida (113) se agrega al frasco de reacción y el frasco se sumerge en un baño de aceite precalentado a 80 °C. La mezcla de reacción se agita durante 1 h a 80 °C, y luego se enfría a temperatura ambiente. La mezcla de reacción se diluye con Et_2O (15 mL) y se lava con agua (10 mL). La capa orgánica se seca sobre $MgSO_4$, se filtra y concentra. El residuo resultante se purifica mediante cromatografía flash (EtOAc al

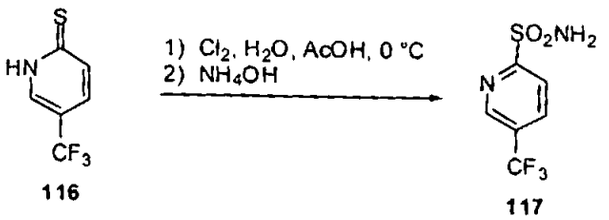
30% en hexanos) para proporcionar (114) (0,05 g, 66%). MS (ES) *m/z* 477,0 $(M+H)^+$.

4-ciclopropil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c][1,5]naftiridina (115).

Se sumerge una solución de (114) (0,05 g, 0,09 mmol) en ácido fórmico (1 mL) en un baño de aceite precalentado a 80 °C. La mezcla de reacción se agita durante 2 h a 80 °C y luego se enfría a temperatura ambiente. La mezcla se concentra y el residuo resultante se disuelve en CH_2Cl_2 (10 mL) y se lava con agua (5 mL). La capa orgánica se seca sobre $MgSO_4$, se filtra y concentra. El residuo resultante se purifica mediante cromatografía flash (EtOAc al 50% en hexanos) para proporcionar (115) (0,03 g, 63%). ^1H NMR (300 MHz, $CDCl_3$) δ 8,62 (dd, *J* = 4,8, 1,2 Hz, 1H), 8,27 (dd, *J* = 8,2, 1,2 Hz, 1H), 7,36 (m, 6H), 5,12 (d, *J* = 7,5 Hz, 1H), 1,05 (m, 1H), 0,45 (m, 2H), 0,19 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147,7, 141,6, 141,0, 136,7, 135,6, 133,5, 129,9, 127,3, 125,5, 125,4, 123,2, 117,7, 58,7, 30,3, 17,0, 3,32, 2,82; MS (ES) *m/z* 420,9 $(M+H)^+$.

Ejemplo 20

5-(Trifluorometil)piridin-2-sulfonamida (117).

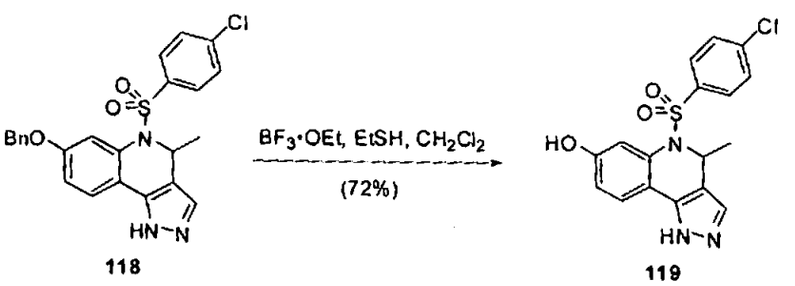


116 117

Se coloca 5-(trifluorometil)piridina-2(1*H*)-tiona (116), 10,0g, 55,8 mmol) en un frasco que contiene 100 mL de agua y 50 mL de ácido acético. La mezcla se enfría a 0 °C y gas de cloro burbujea en la mezcla durante 45-60 minutos. Se agrega agua (100 mL) y se forma un precipitado que se recoge mediante filtración. Este sólido se enfría en un baño de hielo y se enfría también NH_4OH conc. En un frasco de 100 mL en un baño de hielo. Luego de 10 minutos, se agrega una solución enfriada de NH_4OH al sólido y la mezcla se agita durante la noche a temperatura ambiente. La mezcla se extrae luego con Et_2O (100 mL). La capa acuosa se recoge y concentra para dar el producto crudo que se purifica mediante cromatografía de columna en gel de sílice utilizando gradientes de EtOAc/hexanos para proporcionar 1,30 g de (117) (10%) como un sólido blancuzco.

Ejemplo 21

5-(4-Clorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolin-7-ol (119).



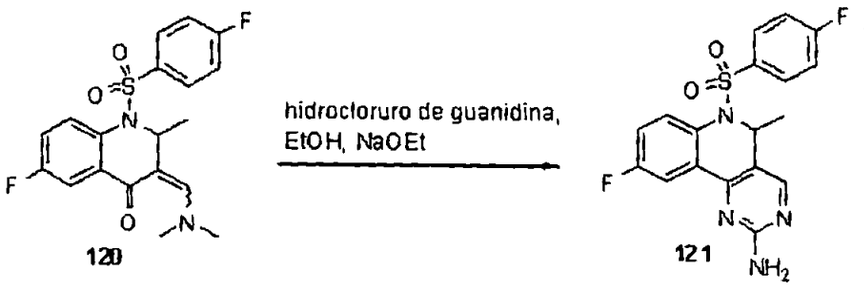
118 119

A una solución de (118) (0,37 g, 0,78 mmol) en CH_2Cl_2 (5 mL) a 0 °C se agrega etanotiol (1 mL) y $BF_3•Et_2O$ (0,39 mL, 3,15 mmol). La mezcla de reacción se agita durante 18 h mientras se calienta a temperatura ambiente. Se agrega una segunda alícuota de $BF_3•Et_2O$ (0,39 mL, 3,15 mmol) y la mezcla de

reacción se calienta a 50 °C durante 3 h. La mezcla se enfría luego a temperatura ambiente, se diluye con EtOAc (10 mL), y se lava con agua (10 mL) y NaCl acuoso saturado (10 mL). La capa orgánica se seca sobre $MgSO_4$, se filtra y concentra. El residuo resultante se purifica mediante HPLC preparativa para proporcionar (119) (0,21 g, 72%). ^{1}H NMR (CD_3CN) δ 7,44 (d, *J* = 8,4 Hz, 1H), 7,27 (s, 1H), 7,17 (d, *J* = 2,5 Hz, 1H), 7,17 (s, 4H), 6,83 (dd, *J* = 8,4, 2,5 Hz, 1H), 6,38 (bs, 1H), 5,57 (q, *J* = 6,9 Hz, 1H), 1,21 (d, *J* = 6,9 Hz, 3H); ^{13}C NMR (75 MHz, CD_3CN) δ 158,1, 139,5, 137,0, 134,8, 129,6, 129,2, 127,2, 124,6, 118,2, 117,8, 117,2, 116,0, 55,2, 50,9, 23,3; MS (ES) *m/z* 375,9 $(M+H)^+$.

Ejemplo 22

9-fluoro-6-(4-fluorofenilsulfonil)-5-metil-5,6-dihidropirimido[5,4-C]quinolin-2-amina (121).



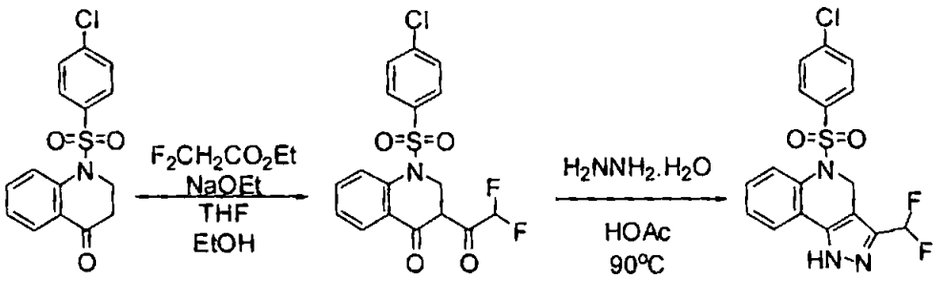
120 121

Se agrega una solución de clorhidrato de guanidina (0,49 mmol) y NaOEt (21% p en EtOH, 1,34 mmol) al frasco de reacción que contenía compuesto (120) (0,45 mmol) en EtOH (1,5 ml). El frasco se calienta durante 5 minutos a 100 °C en un microondas y se filtra subsiguientemente y se purifica mediante HPLC preparativa para proporcionar el compuesto (121) (27%). ^{1}H NMR (CD_3OD) δ 8,13 (s, 1H), 7,85-7,79 (m, 2H), 7,51-7,45 (m, 1H),

7,34-7,29 (m, 2H), 7,17-7,12 (m, 1H), 7,02-6,96 (m, 2H), 6,76-6,69 (m, 1H), 5,57-5,5$_0$ (q, J = 6,9 Hz, 1H), 1,31-1,28 (m, 3H). MS *m/z* 388,9 $(M+H)^+$.

Ejemplo 23

5-(4-Clorofenilsulfonil)-3-(difluorometil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina (123)



5 **122** **123**

1-(4-Clorofenilsulfonil)-3-(2,2-difluoroacetil)-2,3-dihidroquinolin-4(1*H*)-ona (122).

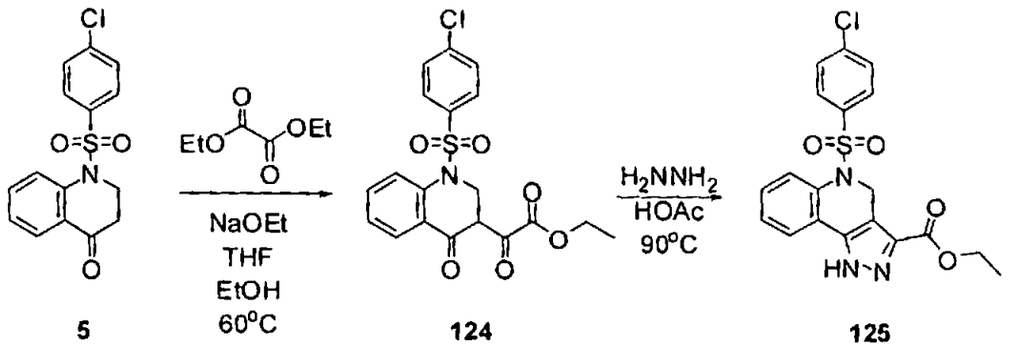
Se disuelve cetona (5) (481 mgs, 1,5 mmol) en difluoroacetato de etilo (3,15 mL, 30 mmol), THF (1 mL) y etanol seco (1 mL). A la mezcla de reacción se agrega etóxido de sodio al 21% en etanol (1,68 mL, 4,5 mmol). La solución se agita entonces a temperatura ambiente. Luego de 4h, el análisis por LC-MS muestra conversión parcial y la reacción continúa a temperatura ambiente durante 14h adicionales. La evaporación de la mezcla de reacción de color ámbar bajo una corriente de nitrógeno produjo el (122) intermedio, MS (ES) *m/z* 422,0 $(M+Na)^+$.

5-(4-Clorofenilsulfonil)-3-(difluorometil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina (123) .

A una suspensión de (122) intermedio (239 mgs, 0,6 mmol) y ácido acético glacial (3 mL) se agrega hidrazina anhidra (30 µL, 0,6 mmol). La solución se agita bajo nitrógeno y se calienta a 90 °C durante 3h, seguido de enfriamiento a temperatura ambiente. Luego del consumo completo de (87) mediante LC-MS, la mezcla de reacción se evapora mediante evaporación rotatoria. El residuo resultante se disuelve en acetonitrilo (5 mL) y se purifica mediante HPLC preparativa de fase inversa, lo que produjo 172 mgs del compuesto (123). MS (ES) *m/z* 396,0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7,90-7,83 (m, 2H), 7,52-7,43 (m, 1H), 7,42-7,35 (m, 2H), 7,27 (m, 1H), 7,19-7,04 (m, 3H), 5,05 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 139,2, 138,8, 135,8, 134,4, 129,5, 129,4, 128,4, 128,3, 128,0, 122,1, 121,7, 113,9, 110,8, 110,7, 107,7, 50,6, 42,8.

Ejemplo 24

5-(4-Clorofenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolin-3-carboxilato de etilo (125)



5 124 125

2-(1-(4-Clorofenilsulfonil)-4-oxo-1,2,3,4-tetrahidroquinolin-3-il)-2-oxoacetato de etilo (124).

Se disuelve la cetona (5) (963 mgs, 3,0 mmol) en oxalato de dietilo (4,1 mL, 30 mmol), THF (2 mL) y etanol seco (2 mL). A la mezcla de reacción se agrega etóxido de sodio al 1% en etanol (3,36 mL, 9,0 mmol). La solución se coloca bajo nitrógeno y se deja agitar a temperatura ambiente durante 1h, seguido de calentamiento a 60 °C durante 1h. La mezcla resultante se concentra mediante evaporación rotatoria, se disuelve en MeOH (14 mL) y se purifica mediante HPLC preparativa de fase inversa para proporcionar 260 mgs de compuesto (124). MS (ES) *m/z* 421,9 $(M+H)^+$.

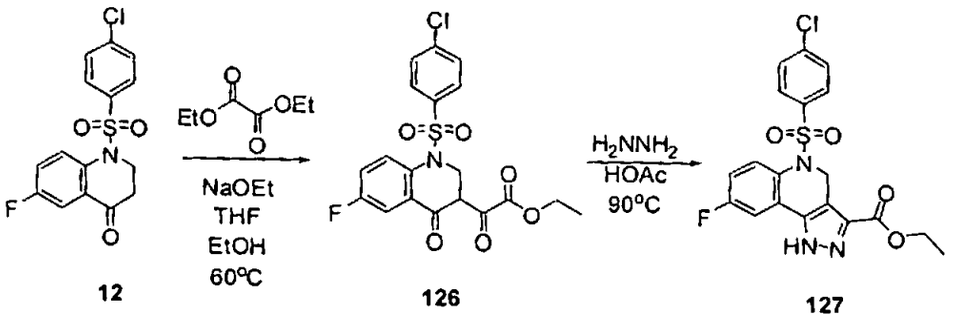
5-(4-Clorofenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolin-3-carboxilato de etilo (125).

A una suspensión de (124) intermedio (260 mgs, 0,62 mmol) y ácido acético glacial (2 mL) se agrega hidrazina anhidra (35 µL, 0,62 mmol). La solución se agita bajo nitrógeno y se calienta a 90 °C durante 6h, seguido de enfriamiento a temperatura ambiente. Luego del consumo completo de (124) mediante LC-MS, la mezcla de reacción se evapora mediante evaporación rotatoria. El residuo resultante se disuelve en metanol (6 mL) y se purifica mediante HPLC preparativa de fase inversa, lo que produce 107 mgs de compuesto (125). MS (ES) *m/z* 417,9 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7,84-7,80 (dd, 2H), 7,74-7,74 (dd, 2H), 7,49-7,38 (m, 2H), 7,17-7,04 (m, 2H), 5,10 (s, 2H), 4,54-4,47 (q, 2H), 1,53-1,48 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 159,0, 145,2, 139,4, 136,0, 134,9, 129,9, 129,7, 129,3, 129,0,

128,4, 128,3, 128,2, 128,1, 124,3, 122,7, 115,6, 62,0, 43,1, 14,4.

Ejemplo 25

5-(4-Clorofenilsulfonil)-8-fluoro-4,5-dihidro-2*H*-pirazol[4,3-c]quinolin-3-carboxilato de etilo (127).



12 126 127

2-(1-(4-Clorofenilsulfonil)-6-fluoro-4-oxo-1,2,3,4-tetrahidroquinolin-3-il)-2-oxoacetato de etilo (126).

La cetona (12) (1017 mgs, 3,0 mmol) se calienta a disolución en oxalato de dietilo (4,1 mL, 30 mmol), THF (2 mL) y etanol seco (2 mL). A la mezcla de reacción se agrega etóxido de sodio al 21% en etanol (3,36 mL, 9,0 mmol). La solución se agita bajo nitrógeno a temperatura ambiente durante 1h, seguido de calentamiento a 60 °C durante 1h. La mezcla resultante se concentra mediante evaporación rotatoria y lleva al paso siguiente en forma cruda. Compuesto (126) MS (ES) *m/z* 440,0 $(M+H)^+$.

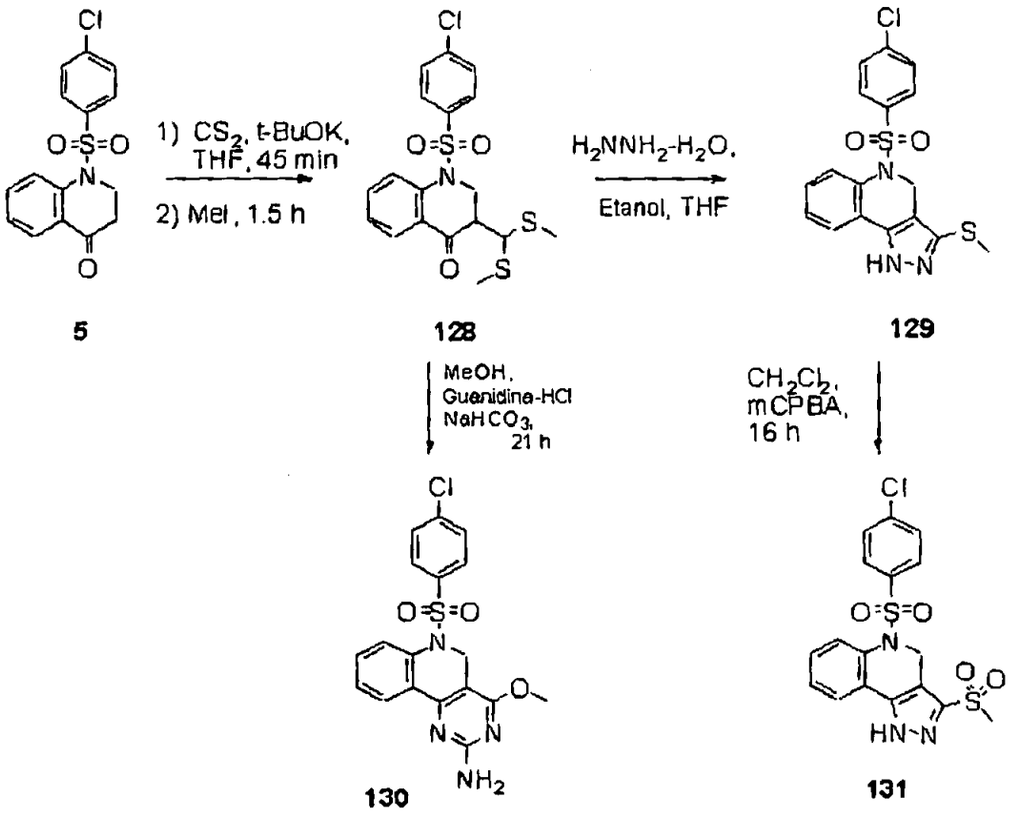
5-(4-Clorofenilsulfonil)-8-fluoro-4,5-dihidro-2*H*-pirazol[4,3-c]quinolin-3-carboxilato de etilo (127).

A una suspensión de (126) intermedio (3,0 mmol) y ácido acético glacial (10 mL) se agrega hidrazina anhidra (168 µL, 3,0 mmol). La solución se agita bajo nitrógeno y se calienta a 90 °C durante 5h, seguido de enfriamiento a temperatura

ambiente. Luego del consumo completo de (126) mediante LC-MS, la mezcla de reacción se evapora mediante evaporación rotatoria. El residuo resultante se disuelve en metanol (12 mL) y se purifica mediante HPLC preparativa de fase inversa, lo que produce 379 mgs de compuesto (127). MS (ES) *m/z* 435,9 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7,81-7,76 (dd, 2H), 7,47-7,43 (dd, 2H), 7,16-7,06 (m, 3H), 5,07 (s, 2H), 4,54-4,46 (q, 2H), 1,53-1,48 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 163,5, 160,2, 159,0, 139,4, 135,8, 131,0, 130,9, 130,7, 128,4, 128,3, 116,0, 115,7, 115,6, 109,7, 109,4, 61,9, 50,8, 43,1, 14,4.

Ejemplo 26

5-(4-Clorofenilsulfonil)-3-(metilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina (131).



3-(bis(metiltio)metil)-1-(4-Clorofenilsulfonil)-2,3-dihidroquinolin-4(1*H*)-ona (128)

Se trata una solución de (5) (506 mg, 1,57 mmol) y disulfuro de carbono (239 mg, 0,189 mL, 3,15 mmol) en tetrahidrofurano (10 mL) con terc-butóxido de potasio (441 mg, 3,93 mmol) y se agita durante 45 min. La mezcla se trata luego con yodometano (1,12g, 0,49 mL), 7,9 mmol) y se agita a temp. ambiente durante 1,5 h. La mezcla se diluye con bicarbonato de sodio ac. saturado (25 mL) y se extrae con acetato de etilo (2 x 25 mL). Los extractos orgánicos combinados se lavan con agua (20 mL) y solución salina (10 mL), luego se secan (sulfato de sodio), se filtran y evaporan al vacío para dar (128) como un aceite amarillo (645 mg, bruto - 92%).

5-(4-Clorofenilsulfonil)-3-(metiltio)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina (129

El ceteno ditioacetal (128) (615 mg, 1,44 mmol) se absorbió en etanol (10 mL) y se trató con hidrato de hidrazina (87 mg, 0,084 mL, 1,73 mmol). Se agrega tetrahidrofurano (2 mL) para dar una solución homogénea, que se agita durante 4 h. La mezcla se diluye con agua (25 mL) y se extrae con acetato de etilo (2 X 25 mL). Los extractos orgánicos combinados se lavan con agua (25 mL) y solución salina (10 mL), luego se secan (sulfato de sodio), se filtran y evaporan al vacío para dar un residuo bruto que se purifica mediante cromatografía flash de gel de sílice (hexanos/acetato de etilo 2:1 eluidos) para dar (129) (373 mg, 66%) como un sólido tostado. Espectro de masa: MS (ES) *m/z* 392,0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7,81 (d, J = 7,7 Hz,

1H), 7,60 (m, 1H), 7,45-7,34 (m, 2H), 7,16 (d, J = 8,2 Hz, 2H), 7,08 (d, J = 8,2 Hz, 2H), 4,87 (s, 2H), 2,41 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 139,2, 136,3, 134,9, 129,1, 128,9, 128,4, 128,0, 122,4, 42,7.

5-(4-Clorofenilsulfonil)-3-(metilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina (131)

Se trató una solución de (129) (307 mg, 0,78 mmol) en cloruro de metileno (10 mL) con mCPBA (ensayo: 77%, 527 mg, 2,35 mmol) y se agita durante 16 h. La mezcla se diluye con acetato de etilo (50 mL) y se lava con bicarbonato de sodio acuoso diluido (2 x 25 mL). Se removieron los volátiles al vacío y el residuo se purifica mediante cromatografía flash sobre gel de sílice (hexanos/etilo acetato 1:1 eluidos) para dar (131) como un sólido blanco (290 mg, 87%) Espectro de masa: MS (ES) *m/z* 424,0 $(M+H)^+$. ^1H NMR (DMSO d_6) δ 7,75 (m, 1H), 7,65-7,54 (m, 3H), 7,35 (d, J = 8,8 Hz, 2H), 7,12 (d, J = 8,2 Hz, 2H), 5,11 (s, 2H), 3,33 (s, 3H). ^{13}C NMR (DMSO d_6) δ 133,7, 130,7, 128,7, 128,1, 124,8, 124,1, 124,1, 123,8, 123,7, 123,3, 117,9, 38,6, 37,6.

6-(4-Clorofenilsulfonil)-4-metoxi-5,6-dihidropirimido[5,4-C]quinolin-2-amina (130)

Se absorbe el ceteno ditioacetal (128) (0,58g, 1,36 mmol) en metanol (10 mL) y se trata con clorhidrato de guanidina (0,260 g, 2,77 mmol). La mezcla se agita durante 16 h con lo cual el análisis por TLC indica que no se ha producido condensación alguna. Se agrega bicarbonato de sodio (300 mg) y la mezcla se calienta a reflujo durante 21 h. La mezcla se enfría a temp.

ambiente y se diluye con agua (15 mL); luego se extrae con acetato de etilo (3 x 25 mL). Los extractos se secan (sulfato de sodio), se filtran y concentran al vacío para dar un residuo, que se purifica mediante cromatografía de gel de sílice (hexanos/etilo acetato 1:1 eluidos) para dar 190 mg de (130). MS *m/z* 403,0 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 7,98 (dd, *J* = 1,1, 7,7 Hz, 1H), 7,75 (d, *J* = 8,2 Hz, 1H), 7,51 (m, 1H), 7,39 (m, 1H), 7,18 (d, *J* = 8,8 Hz, 2H), 7,10 (d, *J* = 8,8 Hz, 2H), 4,87 (br s, 2H), 4,76 (s,2H), 3,92 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 166,0, 162,9, 156,6, 139,5, 137,8, 136,5, 131,1, 128,9, 128,6, 128,2, 128,0, 127,7, 125,3, 99,9, 53,7, 42,4.

Ejemplo 27

5-(4-Clorofenilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolin-3-ol.

Preparado mediante tratamiento de 1-(4-Clorofenilsulfonil)-4-oxo-1,2,3,4-tetrahidroquinolin-3-carboxilato de etilo, que se prepara a partir del compuesto (5) utilizando fosfonoformiato de trietilo y NaH en THF, con hidrazina en AcOH. MS *m/z* 361,9 $(M+H)^+$. ^1H NMR (CD_3OD) δ 7,74 (m, 1H), 7,42-7,37 (m, 3H), 7,25-7,16 (m, 4H), 4,82 (s, 4H).

Ejemplo 28

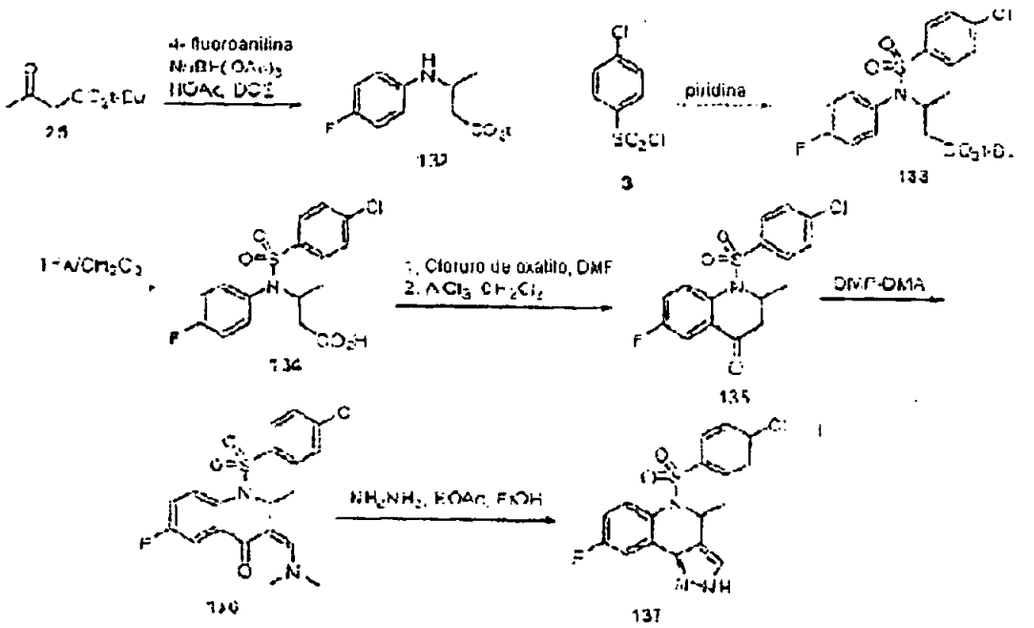
8-fluoro-4-metil-5-(piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina.

Preparado como se describe en el Ejemplo 10 utilizando cloruro de 3-piridinsulfonilo y 3-(4-fluorofenilamino)butanoato de terc-butilo, que se prepara del compuesto (25) y 4-fluoroanilina como se describe para el compuesto (26) en el

Ejemplo 4. MS *m/z* 345,0 $(M+H)^+$. ^1H NMR (CD_3OD) δ8,52-8,50 (dd, J = 4,9, 1,3 Hz, 1H), 8,30-8,29 (d, J = 1,8 Hz, 1H), 7,81-7,77 (dd, J = 8,9, 4,9 Hz, 1H), 7,61-7,57 (m, 1H), 7,46 (s, 1H), 7,37-7,33 (dd, J = 8,7, 3,0 Hz, 1H), 7,27-7,17 (m, 2H), 5,76-5,73 (q, J = 6,9 Hz, 1H), 1,29-1,27 (d, J = 6,9 Hz, 3H).

Ejemplo 29

5-(4-Clorofenilsulfonil)-8-fluoro-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina (149).



3-(4-fluorofenilamino)butanoato de terc-butilo (132). A una solución de 1,2-dicloroetano (146 mL) de 4-fluoroanilina (4.06 g, 36.5 mmol) se agrega acetoacetato de terc-butilo (25) (6.05 mL, 36.5 mmol) y ácido acético glacial (3.0 mL, 47.5 mmol). Se agrega en porciones Triacetoxiborohidruro de sodio (11.6 g, 54.8 mmol) y la reacción se agita durante la noche a temperatura ambiente. Se agrega lentamente $NaHCO_3$ acuoso saturado (250 mL) y la solución de dos fases también se agita.

La porción orgánica separada se lava con $NaHCO_3$ ac. Sat (1 x 100 mL), agua (1 x 100 mL), solución salina (1 x 20 mL), se seca ($MgSO_4$), se filtra y se concentra para producir 132 (9.03 g, 98%) como un aceite. MS m/z: $(M+H)^+$ = 254.1.

3-(4-cloro-N-(4-fluorofenil)fenilsulfonamido)butanoato de terc-butilo (133). A una solución del compuesto 132 (3.08 g, 12.2 mmol) en piridina (35 mL) a 0° C se agrega cloruro de 4-clorobencenosulfonilo (3) (8.98 g, 42.6 mmol) en forma de porciones. La reacción se calienta a temperatura ambiente y luego se calienta a 70° C durante 5.5 horas luego se enfría a temperatura ambiente. Se agrega dimetilaminopropilamina (~ 40 mL) a la mezcla de reacción que luego se agita durante la noche. La mezcla de reacción luego se concentra y el residuo se toma a EtOAc (120 mL). La fase orgánica se lava con con 1N de HCl frío (6 x 100 mL), agua (1 x 100 mL), NaHCO3 ac. Sat (3 x 100 mL), solución salina (1 x 100 mL), se seca ($MgSO_4$), se filtra, y se concentra para producir éster como un aceite 133 (5.2 g, 99%). MS m/z: $(M+Na)^+$ = 450.1.

Ácido 3-(4-Cloro-N-(4-fluorofenil)fenilsulfonamido)butanoico (134). A una solución del éster 133 (5.19 g, 12.13 mmol) en CH_2Cl_2 (10 mL) a 0° C se agrega TFA (35 mL). La mezcla de reacción se le permite calentar a temperatura ambiente, se agita durante la noche y luego se concentra para dar 134 (4.7 g, 105%) como un aceite. MS m/z: $(M+H)^+$ = 372.1.

1-(4-Clorofenilsulfonil)-6-fluoro-2-metil-2,3-dihidroquinolin-4(1H)-ona (135). A una solución enfriada en hielo de 134 (3.91 g, 10.52 mmol) en CH_2Cl_2 (45 mL) y DMF (4 gotas) se agrega cloruro de oxalilo en forma de gotas (3.67 mL, 42.10 mmol). La solución resultante se agita a -5° C durante 15 minutos y luego se calienta a temperatura ambiente y es agitada durante 3 horas. La mezcla de reacción luego se concentra y el residuo se toma en éter de dietilo, se filtra a través de un tapón de lana de vidrio, y se concentra para dar el cloruro ácido (4.09, 99%). Una solución CH_2Cl_2 (20 mL) de cloruro ácido se agrega en forma de gotas durante un operiodo de 20 minutos. A una suspensión enfriada (-5° C) de $AlCl_3$ (1.81 g, 13.6 mmol) en CH_2Cl_2 (20 mL). Después de agitar a 0° C durante una hora la reacción se calienta a temperatura ambiente y se agita durante la noche.

La mezcla de reacción luego se enfría en un baño de hielo al que se agrega 10% HCl (15 mL) en forma de gotas durante 15 minutos. La porción ogánica se lava con 10% HCl (2 x 50 mL), agua (1 x 20 mL), $NaHCO_3$ ac. Sat (3 x 50 mL), solución salina (1 x 20 mL), se seca ($MgSO_4$), se filtra, y se concentra. El producto crudo luego se disuelve en THF (40 mL) al que se le agrega $NaHCO_3$ ac. sat (40 mL). Esta mezcla se agita durante 7 horas y luego se concentra. El residuo se toma en agua y EtOAc. La capa acuosa se extrae con EtOAc (4 x 30 mL) y los

extractos combinados EtOAc se lavan con solución salina (1 x 20 mL), se secan ($MgSO_4$) se filtran, y se concentran para dar el producto crudo que se purifica mediante cromatogafía flash eluyendo con 8:1 hexanos/EtOAc para dar 135 (980 mg, 26%). MS m/z: $(M+H)^+$ = 354.2.

5-(4-Clorofenilsulfonil)-8-fluoro-4-metil-4,5-dihidro-2H-pirazolo [4,3-c]quinolina (137). Una solución de dimetil acetal dimetilformamida (5.2 mL) 135 (922 mg, 2.61 mmol) se calienta a 100° C durante C 3 horas. El análisis HPLC/MS de la mezcla de reacción determina que no permanece material de partida así que la reacción se enfría a temperatura ambiente y se vierte en EtOAc (50 mL) y agua (50 mL). La porción orgánica se lava con agua (3 x 50 mL), solución salina (1 x 20 mL), se seca ($MgSO_4$), se filtra y se concentra para dar 136 como una espuma roja que se utliza directamente en la siguiente reacción. A una solución de EtOH/HOAc glacial (25 : 1 v/v, 12 mL) de 136 (982 mg, 2.40 mmol) se agrega hidrato de hidrazina (582 mL, 12.0 mmol). La mezcla de reacción se agita durante la noche a temperatura ambiente, se concentra, y el residuo se toma en EtOAc (20 mL). La fase orgánica se lava con $NaHCO_3$ ac. Sat (3 x 25 mL), solución salina (1 x 20 mL), se seca (MgSO4), se filtra y se concentra. El producto crudo se purifica mediante cromatogafía flash eluyendo con 2:1 hexanos/EtOAc para dar 137 como un sólido amarillo. ^1H RMN ($CDCl_3$) δ 7.81-7.76 (m, 1H), 7.37 (dd, J = 8.5, 2.7 Hz, 1H), 7.21 (s, 1H),

7.13-7.04 (m, 5H), 5.60 (q, J= 6.6 Hz), 1.28 (d, J= 7.1 Hz, 3H); MS: $(M+H)^+$ = 378.0.

Ejemplo 30

8-Fluoro-4-metil-5-(piridin-2-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina. Preparada como se describe en el Ejemplo 10 utilizando 3-(4-fluorofenilamino)butanoato de terc-butilo, que se preparó a partir del compuesto (25) y 4-fluoroanilina como se describe para el compuesto (26) en el Ejemplo 4. MS *m/z* 345 $(M+H)^+$. ^1H RMN (CD_3OD) δ 8,25-8,24 (m, 1H), 7,78-7,68 (m, 2H), 7,44-7,32 (m, 4H), 7,22-7,10 (m, 2H), 5,75-5,68 (q, J = 6,9 Hz, 1H), 1,28-1,26 (d, J = 6,9 Hz, 3H).

Ejemplo 31

5-(4-Clorofenilsulfonil)-8-fluoro-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina. (Enantiómeros A y B) Preparado como se describe en el Ejemplo 4 utilizando 4-fluoroanilina seguido de separación cromatográfica utilizando el tipo de columna especificado y se analiza utilizando el Método 16.

Enantiómero A Tiempo de retención = 9,8 min.

Enantiómero B Tiempo de retención = 27,1 min.

MS *m/z* 378,0 $(M+H)^+$. ^1H-RMN ($CDCl_3$) δ 7,81-7,76 (m, 1H), 7,37 (dd, J = 8,5, 2,7 Hz, 1H), 7,21 (s, 1H), 7,13-7,04 (m, 5H), 5,60 (q, J = 6,6 Hz), 1,28 (t, J = 7,1 Hz, 3H).

Ejemplo 32

4-Metil-5-(piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina. Preparada como se describe en el Ejemplo 10

utilizando cloruro de 3-piridinsulfonilo en lugar del compuesto (50). MS *m/z* 327,0 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 8,45-8,43 (m, 2H), 7,86-7,83 (dd, J = 7,8, 1,3 Hz, 1H), 7,66-7,63 (dd, J = 7,4, 1,6 Hz, 1H), 7,47-7,28 (m, 4H), 7,03-6,99 (m, 1H), 5,75-5,68 (q, J = 6,9 Hz, 1H), 1,35-1,33 (d, J = 6,9 Hz, 3H).

Ejemplo 33

8-Fluoro-4-metil-5-(piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina. (Enantiómeros A y B)

Preparado como se describe en el Ejemplo 10 utilizando cloruro de 3-piridinsulfonilo y 3-(4-fluorofenilamino)butanoato de terc-butilo, que se prepara del compuesto (25) y 4-fluoroanilina como se describe para el compuesto (26) en el Ejemplo 4 seguido de separación cromatográfica utilizando el tipo de columna especificado y se analiza utilizando el Método 15.

Enantiómero A Tiempo de retención = 15,2 min.

Enantiómero B Tiempo de retención = 17,5 min

MS *m/z* 345 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 10,16 (s, 1H), 8,48-8,45 (d, J = 10,4 Hz, 2H), 7,83-7,79 (dd, J = 8,9, 5,0 Hz, 1H), 7,36-7,28 (m, 3H), 7,16-7,05 (m, 2H), 5,75-5,68 (q, J = 6,9 Hz, 1H), 1,34-1,31 (d, J = 6,9 Hz, 3H).

Ejemplo 34

5-(Piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina. Preparada como se describe en el Ejemplo 1

utilizando cloruro de 3-piridinsulfonilo en lugar del compuesto (3).

^{1}H-RMN ($CDCl_3$) δ 8,47 (br s, 2H), 7,82 (d, J = 7,6 Hz, 1H), 7,66 (d, J = 6,0 Hz, 1H), 7,45-7,39 (m, 2H), 7,31-7,28 (m, 3H), 7,03-6,99 (m, 1H), 4,99 (s, 2H).

Ejemplo 35

8-Fluoro-5-(piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina. Preparada como se describe en el Ejemplo 2 utilizando cloruro de 3-piridinsulfonilo en lugar del compuesto (3).

^{1}H RMN (CD_3OD) δ 8,50-8,49 (1H, d), 8,27 (1H, s), 7,82-7,77 (1H, dd), 7,56-7,53 (1H, d), 7,46 (1H, s), 7,35-7,32 (1H, d), 7,24-7,17 (2H, m), 5,00 (2H, s).

Ejemplo 36

8-Fluoro-4-metil-5-(piridin-2-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina. (Enantiómeros A y B). Preparado como se describe en el Ejemplo 10 utilizando 3-(4-fluorofenilamino)butanoato de *terc*-butilo, que se prepara a partir del compuesto (25) y 4-fluoroanilina como se describe para el compuesto (26) en el Ejemplo 4. Se separan luego los enantiómeros utilizando el tipo de columna especificado y se analizan utilizando el Método 15.

Enantiómero A Tiempo de retención = 16,3 min.

Enantiómero B Tiempo de retención = 21,4 min.

MS m/z 345,0 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 8,31-8,30 (d, J = 4,6 Hz, 1H), 7,83-7,78 (dd, J = 8,9, 5,1 Hz, 1H), 7,60-7,55 (td, J = 7,8, 1,6 Hz, 1H), 7,39-7,33 (m, 2H), 7,23-7,19 (m, 1H), 7,10-7,04 (td, J = 8,7, 2,9 Hz, 1H), 5,83-5,76 (q, J = 6,9 Hz, 1H), 1,34-1,32 (d, J = 6,9 Hz, 3H).

Ejemplo 37

4-Metil-5-(piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina. (Enantiómeros A y B). Preparado como se describe en el Ejemplo 10 utilizando cloruro de 3-piridinsulfonilo en lugar del compuesto (50) seguido de separación cromatográfica utilizando el tipo de columna especificado y se analiza utilizando el Método 15.

Enantiómero A Tiempo de retención = 13,5 min.

Enantiómero B Tiempo de retención = 14,6 min.

MS m/z 326,9 $(M+H)^+$. ^1H RMN ($CDCl_3$) d 9,44 (s, 1H) 8,48-8,43 (m, 2H), 7,86-7,83 (dd, J = 8,0, 1,3 Hz, 1H), 7,64-7,61 (dd, J = 7,4, 1,6 Hz, 1H), 7,47-7,28 (m, 4H), 7,04-7,00 (dd, J = 8,0, 4,9 Hz, 1H), 5,75-5,68 (q, J = 6,9 Hz, 1H), 1,35-1,33 (d, J = 6,9 Hz, 3H).

Ejemplo 38

8-Fluoro-5-(4-fluorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina.

Preparado como se describe en el Ejemplo 4 utilizando cloruro de 4-fluoroanilina y 4-fluorofenilsulfonilo. MS *m/z* 361,9

$(M+H)^+$. ^1H RMN ($CDCl_3$) δ 7,84-7,79 (dd, J = 5,1, 3,8 Hz, 1H), 7,38-7,34 (dd, J = 5,5, 2,9 Hz, 1H), 7,23 (s, 1H), 7,22-7,16 (m, 2H), 7,15-7,08 (dt, J = 5,7, 2,9 Hz, 1H), 6,80-6,75 (m, 2H), 5,67-5,60 (q, J = 6,9 Hz, 1H), 1,33-1,30 (d, J = 6,8, 3H).

Ejemplo 39

4-metil-5-(piridin-2-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina.

Preparado como se describe en el Ejemplo 10 seguido de separación cromatográfica utilizando el tipo de columna especificado y se analiza utilizando el Método 21. Tiempo de retención = 7,9.

MS *m/z* 373,9 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 8,31-8,30 (d, J = 4,6 Hz, 1H), 7,84-7,81 (dd, J = 8,0, 1,0 Hz, 1H), 7,65-7,62 (dd, J = 7,4, 1,5 Hz, 2H), 7,57-7,51 (td, J = 7,8, 1,7 Hz, 1H), 7,41-7,30 (m, 3H), 7,20-7,16 (m, 1H), 5,85-5,78 (q, J = 6,9 Hz, 1H), 1,35-1,33 (d, J = 6,9 Hz, 3H).

Ejemplo 40

5-(4-Clorofenilsulfonil)-4-ciclopropil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina.

Preparado como se describe en el Ejemplo 12 utilizando ácido 2-bromofenilborónico en lugar del compuesto (70). MS *m/z* 386 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 8,88 (s, 1H), 7,91 (dd, J=7,8, 1,2 Hz, 1H), 7,62 (dd, J=7,8, 1,5 Hz, 1H), 7,49 (dt, J=7,8, 1,5 Hz, 1H), 7,39 (dt, J=7,8, 1,2 Hz, 1H), 7,34 (s, 1H), 7,06 (s, 4H),

4,95 (d, J=8,4 Hz, 1H), 1,02 (m, 1H), 0,44 (amplio m, 3H), 0,14 (m, 1H).

Ejemplo 41

5-(4-Clorofenilsulfonil)-4-isopropil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina.

Preparado como se describe en el Ejemplo 12 utilizando ácido 2-bromofenilborónico y bromuro de isopropilmagnesio. MS *m/z* 388,0 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 7,86 (dd, J=7,5, 0,9 Hz, 1H), 7,58 (dd, J=7,5, 1,5 Hz, 1H), 7,48 (dt, J=7,5, 1,5 Hz, 1H), 7,39 (dt, J=7,5, 0,9 Hz, 1H), 7,33 (s, 1H), 7,05 (s, 4H), 4,94 (d, J=9,6 Hz, 1H), 1,51 (m, 1H) 1,09 (d, J=7,2 Hz, 3H), 0,83 (d, J=6,3 Hz, 3H).

Ejemplo 42

8-fluoro-5-(4-fluorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina. (Enantiómeros A y B)

Preparado como se describe en el Ejemplo 4 utilizando cloruro de 4-fluoroanilina y 4-fluorofenilsulfonilo seguido de separación cromatográfica utilizando el tipo de columna especificado y se analiza utilizando el Método 17.

Enantiómero A Tiempo de retención = 7,6 min.

Enantiómero B Tiempo de retención = 10,1 min.

MS *m/z* 361,9 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 7,83-7,78 (dd, J = 5,1, 3,8 Hz, 1H), 7,34-7,30 (dd, J = 5,5, 2,9 Hz, 1H), 7,22 (s,

Ejemplo 52

4-ciclopropil-5-(4-fluorofenilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina. Preparada como se describe en el Ejemplo 12 utilizando ácido 2-bromofenilborónico y 4-fluorofenilsulfonamida. MS *m/z* 371,0 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 7,91 (d, J = 8,6 Hz, 1H), 7,62 (d, J = 7,6 Hz, 1H), 7,48-7,35 (m, 2H), 7,30-7,28 (m, 2H), 7,18-7,11 (m, 1H), 6,74 (dd, J = 9,1, 7,2 Hz, 2H), 4,96 (d, J = 7,6 Hz, 1H), 1,14-0,08 (m, 1H), 0,58-0,32 (m, 3H), 0,20-0,11, 1H).

Ejemplo 53

5-(5-Clorotiofen-2-ilsulfonil)-4-ciclopropil-7,8-difluoro-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina. (Enantiómeros A y B).

Preparada como se describe en el Ejemplo 12 utilizando 5-Clorotiofen-2-sulfonamida seguido de separación cromatográfica utilizando el tipo de columna especificado y se analiza utilizando el Método 22.

Enantiómero A Tiempo de retención = 10,3 min.

Enantiómero B Tiempo de retención = 16,1 min.

MS *m/z* 428,0 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 9,97 (amplios, 1H), 7,70 (dd, J = 11,4, 7,2 Hz, 1H), 7,57 (dd, J = 10,2, 8,7 Hz, 1H), 7,31 (s, 1H), 6,70 (d, J = 4,8 Hz, 1H), 6,56(d, J = 4,8 Hz, 1H), 4,98 (d, J = 7,5 Hz, 1H), 1,03 (m, 1H), 0,53 (m, 1H), 0,40 (m, 2H), 0,10 (m, 1H).

Ejemplo 56

5-(4-Clorofenilsulfonil)-4-etil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina.

Preparada mediante ciclización de ácido 3-(4-Cloro-N-fenilfenilsulfonamido)pentanoico, que se prepara como se describe para el compuesto (27) utilizando 3-oxopentanoato de metilo seguido de hidrólisis con NaOH, en la forma que se describe para el compuesto 55 seguido de la formación de pirazol según se muestra en el Ejemplo 10. MS *m/z* 373,9 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 7,90 - 7,87 (dd, J = 8,1, 0,9 Hz, 1H), 7,66 - 7,63 (dd, 7,7, 1,4 Hz, 1H), 7,56 - 7,39 (m, 3H), 7,14 - 7,11 (m, 4H), 5,39 - 5,34 (ABq, J = 8,5, 6,8 Hz, 1H), 1,67 - 1,43 (m, 2H), 1,02 - 0,95 (t, J = 7,3 Hz, 3H).

Ejemplo 57

5-(4-Clorofenilsulfonil)-4-metil-4,5,5a,6,7,8,9,9a-octahidro-1*H*-pirazol[4,3-c]quinolina.

Preparada por sulfonilación de 2-metilo Ctahidroquinolin-4(1H)-ona seguido de la formación de pirazol como se describe en el Ejemplo 1. MS *m/z* 365,9 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 7,80-7,76 (m, 2H), 7,55 (s, 1H), 7,49-7,45 (m, 2H), 4,21-4,15 (m, 1H), 3,15-3,06 (dt, J = 7,9, 2,4 Hz, 1H), 2,95-2,88 (dt, J = 7,9, 2,4 Hz, 1H), 1,95-1,92 (m, 1H), 1,80-1,70 (m, 3H), 1,56-1,55 (m, 1H), 1,51-1,48 (d, J = 7,0 Hz, 3H), 1,40-1,28 (m, 3H).

Ejemplo 58

5-(4-Clorofenilsulfonil)-9-fluoro-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina. Preparada como se describe en el Ejemplo 4 utilizando 3-fluoroanilina. MS *m/z* 378,0 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 7,70 (d, J = 8,10 Hz, 1H), 7,37 (m, 1H), 7,32 (s, 1H), 7,16-7,04 (m, 5H), 5,70 (q, J = 6,90 Hz, 1H), 1,33 (d, J = 6,93 Hz, 3H).

Ejemplo 59

5-(4-Clorofenilsulfonil)-7-fluoro-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina.

Preparado como se describe en el Ejemplo 4 utilizando 3-fluoroanilina. MS *m/z* 378,0 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 10,40 (br s, 1H), 7,58-7,69 (m, 2H), 7,28-7,16 (m, 3H), 7,11-7,05 (m, 3H), 5,65 (q, J = 6,90 Hz, 1H), 1,33 (d, J = 6,90 Hz, 3H).

Ejemplo 60

5-(4-Clorofenilsulfonil)-4-ciclopropil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina. Preparada como se describe en el Ejemplo 12 utilizando ácido 2-bromofenilborónico en lugar del compuesto (70). MS *m/z* 386,0 $(M+H)^+$. ^1H RMN ($CDCl_3$) d 8,88 (s, 1H), 7,91 (dd, J=7,8, 1,2 Hz, 1H), 7,62 (dd, J=7,8, 1,5 Hz, 1H), 7,49 (dt, J=7,8, 1,5 Hz, 1H), 7,39 (dt, J=7,8, 1,2 Hz, 1H), 7,34 (s, 1H), 7,06 (s, 4H), 4,95 (d, J=8,4 Hz, 1H), 1,02 (m, 1H), 0,44 (amplio m, 3H), 0,14 (m, 1H).

Ejemplo 61

5-(4-Clorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolin-7-ol. (Enantiómeros A y B). Preparado como se describe en el Ejemplo 21 seguido de separación cromatográfica utilizando el tipo de columna especificado y se analiza utilizando el Método 15.

Enantiómero A Tiempo de retención = 13,4 min.

Enantiómero B Tiempo de retención = 17,0 min.

MS *m/z* 375,9(M+H)$^+$. ^{1}H RMN ($CDCl_3$) δ 7,42 (d, J = 8,4 Hz, 1H), 7,23 (s, 1H), 7,18 (d, J = 2,4 Hz, 1H), 7,14 (m, 4H), 6,85 (dd, J = 8,4, 2,5 Hz, 1H), 5,59 (q, J = 6,9 Hz, 1H), 1,22 (d, J = 6,9 Hz, 3H).

Ejemplo 62

5-(4-Clorofenilsulfonil)-4,5-dihidro-1*H*-imidazo[1,2-a]pirazol[4,3-e]pirimidina. Preparada mediante aminación reductiva de aldehído (69) con 4-Clorobencenosulfonamida como se describe para el compuesto (26) en el Ejemplo 4 para proporcionar 4-Cloro-N-((3-yodo-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-il)metil)bencenosulfonamida. Ésta luego se acopla a 2-bromo-1*H*-imidazol y se desprotege como se describe para el compuesto (100) en el Ejemplo 17. MS *m/z* 336,0(M+H)$^+$. ^{1}H RMN (CD_3OD) δ 7,66 (d, J = 1,65 Hz, 1H), 7,61 (d, J = 8,79 Hz, 2H), 7,52 (s, 1H), 7,46 (d, J = 8,79 Hz, 2H), 7,35 (d, J = 1,65 Hz, 1H), 5,36 (s, 2H).

Ejemplo 63

5-(4-Clorofenilsulfonil)-4-etil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina.

(Enantiómeros A y B)

Preparado por ciclización de ácido 3-(4-Cloro-N-fenilfenilsulfonamido)pentanoico, que se prepara como se describe para el compuesto (27) utilizando 3-oxopentanoato de metilo seguido de hidrólisis con NaOH, en la forma que se describe para el compuesto (53) seguido de la formación de pirazol según se muestra en el Ejemplo 10. Se separan luego los enantiómeros utilizando el tipo de columna especificado y se analiza utilizando el Método 17.

Enantiómero A Tiempo de retención = 6,0 min.

Enantiómero B Tiempo de retención = 9,3 min.

MS m/z 373,9$(M+H)^+$. ^1H RMN (CD_3OD) δ 7,77-7,74 (d, J = 7,3 Hz, 1H), 7,65 (s, 1H) 7,44-7,35 (m, 3H), 7,14 (s, 4H), 5,36-5,31 (t, J = 8,3 Hz, 1H), 1,51-1,44 (m, 2H), 1,02-0,98 (t, J = 7,2 Hz, 3H).

Ejemplo 64

5-(4-Clorofenilsulfonil)-7-metil-4,5-dihidro-1*H*-imidazo[1,2-a]pirazol[4,3-e]pirimidina.

5-(4-Clorofenilsulfonil)-8-metil-4,5-dihidro-1*H*-imidazo[1,2-a]pirazol[4,3-e]pirimidina.

Preparado mediante la aminación reductiva del aldehído (69) con 4-Clorobencenosulfonamida como se describe para el compuesto 26 en el Ejemplo 4 para proporcionar 4-Cloro-N-((3-yodo-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-il)metil)bencenosulfonamida. Ésta luego se acopla a 2-bromo-4-metil-1*H*-imidazol y se desprotege como se describe para el compuesto (100) en el Ejemplo 18 para dar una mezcla de regioisómeros. MS *m/z* 350,0 $(M+H)^+$. ^1H RMN (CD_3OD) δ 7,39-7,31 (m, 10H), 7,13-7,11 (s, 1H), 6,75-6,73 (m, 1H), 4,98 (s, 2H), 4,97 (s, 2H), 2,41-2,40 (m, 3H), 2,67-2,50 (m, 3H).

Ejemplo 65

5-(4-Clorofenilsulfonil)-4-ciclopropil-4,5-dihidro-1*H*-imidazo[1,2-a]pirazol[4,3-e]pirimidina.

Preparado mediante la formación de imina utilizando el aldehído 69 y 4-Clorobencenosulfonamida como se describe para el compuesto 73 en el Ejemplo 12 para proporcionar 4-Cloro-*N*-((3-yodo-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-il)metilen)bencenosulfonamida. Éste se hizo reaccionar luego con bromuro de isopropilmagnesio como se describe para compuesto 74 en el Ejemplo 12 para proporcionar 4-Cloro-*N*-(ciclopropil(3-yodo-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-il)metil)bencenosulfonamida que luego se acopla a 2-bromo-1*H*-imidazol y se desprotege como se describe en el Ejemplo 17. MS *m/z* 376,0 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 7,82 (d, J = 6,90 Hz, 2H), 7,71 (s, 1H), 7,40 (d, J = 6,6 Hz, 2H), 6,80 (s,

1H), 6,70 (s, 1H), 3,95 (d, J = 7,6 Hz, 1H), 1,10 - 1,04 (m, 1H), 0,59 - 0,51 (m, 2H), 0,48- 0,41 (m, 1H), 0,21 - 0,13 (m, 1H).

Ejemplo 66

5-(4-Clorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c][1,7]naftiridina.

Preparado como se describe en el Ejemplo 18 utilizando ácido 3-bromopiridin-4-ilborónico, 4-Clorobencenosulfonamida y bromuro de metilmagnesio. MS *m/z* 362,0 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 8,99 (bs, 1H), 8,62 (bs, 1H), 8,03 (bs, 1H), 7,42 (s, 1H), 7,29 (m, 2H), 7,23 (m, 2H), 5,73 (q, J = 6,8 Hz, 1H), 1,28 (d, J = 6,9 Hz, 3H).

Ejemplo 67

4-ciclopropil-7,8-difluoro-5-(5-(trifluorometil)piridin-2-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina.

Preparado como se describe en el Ejemplo 12 utilizando aldehído (103) y sulfonamida (117). MS *m/z* 457,0 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 8,53 (s, 1H), 7,89 (dd, J = 10,6, 8,0 Hz, 1H), 7,82 (dd, J = 18,6, 11,3, 1H), 7,60 (d, J = 8,2 Hz, 1H), 7,45 (dd, J = 18,6, 10,0, 1H), 7,38 (s, 1H), 5,11 (d, J = 8,0 Hz, 1H), 1,06 (m, 1H), 0,58 (m, 1H), 0,47 (m, 2H), 0,20 (m, 1H).

Ejemplo 68

5-(5-Clorotiofen-2-ilsulfonil)-4-ciclopropil-7,8-difluoro-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina.

Preparado como se describe en el Ejemplo 12 utilizando 5-Clorotiofen-2-sulfonamida. MS *m/z* 428,0 $(M+H)^+$. ^1H RMN ($CDCl_3$) d 9,97 (amplios, 1H), 7,70 (dd, J = 11,4, 7,2 Hz, 1H), 7,57 (dd, J = 10,2, 8,7 Hz, 1H), 7,31 (s, 1H), 6,70 (d, J = 4,8 Hz, 1H), 6,56(d, J = 4,8 Hz, 1H), 4,98 (d, J = 7,5 Hz, 1H), 1,03 (m, 1H), 0,53 (m, 1H), 0,40 (m, 2H), 0,10 (m, 1H).

Ejemplo 69

4-ciclopropil-5-(4-fluorofenilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c][1,8]naftiridina.

Preparado como se describe en el Ejemplo 18 utilizando 4-fluorobencenosulfonamida. MS *m/z* 371,0 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 8,42 (dd, J = 4,9, 1,6 Hz, 1H), 8,10 (dd, J = 7,6, 1,6 Hz, 1H), 7,98 (m, 2H), 7,58 (s, 1H), 7,22 (dd, J = 7,6, 4,9 Hz, 1H), 7,08 (m, 2H), 5,42 (d, J = 8,0 Hz, 1H), 1,14 (m, 1H), 0,46 (m, 3H), 0,21 (m, 1H).

Ejemplo 70

4-ciclopropil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-imidazo[1,2-a]pirazol[4,3-e]pirimidina.

Preparada mediante la formación de imina utilizando el aldehído (69) y 4-(trifluorometil)bencenosulfonamida como se describe para el compuesto (73) en el Ejemplo 12 para proporcionar 4-Cloro-*N*-((3-yodo-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-il)metilen)bencenosulfonamida. Éste se hizo reaccionar luego con bromuro de isopropilmagnesio como se describe para el

compuesto (74) en el Ejemplo 12 para proporcionar 4-Cloro-*N*-(ciclopropil(3-yodo-1-((2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-4-il)metil)bencenosulfonamida que luego se acopla a 2-bromo-1*H*-imidazol y se desprotege como se describe en el Ejemplo 17. MS *m/z* 410,0 $(M+H)^+$. ^1H RMN (CD_3OD) δ 8,05 (d, J = 8,3 Hz, 2H), 7,78 (d, J = 9,4 Hz, 2H), 7,76 (s, 1H), 6,86 (dd, J = 13,0, 2,6 Hz, 2H), 3,80 (d, J = 8,2 Hz, 1H), 1,05-1,03 (m, 1H), 0,42-0,37 (m, 1H), 0,31-0,24 (m, 1H), 0,21-0,13 (m, 1H), 0,54-0,14 (m, 1H).

Ejemplo 71

4-ciclopropil-7,8-difluoro-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina. Preparada como se describe en el Ejemplo 12 utilizando el aldehído (103) y la sulfonamida (83). MS *m/z* 457,0 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 8,57 (s, 1H), 7,76 (m, J = 11,0, 7,6 Hz, 1H), 7,52 (m, 3H), 7,43 (d, J = 8,3 Hz, 1H), 7,33 (s, 1H), 5,03 (d, J = 7,6 Hz, 1H), 1,05 (m, 1H), 0,56 (m, 1H), 0,42 (m, 2H), 0,11 (m, 1H).

Ejemplo 72

5-(4-Fluorofenilsulfonil)-4-(trifluorometil)-4,5-dihidro-1*H*-pirazol[4,3-c][1,8]naftiridina.

Preparado como se describe en el Ejemplo 18 utilizando trifluorometanosulfonato de metilo en lugar de bromuro de ciclopropilmagnesio. MS *m/z* 399,0 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 8,30 (dd, J = 4,9, 1,9 Hz, 1H), 8,15 (dd, J = 7,6, 1,9 Hz, 1H),

8,05 (m, 2H), 7,82 (s, 1H), 7,22 (m, 3H), 6,58 (q, J = 7,4 Hz, 1H).

Ejemplo 73

7,8-Difluoro-4-(piridin-3-il)-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina.

Preparado mediante la adición de 3-litiopiridina (Ota, T.; Terashima, M. J. Heterocycl. Chem. 1987, 24(2), 377) al compuesto (73) seguido de la formación de pirazol como se describe en el Ejemplo 12. MS *m/z* 493,0 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 8,52 (d, J = 3,8 Hz, 1H), 8,33 (s, 1H), 7,72-7,48 (m, 7H), 7,40-7,33 (m, 2H), 6,71 (s, 1H).

Ejemplo 74

4-ciclopropil-8-fluoro-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina.

Preparado como se describe en el Ejemplo 12 utilizando ácido 2-bromo-5-fluorofenilborónico en lugar del compuesto (70). MS *m/z* 437,9 $(M+H)^+$. ^1H RMN (CD_3OD) δ 7,85-7,80 (dd, J = 8,9, 5,1 Hz, 1H), 7,50-7,46 (m, 2H) 7,40-7,34 (m, 4H), 7,22-7,16 (td, J = 8,7, 2,9 Hz, 1H), 5,07-5,04 (d, J = 7,5 Hz, 1H), 1,02-0,94 (m, 1H), 0,54-0,47 (m, 1H), 0,41-0,31 (m, 2H), 0,17-0,12 (m, 1H).

Ejemplo 75

4-ciclopropil-7,8-difluoro-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina.

(Enantiómeros A y B)

Preparado como se describe en el Ejemplo 13 utilizando ácido borónico (70) y cloruro de sulfonilo (83). Se separaron luego los enantiómeros utilizando HPLC - Método 19.

Enantiómero A Tiempo de retención = 17,3 min.

Enantiómero B Tiempo de retención = 13,0 min.

MS *m/z* 457,0 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 10,03 (br s, 1H), 8,58 (s, 1H), 7,76 (dd, J=11,0, 7,2 Hz, 1H), 7,49 (m, 2H), 7,44 (s, 1H), 5,03 (d, J=7,6 Hz), 1,04 (m, 1H), 0,56 (m, 1H), 0,41 (m, 2H), 0,11 (m, 1H).

Ejemplo 76

7,8-Difluoro-4-isopropil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina.

Preparado como se describe en el Ejemplo 12 utilizando bromuro de isopropilmagnesio. El producto se analiza mediante HPLC utilizando el Método 7. Tiempo de retención = 8,77 min. MS *m/z* 458,0 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 7,73 (dd, J = 11,1, 7,5 Hz, 1H), 7,35 (amplio m, 5H), 7,25 (s, 1H), 4,92 (d, J = 9,9 Hz, 1H), 4,48 (amplios, 1H), 1,50 (m, 1H), 1,09 (d, J = 6,9 Hz, 3H), 0,83 (d, J = 6,9 Hz, 3H).

Ejemplo 77

4-ciclopropil-7,8-difluoro-5-(4-(trifluorometoxi)fenilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina.

Preparado como se describe en el Ejemplo 12 utilizando 4-trifluorometoxibencenosulfonamida en lugar del compuesto (72). MS *m/z* 472,0 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 7,78 (dd, J = 10,8, 6,8 Hz, 1H), 7,43 (dd, J = 9,8, 8,2 Hz, 1H), 7,26 (s, 1H), 7,23 (d, J = 9,3 Hz, 2H), 6,96 (d, J = 7,9 Hz, 2H), 4,93 (d, J = 7,6 Hz, 1H), 1,07-0,96 (m, 1H), 0,61-0,50 (m, 1H), 0,47-0,37 (m, 2H), 0,13-0,06 (m, 1H).

Ejemplo 78

4-ciclopropil-8-fluoro-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1H-pirazol[4,3-c]quinolina. (Enantiómeros A y B)

Preparado como se describe en el Ejemplo 12 utilizando ácido 2-bromo-5-fluorofenilborónico en lugar del compuesto (70). Se separaron luego los enantiómeros utilizando el tipo de columna especificado y se analizaron utilizando el Método 15.

Enantiómero A Tiempo de retención = 8,0 min.

Enantiómero B Tiempo de retención = 12,6 min.

MS *m/z* 437,9 $(M+H)^+$. ^1H RMN (CD_3OD) δ 7,85-7,80 (dd, J = 8,9, 5,1 Hz, 1H), 7,50-7,46 (m, 2H) 7,40-7,34 (m, 4H), 7,22-7,16 (td, J = 8,7, 2,9 Hz, 1H), 5,07-5,04 (d, J = 7,5 Hz, 1H),

1,02-0,94 (m, 1H), 0,54-0,47 (m, 1H), 0,41-0,31 (m, 2H), 0,17-0,12 (m, 1H).

Ejemplo 79

5-(5-Cloropiridin-2-ilsulfonil)-4-ciclopropil-8-fluoro-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina.

Preparado como se describe en el Ejemplo 12 utilizando 5-Cloro-2-piridinsulfonamida. MS *m/z* 405 $(M+H)^+$.

Ejemplo 80

4-ciclopropil-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina.

Preparado como se describe en el Ejemplo 13 utilizando ácido 2-bromoborónico y cloruro de sulfonilo (83). Se separan luego los enantiómeros utilizando el tipo de columna especificado y se analizan utilizando el Método 17. MS *m/z* 421,1 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 8,51 (s, 1H), 7,87 (d, J = 9,7, 1H), 7,68 (d, J = 7,7 Hz, 1H), 7,49-7,26 (m, 5H), 5,00 (d, J = 7,6 Hz, 1H), 1,07-1,00 (m, 1H), 0,56-0,31 (m, 3H), 0,17-0,08 (m, 1H).

Ejemplo 81

5-(4-Clorofenilsulfonil)-4-metil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolin-8-ol. Preparado a partir de 8-(benciloxi)-5-(4-Clorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina como se describe para el compuesto 119 en el Ejemplo 21. MS *m/z* 376 $(M+H)^+$.

Ejemplo 82

(*R*)-4-(4-ciclopropil-7,8-difluoro-1*H*-pirazol[4,3-c]quinolin-5(4*H*)-ilsulfonil)anilina. Preparada como se describe en el Ejemplo 13 utilizando ácido borónico (70) y cloruro de 4-nitrobencenosulfonilo seguido de la reducción del grupo nitro utilizando hidrógeno sobre Pt_2O en MeOH. MS *m/z* 403,1 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 7,77 (dd, J = 11,2, 7,4 Hz, 1H), 7,41 (dd, J = 10,0, 8,0 Hz, 1H), 7,29 (s, 1H), 6,94 (d, J = 8,4 Hz, 2H), 6,27 (d, J = 9,0 Hz, 2H), 4,95 (d, J = 7,7 Hz, 1H), 1,05-0,96 (m, 1H), 0,54-0,48 (m, 1H), 0,44-0,33 (m, 2H), 0,13-0,04 (m, 1H).

Ejemplo 83

(*R*)-4-ciclopropil-7,8-difluoro-5-(4-nitrofenilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina.

Preparado como se describe en el Ejemplo 13 utilizando ácido borónico (70) y cloruro de 4-nitrobencenosulfonilo. MS *m/z* 432,2 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 7,78 (dd, J = 11,0, 7,0 Hz,1H), 7,41 (dd, J = 9,7, 8,0 Hz, 1H), 7,28 (s, 1H), 6,95 (d, J = 8,9 Hz, 2H), 6,17 (d, J = 8,6 Hz, 2H) 4,97 (d, J = 7,1 Hz, 1H), 1,04-0,94 (m, 1H), 0,57-0,47 (m, 1H), 0,45-0,31 (m, 2H), 0,129 - 0,05 (m, 1H).

Ejemplo 84

5-Cloro-2-(4-ciclopropil-7,8-difluoro-1*H*-pirazol[4,3-c]quinolin-5(4*H*)-ilsulfonil)tiazol.

Preparado como se describe en el Ejemplo 13 utilizando ácido borónico (70), aldehído (103), y cloruro de 5-Clorotiazol-2-sulfonilo. MS *m/z* 429 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 7,71 (dd, J = 11,2, 7,4 Hz, 1H), 7,58 (dd, J = 10,3, 8,8 Hz, 1H), 7,38 (s, 1H), 7,33 (s, 1H), 5,07 (d, J = 7,5 Hz, 1H), 1,09-1,02 (m, 1H), 0,56-0,32 (m, 2H), 0,21-0,08 (m, 1H).

Ejemplo 85

(*R*)-4-ciclopropil-5-(4-(difluorometoxi)fenilsulfonil)-7,8-difluoro-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina.

Preparado como se describe en el Ejemplo 13 utilizando ácido borónico (70) y cloruro de 4-(difluorometoxi)bencenosulfonilo. MS *m/z* 454,1 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 7,78 (dd, J = 7,9, 4,3 Hz, 1H), 7,42 (dd, J = 9,9, 8,1 Hz, 1H), 7,27 (s, 1H), 7,20 (d, J = 8,8 Hz, 2H), 6,85 (d, J = 8,9 Hz, 2H), 6,45 (t, J = 72,6 Hz, 1H), 4,94 (d, J = 7,7 Hz, 1H), 1,05-0,96 (m, 1H), 0,60-0,49 (m, 1H), 0,46 - 0,35 (m, 2H), 0,15-0,06 (m, 1H).

Ejemplo 86

4-ciclopropil-8-fluoro-5-(5-(trifluorometil)piridin-2-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina.
(Enantiómeros A y B)

Preparado como se describe en el Ejemplo 12 utilizando ácido borónico (77) y sulfonamida (117). Se separan luego los enantiómeros utilizando el tipo de columna especificado y se analizan utilizando el Método 20.

Enantiómero A Tiempo de retención = 7,6 min.

Enantiómero B Tiempo de retención = 13,7 min.

MS *m/z* 439,1 $(M+H)^+$. ^1H RMN (300 MHz, $CDCl_3$) δ 10,14 (br s, 1H), 8,53 (m, 1H), 7,86 (dd, J=9,3 Hz y 5,7 Hz, 1H), 7,81 (m, 1H), 7,46 (d, J=8,2 Hz, 1H), 7,38 (dd, J=8,5 Hz y 3,2 Hz, 1H), 7,10 (m, 1H), 5,10 (m, J=7,8 Hz, 1H), 1,06 (m, 1H), ,48 /sic/ (m, 3H), ,16 /sic/(m, 1H),

Ejemplo 87

4-ciclopropil-5-(4-(difluorometoxi)fenilsulfonil)-8-fluoro-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina.

Preparado como se describe en el Ejemplo 13 utilizando cloruro de 4-(difluorometoxi)bencenosulfonilo en lugar del compuesto 83. MS *m/z* 436,1 $(M+H)^+$. ^1H RMN (300 MHz, $CDCl_3$) δ 7,89 (dd, J = 8,5, 4,8 Hz, 1H), 7,29 (d, J = 8,5 Hz, 2H), 7,21-7,12 (m, 1H), 7,14 (d, J = 8,6 Hz, 2H), 6,83 (d, J = 8,7 Hz, 1H), 6,65 (s, 1H), 6,44 (t, J = 7,25 Hz, 1H), 4,93 (d, J = 8,2 Hz, 1H), 1,02-0,99 (m, 1H), 0,54-0,51 (m, 1H), 0,46-0,37 (m, 2H), 0,13 - 0,11 (m, 1H).

Ejemplo 88

7-(Benciloxi)-5-(4-Clorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina.

Preparado como se describe en el Ejemplo 4 utilizando 3-benciloxianilina. MS *m/z* 467,8 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 7,47 (m, 4H), 7,35 (m, 3H), 7,19 (s, 1H), 7,01 (m, 5H), 5,62 (q, J = 6,87 Hz, 1H), 5,16 (s, 2H), 1,30 (d, J = 6,93 Hz, 3H).

Ejemplo 89

5-(4-Fluorofenilsulfonil)-4-metil-4,5,5a,6,7,8,9,9a-octahidro-1*H*-pirazol[4,3-c]quinolina.

Preparado por sulfonilación de 2-metilo Ctahidroquinolin-4(1H)-ona seguido de la formación de pirazol como se describe en el Ejemplo 1. MS *m/z* 350 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 7,88-7,83 (m, 2H), 7,56 (s, 1H), 7,20-7,15 (m, 2H), 5,16-5,09 (q, J = 6,8 Hz, 1H), 4,21-4,14 (m, 1H), 2,77 (m, 1H), 2,40-2,35 (m, 1H), 1,80-1,73 (m, 1H), 1,70-1,69 (m, 2H), 1,65-1,63 (d, J = 6,0 Hz, 3H), 1,55-1,52 (m, 1H), 1,44-1,27 (m, 2H), 1,08-0,99 (m, 1H).

Los siguientes compuestos se preparan esencialmente de acuerdo con los métodos anteriores y esquemas descritos anteriormente.

Ejemplo 90

5'-(4-(Trifluorometil)-fenilsulfonil)-1',5'-dihidrospiro[ciclopropan-1,4'-pirazol[4,3-c]quinolina].

MS *m/z* 439,1 $(M+H)^+$. ^1H RMN ($CDCl_3$) d 7,75-7,73 (m, 1H), 7,61-7,45 (m, 3H), 7,36 (d, J = 8,0 Hz, 2H), 7,26 (d, J = 8,0 Hz, 2H), 7,0 (s, 1H), 2,70-2,60 (m, 1H), 1,68-1,60 (m, 1H), 1,29-1,19 (m, 1H), 0,58-0,51 (m, 1H).

Ejemplo 91

5'-(4-Clorofenilsulfonil)-1',5'-dihidrospiro[ciclopropan-1,4'-pirazol[4,3-c]quinolina].

MS *m/z* 372,1 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 7,72 - 7,69 (m, 1H), 7,64 - 7,61 (m, 1H), 7,52 - 7,42 (m, 2H), 7,28 - 7,25 (m, 2H), 7,08 - 7,04 (m, 2H), 7,0 (s, 1H), 2,64 - 2,56 (m, 1H), 1,64 - 1,56 (m, 1H), 1,29 - 1,19 (m, 1H), 0,56 - 0,52 (m, 1H).

Ejemplo 92

7,8-Difluoro-4-metil-5-(tiofen-2-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina. MS *m/z* 368 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 7,72 (dd, J=10,8, 7,2 Hz, 1H), 7,57 (dd, J=9,9, 8,1 Hz, 1H), 7,29 (m, 2H), 6,98 (dd, J=3,9, 1,2 Hz, 1H), 6,75 (d, J=4,8, 3,9 Hz, 1H), 5,84 (amplios, 1H), 5,69 (q, J=7,2 Hz, 1H), 1,32 (q, J=7,2 Hz, 3H).

Ejemplo 93

5-(4-Clorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c][1,8]naftiridina.

MS *m/z* 368 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 8,30 (dd, J = 4,9, 1,8 Hz, 1H), 8,07 (dd, J = 7,6, 1,8 Hz, 1H), 7,95 (m, 2H), 7,43 (s, 1H), 7,38 (m, 2H), 7,10 (dd, J = 7,6, 4,9 Hz, 1H).

Ejemplo 94

Dimetilcarbamato de 5-(4-Clorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolin-7-il.

MS *m/z* 447(M+H)$^+$. ^{1}H RMN ($CDCl_3$) δ 7,65 (d, J=11,7 Hz, 1H), 7,64 (s, 1H), 7,22 (s, 1H), 7,18 (d, J=8,6 Hz, 1H) 7,17 (d, J=8,8 Hz, 2H), 7,06 (d, J=8,8 Hz, 2H), 5,64 (q, J=6,8 Hz, 1H), 3,17 (s, 3H), 3,07 (s, 3H), 1,32 (d, J=7,0 Hz, 3H).

Ejemplo 95

7-Cloro-4-metil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-pirazol[3,4-d]tieno[2,3-b]piridina.

MS *m/z* 434,0(M+H)$^+$. ^{1}H RMN ($CDCl_3$) δ 8,58 (s, 1H), 7,62 (d, J=9,0 Hz, 2H), 7,54 (dd, J=9,0 Hz, 2H), 7,36 (s, 1H), 7,03 (s, 1H), 5,66 (q, J=6,3 Hz, 1H), 1,43 (q, 6,3 Hz, 3H).

Ejemplo 96

4-etil-7,8-difluoro-5-(5-(trifluorometil)piridin-2-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina.

MS *m/z* 445,0(M+H)$^+$. ^{1}H RMN ($CDCl_3$) δ 8,53 (s, 1H), 7,89 (dd, J = 10,6, 8,0 Hz, 1H), 7,74 (dd, J = 18,6, 11,3, 1H), 7,60 (d, J = 8,2 Hz, 1H), 7,46 (dd, J = 18,6, 10,0, 1H), 7,34 (s, 1H), 5,45 (dd, J = 15,3, 8,5 Hz, 1H), 1,64 (m, 1H), 1,5$_0$ (m, 1H), 1,00 (t, J=7,3 Hz, 3H).

Ejemplo 97

4-ciclopropil-7,8-difluoro-5-(tiofen-2-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina.

MS *m/z* 394,0 $(M+H)^+$. ^1H RMN ($CDCl_3$) d 7,75 (dd, J = 11,4, 7,5 Hz, 1H), 7,57 (dd, J = 10,5, 8,7 Hz, 1H), 7,29 (m, 2H), 7,08 (amplios, 1H), 6,96 (dd, J = 3,9, 1,2 Hz, 1H), 6,73 (d, J = 5,1, 3,9 Hz, 1H), 5,01 (d, J = 8,1 Hz, 1H), 1,03 (m, 1H), 0,53 (m, 1H), 0,40 (m, 2H), 0,11 (m, 1H).

Ejemplo 98

7,8-Difluoro-5-(4-(trifluorometil)-fenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina.

MS *m/z* 416 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 7,69 (dd, J=11,1, 7,2 Hz, 1H), 7,48 (dd, J=10,2, 8,4 Hz, 1H), 7,38 (d, 11,4 Hz, 4H), 7,20 (s, 1H), 4,93 (s, 2H), 2,69 (amplios, 1H).

Ejemplo 99

4-ciclopropil-7-(trifluorometoxi)-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina.

Preparado como se describe en el Ejemplo 13 utilizando ácido 2-bromo-4-(trifluorometoxi)fenilborónico. MS *m/z* 506,1 $(M+H)^+$. ^1H RMN (CD_3OD) δ 8,45 (s, 1H), 7,78-7,73 (m, 3H), 7,62-7,59 (m, 1H), 7,47 (s, 1H), 7,41-7,37 (m, 1H), 5,18-5,16 (d, J = 7,6 Hz, 1H), 1,06-0,98 (m, 1H), 0,60-0,52 (m, 1H), 0,45-0,34 (m, 2H), 0,23-0,14 (m, 1H).

Ejemplo 100

(*R*)-4-ciclopropil-7-(trifluorometil)-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-1*H*-

pirazolo[4,3-c]quinolina. Preparada como se describe en el Ejemplo 13 utilizando ácido 2-bromo-4-(trifluorometil)fenilborónico y cloruro de sulfonilo. MS *m/z* 488,9 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 8,53 (s, 1H), 8,17 (s, 1H), 7,84-7,81 (m, 1H) 7,68-7,65 (m, 1H), 7,5$_0$-7,28 (m, 3H), 5,08-5,05 (d, *J* = 7,7 Hz, 1H), 1,09-0,93 (m, 1H), 0,64-0,55 (m, 1H), 0,50-0,36 (m, 2H), 0,18-0,13 (m, 1H).

Ejemplo 101

(*R*)-4-ciclopropil-7-(trifluorometoxi)-5-(4-(trifluorometoxi)fenilsulfonil)-4,5-dihidro-2*H*-pirazolo[4,3-c]quinolina. Preparada como se describe en el Ejemplo 13 utilizando ácido 2-bromo-4-(trifluorometoxi)fenilborónico y cloruro de 4-(trifluorometoxi)-bencenosulfonilo. MS *m/z* 520,1 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 7,85 (s, 1H), 7,71-7,68 (m, 1H), 7,43 (s, 1H), 7,31-7,24 (m, 3H) 6,99-6,96 (m, 2H), 5,02-4,99 (d, J = 8,0 Hz, 1H), 1,09-1,00 (m, 1H), 0,66-0,57 (m, 1H), 0,55-0,40 (m, 2H), 0,23-0,16 (m, 1H).

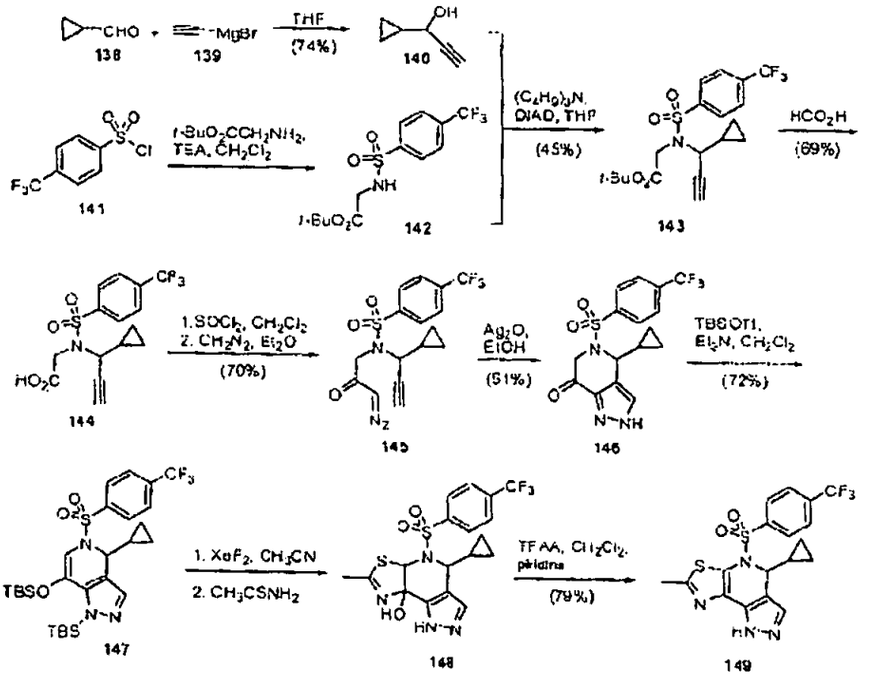
Ejemplo 102

(*R*)-4-ciclopropil-8-(trifluorometil)-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina. Preparada como se describe en el Ejemplo 13 utilizando ácido 2-bromo-5-(trifluorometil)fenilborónico. MS *m/z* 489,1 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 8,59 (s, 1H), 8,11-8,08 (m, 1H), 7,91 (s, 1H) 7,82-7,79 (m, 1H), 7,61-7,49 (m, 3H), 5,08-5,05 (d, J = 8,0 Hz,

1H), 1,08-1,01 (m, 1H), 0,67-0,58 (m, 1H), 0,55-0,44 (m, 2H), 0,23-0,17 (m, 1H).

Ejemplo 103

4-ciclopropil-7-metil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1H-pirazolo[3,4-d]tiazolo[5,4-b]piridina(149).



1-ciclopropilprop-2-in-1-ol (140). A una solución del aldehído en THF se agrega bromuro de etinilmagnesio 138 (5.00 g, 71.3 mmol) (50 niL) a 0° C (139) (0.5M en THF, 178 mL, 89.2 mmol), en forma de gotas por vía de un embudo de adición que equaliza a presión. La mezcla de reacción se agita durante 3 h a 0 0C, y luego se apaga con NH4Cl (100 mL) acuoso saturado y se calienta a temperatura ambiente. La mezcla de reacción se fltra a través de una almohadilla de Celita. El filtrado se diluye con EtOAc (100 mL) y las capas se separan. La capa orgánica se lava con NaCl acuoso saturado (100 mL), se seca

sobre $MgSO_4$, se filtra y se concentra. El residuo resultante se purifica por cromatografía flash (20% EtOAc en hexanos) para proporcionar 6.15 g de alcohol 140 (90%). ^1H RMN (300 MHz, $CDCl_3$) δ 4.20 (bd, J = 5.6 Hz, 1H), 2.44 (d, J = 2.1 Hz, 1H), 1.90 (bs, 1H), 1.25 (m, 1H), 0.57 (m, 2H), 0.52 (m, 2H).

2-(4-(trifluorometil)fenilsulfonamido)acetato de terc-Butilo (142) . A una solución de terc-butil éster de glicina (10.0 g, 76.2 mmol) en CH2Cl2 (150 mL) a 0°C se agrega trietilamina (12.7 mL, 91.5 mmol) seguido por cloruro de sulfonlo 141 (18.6 g, 76.2 mmol). La mezcla de reacción se agita durante 18 h mientras se calienta a temperatura ambiente. La mezcla de reacción se apaga con la adición H_2O (100 mL), y las dos capas se separan.

La capa orgánica se seca sobre MgSO4, se fltra y se concentra para proporcionar 25.9 g de 142 (100%). MS (ES) m/z: 340.0 (M+H)+.

2-(N-(1-ciclopropilprop-2-vinil)-4-(trifluorometil)fenilsulfonamido)acetato de terc-Butilo (143). A una solución de 142 en THF (150 niL) a 0° C se agrega tributilfosfino (29.1 g, 143.6 mmol) y alcohol 140 (5.06 g, 52.6 mmol). Luego se agrega en una forma de gota diisopropil azodicarboxilato (27.8 mL, 143.6 mmol). La mezcla de reacción se agita a 0° C durante 2 h, y luego se concentra. El residuo resultante se purifica mediante cromatografía flash (10% EtOAc

y 10% CH_2Cl_2 en hexanos) para proporcionar 9.84 g de 143 (45%). MS (ES) m/z: 440.2 (M+Na)+.

Ácido 2-(N-(1-ciclopropilprop-2-inil)-4-(trifluorometil)fenilsulfonamido) acético (144). Compuesto 143 (8.34 g, 20.0 mmol) se disuelve en ácido fórmico y se le permite reposar durante 24 h a temperatura ambiente. Se forma un precipitado blanco, que se aisla mediante filtración. El sólido se lava con EtOAc frío (10 mL) para proporcionar 5.08 g de 144 (69%). MS (ES) m/z: 362.0 (M+H)+.

N-(1-ciclopropilprop-2-inil)-N-(3-diazo-2-oxopropil)-4-(trifluorometil)benzenosulfonamida (145). Al cloruro de tionilo se agrega (2 mL) se agrega el compuesto 144 (0.50 g, 1.38 mmol). La mezcla de reacción se calienta a 70°C durante 2 h. La mezcla de reacción se enfría a temperatura ambiente y se concentra. El residuo resultante se disuelve en ET_2O (5 mL) y se agrega una solución preparada por ésta de diazometano en Et2O (30 mL) a 0°C. El diazometano se prepara en la siguiente forma; a una solución de 40% $KOH_{(ac)}$ (15 mL) y Et_2O (30 mL) a 0°C se agrega 1-metil-3-nitro-1-nitrosoguanadina (1.01 g, 6.91 mmol). La mezcla de reacción se le permite reposar a 0°C durante 45 minutes. La temperatura se reduce a -40°C, y la apa acuosa se congela. La capa orgánica se decanta en un recipiente fresco a 0°C que contiene KOH sólido (2.50 g). La mezcla de reacción se le permite reposar a 0°C durante 15 minutos. La mezcla de reacción luego se decanta en un

recipiente limpio a 0°C, tiempo durante que la solución de ET_2O de cloruro ácido se agrega. La mezcla de reacción se le permite reposar durante 30 minutes a 0°C, y luego se apaga con ácido acético (2 mL). La mezcla de reacción se calienta a tempertura ambiente y se diluye con EtOAc (25 mL) y H_2O (25 mL). Las dos capas se separan. La capa orgánica se lava con $NaHCO_3$ saturado (2x 30 mL) y NaCl acuoso saturado (30 mL). La capa orgánica se seca sobre MgSO4, se filtra y se concentra. El residuo resultante se purifica por cromatografía flash (20% EtOAc en hexanos) para proporcionar 0.37 g de 145 (70%). MS (ES) m/z: 408.1 $(M+Na)^+$.

4-ciclopropil-5-(4-(trifluorometil)fenilsulfonil)-5,6-dihidro-2H-pirazolo-[4,3]piridin-7(4H)-ona (146). A una solución del compuesto 145 (0.37 g, 0.96 mmol) en EtOH (5 mL) se agrega óxido de plata (I) (0.02 g, 0.09 mmol). La mezcla de reacción se calienta a 80°C durante 18 h, y luego se enfría a temperatura ambiente. La mezcla de reacción se filtra a través de una almohadilla de Celita y se concentra. El residuo resultante se purifica mediante cromatografía flash (40% EtOAc en hexanos) para proporcionar 0.19 g de 146 (51%). MS (ES) m/z: 386.1 $(M+H)^+$.

1-(terc-Butildimetilsilil)-7-(terc-butildimetilsililoxi)-4-ciclopropil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1H-pirazolo[4,3]-piridina (147). A una solución del compuesto

146 (0.33 g, 0.87 mmol) en CH_2Cl_2 (2.5 mL) a 0°C se agrega trietilamina (0.14 mL, 1.04 mmol) seguido por trifluorometanosulfonato de terc-butildimetisilil (0.21 mL, 0.87 mmol). La mezcla de reacción se agita a 0°C durante 1.5 h, y luego se apaga con H_2O (1 mL). La mezcla de reacción se calienta a temperatura ambiente y las capas se separan. La capa orgánica se seca sobre MgSO4, se filtra y se concentra. El residuo resultante se purifica por cromatografía flash (10% EtOAc en hexanos) para proporcionar 0.38 g de 147 (72%). MS (ES) m/z: 500.1 $(M-TBS)^+$.

4-ciclopropil-7-metil-5-(4-(trifluorometil)fenilsulfonil)-4,5,5a,8a-tetrahidro-1H- pirazolo[3,4d] tiazolo[5,4-b] piridin-8a-ol (148). A una solución del compuesto (0.05 g, 0.08 mmol) en CH_3CN (1 mL) se agrega difluoruro de xenón (0.05 g, 0.28 mmol). La mezcla de reacción se agita durante 3 h a temperatura ambiente y luego se agrega tioacetamida en volumen (0.03 g, 0.41 mmol). La mezcla de reacción se agita durante 18 h a temperatura ambiente y luego se apaga con $NaHCO_3$ acuoso saturado (1 mL). La mezcla de reacción se diluye con EtOAc (5 mL) y las capas se separan. La capa orgánica se seca sobre MgSO4, se filtra y se concentra. El residuo resultante se purifica mediante cromatografía flash (50% EtOAc en hexanos) para proporcionar 0.03 g de 148 (80%). MS (ES) m/z: 459.0 $(M+H)^+$.

4-ciclopropil-7-metil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1H-pirazolo[3,4-d] tiazolo [5,4-b] piridina (149). A una solución del compuesto 148 (0.03 g, 0.06 mmol) en CH_2Cl_2 (1 mL) a 0° C se agrega anhídrido trifluoroacético (0.04 mL, 0.32 mmol) seguido por piridina (0.05 mL, 0.65 mmol). La mezcla de reacción se agita durante 1 h a 0°C, y luego se apaga con $NaHCO_3$ acuoso saturado (1 mL) y se diluye con CH_2Cl_2 (5 mL). las capas se separan. La capa orgánica se lava con H_2O (2 mL), se seca sobre MgSO4, se filtra y se concentra. El residuo resultante se purifica mediante cromatografía flash (50% EtOAc en hexanos) para proporcionar 0.03 g de 149 (79%). ^1H RMN (300 MHz, CD_3Cl_3) δ 7.62 (d, J = 8.3 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.36 (s, 4H), 5.06 (d, J = 7.5 Hz, 1H), 2.78 (s, 3H), 1.24 (m, 2H), 0.46 (m, 3H), 0.22 (m, 1H); 13C RMN (75 MHz, CD3Cl3) δ 163.7, 140.9, 137.6, 136.8, 135.0, 134.6, 130.4, 127.4, 126.0, 121.8, 113.4, 61.0, 21.2, 17.6, 3.47, 2.92; MS (ES) m/z: 441.1 $(M+H)^+$.

Ejemplo 104

5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro- 1H-pirazolo [4,3-c] quinolina-7,8-diol.

MS m/z: 391.9 $(M+H)^+$. ^1H RMN (CD_3CN) δ 7.28 (s, 1H), 7.18 (s, 1H), 7.13 (s 4H), 7.00 (s, 1H), 5.54 (q, J= 6.8Hz, 1H), 1.24 (d, J= 6.8 Hz, 1H)

Ejemplo 105 5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-2H-pirazolo[4,3-c]quinolin-8-ol.

Preparado a partir de 8-(benciloxi)-5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-1H- pirazolo[4,3-c]quinolina como se describe para el compuesto 119 en el Ejemplo 21. MS m/z: 375.9 $(M+H)^+$. ^1H RMN (CD_3OD) δ 7.55 (d, J= 8.7 Hz, 1H), 7.45 (s, 1H), 7.11 (m, 4H), 6.84 (dd, J= 8.7, 2.8 Hz, 1H), 5.60 (q, J= 6.9 Hz, 1H), 1.25 (d, J= 7.0 Hz, 3H).

Ejemplo 106

4-(8-fluoro-4-metil-1H-pirazolo[4,3-c]quinolin-5(4H)-ilsulfonil)-3,5- dimetilisoxazol. Preparado como se describe en el Ejemplo 29 utilizando cloruro de 3,5-dimetilisoxazol-4-sulfonilo. ^1H RMN ($CDCl_3$) δ 11.09 (s, 1η) 7.79-7.74 (dd, J = 8.9, 5.1 Hz, 1H), 7.53-7.49 (dd, J = 8.5, 3.0 Hz, 1H), 7.40 (s, 1H), 7.16-7.09 (dt, J = 8.4, 3.0 Hz, 1H), 5.64- 5.57 (q, J = 6.9 Hz, 1H), 2.03 (s, 3H), 1.97 (s, 3H), 1.35-1.33 (d, J = 6.9 Hz, 3H).

Ejemplo 107

8-fluoro-4-metil-5-(1-metil-1H-pirazol-4-ilsulfonil)-4,5-dihidro-1H-pirazolo[4,3- c]quinolina. Se prepara como se describe en el Ejemplo 29 utilizando cloruro de 1 -metil- 1H-

pirazol-4-sulfonil. ^{1}H RMN ($CDCl_3$) δ 7.79-7.74 (dd, J = 8.9, 5.1 Hz, 1H), 7.45-7.41 (dd, J = 8.4, 2.7 Hz, 1H), 7.36 (s, 1H), 7.15-7.07 (m, 2H), 6.98 (m, 1H), 5.70-5.63 (q, J = 6.9 Hz, 1H), 3.67 (s, 3H), 1.33-1.31 (d, J = 6.9 Hz, 3H).

Ejemplo 108

8-fluoro-4-metil-5-(5-(piridin-2-yl)tiofen-2-ilsulfonil)-4,5-dihidro-1H- pirazolo[4,3-c]quinolina. Se prepara como se describe en Ejemplo 29 utilizando cloruro de 5-pirid-2-iltiofeno-2-sulfonilo. ^{1}H RMN ($CDCl_3$) δ 10.25 (s, 1η) 8.51-8.49 (d, J = 4.0 Hz, 1H), 7.83-7.79 (dd, J = 8.8, 5.1 Hz, 1H), 7.69-7.65 (m, 1H), 7.49-7.41 (m, 2H), 7.28-7.11 (m, 5H), 6.82-6.80 (d, J = 3.8 Hz, 1H), 5.73-5.68 (q, J = 6.8 Hz, 1H), 1.36-1.34 (d, J = 6.8 Hz, 3H).

Ejemplo 109

8-fluoro-4-metil-5-(1-metil-1H-imidazol-4-ilsulfonil)-4,5-dihidro-1H-pirazolo[4,3- c]quinolina. MS m/z: 348.1 (M+H)+. 1H RMN (DMSO-d6) δ 12.83 (s, 1H), 7.67-7.63 (dd, J = 9.0, 5.4 Hz, 1H), 7.54-7.48 (m, 2H), 7.40-7.36 (dd, J = 9.0, 3.0 Hz, 1H), 7.17-7.10 (td, J = 8.7, 3.0 Hz, 1H), 5.58-5.51 (q, J = 7.2 Hz, 1H), 1.14-1.12 (d, J = 7.2 Hz, 3H).

Ejemplo 110

(R)-4-etil-7,8-difluoro-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1H- pirazolo[4,3-c]quinolina. Se prepara como se describe en el Ejemplo 13 utilizando ácido 2-bromo-4,5-difluorofenilborónico, bromuro de etilmagnesio, y sulfonamida 72. MS m/z: 444.1 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 7.70 (dd, 1H, J=7.5, 11.1 Hz), 7.47 (t, J = 8.4 Hz, 1H), 7.40- 7.34 (m, 4H), 7.19 (s, 1H), 5.25 (t, J = 8.4 Hz, 1H), 1.64-1.54(m, 1H), 1.47-1.38 (m, 1H), 0.97(t, J = 7.2Hz, 3H)

Ejemplo 111

(R)-4-ciclopropil-8-fluoro-5-(4-(trifluorometoxi)fenilsulfonil)-4,5-dihidro-1H- pirazolo[4,3-c]quinolina. Se prepara como se describe en el Ejemplo 13 utilizando cloruro de 4- (trifluorometoxi)bencenosulfonilo. MS m/z: 454.0. ^1H RMN ($CDCl_3$) δ 7.69 (dd, J = 9.5 Hz, 2.2 Hz, 1H), 7.66 (dd, J = 8.4, 5.9 Hz, 1H), 7.27 (s, 1H), 7.20 (d, J = 8.7, 2H), 7.16-7.10 (m, 1H) 6.94 (d, J= 8.4 Hz, 2H), 4.95 (d, J= 8.1 Hz, 1H), 1.07-1.0 (m, 1H), 0.58- 0.42 (m, 3H), 0.15-0.12 (m, 1H).

Ejemplo 112

(R)-4-ciclopropil-8-fluoro-5-(4-metoxifenilsulfonil)-4,5-dihidro-1H-pirazolo[4,3- c]quinolina. Se prepara como se

describe en el Ejemplo 13 utilizando cloruro de 4-metoxibencenosulfonilo. MS m/z: 400.1 $(M+H)^+$. ^1H RMN ($CDCl_3$) δ 7.69 (dd, J = 4.0, 2.6 Hz, 1H), 7.60 (dd, J = 8.4, 5.9 Hz, 1H), 7.30 (s, 1H), 7.15-7.12 (m, 2H), 7.12-7.04 (m, 1H), 6.60-6.55 (m, 2H), 5.0 (d, J = 7.6 Hz, 1H), 3.71 (s, 3H), 1.20-0.92 (m, 1H), 0.60-0.35 (m, 3H), 0.19-0.14 (m, 1H).

La cromatografía quiral se desarrolló en un eluyente isocrático etanol:hexanos 10:90 a 1 mL/min en un CHIRALCEL #ODHOCE-EF074.

EJEMPLOS BIOLÓGICOS

Ensayo gama-secretasa

El ensayo gama-secretasa de la proteína precursora amiloide APP se diseña para medir la división proteolítica específica de un sustrato APP (proteína de fusión MBP-C125 Swe) en el sitio Aβ40. En el ensayo se utilizó un extracto parcialmente purificado de membranas de células IMR-32 como preparación enzimática de gama-secretasa y una proteína de fusión recombinante que contiene el terminal-C de aminoácidos 125 de la variante sueca de APP (MBP-C125swe) como sustrato. Este ensayo involucra 2 etapas que comienzan con la reacción enzimática que genera un producto de división que se captura con un anticuerpo inmovilizado específico para el sitio del nuevo epítopo Aβ40. El producto del división capturado se detecta luego en un ensayo ELISA emparedado con un anticuerpo indicador biotinilado específico del Aβ (17-28). Luego se

agregó fosfatasa alcalina unida a estreptavidina para generar una señal fluorescente proporcional a la cantidad de producto de clivaje. Este ensayo se utiliza para descubrir pequeños inhibidores moleculares de gama-secretasa.

Materiales y métodos:

Brevemente, se hace una solución de 149 mg/ml de detergente BIGCHAP con agua a 42°C y luego se rota durante 30 minutos a la misma temperatura. Dicha solución calentada de detergente BigCHAPS (N,N-Bis(3-D-gluconamidopropil)colamida) se utiliza para disolver extracto cerebral de tipo V (lípido que contiene un mínimo de fosfatidiletanolamina al 40%) obtenido de Sigma (St. Louis, Mo.) a una concentración de 8 mg/ml. Esta solución que contenía BigCHAPS y lípido a una concentración de 8 mg/ml se diluye hasta una concentración lipídica de 0,53 mg/ml con una solución previamente calentada de Hepes y cloruro de sodio. Esta solución final con amortiguador Hepes, cloruro de sodio, detergente BigCHAPS y lípido se utilizó para preparar soluciones de trabajo tanto de gama-secretasa (25 unidades) como de sustrato MBP-C125 (0,05 mg/ml).

Luego la gama-secretasa se coloca en una placa de microtítulo de 96 pozos y posteriormente se incuba con varias concentraciones de inhibidor durante 30 minutos a 37°C. El sustrato MBPC125 se agrega luego para iniciar la reacción que se correría durante dos horas a 37°C. La reacción se apaga mediante la adición de SDS hasta una concentración final de 0,1% y luego 100 µl de la mezcla de reacción se transfieren a una placa de captura ELISA y se incuban durante toda la noche

a 4°C. La detección del producto de división se realiza utilizando un ensayo ELISA emparedado estándar y se cuantifica mediante una curva estándar de seis puntos.

Resultados

Los siguientes compuestos, se preparan fundamentalmente según los métodos y esquemas anteriores, al ser sometidos a los ensayos de la manera descrita anteriormente muestran una inhibición en el ensayo de gama-secretasa con un IC_{50} como el descrito en la siguiente tabla. "A" refiere a un IC_{50} de 0,1 a 100 nm, "B" refiere a un IC_{50} de 101 a 500 nm, "C" refiere a un valor de IC_{50} de 501 a 1000 nm y "D" refiere a un valor de IC_{50} de 1000 a 10.000 nm.

TABLA A

Nombre	IC_{50}
5-[(4-clorofenil)sulfonil]-4,5-dihidro-1*H*-pirazolo[4,3-*c*]quinolina	A
5-[(4-clorofenil)sulfonil]-8-fluoro-4,5-dihidro-2*H*-pirazolo[4,3-*c*]quinolina	A
5-[(4-clorofenil)sulfonil]-7-fluoro-4,5-dihidro-2*H*-pirazolo[4,3-*c*]quinolina	A
5-[(4-clorofenil)sulfonil]-9-fluoro-4,5-dihidro-2*H*-pirazolo[4,3-*c*]quinolina	A
5-[(4-clorofenil)sulfonil]-4-metil-4,5-dihidro-2*H*-pirazolo[4,3-*c*]quinolina (racémico)	A
5-[(4-clorofenil)sulfonil]-7-metoxi-4-metil-4,5-dihidro-1*H*-pirazolo[4,3-*c*]quinolina	A

Nombre	IC_{50}
5-[(4-clorofenil)sulfonil]-9-metoxi-4-metil-4,5-dihidro-1*H*-pirazolo[4,3-*c*]quinolina	D
5-[(4-clorofenil)sulfonil]-3-metil-4,5-dihidro-1*H*-pirazolo[4,3-*c*]quinolina	D
8-cloro-5-[(4-clorofenil)sulfonil]-4,5-dihidro-2*H*-pirazolo[4,3-*c*]quinolina	C
4-metil-5-(piridin-2-ilsulfonil)-4,5-dihidro-2*H*-pirazolo[4,3-*c*]quinolina	B
5-[(4-clorofenil)sulfonil]-4,5-dihidro-1*H*-pirazolo[4,3-*c*]quinolin-3-ol	D
6-(4-clorofenilsulfonil)-5-etil-5,6-dihidropirazolo[1,5-c]quinazolina	B
5-[(4-clorofenil)sulfonil]-4-metil-4,5-dihidro-2*H*-pirazolo[4,3-*c*]quinolina; (enantiómero resuelto, tiempo de retención de aproximadamente 9,3 min*.)	A
5-[(4-clorofenil)sulfonil]-4-metil-4,5-dihidro-2*H*-pirazolo[4,3-*c*]quinolina (enantiómero resuelto, tiempo de retención de aproximadamente 20,5 min*.)	D
5-[(4-clorofenil)sulfonil]-8-fluoro-4-metil-4,5-dihidro-2*H*-pirazolo[4,3-*c*]quinolina (racémico)	A
5-[(4-clorofenil)sulfonil]-8-fluoro-4-metil-4,5-dihidro-2*H*-pirazolo[4,3-*c*]quinolina (enantiómero resuelto, tiempo de retención de aproximadamente 9,8 min*.)	A
8-fluoro-4-metil-5-(piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazolo[4,3-*c*]quinolina (racémico)	B

Nombre	IC_{50}
8-fluoro-4-metil-5-(piridin-2-ilsulfonil)-4,5-dihidro-1*H*-pirazolo[4,3-*c*]quinolina	B
4-metil-5-(piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazolo[4,3-*c*]quinolina	B
8-fluoro-4-metil-5-(piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazolo[4,3-*c*]quinolina (enantiómero resuelto, tiempo de retención de aproximadamente 15,2 min*.)	A
8-fluoro-4-metil-5-(piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazolo[4,3-*c*]quinolina (enantiómero resuelto, tiempo de retención de aproximadamente 17,2 min*.)	D
5-[(4-clorofenil)sulfonil]-1,5-dihidro-4*H*-pirazolo[4,3-*c*]quinolin-4-ona	B
5-[(4-clorofenil)sulfonil]-4-metil-4,5-dihidro-1*H*-pirazolo[4,3-*c*]-1,5-naftiridina	A
8-fluoro-4-metil-5-(piridin-2-ilsulfonil)-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina	A
5-(4-clorofenilsulfonil)-4-etil-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina	A
5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolin-7-ol	A
5-(4-clorofenilsulfonil)-8-fluoro-1*H*-pirazolo[4,3-c]quinolin-4(5H)-ona	D

Nombre	IC_{50}
5-(4-clorofenilsulfonil)-4-metil-4,5,5a,6,7,8,9,9ª-octahidro-1*H*-pirazolo[4,3-c]quinolina	
Racemato	A
Enantiómero A	B
Enantiómero B	A
5-(4-clorofenilsulfonil)-9-fluoro-4-metil-4,5-dihidro-2*H*-pirazolo[4,3-c]quinolina	A
5-(4-clorofenilsulfonil)-7-fluoro-4-metil-4,5-dihidro-2*H*-pirazolo[4,3-c]quinolina	A
8-fluoro-5-(4-fluorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina	A
4-metil-5-(piridin-2-ilsulfonil)-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina	
Enantiómero A (tiempo de retención de aproximadamente 9,3 min*.)	B
Enantiómero B	D
9-fluoro-6-(4-fluorofenilsulfonil)-5-metil-5,6-dihidropirimido[5,4-c]quinolin-2-amina	
Enantiómero A	D
Enantiómero B	B
5-(4-clorofenilsulfonil)-4-ciclopropil-4,5-dihidro-2*H*-pirazolo[4,3-c]quinolina	A
5-(4-clorofenilsulfonil)-4-(trifluorometil)-4,5-dihidro-2*H*-pirazolo[4,3-c]quinolina	A

Nombre	IC_{50}
5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolin-7-ol Enantiómero A (tiempo de retención de aproximadamente 13,4 min*.) Enantiómero B (tiempo de retención de aproximadamente 17,0 min*.)	 A A
5-(4-clorofenilsulfonil)-4-isopropil-4,5-dihidro-2*H*-pirazolo[4,3-c]quinolina	A
1,5-bis(4-clorofenilsulfonil)-1*H*-pirazolo[4,3-c]quinolin-4(5H)-ona	D
5-(4-clorofenilsulfonil)-4,5-dihidro-1*H*-imidazo[1,2-a]pirazolo[4,3-e]pirimidina	B
8-fluoro-5-(4-fluorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina	A
5'-(4-clorofenilsulfonil)-2',5'-dihidrospiro[ciclopropan-1,4'-pirazolo[4,3-c]quinolina]	A
5-(4-clorofenilsulfonil)-7,8-difluoro-4-metil-4,5-dihidro-2*H*-pirazolo[4,3-c]quinolina Enantiómero A Enantiómero B	 A A
7,8-difluoro-4-metil-5-(tiofen-2-ilsulfonil)-4,5-dihidro-2*H*-pirazolo[4,3-c]quinolina	A
5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-2*H*-pirazolo[4,3-c][1,8]naftiridina	A

Nombre	IC_{50}
5-(4-clorofenilsulfonil)-4-etil-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina	A
5-(5-clorotiofen-2-ilsulfonil)-7,8-difluoro-4-metil-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina	A
5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolin-7-il dimetilcarbamato	A
4-ciclopropil-7,8-difluoro-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina Racemato Enantiómero A (tiempo de retención de aproximadamente 6,0 min*.) Enantiómero B (tiempo de retención de aproximadamente 9,3 min*.)	A A A
7-cloro-4-metil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-pirazolo[3,4-d]tieno[2,3-b]piridina	A
5-(4-clorofenilsulfonil)-4-ciclopropil-4,5-dihidro-1*H*-imidazo[1,2-a]pirazolo[4,3-e]pirimidina	B
4-etil-7,8-difluoro-5-(5-(trifluorometil)piridin-2-ilsulfonil)-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina	A

Nombre	IC_{50}
7,8-difluoro-4-metil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina Enantiómero A (tiempo de retención de aproximadamente 7,0 min*.) Enantiómero B (tiempo de retención de aproximadamente 9,5 min*.)	A B
5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-2*H*-pirazolo[4,3-c][1,7]naftiridina	A
5'-(4-(trifluorometil)fenilsulfonil)-1',5'-dihidrospiro[ciclopropan-1,4'-pirazolo[4,3-c]quinolina]	A
4-ciclopropil-7,8-difluoro-5-(5-(trifluorometil)piridin-2-ilsulfonil)-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina	A
5-(5-clorotiofen-2-ilsulfonil)-4-ciclopropil-7,8-difluoro-4,5-dihidro-2*H*-pirazolo[4,3-c]quinolina	A
4-ciclopropil-7,8-difluoro-5-(4-fluorofenilsulfonil)-4,5-dihidro-2*H*-pirazolo[4,3-c]quinolina	A
4-ciclopropil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-2*H*-pirazolo[4,3-c][1,8]naftiridina	A
4-ciclopropil-5-(4-fluorofenilsulfonil)-4,5-dihidro-2*H*-pirazolo[4,3-c][1,8]naftiridina	A
4-ciclopropil-5-(4-fluorofenilsulfonil)-4,5-dihidro-2*H*-pirazolo[4,3-c]quinolina	A

Nombre	IC_{50}
4-ciclopropil-7,8-difluoro-5-(tiofen-2-ilsulfonil)-4,5-dihidro-2*H*-pirazolo[4,3-c]quinolina	A
4-ciclopropil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-imidazo[1,2-a]pirazolo[4,3-e]pirimidina	C
4-ciclopropil-7,8-difluoro-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina	A
5-(4-fluorofenilsulfonil)-4-(trifluorometil)-4,5-dihidro-2*H*-pirazolo[4,3-c][1,8]naftiridina	A
7,8-difluoro-4-(piridin-3-il)-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina	A
4-ciclopropil-8-fluoro-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina Racemato Enantiómero A (tiempo de retención de aproximadamente 8,0 min*.) Enantiómero B (tiempo de retención de aproximadamente 12,6 min*.)	 A A B
5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-2*H*-[1,3]dioxolo[4,5-g]pirazolo[4,3-c]quinolina	A

Nombre	IC_{50}
5-(5-cloropiridin-2-ilsulfonil)-4-ciclopropil-7,8-difluoro-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina	A
5-(5-clorotiofen-2-ilsulfonil)-4-ciclopropil-7,8-difluoro-4,5-dihidro-2*H*-pirazolo[4,3-c]quinolina	
Enantiómero A (tiempo de retención de aproximadamente 10,3 min*.)	A
Enantiómero B (tiempo de retención de aproximadamente 16,1 min*.)	A
4-ciclopropil-7,8-difluoro-5-(4-fluorofenilsulfonil)-4,5-dihidro-2*H*-pirazolo[4,3-c]quinolina	
Enantiómero A (tiempo de retención de aproximadamente 16,9 min*.)	A
Enantiómero B (tiempo de retención de aproximadamente 19,7 min*.)	A
4-ciclopropil-8-fluoro-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-2*H*-pirazolo[4,3-c]quinolina	
Enantiómero A	A
Enantiómero B	A

Nombre	IC_{50}
4-ciclopropil-7,8-difluoro-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina Enantiómero A (tiempo de retención de aproximadamente 17,3 min*.) Enantiómero B (tiempo de retención de aproximadamente 13,0 min*.)	A A
7,8-difluoro-4-isopropil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-2*H*-pirazolo[4,3-c]quinolina	A
4-ciclopropil-7,8-difluoro-5-(4-(trifluorometoxi)fenilsulfonil)-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina	A
7,8-difluoro-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-2*H*-pirazolo[4,3-c]quinolina	A
5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazolo[4,3]quinolin-7,8-diol	A
5-(5-cloropiridin-2-ilsulfonil)-4-ciclopropil-8-fluoro-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina	A
4-ciclopropil-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina	A
(R)-4-ciclopropil-7-(trifluorometoxi)-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-2*H*-pirazolo[4,3-c]quinolina	A

Nombre	IC_{50}
óxido de 4-ciclopropil-5-(4-(trifluorometilfenilsulfonil)-4,5-dihidro-2*H*-pirazolo[4,3-c][1,7]naftiridina 7	A
5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-2*H*-pirazolo[4,3-c]quinolin-8-ol	A
4-(8-fluoro-4-metil-1*H*-pirazolo[4,3-c]quinolin-5(4*H*)-ilsulfonil)-3,5-dimetilisoxazol	C
8-fluoro-4-metil-5-(1-metil-1*H*-pirazol-4-ilsulfonil)-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina	B
8-fluoro-4-metil-5-(5-(piridin-2-il)tiofen-2-ilsulfonil)-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina	D
(R)-4-ciclopropil-7-(trifluorometil)-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina	A
(*R*)-4-ciclopropil-7-(trifluorometoxi)-5-(4-(trifluorometoxi)fenilsulfonil)-4,5-dihidro-2*H*-pirazolo[4,3-c]quinolina	A
(*R*)-4-(4-ciclopropil-7,8-difluoro-1*H*-pirazolo[4,3-c]quinolin-5(4*H*)-ilsulfonil)anilina	A
(*R*)-4-ciclopropil-7,8-difluoro-5-(4-nitrofenilsulfonil)-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina	A
(*R*)-4-ciclopropil-8-(trifluorometil)-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina	A

Nombre	IC_{50}
5-cloro-2-(4-ciclopropil-7,8-difluoro-1*H*-pirazolo[4,3-c]quinolin-5(4*H*)-ilsulfonil)tiazol	A
(*R*)-4-ciclopropil-5-(4-(difluorometoxi)fenilsulfonil)-7,8-difluoro-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina	A
4-ciclopropil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-2*H*-pirazolo[4,3-c][1,5]naftiridina	A
4-ciclopropil-8-fluoro-5-(5-(trifluorometil)piridin-2-ilsulfonil)-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina Enantiómero A (tiempo de retención de aproximadamente 13,7 min*.) Enantiómero B (tiempo de retención de aproximadamente 7,6 min*.)	 B A
4-ciclopropil-5-(4-(difluorometoxi)fenilsulfonil)-8-fluoro-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina	A
4-ciclopropil-7,8-difluoro-5-(5-(trifluorometil)piridin-2-ilsulfonil)-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina	A
5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolin-7,8-diol Enantiómero A Enantiómero B	 A B
8-fluoro-4-metil-5-(1-metil-1*H*-imidazol-4-ilsulfonil)-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina	D

Nombre	IC_{50}
(*R*)-4-etil-7,8-difluoro-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina	A
(R)-4-ciclopropil-8-fluoro-5-(4-(trifluorometoxi)fenilsulfonil)-4,5-dihidro-1H-pirazolo[4,3-c]quinolina	A
4-ciclopropil-7-metil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1H-pirazolo[3,4-d]tiazolo[5,4-b]piridina	A
(R)-4-ciclopropil-8-fluoro-5-(4-(metoxifenilsulfonil)-4,5-dihidro-1H-pirazolo[4,3-c]quinolina	A

Ensayo de señalizaciones del Notch de inhibidores selectivos de la gama-secretasa.

La convergencia de resultados indica que el complejo gama-secretasa, el cual es parte de las subunidades de presenilina, actúa de mediador en la división del interior de la membrana de la proteína precursora amiloide (APP) y la familia de proteínas Notch (De Strooper, B., P. Saftig, K. Craessaerts, H. Vanderstichele, G. Guhde, W. Annaert, K. Von Figura y F. Van Leuven (1998). " Deficiency of presenilin-1 inhibits the noral cleavage of amyloid precursor protein" Nature **391** (6665): 387-90; De Strooper, B., W. Annaert, P. Cupers, P. Saftig, K. Craessaerts, J. S. Mumm, E. H. Schroeter, V. Schrijvers, M. S. Wolfe, W. J. Ray et al. (1999). " A

presenilin-1-dependet gamma-secretase-lik protease mediates release of Notch intracellular domain" Nature **398** (6727): 518-22; Mumm, J. S., E. H. Schroeter, M. T. Saxena, A. Griesemer, X. Tian, D. J. Pan, W. J. Ray y R. Kopan (2000). " A ligand-induced extracellular cleavage regulates gamm-secretase-like proteolytic activation of Nochl." Mol Cell **5**(2): 197-206; Zhang, Z., P. Nadeau, W. Song, D. Donoviel, M. Yuan, A. Bernstein y B. A. Yankner (2000). " Presenilins are required formulación gamma-secrettase cleavage of beta-APP and transmembrane cleavage of Notch-1." Nat Cell Biol **2**(7): 463-5). La división del APP mediante gama-secretasa conduce a la síntesis de beta-amiloide. La división del Notch1 mediante la gama-secretasa produce la liberación del dominio intracelular del Notch (NICD), el cual transloca hacia el núcleo y activa la expresión genética (Jarriault, S., C. Brou, F. Logeat, E. H. Schroeter, R. Kopan y A. Israel (1995). "Signalling downstream of activated mammalian Notch." Nature **377**(6547): 355-8; Kopan, R., E. H. Schroeter, H. Weintraub y J. S. Nye (1996). "Signal transduction by activated Notch: importance of proteolytic processing and its regulation by the extracellular domain." Proc Natl Acad Sci U S A **93**(4): 1683-8; Schroeter, E. H., J. A. Kisslinger y R. Kopan (1998). " Notch-1 signalling requires ligand-induced proteolytic release of intracellular domain" Nature **393**(6683): 382-6). En particular la señalización del Notch activa la transcripción del homólogo mamífero del mejorador de la división de tricoleucocito del factor de transcripción *Drosophila* split (*Hes*). La activación

transcripcional del *Hes1* es mediada por la desrepresión del CBF1/RBPJk ante la unión del NICD en el núcleo. Estos hechos se han explotado para desarrollar un ensayo con el gen indicador para la señalización del Notch. Hsieh, J. J., T. Henkel, P. Salmon, E. Robey, M. G. Peterson y S. D. Hayward (1996). " Truncated mammalian Notch1 activates CBF1/RBPJk-repressed genes by a mechanism resembling that of Epstein-Barr virus EBNA2." Mol Cell Biol **16**(3): 952-9; Lu, F. M. y S. E. Lux (1996). " Constitutively active human Notch1 binds to the transcription factor CBF1 and stimulates transcription through a promoter containing a CBF1-responsive element " Proc Natl Acad Sci U S A **93**(11): 5663-7).

Nature **391** (6665): 387-90; De Strooper, B., W. Annaert, P. Cupers, P. Saftig, K. Craessaerts, J. S. Mumm, E. H. Schroeter, V. Schrijvers, M. S. Wolfe, W. J. Ray et al. (1999). (1999). " A presenilin-1-dependent gamma-secretase-like protease mediates release of Notch intracellular domain." Nature **398**(6727): 518-22). Debido a la importancia de la señalización del Notch en la determinación del destino de la célula y la diferenciación tisular durante el desarrollo y en el adulto, la inhibición de la señalización del Notch mediante inhibidores de la gama-secretasa presupone ser un factor limitante en su utilidad terapéutica. De manera de identificar a los inhibidores selectivos de la gama-secretasa, se utilizó un gen indicador basado en el ensayo de indicación del Notch mediante la utilizando una rata constitutivamente activa de una construcción Notch (ZEDN1) proporcionado por el Dr. Gerry

Weinmaster, quien se encuentra en la Universidad de California en Los Ángeles (UCLA), tal y como se describe en Shawber, C., D. Nofziger, J. J. Hsieh, C. Lindsell, O. Bogler, D. Hayward y G. Weinmaster (1996). " Notch signaling inhibits muscle cell differentiation thrugh a CBF1-indepent pathway." Development **122**(12): 3765-73 en combinación con el gen represible indicador CBF1 Luciferasa 4xwtCBF1Luc (Hsieh, J. J., T. Henkel, P. Salmon, E. Robey, M. G. Peterson y S. D. Hayward (1996). " Truncated mammalian Notch1 activates CBF1/RBPJk-repressed genes by a mechanism resembling that of Epstein Barr virus EBNA2" Mol Cell Biol **16**(3): 952-9).

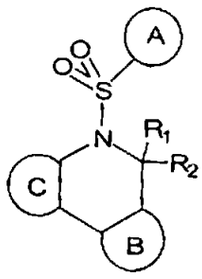
Cuando el Luciferasa 4xwtCBF1 es co-transfectado con el NotchδE (ZEDN1), la división de NotchδE de la gama-secretasa libera el dominio intracelular del Notch (NICD) , el cual se transloca hacia el núcleo y desreprime la represión transcripcional mediada por el CBF1, lo cual a su vez conduce a la transcripción del gen indicador Luciferasa. La actividad del Luciferasa es fácilmente estudiable en los extractos celulares utilizando kits disponibles comercialmente. La actividad del gen indicador tiene correlación directa con la división del NotchδE de la gama-secretasa, y como tal, una reducción de la actividad del Luciferasa, proporciona una medida conveniente de división del NotchδE de la gama-secretasa. Una comparación de los valores de IC_{50} de los compuestos para la inhibición de la señalización del Notch con la inhibición de la producción de beta-amiloides en las células 293sw se utiliza como guía en la selección de los

compuestos que cumplen con la propiedad deseada de ser potentes inhibidores de la síntesis de los beta-amiloides con una mínima inhibición de las señalizaciones del Notch.

La invención y los modos y procesos para su preparación y uso se describen a continuación de una manera tan completa, clara, concisa y exacta que cualquier persona experta en la técnica a la cual pertenece, podrá prepararla y utilizarla. Se entiende que lo anterior describe realizaciones preferidas de la invención y que podrán realizárseles modificaciones sin que éstas se aparten del espíritu o el alcance de la invención, tal y como se establece en las reivindicaciones. De manera de señalar y reivindicar especial y particularmente el tema tratado como invención, las siguientes reivindicaciones concluyen la presente memoria descriptiva.

Lo que se reivindica es:

1. Un compuesto de la Fórmula:



estereoisómeros, tautómeros, mezclas de estereoisómeros y/o tautómeros o sus sales farmacéuticamente aceptables, en donde el anillo C es cicloalquilo, arilo, heterocicloalquilo, o heteroarilo, cada uno de los cuales se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente halógeno, alquilo C_1-C_6, alcoxi C_1-C_6, ariloxi, aril-(alcoxi C_1-C_6), haloalquilo C_1-C_6, haloalcoxi C_1-C_6, hidroxilo, hidroxi-(alquilo C_1-C_6), -NR'R", -(alquilo C_1-C_6)-NR'R", -NR'C(O)OR', -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, oxo, aril-(alquilo C_1-C_6), arilo, heteroarilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$ arilo o -S(O)$_z$(alquilo C_1-C_6), en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1, 2 ó 3 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_6, y en donde las porciones arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno,

haloalquilo C_1-C_6, haloalcoxi C_1-C_6, hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R";

o donde dos sustituyentes adyacentes forman $-O-(CH_2)_{1-3}-O-$;

el anillo A es arilo, cicloalquilo, heteroarilo o heterocicloalquilo, en donde cada anillo se sustituye opcionalmente en una posición sustituible con halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, alcoxi C_1-C_6, haloalquilo C_1-C_6, haloalcoxi C_1-C_6, hidroxilo, hidroxi-(alquilo C_1-C_6), CN, NO_2, ariloxi, aril-(alcoxi C_1-C_6), $-SO_2$-(alquilo C_1-C_6), -NR'R", alcanoilo C_1-C_6, -C(O)OR', -(alquilo C_1-C_6)-C(O)OR', heteroarilo, arilo, aril-(alquilo C_1-C_6), $-SO_2$-NR'R", -C(O)NR'R", -OC(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", o -NR'C(O)OR';

el anillo B es un anillo heteroarilo o heterocicloalquilo, cada uno de los cuales se sustituye opcionalmente en una posición sustituible con un grupo que es independientemente alquilo C_1-C_6, alcoxi C_1-C_6, -NR'R", $-SO_2$-NR'R", -C(O)NR'R", -NR'SO_2R", -NR'SO_2NR'R", -NR'SO_2-(alquilo C_1-C_6), -NR'SO_2-fenilo, -NR'C(O)R", -NR'C(O)NR'R", -NR'C(O)OR', -(alquilo C_1-C_6)-NR'R", -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", NO_2, CN, -C(O)OR', hidroxilo, hidroxi-(alquilo C_1-C_6), $-S(O)_z$ arilo, $-S(O)_z$ (alquilo C_1-C_6), halógeno, haloalquilo C_1-C_6, haloalcoxi C_1-C_6, fenilo, alcanoilo C_1-C_6, aril-alcanoilo C_1-C_6, aril-(alquilo C_1-C_6), arilcarbonilo, heteroarilcarbonilo, o heteroaril-alcanoilo C_1-C_6, en donde los grupos arilo o heteroarilo se sustituyen opcionalmente con 1 a 5 grupos que son independientemente halógeno, hidroxilo, alquilo C_1-C_6,

alcoxi C_1-C_6, alcanoilo C_1-C_6, haloalquilo C_1-C_6, haloalcoxi C_1-C_6, CN o NO_2; y

en donde cada z es independientemente 0, 1, ó 2;

R_1 es hidrógeno o alquilo C_1-C_6;

R_2 es hidrógeno, alquilo C_1-C_6, haloalquilo C_{1-4}, hidroxilo, hidroxi-(alquilo C_1-C_4), $-NO_2$, -CN, alquenilo C_2-C_6, alquinilo C_2-C_6, alcanoilo C_1-C_6, -C(O)OR', -NR'R", -X(CO)Y, $-(C(R_{30})_2)_{1-4}$X(CO)Y, cicloalquilo C_{3-6} no sustituido, cicloalquilo C_{3-6} sustituido con de uno a cuatro grupos R_{50}, arilo no sustituido, arilo sustituido con de uno a cuatro grupos R_{50}, heteroarilo no sustituido; o heteroarilo sustituido con de uno a cuatro grupos R_{50}, heterocicloalquilo no sustituido; o heterocicloalquilo sustituido con de uno a cuatro grupos R_{50}; en donde

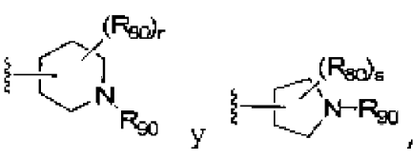
cada R_{30} es independientemente hidrógeno o alquilo C_1-C_6;

cada R_{50} se selecciona independientemente de: halógeno, alquilo C_1-C_6, haloalquilo C_1-C_6, -OH, -O-(alquilo C_1-C_6), $-OCF_3$, -CN, $-NR_{60}R_{70}$, -C(O)O-alquilo C_1-C_6, $-CONR_{60}R_{70}$, -(alquilo C_1-C_6)-$NR_{60}R_{70}$, $-NR_{60}$COalquilo, $-NR_{60}$COarilo, $-NR_{60}$COheteroarilo, $-NR_{60}CONR_{60}R_{70}$,

X es: -O-, -NH-, o -N(alquilo)-;

Y se selecciona de -O-(alquilo C_1-C_6), -O-fenilo, $-NR_{60}R_{70}$, o $-N(R_{30})(CH_2)_{2-6}NR_{60}R_{70}$;

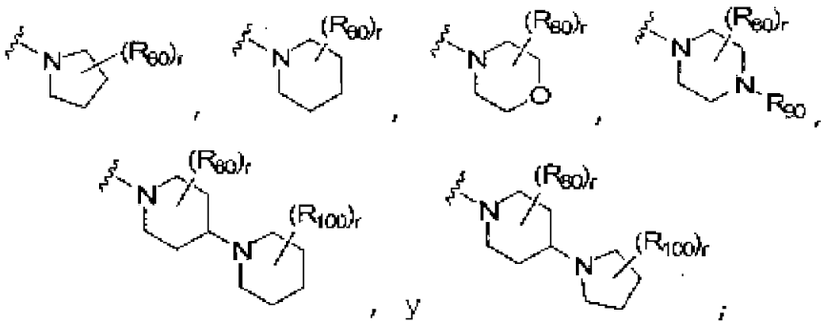
R_{60} y R_{70} se seleccionan independientemente de: hidrógeno, alquilo C_1-C_6, cicloalquilo, arilalquilo; heteroarilalquilo;



y

, o

R_{60} y R_{70} tomados junto con el átomo de nitrógeno al que están unidos forman un grupo heterocicloalquilo seleccionado de:



en donde

cada R_{80} es independientemente alquilo C_1-C_6 no sustituido o alquilo C_1-C_6 sustituido con hidroxilo o halógeno;

cada R_{90} es independientemente H; alquilo C_1-C_6 no sustituido; alquilo C_1-C_6 sustituido con hidroxilo o halógeno; cicloalquilo no sustituido; cicloalquilo sustituido con de uno a cuatro grupos R_{50}; aril-(alquilo C_1-C_6); heteroarilalquilo; -C(O)O-(alquilo C_1-C_6); -C(O)O-arilo; $-SO_2$-(alquilo C_1-C_6); $-SO_2$-arilo; arilo no sustituido; arilo sustituido con de uno a cuatro grupos R_{50}; heteroarilo; o heteroarilo sustituido con de uno a cuatro grupos R_{50};

cada R_{100} es independientemente hidrógeno o alquilo C_1-C_6 ;

cada r es de 0 a 4;

cada s es de 0 a 3;

o R_1 y R_2 combinados son oxo o =N-OR donde R es hidrógeno, alquilo C_1-C_6, arilo o arilalquilo;

o R_1 y R_2 junto con el carbono al que están unidos forman un grupo cicloalquilo C_3-C_6 donde uno de los carbonos puede remplazarse con un heteroátomo seleccionado de N, O o S y en

donde dicho anillo de cicloalquilo C_3-C_6 puede sustituirse opcionalmente con alquilo C_1-C_6 ; y

R' y R" son independientemente hidrógeno, alquilo C_1-C_6, o fenilo, en donde el fenilo se sustituye opcionalmente con 1 a 5 grupos que son independientemente halógeno, hidroxilo, alquilo C_1-C_6, alcoxi C_1-C_6, alcanoilo C_1-C_6, haloalquilo C_1-C_4, haloalcoxi C_1-C_4, CN o NO_2, o

R' y R" tomados junto con el átomo de nitrógeno al que están unidos forman un grupo heterocicloalquilo de 3 a 7 miembros que puede tener un heteroátomo adicional seleccionado de N, O o S y que puede sustituirse opcionalmente con 1 a 3 grupos R_{80} o R_{90};

siempre que 5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina, 2-fenil-5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina, 7-metoxi-2-fenil-5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina, 8-metoxi-5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina, 8-metoxi-2-fenil-5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina, 3-(metiltio)-5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina, 7-metoxi-5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina, 5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina, 1-(4-sulfamoilfenil)-5-tosil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolin-3-carboxilato de etilo, 1-(4-sulfamoilfenil)-5-tosil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolin-3-carboxamida y 1-metil-5-tosil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolin-3-carboxilato de etilo, no se encuentran abarcados por la Fórmula I.

2. Compuestos o sales de acuerdo con la reivindicación 1, en donde

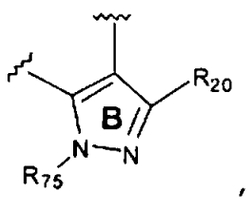
el anillo B es pirazolilo, imidazolilo, pirrolilo, triazolilo, pirrolidinilo, pirazolidinilo, imidazolidinilo, piridilo, pirimidilo, o isoxazolilo, cada uno de los cuales se sustituye opcionalmente en una posición sustituible con un grupo que es independientemente alquilo C_1-C_6, alcoxi C_1-C_6, -NR'R", -SO_2-NR'R", -C(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, NO_2, CN, -C(O)OR', hidroxilo, hidroxi-(alquilo C_1-C_6), halógeno, -S(O)$_z$(alquilo C_1-C_6), -S(O)$_z$arilo, halógeno, haloalquilo C_1-C_2, haloalcoxi C_1-C_2, bencilo, o fenilo.

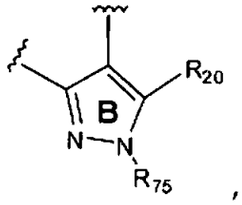
3. Compuestos o sales de acuerdo con la reivindicación 1, en donde

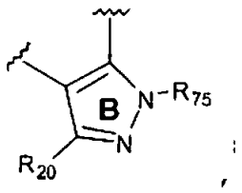
el anillo C es ciclohexilo, ciclopentilo, fenilo, naftilo, tienilo, imidazolilo, pirimidilo, pirazinilo, furanilo, o piridilo, cada uno de los cuales se sustituye opcionalmente en cada posición sustituible con grupos que son independientemente halógeno, alquilo C_1-C_6, alcoxi C_1-C_6, ariloxi, aril-(alcoxi C_1-C_4), haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), -NR'R", -(alquilo C_1-C_4)-NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R", -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, oxo, bencilo, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo, furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -NR'SO_2R", -SO_2-NR'R", -S(O)$_z$(alquilo C_1-C_6), o -S(O)$_z$ arilo, en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen

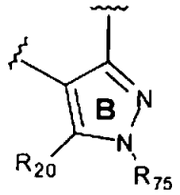
o no se sustituyen con 1, 2 ó 3 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_6, y en donde las porciones arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R"; o en donde dos sustituyentes adyacentes del anillo CC-O-$(CH_2)_{1-3}$-O- /sic/.

4. Compuestos o sales de acuerdo con la reivindicación 3, en donde el anillo B tiene la Fórmula:



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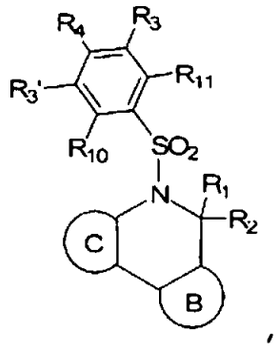
, o


en donde

R_{20} es hidrógeno, alquilo C_1-C_6, alcoxi C_1-C_6, -NR'R", -(alquilo C_1-C_4)-NR'R", -S(O)$_z$(alquilo C_1-C_6), hidroxilo, halógeno, CN, NO_2, CH_2F, CHF_2, CF_3, -C(O)OR', -C(O)NR'R", -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", o fenilo, y

R_{75} es hidrógeno, alquilo C_1-C_6, alcanoilo C_1-C_6, fenil-(alcanoilo C_1-C_6)-, -C(O)NR'R", -S(O)$_2$(alquilo C_1-C_6), -S(O)$_z$-arilo, $-SO_2NR'R"$, fenilo, fenil-(alquilo C_1-C_6) (preferiblemente fenetilo o bencilo, más preferiblemente, bencilo), fenilcarbonilo, bencilcarbonilo, o heteroarilcarbonilo, en donde el grupo heteroarilo es piridilo, pirimidilo, tienilo o furanilo.

5. Compuestos o sales de acuerdo con la reivindicación 4, que tienen la siguiente Fórmula:



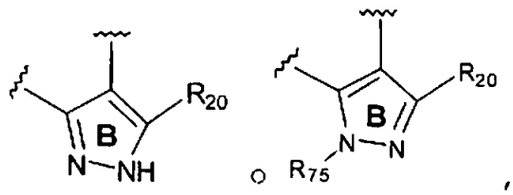
,

en donde

R_3, $R_{3'}$, R_4, R_{10} o R_{11} son independientemente hidrógeno, halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, alcoxi C_1-C_6, haloalquilo C_1-C_6, haloalcoxi C_1-C_6, hidroxilo, hidroxi-(alquilo C_1-C_4), CN, NO_2, ariloxi (tal como feniloxi), aril-(alcoxi C_1-C_4) como benciloxi, $-SO_2$-(alquilo C_1-C_6), -NR'R", alcanoilo C_1-C_6, -C(O)OR', -(alquilo C_{1-4})-C(O)OR', piridilo, fenilo, fenil-(alquilo C_{1-4})-, $-SO_2$-NR'R", -C(O)NR'R", -OC(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", o -NR'C(O)O-R', en donde cada R' y R" es independientemente hidrógeno, alquilo C_1-C_6, o fenilo, en donde el fenilo se sustituye opcionalmente con 1 a 5 grupos que son independientemente halógeno, hidroxilo, alquilo C_1-C_6, alcoxi C_1-C_6, alcanoilo C_1-C_6, haloalquilo C_{1-4}, haloalcoxi C_{1-4}, CN o NO_2; o

R_4 y $R_{3'}$, o R_{10} y $R_{3'}$ y los carbonos al que están unidos forman un anillo benzo.

6. Compuestos o sales de acuerdo con la reivindicación 5, en donde el anillo B tiene la Fórmula:



en donde R_{20} y R_{75} son ambos hidrógeno.

7. Compuestos o sales de acuerdo con la reivindicación 6, en donde el anillo C es fenilo, que se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, ariloxi, aril-(alcoxi C_1-C_4), haloalquilo C_1-C_4 (en otro aspecto, CF_3), haloalcoxi C_1-C_4 (en otro aspecto, OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_4), -NR'R", -(alquilo C_1-C_4)-NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, oxo, bencilo, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo, furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -S(O)$_z$fenilo, o -S(O)$_z$(alquilo C_1-C_6), en donde las porciones alquilo, alquenilo y alquinilo de los anteriores se sustituyen o no se sustituyen con 1, 2 ó 3 grupos que son independientemente halógeno, hidroxi, -NR'R" o alcoxi C_1-C_6, y en donde las porciones arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6 (tal como CF_3), haloalcoxi C_1-C_6 (tal como OCF_3), hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R" o en donde dos sustituyentes adyacentes del anillo C forman -O-$(CH_2)_{1-3}$-O-.

8. Compuestos o sales de acuerdo con la reivindicación 7, en donde R_4 es Cl, F, CH_2F, CHF_2, CF_3, OCH_2F, $OCHF_2$, o OCF_3; R_3, $R_{3'}$, R_{10} y R_{11} son independientemente Cl, F, metilo o hidrógeno; R_2 es independientemente hidrógeno, metilo, etilo, propilo, isopropilo, o ciclopropilo; y R_1 es H o metilo.

9. Compuestos o sales de acuerdo con la reivindicación 8, en donde el anillo C es fenilo sustituido con 1 ó 2 grupos que son Cl, F, metilo, etilo, isopropilo, metoxi, CF_3, OCF_3, OH, $-OC(O)N(CH_3)_2$ o con dos sustituyentes adyacentes que forman $-O-(CH_2)_{1-3}-O-$, en donde el anillo C está sustituido al menos en la posición 8.

10. Compuestos o sales de acuerdo con la reivindicación 6, donde

R_4 es halógeno o alquilo C_1-C_4; R_1 es H; R_2 es H, alquilo C_1-C_4, o cicloalquilo C_{3-6}; y el anillo C es fenilo sustituido con uno o dos halógenos.

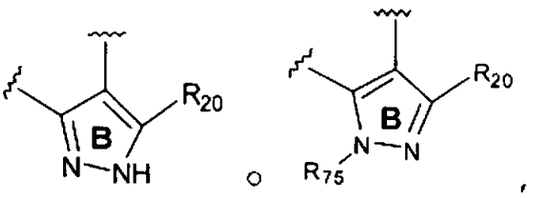
11. Compuestos o sales de acuerdo con la reivindicación 6, donde

R_4 es F, Cl, o CF_3; R_2 es H, metilo, etilo, isopropilo, o ciclopropilo; y el anillo C es fenilo sustituido con uno o dos halógenos.

12. Compuestos o sales de acuerdo con la reivindicación 4, en donde el anillo A es heteroarilo, que es piridilo, pirimidilo, quinolinilo, isoquinolinilo, tienilo, tiazolilo, imidazolilo, pirazolilo, isoxazolilo, o oxazolilo, cada uno de los cuales se sustituye opcionalmente en una posición sustituible con halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6,

alcoxi C_1-C_6, haloalquilo C_1-C_6, haloalcoxi C_1-C_6, hidroxilo, hidroxi-(alquilo C_1-C_4), CN, NO_2, ariloxi, aril-(alcoxi C_1-C_4) (tal como benciloxi),-SO_2-(alquilo C_1-C_6), -NR'R", alcanoilo C_1-C_6, -C(O)OR', -(alquilo C_1-C_4)-C(O)OR', heteroarilo, arilo, aril-(alquilo C_1-C_4), -SO_2-NR'R", -C(O)NR'R", -OC(O)NR'R", -NR'C(O)R", -NR'C(O)NR'R", -NR'C(O)O-(alquilo C_1-C_6) o -NR'C(O)O-fenilo, en donde cada R' y R" son independientemente hidrógeno o alquilo C_1-C_6 .

13. Compuestos o sales de acuerdo con la reivindicación 12, en donde el anillo B tiene la Fórmula:



en donde R_{20} y R_{75} son ambos hidrógeno.

14. Compuestos o sales de acuerdo con la reivindicación 13, en donde el anillo C es fenilo, que se sustituye opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente halógeno, alquilo C_1-C_4, alcoxi C_1-C_4, ariloxi, aril-(alcoxi C_1-C_4), haloalquilo C_1-C_4, haloalcoxi C_1-C_4, hidroxilo, hidroxi-(alquilo C_1-C_4), -NR'R", -(alquilo C_1-C_4)-NR'R", -NR'C(O)O-(alquilo C_1-C_6), -NR'C(O)O-fenilo, -COR', -C(O)OR', -C(O)NR'R", -OC(O)NR'R", -NR'C(O)NR'R"; -(alquilo C_1-C_6)-C(O)OR', -(alquilo C_1-C_6)-C(O)NR'R", -NR'C(O)R", NO_2, CN, fenilo, oxazolilo, pirazolilo, tiazolilo, piridilo, furanilo, tienilo, alquenilo C_2-C_6, alquinilo C_2-C_6, -NR'SO_2R", -SO_2-NR'R", -S(O)$_2$fenilo, o -S(O)$_2$(alquilo C_1-C_6), en donde las porciones alquilo, alquenilo

y alquinilo de los anteriores se sustituyen o no se sustituyen con 1 ó 2 grupos que son independientemente halógeno, hidroxilo, -NR'R" o alcoxi C_1-C_6, y en donde las porciones arilo o heteroarilo de los anteriores se sustituyen opcionalmente con 1, 2, 3, ó 4 grupos que son independientemente alquilo C_1-C_6, alcoxi C_1-C_6, halógeno, haloalquilo C_1-C_6, haloalcoxi C_1-C_6, hidroxilo, hidroxi-(alquilo C_1-C_6), o -NR'R.

15. Compuestos o sales de acuerdo con la reivindicación 14, en donde R_2 es independientemente hidrógeno, metilo, etilo, propilo, isopropilo, o ciclopropilo; y R_1 es H o metilo.

16. Compuestos o sales de acuerdo con la reivindicación 15, en donde el anillo C es fenilo sustituido con 1 ó 2 grupos que son Cl, F, metilo, etilo, isopropilo, metoxi, CF_3, OCF_3, OH, o $-OC(O)N(CH_3)_2$, en donde el anillo C está sustituido al menos en la posición 8.

17. Compuestos o sales de acuerdo con la reivindicación 13, donde

R_4 es halógeno o alquilo C_1-C_4; R_1 es H; R_2 es H, alquilo C_1-C_4, o cicloalquilo C_{3-6}; y el anillo C es fenilo sustituido con uno o dos halógenos.

18. Compuestos o sales de acuerdo con la reivindicación 13, donde

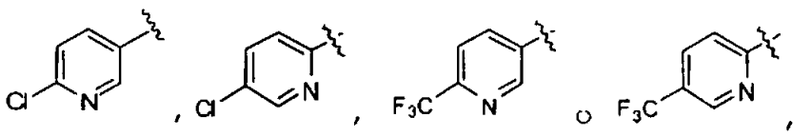
R_4 es F, Cl, o CF_3; R_2 es H, metilo, etilo, isopropilo, o ciclopropilo; y el anillo C es fenilo sustituido con uno o dos halógenos.

19. Compuestos o sales de acuerdo con la reivindicación 13, en donde

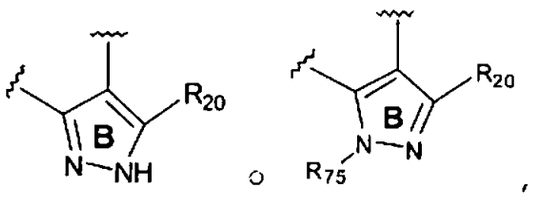
el anillo A es heteroarilo, que es piridilo, o tienilo, cada uno de los cuales se sustituye opcionalmente con 1 ó 2 grupos que son independientemente halo, metilo, metoxi, CF_3, o OCF_3.

20. Compuestos o sales de acuerdo con la reivindicación 12, en donde

el anillo A es un grupo heteroarilo, que presenta las siguientes estructuras:



R_1 es hidrógeno o metilo; R_2 es H, alquilo C_1-C_4, o cicloalquilo C_{3-6}; el anillo C es fenilo sustituido con 1 ó 2 grupos que son independientemente Cl, F, metilo, etilo, isopropilo, metoxi, etoxi, CF_3, OCF_3, OH, CH_2OH, NH_2, $NH(CH_3)$, o $N(CH_3)_2$; y el anillo B tiene la Fórmula:



en donde R_{20} y R_{75} son ambos hidrógeno.

21. Compuestos, estereoisómeros, tautómeros, mezclas de estereoisómeros y/o tautómeros o sus sales farmacéuticamente aceptables, de la reivindicación 1 que son

5-[(4-clorofenil)sulfonil]-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

5-[(4-clorofenil)sulfonil]-8-fluoro-4,5-dihidro-2*H*-pirazol[4,3-*c*]quinolina;

5-[(4-clorofenil)sulfonil]-7-fluoro-4,5-dihidro-2*H*-pirazol[4,3-*c*]quinolina;

5-[(4-clorofenil)sulfonil]-9-fluoro-4,5-dihidro-2*H*-pirazol[4,3-*c*]quinolina;

5-[(4-clorofenil)sulfonil]-4-metil-4,5-dihidro-2*H*-pirazol[4,3-*c*]quinolina (racémico);

5-[(4-clorofenil)sulfonil]-7-metoxi-4-metil-4,5-dihidro-1*H*-pirazol[4,3-*c*]quinolina;

5-[(4-clorofenil)sulfonil]-9-metoxi-4-metil-4,5-dihidro-1*H*-pirazol[4,3-*c*]quinolina ;

5-[(4-clorofenil)sulfonil]-3-metil-4,5-dihidro-1*H*-pirazol[4,3-*c*]quinolina;

8-cloro-5-[(4-clorofenil)sulfonil]-4,5-dihidro-2*H*-pirazol[4,3-*c*]quinolina;

4-metil-5-(piridin-2-ilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-*c*]quinolina;

5-[(4-clorofenil)sulfonil]-4,5-dihidro-1*H*-pirazol[4,3-*c*]quinolin-3-ol;

5-[(4-clorofenil)sulfonil]-4-metil-4,5-dihidro-2*H*-pirazol[4,3-*c*]quinolina; (enantiómero resuelto, con un tiempo de retención de aproximadamente 9,3 min.*)

5-[(4-clorofenil)sulfonil]-4-metil-4,5-dihidro-2*H*-pirazol[4,3-*c*]quinolina (enantiómero resuelto, con un tiempo de retención de aproximadamente 20,5 min.*);

5-[(4-clorofenil)sulfonil]-8-fluoro-4-metil-4,5-dihidro-2*H*-pirazol[4,3-*c*]quinolina (racémico);

5-[(4-clorofenil)sulfonil]-8-fluoro-4-metil-4,5-dihidro-2*H*-pirazol[4,3-*c*]quinolina (enantiómero resuelto, con un tiempo de retención de aproximadamente 9,8 min.*);

8-fluoro-4-metil-5-(piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-*c*]quinolina (racémico);

8-fluoro-4-metil-5-(piridin-2-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-*c*]quinolina;

4-(4-ciclopropil-1*H*-pirazol[4,3-c]quinolin-5(4*H*)-ilsulfonil)benzonitrilo;

4-metil-5-(piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-*c*]quinolina;

8-fluoro-4-metil-5-(piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-*c*]quinolina (enantiómero resuelto, con un tiempo de retención de aproximadamente 15,2 min.*);

8-fluoro-4-metil-5-(piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-*c*]quinolina (enantiómero resuelto, con un tiempo de retención de aproximadamente 17,2 min.*);

5-[(4-clorofenil)sulfonil]-1,5-dihidro-4*H*-pirazol[4,3-c]quinolin-4-ona;

5-[(4-clorofenil)sulfonil]-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]-1,5-naftiridina;

8-fluoro-4-metil-5-(piridin-2-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

5-(4-clorofenilsulfonil)-4-etil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolin-7-ol;

5-(4-clorofenilsulfonil)-8-fluoro-1*H*-pirazol[4,3-c]quinolin-4(5*H*)-ona;

5-(4-clorofenilsulfonil)-4-metil-4,5,5a,6,7,8,9,9a-octahidro-1*H*-pirazol[4,3-c]quinolina;

5-(4-clorofenilsulfonil)-9-fluoro-4-metil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

5-(4-clorofenilsulfonil)-7-fluoro-4-metil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

8-fluoro-5-(4-fluorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

4-metil-5-(piridin-2-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

5-(4-clorofenilsulfonil)-4-ciclopropil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

5-(4-clorofenilsulfonil)-4-(trifluorometil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolin-7-ol;

5-(4-clorofenilsulfonil)-4-isopropil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

1,5-bis(4-clorofenilsulfonil)-1*H*-pirazol[4,3-c]quinolin-4(5*H*)-ona;

8-fluoro-5-(4-fluorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

5'-(4-clorofenilsulfonil)-2',5'-dihidrospiro[ciclopropan-1,4'-pirazol[4,3-c]quinolina];

5-(4-clorofenilsulfonil)-7,8-difluoro-4-metil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

7,8-difluoro-4-metil-5-(tiofen-2-ilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-2*H*-pirazol[4,3-c][1,8]naftiridina;

5-(4-clorofenilsulfonil)-4-etil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

5-(5-clorotiofen-2-ilsulfonil)-7,8-difluoro-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

dimetilcarbamato de 5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolin-7-ilo;

4-ciclopropil-7,8-difluoro-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

7-cloro-4-metil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-pirazol[3,4-d]tieno[2,3-b]piridina;

4-etil-7,8-difluoro-5-(5-(trifluorometil)piridin-2-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

7,8-difluoro-4-metil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-2*H*-pirazol[4,3-c][1,7]naftiridina;

5'-(4-(trifluorometil)fenilsulfonil)-1',5'-dihidrospiro[ciclopropan-1,4'-pirazol[4,3-c]quinolina];

5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-imidazo[1,2-a]pirazol[4,3-e]pirimidina;

4-ciclopropil-7,8-difluoro-5-(5-(trifluorometil)piridin-2-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

5-(5-clorotiofen-2-ilsulfonil)-4-ciclopropil-7,8-difluoro-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-7,8-difluoro-5-(4-fluorofenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c][1,8]naftiridina;

4-ciclopropil-5-(4-fluorofenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c][1,8]naftiridina;

4-ciclopropil-5-(4-fluorofenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-7,8-difluoro-1-(metoximetil)-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-7,8-difluoro-5-(tiofen-2-ilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-imidazo[1,2-a]pirazol[4,3-e]pirimidina;

4-ciclopropil-7,8-difluoro-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

5-(4-fluorofenilsulfonil)-4-(trifluorometil)-4,5-dihidro-2*H*-pirazol[4,3-c][1,8]naftiridina;

7,8-difluoro-4-(piridin-3-il)-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-8-fluoro-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-2*H*-[1,3]dioxol[4,5-g]pirazol[4,3-c]quinolina;

5-(5-cloropiridin-2-ilsulfonil)-4-ciclopropil-7,8-difluoro-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

5-(5-clorotiofen-2-ilsulfonil)-4-ciclopropil-7,8-difluoro-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-7,8-difluoro-5-(4-fluorofenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-8-fluoro-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-7,8-difluoro-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

7,8-difluoro-4-isopropil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-7,8-difluoro-5-(4-(trifluorometoxi)fenilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

7,8-difluoro-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolin-7,8-diol;

5-(5-cloropiridin-2-ilsulfonil)-4-ciclopropil-8-fluoro-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-7-(trifluorometoxi)-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

7-óxido de 4-ciclopropil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c][1,7]naftiridina;

5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolin-8-ol;

4-(8-fluoro-4-metil-1*H*-pirazol[4,3-c]quinolin-5(4*H*)-ilsulfonil)-3,5-dimetilisoxazol;

8-fluoro-4-metil-5-(1-metil-1*H*-pirazol-4-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

8-fluoro-4-metil-5-(5-(piridin-2-il)tiofen-2-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-7-(trifluorometil)-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-7-(trifluorometoxi)-5-(4-(trifluorometoxi)fenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina;

4-(4-ciclopropil-7,8-difluoro-1*H*-pirazol[4,3-c]quinolin-5(4*H*)-ilsulfonil)anilina;

4-ciclopropil-7,8-difluoro-5-(4-nitrofenilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-8-(trifluorometil)-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

5-cloro-2-(4-ciclopropil-7,8-difluoro-1H-pirazol[4,3-c]quinolin-5(4H)-ilsulfonil)tiazol;

4-ciclopropil-5-(4-(difluorometoxi)fenilsulfonil)-7,8-difluoro-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-2*H*-pirazol[4,3-c][1,5]naftiridina;

4-ciclopropil-8-fluoro-5-(5-(trifluorometil)piridin-2-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-8-fluoro-5-(5-(trifluorometil)piridin-2-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-5-(4-(difluorometoxi)fenilsulfonil)-8-fluoro-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

4-ciclopropil-7,8-difluoro-5-(5-(trifluorometil)piridin-2-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

5-(4-clorofenilsulfonil)-4-metil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolin-7,8-diol;

8-fluoro-4-metil-5-(1-metil-1H-imidazol-4-ilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3-c]quinolina;

(*R*)-4-etil-7,8-difluoro-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-pirazol[4,3]quinolina.

(*R*)-4-ciclopropil-8-fluoro-5-(4-(trifluorometoxi)fenilsulfonil)-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina

4-ciclopropil-7-metil-5-(4-(trifluorometil)fenilsulfonil)-4,5-dihidro-1*H*-pirazolo[3,4-d]tiazolo[5,4-b]piridina o

(*R*)-4-ciclopropil-8-fluoro-5-(4-(metoxifenilsulfonil)-4,5-dihidro-1*H*-pirazolo[4,3-c]quinolina

22. Una composición farmacéutica que comprende un compuesto de la reivindicación 1, una sal farmacéuticamente aceptable de la reivindicación 1, o una combinación de un compuesto y una sal farmacéuticamente aceptable de la reivindicación 1, que comprende adicionalmente por lo menos un disolvente, excipiente, adyuvante o una mezcla de los mismos.

23. Un método para tratar una enfermedad relacionada con beta A que comprende administrar una cantidad terapéuticamente efectiva de un compuesto o sal de la reivindicación 1 a un paciente en necesidad de tal tratamiento.

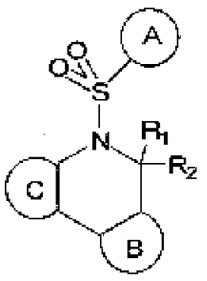
24. Un método para tratar enfermedad de Alzheimer, daño cognitivo leve, demencia o síndrome de Down, que comprende administrar una cantidad terapéuticamente efectiva de un compuesto o sal de la reivindicación **1** a un paciente en necesidad de tal tratamiento.

25. Un método para tratar la enfermedad de Alzheimer, daño cognitivo leve, demencia, o síndrome de Down, que comprende

administrar una cantidad terapéuticamente efectiva de un compuesto o sal de la reivindicación 1, en donde la reivindicación 1 comprende adicionalmente 5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina, 2-fenil-5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina, 7-metoxi-2-fenil-5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina, 8-metoxi-5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina, 8-metoxi-2-fenil-5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina, 3-(metiltio)-5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina, 7-metoxi-5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina, 5-tosil-4,5-dihidro-2*H*-pirazol[4,3-c]quinolina, 1-(4-sulfamoilfenil)-5-tosil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolin-3-carboxilato de etilo, 1-(4-sulfamoilfenil)-5-tosil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolin-3-carboxamida, 1-metil-5-tosil-4,5-dihidro-1*H*-pirazol[4,3-c]quinolin-3-carboxilato de etilo, y sus sales farmacéuticamente aceptables, o una combinación de un compuesto y una sal farmacéuticamente aceptable, para un paciente en necesidad de dicho tratamiento.

Resumen

La invención proporciona compuestos de la Fórmula I:



o sus sales farmacéuticamente aceptables, en donde R_1, R_2 y los anillos A, B y C son según se define aquí. Los compuestos de la Fórmula I son útiles en el tratamiento o prevención de trastornos cognitivos, como enfermedad de Alzheimer. La invención abarca también composiciones farmacéuticas que comprenden compuestos o sales de la Fórmula I, métodos para preparar los compuestos deseados y métodos para tratar trastornos cognitivos, como enfermedad de Alzheimer, utilizando los compuestos o sales de la Fórmula I.

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 C07D471/14 C07D513/14 A61K31/519 A61K31/4745
A61K31/437 A61K31/4375 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BARUN O ET AL: "An Expeditious Synthesis of Substituted and Annelated. Pyrido[2,3-b]indoles" TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 40, no. 19, 7 May 1999 (1999-05-07), pages 3797-3800, XP004163835 ISSN: 0040-4039 compounds 13A,13B -/--	1,3,5

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 April 2008	17/04/2008

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Moriggi, J

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MAJUMDAR S ET AL: "Expeditions Synthesis of Chiral Six and Seven Membered Nitrogen Heterocycles from Carbohydrate Amines by N-Allyl Carbohydrate Nitrone Cycloaddition : Tuning of Regioselectivity by N-Substitution" TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 38, no. 49, 8 December 1997 (1997-12-08), pages 8581-8584, XP004096004 ISSN: 0040-4039 compounds 6A;6B	1,5
X	JP 09 077752 A (KAO CORP) 25 March 1997 (1997-03-25) page 6, column 2, paragraph 37; figure 13	1,3,5
X	KELKAR P M ET AL: "Studies in antifertility agents: Part XXVII. Synthesis of 2-acetyl-3-aryl-5-tosyl-7/8-H(or methoxy)-3,3a,4,5-tetrahydropyrazolo (4,3-c)quinoline" INDIAN JOURNAL OF CHEMISTRY, SECTION B: ORGANIC, INCL. MEDICINAL, PUBLICATIONS & INFORMATIONS DIRECTORATE, NEW DELHI, IN, vol. 19, no. 4, 1980, pages 297-300, XP009096891 ISSN: 0019-5103 compounds 19-22	1,3,5
X	SANGWAN N K ET AL: "Antifertility agents: Part XLIII. Synthesis of 3-aryl-4,5-dihydro-2-substituted-5-tosyl-2 H-pyrazolo(4,3-c)quinolines & 2,4-dihydro-3-phenyl(1)benzopyrano(4,3-c)p yrazoles & their derivatives" INDIAN JOURNAL OF CHEMISTRY, SECTION B: ORGANIC, INCL. MEDICINAL, PUBLICATIONS & INFORMATIONS DIRECTORATE, NEW DELHI, IN, vol. 24B, June 1985 (1985-06), pages 639-644, XP009096892 ISSN: 0019-5103 compounds 19, 41-45	1-7
X	WO 2004/058772 A (DAIICHI SUNTORY PHARMA CO LTD [JP]; DAIICHI SUNTORY BIOMEDICAL RES [JP) 15 July 2004 (2004-07-15) intermediate compounds 13-23; compounds 1-19	1,3,5

-/—

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2006/068928 A (WYETH CORP [US]; SABATUCCI JOSEPH PETER [US]; YE FEI [US]; MAHANEY PAI) 29 June 2006 (2006-06-29) claim 1; examples 15,18,21	1-3,5
A	WO 2005/113542 A (ELAN PHARM INC [US]; NEITZEL MARTIN L [US]; MARUGG JENNIFER L [US]) 1 December 2005 (2005-12-01) page 1, line 5 - line 11; claims 1,21,22	1-25

INTERNATIONAL SEARCH REPORT

PCT/US2007/070176

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 23-25 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 9077752 A	25-03-1997	NONE	
WO 2004058772 A	15-07-2004	AU 2003292720 A1	22-07-2004
		JP 2006151810 A	15-06-2006
WO 2006068928 A	29-06-2006	AR 051849 A1	14-02-2007
		US 2006160815 A1	20-07-2006
WO 2005113542 A	01-12-2005	CA 2567343 A1	01-12-2005
		EP 1758884 A2	07-03-2007
		JP 2007538106 T	27-12-2007
		US 2006035884 A1	16-02-2006

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 08-138163- -00000-0000

Fecha: 2008-12-30 17:08:07 Dep: 2020 NUECREACION
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 659

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 97,011
FECHA : DICIEMBRE 15 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
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	102218944	15/12/2008	19,210,000.00

C O N C E P T O

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN		501,000.00
		TOTAL :	$	501,000.00

SON: QUINIENTOS UN MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

COLO. 13170 - 841 - 008 - 2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-138163- -00000-0000
Fecha: 2008-12-30 17:08:07 Dep: 2020 NUECREACION
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 659

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION [✓] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [✓]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [✓]
- Descripción de la invención [✓]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [✓]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecha 30 Dic 2008

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

Bogotá,
2020

Doctor(a)
FERRERO EMILIO
Apoderado(a) y/o Representante de
ELAN PHARMACEUTICAL, INC.

REFERENCIA	Radicación No.	8 138163
	Solicitud internacional	PCT/US2007/070176
	Fecha inicio fase nacional	02/01/2009
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	1066

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 30 ENE. 2009
adpall