SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-039494- -00000-0000
Fecha: 2011-03-31 10:49:34 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 679

DVN

Industria y Comercio

SUPERINTENDENCIA

NOV

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

División de Nuevas Creaciones

SOLICITUD
PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 11-39494

54. **TÍTULO** COMPUESTOS N-SULFONAMIDO PIRAZOLIL POLICICLICOS

51. **CLASIFICACIÓN INTERNACIONAL**

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

DOMICILIO SOUTH SAN FRANCISCO, CALIFORNIA, ESTADOS UNIDOS DE AMERICA

DERADO LUZ CLEMENCIA DE PAEZ
C.C. 35.456.344 de Usaquén

Á, D.C.,

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-039494- -00000-0000
Fecha: 2011-03-31 10:49:34 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 679

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: LUZ CLEMENCIA DE PÁEZ
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 35.456.344 T. P. 23.555

4 INVENTOR (ES) (72)

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12. Michael S. DAPPEN
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Emerald Hills,
California 94062,
Estados Unidos de América

5 **PCT (86)**
Solicitud Internacional No. PCT/US2009/055987 Fecha: 4 de septiembre de 2009
Publicación Internacional No. WO 2010/028213 A3 Fecha: 11 de marzo de 2010

6 **Título (54)**
COMPUESTOS N- SULFONAMIDO PIRAZOLIL POLICÍCLICOS

7 **Clasificación Internacional (51)** C07D 451/000

8 **Prioridad**
SI☒ NO☐

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	5 de septiembre de 2008	61/094,799
US	23 de septiembre de 2008	61/099,241
US	28 de abril de 2009	61/173,278
US	17 de julio de 2009	61/226,532

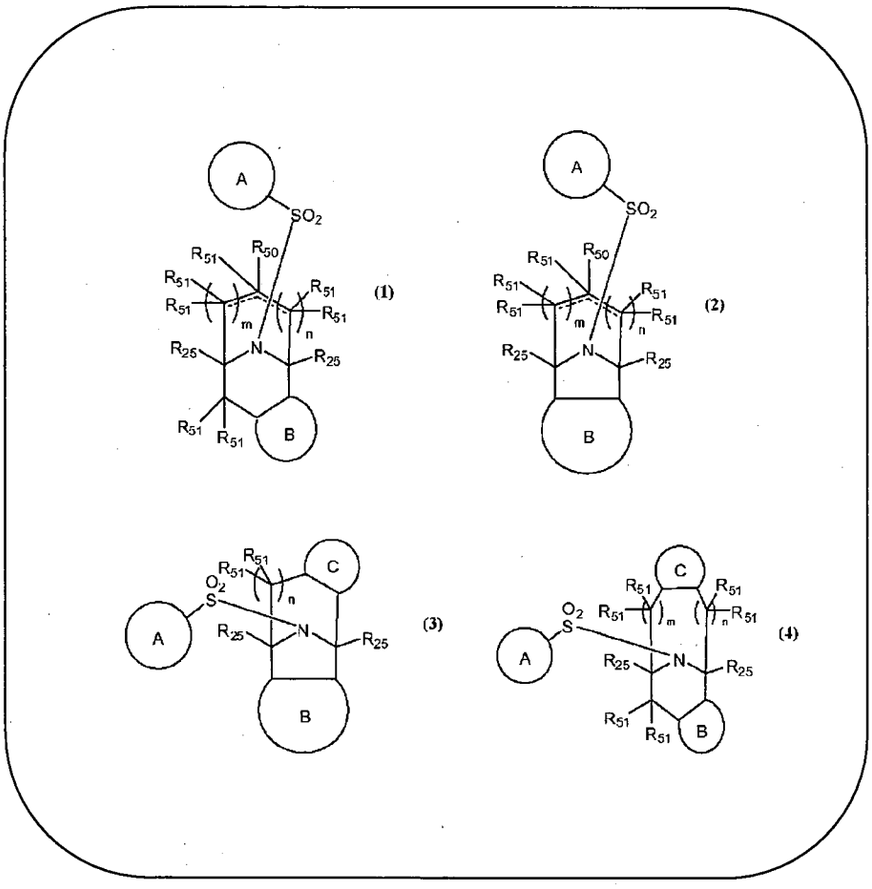
9
Comprobante de pago No.: 10-96,485 **Fecha:** 12 de noviembre de 2010
Comprobante de pago No.: 11-23111 **Fecha:** 14 de marzo de 2011
Comprobante de pago No.: 11-27996 **Fecha:** 29 de marzo de 2011
Comprobante de pago No.: 11-28009 **Fecha:** 29 de marzo de 2011
Comprobante de pago No.: 11-28095 **Fecha:** 29 de marzo de 2011
Comprobante de pago No.: 11-28096 **Fecha:** 29 de marzo de 2011

10 **Anexos:**

☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 571.000.oo.
☒ Comprobante de pago por 33 reivindicaciones adicionales después de la décima reivindicación por $891.000.oo.
☒ 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



12 Solicito la concesión de la patente,

NOMBRE: LUZ CLEMENCIA DE PAEZ

FIRMA : Luz Clemencia de Páez

C.C. 35.456.344 de Usaquén T.P. 23.555

JGG

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2010/028213 A3

   Descripción:

   Páginas 253 en el idioma original

   Páginas 320 en español

   Reivindicaciones: Número (s) 43

   Figuras: Número (s)

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

3. ☒ Extracto de publicación.

NO SE REALIZARON MODIFICACIONES EN LA FASE INTERNACIONAL

Notaría Sexta (6) DEL CIRCULO DE BOGOTA, D.C.

COPIA NUMERO 3ª

DE LA ESCRITURA NUMERO 2.833
FECHA: 28/MAYO/2.010
ACTO O CONTRATO:
PODER ESPECIAL
OTORGANTES:
CAVELIER ABOGADOS
LUZ CLEMENCIA DE PAEZ Y OTROS

ICONTEC
CERTIFICADO DE GESTION DE LA CALIDAD
CERTIFICADO SC 3980-1
PRESTACION DEL SERVICIO PUBLICO NOTARIAL
ISO 9001:2000
NTC-ISO 9001:2000

CERTIFIED IQNet MANAGEMENT SYSTEM

AMPARO QUINTERO ARTURO
NOTARIA SEXTA

CARRERA 9 No. 69-31 - PBX: 317 01 00 - FAX: 314 56 41
Correo Electrónico: notariasexta@etb.net.co

7 700034 715026

ESCRITURA PUBLICA NUMERO: 2833 - - - -

DOS MIL OCHOCIENTOS TREINTA Y TRES - - -

FECHA: VEINTIOCHO (28) DE MAYO - - - - -

DEL AÑO DOS MIL DIEZ (2010) ----------

NOTARIA SEXTA (6ª) DEL CIRCULO NOTARIAL DE BOGOTA D.C.----------

CLASE DE ACTO: PODER ESPECIAL

RAZON SOCIAL : CAVELIER ABOGADOS **NIT :** 860.041.367-3

En la ciudad de Bogotá, Distrito Capital, ante mí JAIME VARGAS CHAMBO - - - - - - - - - - - - - - Notario Sexto (6°) Encargado de éste Círculo Notarial, se otorgó la escritura pública que se consigna en los siguientes términos: -

CONSTANCIA SOBRE COMPARECENCIA Y DECLARACIONES ANTE EL NOTARIO : -

COMPARECIO : Con minuta (e-mail) la señora **ADRIANA ZAPATA GIRALDO,** mayor de edad, vecina de esta ciudad, casada, identificada con la cédula de ciudadanía No. 51.680.061 de Bogotá, y dijo: ----------

ESTIPULACIONES:

PRIMERA.- Que obra en su calidad de representante legal de la sociedad denominada **CAVELIER ABOGADOS** domiciliada en la Carrera 4 No. 72-35, Bogotá, Colombia. **SEGUNDA:** Que **ELAN PHARMACEUTICALS, INC.**, sociedad constituida y existente bajo las leyes del Estado de Delaware, Estados unidos de América, domiciliada en 800 Gateway Boulevard, South San Francisco, California 94080, Estados Unidos de América, designó a **CAVELIER ABOGADOS** como su representante para la Propiedad Industrial en Colombia con facultades de nombrar apoderados tal como consta en la copia auténtica del documento de representación que se protocoliza. **TERCERA.-** Que en su carácter de representante legal de **CAVELIER ABOGADOS,** y en desarrollo de la facultad otorgada por **ELAN PHARMACEUTICALS, INC.**, confiere poder a los abogados **LUZ CLEMENCIA DE PAEZ,** T.P.A. No. 23.555, identificada con cédula de ciudadanía número 35.456.344 de Usaquen, **NIDIA OSORIO LOPEZ,** T.P.A. No.73.366, identificada con cédula de ciudadanía número 39.787.682 de

NOTARIA SEXTA DE BOGOTA

PAPEL DE USO EXCLUSIVO DEL PROTOCOLO NOTARIAL . NO TIENE COSTO PARA EL USUARIO

Bogotá, **OSCAR FERNANDO CORREA BARBOSA**, T.P.A. No. 71.027 identificado con cédula de ciudadanía número 79.524.634 de Bogotá, **EDNA DARMELY SARMIENTO CHARRY**, T.P.A. 65.794 identificada con cédula de ciudadanía número 52.006.265 de Bogotá y **JORGE CHAVARRO ARISTIZABAL**, T.P.A. No. 40.119, identificado con cédula de ciudadanía número 16.209.380 de Cartago (Valle), mayores de edad, vecinos de Bogotá, para que representen a la sociedad a cuyo nombre actúa, ante cualesquiera entidades o personas, ejerzan o no jurisdicción, incluyendo 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, diseños industriales, trazado de circuitos integrados, secretos industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, variedades vegetales, denominaciones de origen e indicaciones de procedencia, 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 consumidor, oposiciones, cancelación administrativa o judicial, nulidad, medidas cautelares, acción por infracción, concesión de licencias, la protección de secretos industriales y de nombres de dominio junto con su administración y pago; acciones populares, de tutela y de cumplimiento; y en general los procesos civiles, penales, administrativos o contencioso-administrativos, de conciliación, arbitramento, tutela relacionados con estos derechos; acciones y procesos que promovamos o se nos promuevan. **CUARTO.**-Que los apoderados designados están facultados en todos los asuntos arriba determinados para sustituir este mandato, transigir, conciliar, arbitrar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar y ratificar los actos de agentes oficiosos. **QUINTO-** Que protocoliza con la presente escritura, un certificado expedido por la Cámara de Comercio de Bogotá, que acredita la constitución y personería de la sociedad **CAVELIER ABOGADOS**, igualmente protocoliza copia autenticada del documento de representación otorgado el día 11 de enero

ELA 6

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a N° 72-35
BOGOTA, 8 – COLOMBIA

REPRESENTACION

REPRESENTATION

13170

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 CAVELIER ABOGADOS, sociedad colectiva constituida de conformidad con las leyes de la República de Colombia, mediante Escritura Pública No. 6233 del 10 de septiembre de 1974, otorgada en la Notaría Sexta del Círculo de Bogotá, domiciliada en Bogotá D.C., con matrícula mercantil No. 00820237 y NIT 860041367-3, domiciliada en la Carrera 4a N° 72-35, Bogotá, Colombia, como nuestra representante en todos los asuntos de Propiedad Industrial, con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales.

CAVELIER ABOGADOS también podrá representarnos, con las mismas facultades arriba indicadas, ante cualesquiera entidades o personas, ejerzan o no jurisdicción, autoridades administrativas o jurisdiccionales, tribunales de arbitramento, en asuntos de naturaleza civil, comercial, penal, constitucional, competencia, competencia desleal, administrativa, contencioso administrativa, protección del consumidor, variedades vegetales, nombres de dominio, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, acciones de tutela, la protección de secretos industriales, derecho regulatorio y en general para que nos represente en cualesquiera acciones y procesos que promovamos o se nos promuevan.

La representante podrá, en nuestro nombre, designar apoderados para actuar ante autoridades administrativas y judiciales, por vía extrajudicial y también procesalmente en nuestro nombre, como demandantes, como demandados, como litisconsortes, como agentes oficiosos, como terceros, por llamamiento en garantía o como intervinientes ad excludendum. Dentro de esta

Do hereby appoint CAVELIER ABOGADOS, a general partnership organized under the laws of the Republic of Colombia by means of Public Deed No. 6233 of September 10, 1974, granted at Notary Sixth of the Bogota Circuit, domiciled in Bogota D.C., with Mercantile Registration No. 00820237 and Taxpayer Identification Number 860041367-3, domiciled at Carrera 4a N° 72-35, Bogota, Colombia, as our representative for all Industrial Property matters with faculty to receive notifications and appoint attorneys in and out of Court.

CAVELIER ABOGADOS may also represent us, with the same faculties stated above, before any entities or persons, with or without jurisdiction, administrative or jurisdictional authorities, courts of arbitration, in civil, commercial, criminal, constitutional, competition, unfair competition, administrative, administrative contentious, consumer protection, plant varieties, domain names, opposition or observation matters, administrative and Court cancellation, nullity, precautionary measures, licensing, action for writ mandamus, protection of trade secrets, regulatoty law and in general represent us in any actions and suits instituted by us or against us.

The representative may, in our name, designate attorneys to act before administrative and judicial authorities, through out-of-court channels, and also procedurally in our name as plaintiff, defendant, joint litigant, representative without power of attorney, third party, when summoned to appear in court or as intervener, ad excludendum. Under this authorization,

© CAVELIER ABOGADOS

28 MAY 2010

NOTARIO ENCARGADO

REPUBLICA DE COLOMBIA
Jaime Vargas
NOTARIO ENCARGADO
NOTARIA SEXTA DE BOGOTA

NOTARIA SEXTA DE BOGOTA

autorización, la representante podrá facultar a los apoderados que ella designe para transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar y sustituir el poder que se le otorgue. Así mismo, la representante tendrá la facultad para revocar el poder así otorgado en el momento que considere pertinente. La representante en todo caso podrá ratificar los actos de agentes oficiosos.

the representative may empower the attorneys appointed thereby to compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign and substitute the power of attorney granted thereto. Likewise, the representative shall have the faculty of revoking the power of attorney thus granted at any time it may deem convenient. The representative may in any case ratify the acts of representatives without a power of attorney.

Dado y firmado hoy/Given and signed this January 11, 2010

En/in Sq. San Francisco, California 94080, USA

Por/by Carl W. Battle, Senior Vice President & Chief Intellectual Property Counsel

Firma/Signature

Nota:

PARA SOCIEDADES

El documento de Representación deberá ser firmado por el representante legal de la compañía. Deberá ser presentado ante Notario Público para que certifique que la persona que firma es quien dice ser. La firma del señor Notario deberá ser legalizada*.

Adicionalmente deberá anexarse copia legalizada* del documento que pruebe la existencia y representación legal de la sociedad.

*La legalización podrá ser por Apostilla si el país del otorgante hace parte de la Convención de La Haya del 5 de octubre de 1961 o ante el Cónsul de Colombia en caso contrario. Una sola legalización que incluya ambos documentos sería suficiente.

PARA PERSONAS NATURALES

El documento de Representación deberá ser firmado por el otorgante: El Notario Público deberá certificar que la persona que firma es quien dice ser.

Posteriormente el documento de Representación deberá ser legalizado por Apostilla si el país del otorgante hace parte de la Convención de La Haya del 5 de octubre de 1961 o ante el Cónsul de Colombia en caso contrario.

Note:

FOR CORPORATIONS

The Representation document should be signed by the Legal Representative of the company. It should be produced before a Notary Public, who should certify that the person signing the same is in fact who he/she purports to be. The Notary's signature should then be legalized*.

In addition a legalized copy* of the document proving the existence and legal representation of the company should also be attached.

*Legalization may be made by Apostille if the issuing country is a member of the The Hague Convention of October 5, 1961, or before the Colombian Consulate if otherwise. A single legalization that would include both documents would be sufficient.

FOR INDIVIDUALS

The Representation should be signed by the grantor. The Notary Public should certify that the person signing is who he/she purports to be.

Subsequently, the Representation document should be legalized by Apostille if the issuing country is a member of the The Hague Convention of October 5, 1961 or before the Colombian Consulate if otherwise.

28 MAY 2010

Jaime Vargas

© CAVELIER ABOGADOS

7

State of California

SECRETARY OF STATE

Requested for use in Colombia.
Not for use within the United States of America.
The purpose of the Apostille is to certify the authenticity of the signature of the official signing the document, the capacity in which the official signing the document has acted, and, where appropriate, the identity of the seal or stamp.

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

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

CERTIFIED

5. *At Sacramento, California*
6. *the 15th day of January 2010*
7. *by Deputy Secretary of State, State of California*
8. *No. 771342*
9. *Seal/Stamp:*

10. *Signature*

28 MAY 2010

Jena Bowen
Secretary of State

BY P Johnson

NP-24 A (REV. 1-07)

OSP 06 99602

CALIFORNIA ALL-PURPOSE ACKNOWLEDGMENT

State of California
County of San Mateo

On Jan. 11, 2010 (Date) before me, Beverly A. Dynes, Notary Public (Here Insert Name and Title of the Officer)

personally appeared Carl W. Battle (Name(s) of Signer(s))

who proved to me on the basis of satisfactory evidence 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.

BEVERLY A. DYNES
Commission # 1872213
Notary Public - California
San Mateo County
My Comm. Expires Nov 27, 2013

I certify under PENALTY OF PERJURY under the laws of the State of California that the foregoing paragraph is true and correct.

WITNESS my hand and official seal.

Signature Beverly A. Dynes (Signature of Notary Public)

Place Notary Seal Above

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

Document Date: — Number of Pages: two (2)

Signer(s) Other Than Named Above: None

Capacity(ies) Claimed by Signer(s)

Signer's Name: Carl W. Battle
☐ Individual
☒ Corporate Officer — Title(s): Sr. Vice President — 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

Signer's Name:
☐ Individual
☐ Corporate Officer — Title(s):
☐ Partner — ☐ Limited ☐ General
☐ Attorney in Fact
☐ Trustee
☐ Guardian or Conservator
☐ Other:
Signer Is Representing:

RIGHT THUMBPRINT OF SIGNER
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28 MAY 2010

NOTARIO ENCARGADO

REPUBLICA DE COLOMBIA
Jaime Vargas
NOTARIO ENCARGADO
NOTARIA SEXTA DE BOGOTA

714

8

Apostille

(Convention de La Haye du 5 Octobre 1961)

1. Country: United States of America

This public document:

2. has been signed by Jeffrey W. Bullock

3. acting in the capacity of Secretary of State of Delaware

4. bears the seal/stamp of Office of Secretary of State

Certified

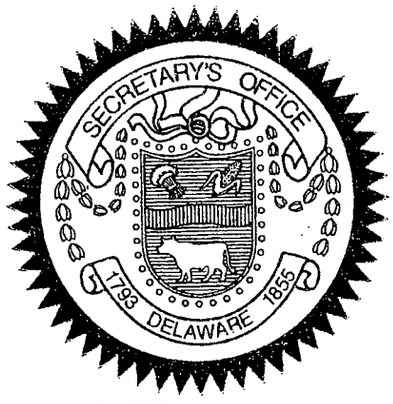
5. at Dover, Delaware

6. the eleventh day of March, A.D. 2010

7. by Secretary of State, Delaware Department of State

8. No. 0409250

9. Seal/Stamp:



10. Signature:

Secretary of State

28 MAY 2010

REPUBLICA DE COLOMBIA
Jaime Vargas
NOTARIO ENCARGADO
NOTARIA SEXTA DE BOGOTA

NOTARIA SEXTA DE BOGOTA

Delaware

The First State

I, JEFFREY W. BULLOCK, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY "ELAN PHARMACEUTICALS, INC." IS DULY INCORPORATED UNDER THE LAWS OF THE STATE OF DELAWARE AND IS IN GOOD STANDING AND HAS A LEGAL CORPORATE EXISTENCE SO FAR AS THE RECORDS OF THIS OFFICE SHOW, AS OF THE ELEVENTH DAY OF MARCH, A.D. 2010.

28 MAY 2010

Jaime Vargas

Jeffrey W. Bullock, Secretary of State

2104559 8300 AUTHENTICATION: 7865147

100272339 DATE: 03-11-10

You may verify this certificate online at corp.delaware.gov/authver.shtml

9

TRADUCCIÓN OFICIAL 098/2010 DE UN DOCUMENTO EN IDIOMA INGLÉS REALIZADA POR EDUARDO CALADO NOGUERA, TRADUCTOR OFICIAL APROBADO POR RESOLUCION 541 DEL 27 DE FEBRERO DE 1976 EXPEDIDA POR EL MINISTERIO DE JUSTICIA DE COLOMBIA Y DEBIDAMENTE REGISTRADO ANTE EL MINISTERIO DE RELACIONES EXTERIORES DE COLOMBIA, POR EL CUAL **ELAN PHARMACEUTICALS, INC**, DOMICILIADA EN 800 GATEWAY BOULEVARD, SOUTH SAN FRANCISCO CALIFORNIA 94080, ESTADOS UNIDOS DE AMÉRICA, OTORGA REPRESENTACIÓN EN ASUNTOS RELACIONADOS CON PROPIEDAD INDUSTRIAL A **CAVELIER ABOGADOS**.

DADO Y FIRMADO HOY ONCE DE ENERO DE 2010 EN SO. SAN FRANCISCO, CALIFORNIA 94080, ESTADOS UNIDOS DE AMÉRICA POR CARL W. BATTLE, VICEPRESIDENTE PRINCIPAL Y ABOGADO JEFE DE PROPIEDAD INTELECTUAL. FIRMADO: CARL W. BATTLE

RECONOCIMIENTO MULTIPROPÓSITO DE CALIFORNIA

ESTADO DE CALIFORNIA

CONDADO DE SAN MATEO

HOY 11 DE ENERO DE 2010, ANTE MI, BEVERLY A. DYNES, NOTARIO PÚBLICO, COMPARECIÓ PERSONALMENTE CARL W. BATTLE, QUIEN DEMOSTRÓ ANTE MÍ CON BASE EN EVIDENCIA SATISFACTORIA SER LA PERSONA CUYO NOMBRE APARECE ESCRITO EN EL DOCUMENTO ADJUNTO Y RECONOCIÓ ANTE MÍ HABER FIRMADO EL MISMO EN SU CALIDAD AUTORIZADA. Y QUE MEDIANTE SU FIRMA EN EL DOCUMENTO, LA PERSONA O ENTIDAD A CUYO NOMBRE LA PERSONA ACTUABA, FIRMÓ EL DOCUMENTO.

28 MAY 2010

Eduardo Calado N.

Eduardo Calado Noguera
TRADUCTOR OFICIAL
Inglés - Español - Inglés
Res. 541 Febrero de 1976

NOTARÍA SEXTA DE BOGOTÁ

ESPACIO

EN

BLANCO

10

CERTIFICO BAJO LA PENA DE PERJURIO DE CONFORMIDAD CON LAS LEYES DEL ESTADO DE CALIFORNIA QUE EL PÁRRAFO PRECEDENTE ES VERÍDICO Y CORRECTO. ATESTIGUO MEDIANTE MI FIRMA Y SELLO OFICIAL. FIRMA: BEVERLY A. DYNES

SELLO: BEVERLY A. DYNES, CARGO # 1872213, NOTARIO PÚBLICO, CALIFORNIA. CONDADO SAN MATEO, MI CARGO VENCE EL 27 DE NOVIEMBRE DE 2013.

DESCRIPCIÓN DEL DOCUMENTO ADJUNTO.

TITULO: REPRESENTACION. NÚMERO DE PÁGINAS 2. FIRMANTE DIFERENTE AL ARRIBA MENCIONADO: NINGUNO. CALIDAD RECLAMADA POr EL FIRMANTE: NOMBRE DEL FIRMANTE: CARL W. BATTLE, FUNCIONARIO DE LA SOCIEDAD: VICEPRESIDENTE PRINCIPAL, JEFE DE ABOGADOS DE PROPIEDAD INTELECTUAL.

EL FIRMANTE REPRESENTA A ELAN PHARMACEUTICALS INC.

ESTADO DE CALIFORNIA

SECRETARIA DE ESTADO

SOLICITADO PARA USO EN COLOMBIA

NO ES PARA USAR DENTRO DE LOS ESTADOS UNIDOS DE AMÉRICA

El objetivo de la apostilla es certificar la autenticidad de la firma del funcionario firmante del documento, la calidad en la cual el mismo actuaba y donde fuere apropiado, la identidad del sello o estampilla.

28 MAY 2010

APOSTILLA

(CONVENCION DE LA HAYA DEL 5 DE OCTUBRE DE 1961)

1. PAIS: ESTADOS UNIDOS DE AMERICA

2. Este documento público ha sido firmado por BEVERLY A. DYNES

Eduardo Calado N.

Eduardo Calado Noguera
TRADUCTOR OFICIAL
Inglés - Español - Inglés
Res. 541 Febrero de 1976

NOTARÍA SEXTA DE BOGOTÁ

REPÚBLICA DE COLOMBIA
Jaime Vargas
NOTARIO
ENCARGADO
NOTARÍA SEXTA DE BOGOTÁ

28 MAY 2010

MINISTERIO DE
RELACIONES EXTERIORES

2010 MAR -6 A 8:25

JEFE DE LEGALIZACIONES
BOGOTA D.C.

RESPONSABILIDAD
DEL TEXTO

014025

Eduardo Calado
CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

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

4. lleva el sello/estampilla de BEVERLY A. DYNES, NOTARIO PÚBLICO, ESTADO DE CALIFORNIA

CERTIFICADO

5. En SACRAMENTO, CALIFORNIA 6. el 15 de enero de 2010.

7. El secretario de estado suplente del Estado de California

8. No. 771342

9. Sello/estampilla: EL GRAN SELLO DEL ESTADO DE CALIFORNIA

10. Firma: DEBRA BOWEN, SECRETARIA DE ESTADO

POR: FIRMA ILEGIBLE

DELAWARE, EL PRIMER ESTADO

Yo, Jeffrey W. Bullock, secretario de estado para el estado de Delaware, por el presente certifico que "ELAN PHARMACEUTICALS, INC" es una empresa debidamente constituida de conformidad con las leyes del estado de Delaware y es de buena reputación y cumplidora de sus obligaciones y actualmente existe legalmente, de acuerdo con lo mostrado en los registros de esta oficina, a 11 de marzo de 2010 de la Era Cristiana.

Firmado: JEFFREY W. BULLOCK, SECRETARIO DE ESTADO

2104559

100272339. FECHA 11 DE MARZO DE 2010

COMO NOTARIO SEXTO (6) DEL CIRCULO DE BOGOTA, DOY FE: QUE LA FOTOCOPIA CORRESPONDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA - COLOMBIA
28 MAY 2010
NOTARIO ENCARGADO

APOSTILLA

(CONVENCION DE LA HAYA DEL 5 DE OCTUBRE DE 19

1. PAIS: ESTADOS UNIDOS DE AMERICA

Este documento público

REPUBLICA DE COLOMBIA
Jaime Vargas
NOTARIO ENCARGADO
NOTARIA SEXTA DE BOGOTA

NOTARIA SEXTA DE BOGOTA

Eduardo Calado Noguera
TRADUCTOR OFICIAL
Inglés - Español - Inglés
Res. 541 Febrero de 1976

ESPACIO

EN

BLANCO

12

2. ha sido firmado por JEFFREY W. BULLOCK

3. quien actúa en su calidad de SECRETARIO DE ESTADO DE DELAWARE

4. lleva el sello/estampilla del SECRETARIO DE ESTADO

CERTIFICADO

5. En Dover, Delaware. 6. el 11 de marzo de 2010, de la Era Cristiana

7. Por el secretario de estado, Departamento de Estado de Delaware

8. No. 0409250

9. Sello/estampilla: OFICINA DEL SECRETARIO, DELAWARE 1793, 1855.

10. Firma: ILEGIBLE, SECRETARIO DE ESTADO

ECN\ECN\ID-168482\WPCL002G

COLO-13170-841-009-0

Bogotá, 5 de abril de 2010.

Eduardo Calado N.

Eduardo Calado Noguera
TRADUCTOR OFICIAL
Inglés - Español - Inglés
Res. 541 Febrero de 1976

28 MAY 2010

NOTARIO ENCARGADO

REPÚBLICA DE COLOMBIA
Jaime Vargas
NOTARIO
ENCARGADO
NOTARÍA SEXTA DE BOGOTÁ

NOTARÍA SEXTA DE BOGOTÁ

28 MAY 2010

REPUBLICA DE COLOMBIA
NOTARIA SEXTA DE BOGOTA
Jaime Vargas Ramírez
NOTARIO
ENCARGADO

MINISTERIO DE
RELACIONES EXTERIORES

2010 MAR -6 A 8:25

JEFE DE LEGALIZACIONES
BOGOTA D.C.

NO SE ACEPTA
RESPONSABILIDAD
DEL TEXTO

01402b

Eduardo Caicedo
CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
AS FUNCIONES INDICADAS

13

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91908772

CAMARA DE COMERCIO DE BOGOTA

SEDE CHAPINERO

24 DE MAYO DE 2010 HORA 14:47:47

R028450262 PAGINA: 1 de 3

* *

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* EN JUNIO DE ESTE AÑO SE ELEGIRAN JUNTA DIRECTIVA Y REVISOR FISCAL *
* DE LA CAMARA DE COMERCIO DE BOGOTA. LAS INSCRIPCIONES DE *
* CANDIDATOS DEBEN HACERSE EN LA PRIMERA QUINCENA DE MAYO. *
* PARA INFORMACION DETALLADA DIRIGIRSE A LA SEDE PRINCIPAL, QUINTO *
* PISO, O COMUNICARSE AL SIGUIENTE TELEFONO: 5941000 EXTENSION 2899.*
****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O INSCRIPCION DE DOCUMENTOS

CERTIFICA:

NOMBRE : CAVELIER ABOGADOS
N.I.T. : 860041367-3
DOMICILIO : BOGOTA D.C.

CERTIFICA:

NO: 00820237

CERTIFICA:

CONSTITUCION : QUE POR ESCRITURA PUBLICA NO. 0006233 DE NOTARIA SEXTA DE BOGOTA D.C. DEL 10 DE SEPTIEMBRE DE 1974 , INSCRITA EL 26 DE SEPTIEMBRE DE 1974 BAJO EL NUMERO 00021234 DEL LIBRO IX, SE CONSTITUYO LA SOCIEDAD CIVIL DENOMINADA: CAVELIER PERDOMO Y CAVELIER.

CERTIFICA :

QUE POR ESCRITURA PUBLICA NO. 0001000 DE NOTARIA SEXTA DE BOGOTA D.C. DEL 10 DE MARZO DE 1983 , INSCRITA EL 5 DE ABRIL DE 1983 BAJO EL NUMERO 00130769 DEL LIBRO IX, LA SOCIEDAD CAMBIO SU NOMBRE DE : CAVELIER PERDOMO Y CAVELIER. POR EL DE : CAVELIER ABOGADOS

CERTIFICA:

QUE POR ESCRITURA PUBLICA NUMERO 1.000 OTORGADA EN LA NOTARIA 6A DE BOGOTA EL 10 DE MARZO DE 1.983, INSCRITA EN ESTA CAMARA DE COMERCIO EL 5 DE ABRIL DE 1.983 BAJO EL NUMERO 130769 DEL LIBRO IX, LA SOCIEDAD CAMBIO SU NOMBRE DE: CAVELIER PERDOMO Y CAVELIER, POR EL DE: CAVELIER ABOGADOS, E INTRODUJO OTRAS REFORMAS.

CERTIFICA:

CERTIFICA

QUE POR E.P.NO. 2.034 DE LA NOTARIA 6 DE SANTAFE DE BOGOTA DEL 18 DE ABRIL DE 1.995, INSCRITA EL 27 DE ABRIL DE 1.995 BAJO EL NO. 5.937 DEL LIBRO XIII,LA SOCIEDAD TRASLADO SU DOMICILIO DE LA CIUDAD DE SANTAFE DE BOGOTA D.C. AL MUNICIPIO DE TABIO (CUNDINAMARCA).-.

CERTIFICA:

QUE POR ESCRITURA PUBLICA NO. 7710 DE LA NOTARIA SEXTA DE BOGOTA DEL 10 DE OCTUBRE DE 1984, INSCRITA EL 15 DE NOVIEMBRE DE 1984 BAJO EL NO. 1559 DEL LIBRO XIII, LA SOCIEDAD CAMBIO SU

NOTARIA SEXTA DE BOGOTA

NATURALEZA JURIDICA DE SOCIEDAD COMERCIAL A SOCIEDAD CIVIL.

CERTIFICA:

REFORMAS:

ESCRITURAS NO.	FECHA	NOTARIA	INSCRIPCION
842	10-V-1.977	18. BTA.	27-V-1.977-NO. 46.204
3.430	1-VII-1.980	6A. BTA.	3-IX-1.980-NO. 89.582
4.844	10-IX-1.980	6A. BTA.	8-X-1.980-NO. 91.261
432	10-II-1.983	6A. BTA.	1-III-1.983-NO.129.337
7.710	10-X-1.984	6A. BTA.	15-XI-1.984-NO. 1.559
7.305	21-X-1.985	6A. BTA.	18-XI-1.985-NO. 1.906
2.567	29-IV-1.987	6A. BTA.	7-V- 1.987-NO. 2.386
4.278	3-VII-1.987	6A. BTA.	23-VII-1987 NO.215.652
2.657	25- IV-1.988	6A. BTA.	19- V -1988-NO. 2,740
9.033	21-XII-1.990	6A. BTA.	10- I - 1991-NO. 3.786
25	3- I -1.991	6A. BTA.	10- I - 1991-NO. 3.787
1.608	8-III-1.991	6A. BTA.	14-III- 1991-NO. 3.841
2.155	2-IV- 1.991	6A. BTA.	8-IV - 1991-NO. 3.862
797	7-II -1.991	6A. BTA.	7- V -1991-NO. 3.882
1.739	14-III-1.991	6A. BTA.	7- V -1991-NO. 3.881
5.886	21-VIII-1.991	6A. BTA	27-VIII-1991 NO. 4.019
8.596	4-XII -1.991	6A. BTA	16-III -1992 NO. 4.430
1.494	10-III -1.992	6A. BTA.	19-III -1992 NO. 4.436
4.205	8 -VII -1.992	6A. BTA.	15-VII -1992 NO. 4.554
8.829	16-XII -1.992	6A. BTA.	24-XII -1992 NO. 4.819
12	5-I -1.993	6 STAFE BTA	13-I -1993 NO. 4.850
4.877	29-VI -1.993	6 STAFE BTA	7-VII -1993 NO. 5.065
5.216	12-VII -1.993	6 STAFE BTA	16-VII -1993 NO. 5.077
ACTA NO.71	2-IX- 1.993	JUNTA DE SOCIOS	29-IX- 1993 NO. 5.174
2.034	18-IV- 1.995	6 STAFE BTA	27- IV -1995 NO. 5.937
2.227	25-IV-1.995	6 STAFE BTA	18-VIII-1.995 NO. 6.092
7.594	12-XII-1.995	6 STAFE BTA	19- XII-1.995 NO. 6.294
676	11- II-1.997	6 STAFE BTA	14- II -1.997 NO. 6.873

CERTIFICA:

REFORMAS:

E.P. NO.	FECHA	NOTARIA	CIUDAD	FECHA	NO.INSC.
0004506	1997/07/28	0006	BOGOTA D.C.	1997/09/02	00007115
0002103	1998/04/08	0006	BOGOTA D.C.	1998/04/21	00007426
0005326	1998/08/06	0006	BOGOTA D.C.	1998/08/13	00007544
0005538	1998/08/14	0006	BOGOTA D.C.	1998/08/27	00007564
0007760	1998/11/10	0006	BOGOTA D.C.	1998/11/12	00007644
0006709	1997/11/04	0006	BOGOTA D.C.	2000/12/04	00008481
0003034	2003/05/30	0006	BOGOTA D.C.	2003/06/04	00882729
0003786	2004/07/16	0006	BOGOTA D.C.	2004/07/28	00009703
0001432	2005/03/18	0006	BOGOTA D.C.	2005/04/07	00009917
0004818	2005/08/22	0006	BOGOTA D.C.	2005/08/26	00010008
0005506	2007/07/17	0006	BOGOTA D.C.	2007/07/24	00010841
5453	2009/10/19	0006	BOGOTA D.C.	2009/10/21	00012243
1336	2010/03/16	0006	BOGOTA D.C.	2010/03/24	00012506

CERTIFICA:

VIGENCIA: QUE LA SOCIEDAD NO SE HALLA DISUELTA. DURACION HASTA EL 10 DE SEPTIEMBRE DE 2024 .

28 MAY 2010

CERTIFICA:

OBJETO SOCIAL: LA SOCIEDAD TENDRA POR OBJETO : EL EJERCICIO DE LA ACTIVIDAD PROFESIONAL DE ABOGADOS. EN DESARROLLO DE ESTE OBJETO LA SOCIEDAD PODRA ADQUIRIR, CONTRAER OBLIGACIONES Y CELEBRAR TODA CLASE DE CONTRATOS DIRECTAMENTE RELACIONADOS Y SUBORDINADOS AL

Jaime Vargas Ramírez NOTARIO ENCARGADO NOTARIA SEXTA DE BOGOTÁ

14

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CAMARA DE COMERCIO DE BOGOTA

SEDE CHAPINERO

24 DE MAYO DE 2010 HORA 14:47:47

R028450262 PAGINA: 2 de 3

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MISMO, INCLUSIVE LOS DE ARRENDAMIENTO, HIPOTECA, MUTUO CON O SIN INTERES, MANDATO CIVIL Y COMERCIAL, Y SOCIEDAD, ASI COMO PARTICIPAR EN ASOCIACIONES CIENTIFICAS, GREMIALES O PROFESIONALES SIN ANIMO DE LUCRO.

CERTIFICA:

CAPITAL Y SOCIOS: $10,000.00 DIVIDIDO EN 10,000.00 CUOTAS CON VALOR NOMINAL DE $1.00 CADA UNA, DISTRIBUIDO ASI :

- SOCIO CAPITALISTA (S)

ASOCIACION CAVELIER DEL DERECHO N.I.T. 000008001722568
NO. CUOTAS: 8,800.00 VALOR: $8,800.00
GAUDEBERT DE CAVELIER AGNES JEANNE C.E. 000000000131100
NO. CUOTAS: 1,200.00 VALOR: $1,200.00

- SOCIO INDUSTRIAL (S)

SUAREZ DE PAEZ LUZ CLEMENCIA C.C. 000000035456344
NO. CUOTAS: 0.00 VALOR: $0.00
CHAVARRO JORGE C.C. 000000016209380
NO. CUOTAS: 0.00 VALOR: $0.00
TOTALES
NO. CUOTAS: 10,000.00 VALOR: $10,000.00

CERTIFICA:

QUE POR ESCRITURAS PUBLICAS NO. 001431 Y 001432 DEL 18 DE MARZO DE 2005 DE LA NOTARIA 06 DE BOGOTA D.C., INSCRITA EL 07 DE ABRIL DE 2005 BAJO EL NO. 0009918 Y 0009917, RESPECTIVAMENTE DEL LIBRO XIII, DE LAS MIL DOSCIENTAS (1200) PARTES DE INTERES SOCIAL RADICADAS EN CABEZA DE AGNES GAUDEBERT DE CAVELIER, SEISCIENTAS (600) PARTES ESTAN GRAVADAS O AFECTADAS EN PROPIEDAD FIDUCIARIA A FAVOR DE LAS SIGUIENTES PERSONAS : GERMAN CAVELIER FRANCO, ERNESTO CAVELIER FRANCO, JORGE CAVELIER FRANCO, INES CAVELIER FRANCO, GUILLERMO CAVELIER FRANCO, ELENA CAVELIER FRANCO, ALEJANDRO CAVELIER FRANCO, BEATRIZ CAVELIER FRANCO, Y LUCIA CAVELIER FRANCO.

CERTIFICA:

REPRESENTACION LEGAL: EL REPRESENTANTE LEGAL ES EL DIRECTOR. EL SOCIO FUNDADOR GERMAN CAVELIER GAVIRIA TENDRA EL CARACTER DE PRESIDENTE DIRECTOR VITALICIO, PARTICIPARA POR DERECHO PROPIO EN EL CONSEJO SUPERIOR Y EN EL CONSEJO DIRECTIVO Y LLEVARA LA REPRESENTACION LEGAL DE LA SOCIEDAD CUANDO LO ESTIME PERTINENTE SIN LIMITACION ALGUNA. IGUAL PARTICIPACION Y ATRIBUCIONES TENDRA SU SUPLENTE AGNES GAUDEBERT DE CAVELIER CUANDO OCUPE EL CARGO, EN CASO DE FALTA ABSOLUTA DE GERMAN CAVELIER GAVIRIA. LOS SOCIOS COLECTIVOS ESTÁN AUTORIZADOS PARA EJERCER LA REPRESENTACIÓN DE LA SOCIEDAD EN CUALQUIER TIEMPO, SIN PERJUICIO DE LAS DELEGACIONS CONFERIDAS A LOS ORGANOS CREADOS POR LOS PRESENTES ESTATUTOS

CERTIFICA:

** NOMBRAMIENTOS **

28 MAY 2010

REPUBLICA DE COLOMBIA NOTARIA SEXTA ENCARGADO Jaime Vargas NOTARIO ENCARGADO

NOTARIA SEXTA DE BOGOTA

QUE POR ESCRITURA PUBLICA NO. 0004818 DE NOTARIA 6 DE BOGOTA D.C. DEL 22 DE AGOSTO DE 2005, INSCRITA EL 26 DE AGOSTO DE 2005 BAJO EL NUMERO 00010008 DEL LIBRO XIII, FUE (RON) NOMBRADO (S):

NOMBRE IDENTIFICACION

PRESIDENTE DIRECTOR VITALICIO

CAVELIER GAVIRIA GERMAN C.C. 000000002877924

QUE POR ACTA NO. 26 DE ASAMBLEA GENERAL DEL 13 DE MAYO DE 2010, INSCRITA EL 24 DE MAYO DE 2010 BAJO EL NUMERO 00012618 DEL LIBRO XIII, FUE (RON) NOMBRADO (S):

NOMBRE IDENTIFICACION

DIRECTORA

ZAPATA GIRALDO ADRIANA C.C. 000000051680061

QUE POR ESCRITURA PUBLICA NO. 0004818 DE NOTARIA 6 DE BOGOTA D.C. DEL 22 DE AGOSTO DE 2005, INSCRITA EL 26 DE AGOSTO DE 2005 BAJO EL NUMERO 00010008 DEL LIBRO XIII, FUE (RON) NOMBRADO (S):

NOMBRE IDENTIFICACION

SUPLENTE DEL PRESIDENTE DIRECTOR VITALICIO

GAUDEBERT DE CAVELIER AGNES JEANNE C.E. 000000000131100

CERTIFICA:

FACULTADES DEL REPRESENTANTE LEGAL: APARTE DE LAS FACULTADES Y DEBERES QUE DE TIEMPO EN TIEMPO SE LE ASIGNEN POR EL CONSEJO SUPERIOR, EL DIRECTOR TENDRA LAS SIGUIENTES FUNCIONES : A) LA DE REPRESENTAR LEGALMENTE A LA SOCIEDAD ANTE LAS AUTORIDADES DE CUALQUIER ORDEN O NATURALEZA Y ANTE OTRAS PERSONAS NATURALES O JURIDICAS, CON FACULTADES PARA NOVAR, TRANSIGIR, COMPROMETER Y DESISTIR Y PARA COMPARECER EN JUICIOS INCLUSIVE EN AQUELLOS EN DONDE SE DISPUTE LA PROPIEDAD DE BIENES INMUEBLES; B) CUMPLIR Y HACER CUMPLIR LOS ESTATUTOS Y REGLAMENTOS DE LA SOCIEDAD; Y C) CREAR O SUPRIMIR TODOS LOS EMPLEOS QUE SEAN NECESARIOS DE ACUERDO CON EL CONSEJO SUPERIOR PARA EL BUEN FUNCIONAMIENTO DE LA SOCIEDAD, ASIGNARLES FUNCIONES, FIJAR SUS SALARIOS Y NOMBRAR LAS PERSONAS QUE DEBAN DESEMPEÑARLOS, ASI COMO RETIRARLOS Y REEMPLAZARLOS CUANDO HAYA LUGAR. CUANDO CUALQUIERA DE LOS ACTOS INDICADOS EN LA CLAUSULA ANTERIOR SE REFIERA A OPERACIONES CUYO MONTO EXCEDA DE LA SUMA EQUIVALENTE A CIENTO OCHENTA (180) SALARIOS MINIMOS MENSUALES, SU CELEBRACION REQUERIRA LA APROBACION PREVIA DEL CONSEJO SUPERIOR.

CERTIFICA:

** REVISOR FISCAL **

QUE POR ACTA NO. 0000071 DEL 2 DE SEPTIEMBRE DE 1993, INSCRITA EL 29 DE SEPTIEMBRE DE 1993 BAJO EL NUMERO 00005175 DEL LIBRO XIII, FUE (RON) NOMBRADO (S):

NOMBRE IDENTIFICACION

REVISOR FISCAL

RINCON FANDIÑO MIGUEL ALFONSO C.C. 000000002877024

CERTIFICA:

DE CONFORMIDAD CON LO ESTABLECIDO POR LA LEY 962 DE 2005, LOS ACTOS DE REGISTRO AQUI CERTIFICADOS QUEDAN EN FIRME CINCO (5) DIAS HABILES DESPUES DE LA FECHA DE INSCRIPCION, SIEMPRE QUE NO SEAN OBJETO DE RECURSOS EN LA VIA GUBERNATIVA.

* * * EL PRESENTE CERTIFICADO NO CONSTITUYE PERMISO DE * * *
* * * FUNCIONAMIENTO EN NINGUN CASO * * *

28 MAY 2010

SEÑOR EMPRESARIO, SI SU EMPRESA TIENE ACTIVOS INFERIORES A 30.000 SMLMV Y UNA PLANTA DE PERSONAL DE MENOS DE 200 TRABAJADORES, USTED

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CAMARA DE COMERCIO DE BOGOTA

SEDE CHAPINERO

24 DE MAYO DE 2010 HORA 14:47:47

R028450262 PAGINA: 3 de 3

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TIENE DERECHO A RECIBIR UN DESCUENTO EN EL PAGO DE LOS PARAFISCALES DE 75% EN EL PRIMER AÑO DE CONSTITUCION DE SU EMPRESA, DE 50% EN EL SEGUNDO AÑO Y DE 25% EN EL TERCER AÑO. LEY 590 DE 2000 Y DECRETO 525 DE 2009.

RECUERDE INGRESAR A www.supersociedades.gov.co PARA VERIFICAR SI SU EMPRESA ESTA OBLIGADA A REMITIR ESTADOS FINANCIEROS. EVITE SANCIONES.

EL SECRETARIO DE LA CAMARA DE COMERCIO,
VALOR : $ 3,600
DE CONFORMIDAD CON EL DECRETO 2150 DE 1995 Y LA AUTORIZACION IMPARTIDA POR LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, MEDIANTE EL OFICIO DEL 18 DE NOVIEMBRE DE 1996, LA FIRMA MECANICA QUE APARECE A CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES

28 MAY 2010

NOTARIA SEXTA DE BOGOTA

de 2010 por ELAN PHARMACEUTICALS, INC. documento que está debidamente legalizado por. Apostilla. ----------

Presente la señora **ADRIANA ZAPATA GIRALDO**, domiciliada en Bogotá, identificada como aparece al pie de su firma y manifestó que está conforme con el contenido de esta escritura pública. ----------

hasta aquí la minuta presentada (e-mail)

OTORGAMIENTO Y AUTORIZACION.- Leída la presente escritura por la compareciente y advertidos sobre las formalidades y trámites de rigor, le impartió su aprobación y en constancia la firma por ante mí y conmigo el Notario que la autoriza. ----------

COMPROBANTES FISCALES.- El Notario certifica que se cumplió con lo dispuesto al respecto por las disposiciones legales vigentes sobre la materia. ----------

DERECHOS NOTARIALES.- Resolución N° 10301 del 17 diciembre de 2009 $ 42.860 IVA $ 19.782 - - - - - - - - - - - - - - - - - -

PAPEL NOTARIAL : Esta escritura se extendió de acuerdo con la minuta presentada y queda protocolizada en las hojas de papel autorizado números 7 700034 715026 - 7 700034 715019 - - - - - - - - - -

EN BLANCO... EN BLANCO

ADRIANA ZAPATA GIRALDO

CC.No. 51680061

Representante legal **CAVELIER ABOGADOS**

NOTARÍA SEXTA DE BOGOTÁ

IMPRESO EN ABRIL 1° DE 2010 POR POLYPRINT EDITORIAL LTDA. - NIT 830.029.959-5

PAPEL DE USO EXCLUSIVO DEL PROTOCOLO NOTARIAL . NO TIENE COSTO PARA EL USUARIO

REPÚBLICA DE COLOMBIA
Jaime Vargas Chambo
NOTARIO
ENCARGADO
NOTARÍA SEXTA DE BOGOTÁ

JAIME VARGAS CHAMBO

NOTARIO SEXTO (6º) (E) DE BOGOTA D.C.

ELABORO : Mac.2010-PODER poder ELAN

ES FIEL Y TERCERA (3ª) (FOTOCOPIA) TOMADA DE LA ESCRITURA PUBLICA NUMERO 2.833 DE FECHA 28 DE MAYO DE 2.010

COPIA QUE EXPIDO EN 13 HOJAS RUBRICADAS EN SUS MARGENES, LA CUAL CARECE DE NOTAS DE REVOCATORIA, MODIFICACIÓN O SUSTITUCIÓN, POR TANTO SE PRESUME VIGENTE EL PODER EN ELLA CONTENIDO.

BOGOTÁ, D.C. 17 DE MARZO DE 2.011

RESOLUCIÓN 01 DE 2008

POR EL(LA) NOTARIO(A) SEXTO(A) (6ª) DE BOGOTÁ D.C.

REPÚBLICA DE COLOMBIA
Amparo Quintero Arturo
NOTARIA
NOTARIA SEXTA DE BOGOTÁ

AMPARO QUINTERO ARTURO
NOTARIO(A) SEXTO(A) (6ª) DE BOGOTÁ D.C.

18

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 March 2010 (11.03.2010)

PCT

(10) International Publication Number
WO 2010/028213 A3

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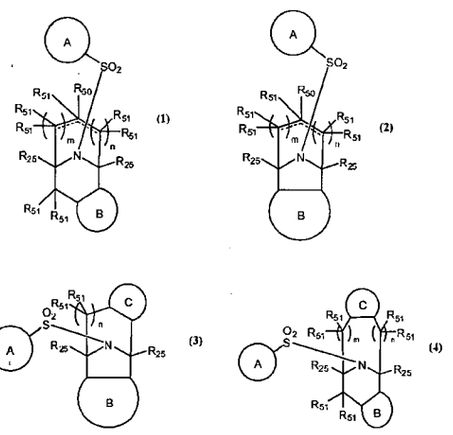
(54) Title: N-SULFONAMIDO POLYCYCLIC PYRAZOLYL COMPOUNDS



(57) Abstract: The current invention provides compounds having a structure according to Formulae (1), (2), (3), and (4): wherein the A-ring, B-ring, C-ring, m, n, R_{25}, R_{50}, and R_{51} are as described in the specification. The invention also provides pharmaceutical compositions comprising compounds of Formulae (1), (2), (3), and (4), as well as methods of treating cognitive disorders, such as Alzheimer's disease. The invention further provides intermediates useful in preparing the compounds of Formulae (1), (2), (3), and (4).

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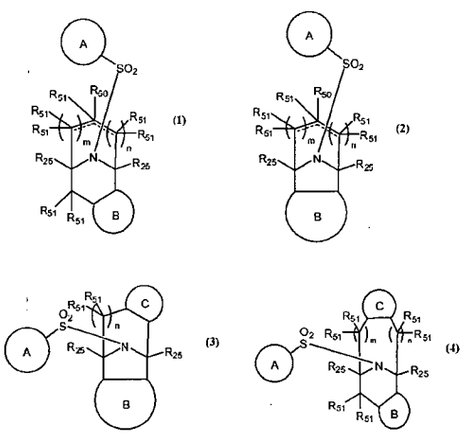

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N-Sulfonamido Polycyclic Pyrazolyl Compounds

BACKGROUND OF THE INVENTION

Field of the Invention

The invention relates to N-sulfonamido polycyclic pyrazolyl compounds having a pendant or fused aryl or heteroaryl ring on the polycyclic ring, which inhibit gamma secretase and ß-amyloid peptide release and/or its synthesis. Therefore, the N-sulfonamido polycyclic pyrazolyl compounds of the present invention are useful in the prevention of cognitive disorders 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.

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, gives 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, *e.g.*, 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 (Goate et al., Nature, 349:704-706 (1990); Chartier Harlan et al., Nature, 353:844-846 (1989); 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.)

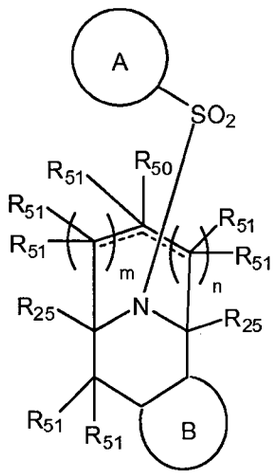
Current evidence indicates that in addition to APP processing leading to β-amyloid synthesis, gamma-secretase also mediates the intra-membrane cleavage of other type I transmembrane proteins (reviewed in Fortini, M. E. (2002). "Gamma-secretase-mediated proteolysis in cell-surface-receptor signaling." 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.

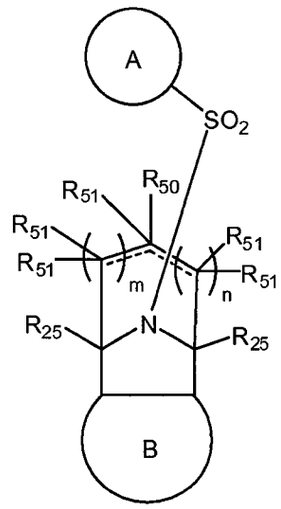
Disruption of Notch signaling via genetic knock-out (KO) results in embryonic lethal phenotype in mice (Swiatek, P. J., C. E. Lindsell, F. F. del Amo, G. Weinmaster and T. Gridley (1994). "Notch1 is essential for postimplantation development in mice." Genes Dev 8(6): 707-19; Conlon, R. A., A. G. Reaume 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.

SUMMARY OF THE INVENTION

Provided herein are compounds of Formulas 1, 2, 3, and 4, which have the following formulas:



Formula 1



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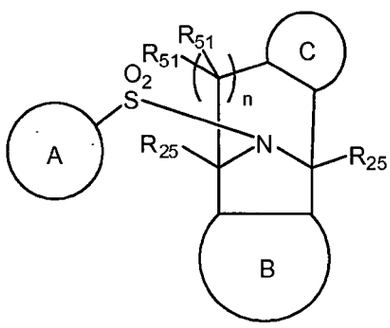

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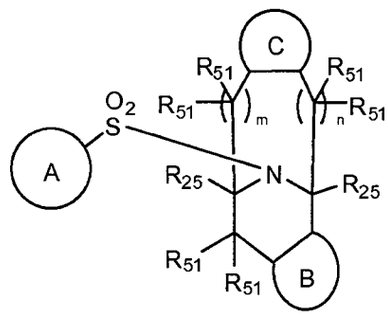


Formula 4

or stereoisomers, enantiomers, pharmaceutically acceptable salts, or solvates thereof, wherein in Formulae 1 and 2, m and n are independently selected from 0, 1 and 2, with the proviso that (m + n) is 1 or 2; in Formula 3 n is 0 or 1; in Formula 4, m and n are independently 0 or 1, provided that m + n = 0 or 1;

wherein the C-ring is aryl (*e.g.*, phenyl) substituted with R_{30}, R_{35}, R_{40}, and R_{45}, heteroaryl, heterocycloalkyl or cycloalkyl, wherein the heteroaryl, heterocycloalkyl and cycloalkyl groups are optionally substituted *e.g.*, with halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, -C(O)OR_{11}, CN, hydroxyl, C_1-C_6 alkoxy, -C_1-C_6 alkyl-OH, -C_1-C_6 alkyl-C_1-C_6 alkoxy, aryloxy (*e.g.*, phenyloxy), -S(O_2)R_{10}, -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alkanoyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl,

pyrimidinyl, imidazolyl, indolyl, furanyl, thienyl, phenyl or phenyl C_1-C_4 alkyl, wherein the phenyl portions of the above are optionally substituted *e.g.*, with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalkyl (*e.g.* CF_3), C_1-C_4 haloalkoxy (*e.g.* OCF_3), hydroxyl, CN, NO_2 or halogen;

R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen, C_1-C_6 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, -C(O)OR_{11}, -$SO_2NR_{11}R_{11}$, arylalkyl, cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, CN, NO_2, hydroxyl, C_1-C_6 alkoxy, -C_1-C_6 alkyl-OH, -C_1-C_6 alkyl-C_1-C_6 alkoxy, aryloxy, -$S(O_2)R_{10}$, -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alkanoyl, heteroarylalkyl, heteroaryl, wherein each heteroaryl group is optionally substituted with a C_1-C_6 alkyl group, heterocycloalkyl C_1-C_6 alkyl, heterocycloalkyl (*e.g.*, pyrrolidinyl, imidazolidinyl, piperidinyl, morpholinyl), wherein each heterocycloalkyl group is optionally substituted *e.g.*, with one or two groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy or halogen, aryl (*e.g.*, phenyl or naphthyl), aryloxy (*e.g.*, phenyloxy or naphthyloxy) or arylalkyl (*e.g.*, phenyl C_1-C_6 alkyl), where the aryl portions of the above are optionally substituted *e.g.*, with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky (*e.g.* CF_3), C_1-C_4 haloalkoxy (*e.g.* OCF_3), hydroxyl, CN, NO_2 or halogen; and

wherein when the C-ring is aryl or heteroaryl, two adjacent substituents of the C-ring, together with the carbons to which they are attached, optionally form a heterocycloalkyl (*e.g.*, -OCH_2O-, -OC(O)O- or –OCH_2CH_2O-) or a heteroaryl ring, each of which is optionally substituted *e.g.*, with one or more groups that are independently alkyl, alkoxy, halogen or C_2-C_4 alkanoyl wherein the alkanoyl group is optionally further substituted with up to 3 halogen atoms; or two adjacent carbons of the C-ring optionally form a benzo ring which is optionally substituted *e.g.*, with 1 to 4 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2;

dashed bonds may be a single or double bond;

the A-ring is aryl, cycloalkyl, heteroaryl or heterocycloalkyl, where each ring is optionally substituted *e.g.*, 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, haloalkyl, haloalkoxy, hydroxyl, hydroxyalkyl, CN, aryloxy, -$S(O)_{0\text{-}2}$-(C_1-C_6 alkyl), -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, NO_2, CN, C_2-C_6 alkanoyl, C_0-C_3alkylCO_2R_{11}, heteroaryl, heterocycloalkyl, aryl, arylalkyl, -OCH_2O-, -OCH_2CH_2O- or -$SO_2NR_{11}R_{11}$;

the B-ring is a heteroaryl ring (*e.g.*, imidazolyl or pyrazolyl) or a heterocycloalkyl ring (*e.g.* dihydropyrazolyl, pyrazolonyl or pyrazolidinonyl) each of which is optionally

substituted at a substitutable position *e.g.*, with one or more R_{20} groups, which are independently selected from $-NR_{11}$-C_2-C_6 alkanoyl, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, C_1-C_6 alkylamino, C_1-C_6 dialkylamino, $-S(O)_{0-2}R_{10}$, hydroxy, hydroxyalkyl, halo, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-C(O)R_{10}$, $-C(O)OR_{11}$, $-C(O)alkylOC(O)R_{10}$; $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, oxo, CN or C_0-C_1alkylaryl (where the aryl group is, *e.g.*, phenyl or naphthyl, where phenyl is preferred), where the aryl is optionally substituted *e.g.*, with 1, 2, 3, 4 or 5 groups that are independently selected from halogen, C_1-C_6 alkyl, $-CO_2R_{11}$, C_1-C_6 alkoxy, haloalkyl, haloalkoxy, hydroxyl, CN, NO_2, aryloxy, $-S(O)_{0-2}$-(C_1-C_6 alkyl), $-NR_{11}R_{11}$, C_2-C_6 alkanoyl, pyridyl, phenyl, and $-SO_2NR_{11}R_{11}$;

R_{50} is oxo, $=N-NHR_{12}$ or $=N-O-R_{13}$ (provided that R_{51} is absent, and R_{50} is not attached to a carbon-carbon double bond) or R_{50} is halogen, C_1-C_6 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, hydroxy, hydroxy C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 haloalkyl, halo C_2-C_8 alkenyl, C_2-C_6 alkanoyl, halo C_2-C_8 alkynyl, $-C(O)OR_{11}$, -(C_1-C_4 alkyl)-$C(O)OR_{11}$, $-CONR_{11}R_{11}$, $-OC(O)NR_{11}R_{11}$, $-NR_{11}C(O)OR_{10}$, $-NR_{11}S(O)_2R_{10}$, $-OS(O)_2R_{10}$, $-S(O)_2R_{10}$, $-NR_{11}C(O)R_{10}$, CN, $-NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, heteroaryl, for instance, pyrazolyl, thiadiazolyl, triazolyl, isoxazolyl, isothiazolyl, imidazolyl, thiazolyl, oxadiazolyl, and pyridyl, heterocycloalkyl, for instance, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, morpholinyl, and imidazolidinyl, C_3 –C_6 cycloalkyl, aryl, for instance, phenyl and naphthyl; wherein the aforementioned heteroaryl, heterocycloalkyl, cycloalkyl and aryl groups are optionally substituted with 1 or more groups that are independently halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxy, hydroxyC_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 haloalkyl, halo C_2-C_6 alkenyl, halo C_2-C_6 alkynyl, $-C(O)OR_{11}$, -(C_1-C_4 alkyl)-$C(O)OR_{11}$, $-CONR_{11}R_{11}$, $-OC(O)NR_{11}R_{11}$, $-NR_{11}C(O)OR_{10}$, $-NR_{11}S(O)_2R_{10}$, $-OS(O)_2R_{10}$, $-S(O)_2R_{10}$, $-NR_{11}C(O)R_{10}$, CN, $=N-NHR_{12}$, $-NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, heteroaryl that is selected from pyrazolyl, thiadiazolyl, triazolyl isoxazolyl, isothiazolyl, imidazolyl, thiazolyl, oxadiazolyl, oxazolyl, tetrazolyl, and pyridyl, heterocycloalkyl that is selected from tetrahydrofuranyl, pyrrolidinyl, piperidinyl, morpholinyl, and imidazolidinyl, C_3 –C_6 cycloalkyl, aryl that is selected from phenyl, benzo[d][1,3]dioxolyl, and naphthyl or $=N-O-R_{13}$; wherein the aforementioned heteroaryl, heterocycloalkyl, cycloalkyl and aryl substituents are optionally substituted with 1 or more groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkoxy or C_1-C_6 haloalkyl;

each R_{51} is independently absent, H, C_1-C_4 alkyl, halogen (*e.g.*, F or Cl), OH, C_1-C_4 alkoxy, CN, amino, mono alkylamino, dialkylamino, C_1-C_4 haloalkoxy (*e.g.*, OCF_3) or C_1-

C_4 haloalkyl (*e.g.*, CF_3); or when there are two R_{51} groups on a carbon atom, the two R_{51} groups and the carbon to which they are attached may form a 3- to 6-membered cycloalkyl or heterocycloalkyl ring; or when there are two R_{51} groups on a carbon, the two R_{51} groups may form an oxo group; or when there are two R_{51} groups on a carbon, the two R_{51} groups may form an alkene group; or when there are two R_{51} groups on a carbon, the two R_{51} groups may form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime);

a non-bridgehead carbon (and any substituent or substituents thereon) in the [3.3.1], [3.2.1] or [2.2.1] ring systems may be replaced with an NR_{15} group;

R_{10} and R_{11} at each occurrence are independently C_3-C_6 cycloalkyl, heteroaryl, heterocycloalkyl, aryl, C_2-C_6 alkanoyl or C_1-C_6 alkyl optionally substituted *e.g.*, with -C(O)OR_{11} or alkoxy, where the alkoxy group is optionally further substituted with -C(O)OR_{11}, and where the heteroaryl and aryl groups are optionally substituted *e.g.*, with 1 to 3 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2; or if two R_{11} groups are on a nitrogen, then the two R_{11} groups together with the nitrogen to which they are attached, may form a 3-8 membered ring optionally including an additional heteroatom such as *e.g.*, NH, NR_{12}, NR_{13}, O or S, and additionally R_{11} may be H;

R_{12} is H, C_1-C_6 alkyl, aryl or –SO_2-aryl, where each aryl is optionally substituted *e.g.*, with 1 to 5 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2;

R_{13} is H, aryl or C_1-C_6 alkyl optionally substituted *e.g.*, with aryl (such as phenyl or naphthyl, more preferably, phenyl), hydroxyl, C_1-C_6 alkoxy or halogen, where each aryl group is optionally substituted *e.g.*, with 1 to 5 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2;

R_{15} is H, phenyl, pyridyl, pyrimidinyl, oxazolyl, thiazolyl, imidazolyl, thienyl, furanyl, pyrrolyl, piperidinyl, piperazinyl, pyrrolidinyl, imidazolidinyl, indolyl, quinolinyl, -SO_2R_{10}, -C(O)R_{10}, –C(O)OR_{11} or C_1-C_6 alkyl optionally substituted *e.g.*, with phenyl, hydroxyl or halogen, where the above cyclic groups are optionally substituted *e.g.*, with 1 to 5 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl (*e.g.*, CF_3 or CH_2CF_3), C_1-C_4 haloalkoxy (*e.g.*, OCF_3 or OCH_2CF_3), CN, amino, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl) (C_1-C_6 alkyl) or NO_2; and

each R_{25} is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -C(O)OR_{11}, -(C_1-C_6 alkyl)-C(O)OR_{11}, C_1-C_6 alkoxy C_1-C_6 alkyl, -$CONR_{11}R_{11}$, CN or hydroxy C_1-C_6 alkyl. One bridgehead carbon and the corresponding R_{25} group in Formulas 1, 2, 3, 4 and/or 5 is

optionally replaced with an N; and in an [3.3.1] core, a non-bridgehead carbon may be replaced with a Z group, where Z is N.

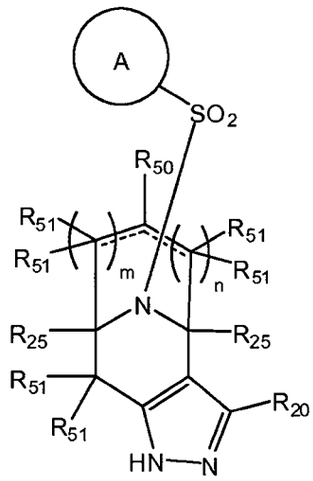
The compounds of Formulas 1, 2, 3, and 4 inhibit β-amyloid peptide release and/or its synthesis and, therefore, are useful in the prevention of neurodegenerative diseases, such as Alzheimers Disease (AD), *e.g.*, in patients susceptible to AD and/or in the treatment of patients with AD in order to inhibit further deterioration in their condition. The invention also encompasses pharmaceutical compositions containing a compound of the invention and methods employing such compounds or compositions in the treatment of cognitive diseases, including Alzheimers disease.

The compounds of Formulas 1, 2, 3, and 4, also provide methods of treating a patient who has AD, methods of preventing a patient from getting Alzheimers disease, methods of helping to prevent or delay the onset of Alzheimers disease, for treating patients with mild cognitive impairment (MCI) and preventing or delaying the onset of Alzheimers 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 Alzheimers disease and who is in need of such treatment which comprises administration of a therapeutically effective amount of a compound of the invention.

In another aspect, provided herein are methods of preparing the compounds of the invention, as well as intermediates useful in preparing the compounds of the invention.

DETAILED DESCRIPTION OF THE INVENTION

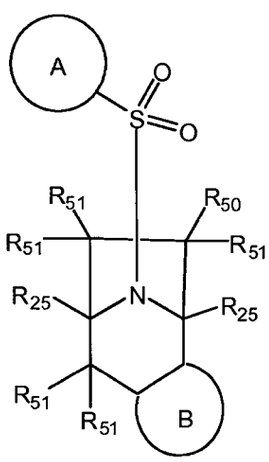
In one aspect, provided herein are compounds of Formula 1a, *i.e.*, compounds of Formula 1 having the formula:



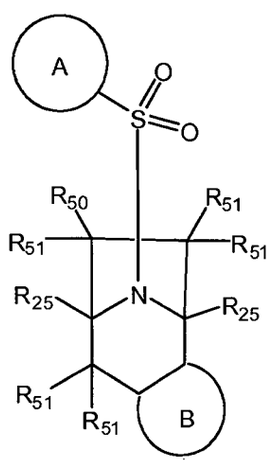
Formula 1a

or stereoisomers, enantiomers or pharmaceutically acceptable salts thereof, wherein R_{25}, R_{50}, R_{51}, m, n, the dashed bonds and the A-ring is as defined above, and wherein R_{20} is H, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, C_1-C_6 alkylamino, C_1-C_6 dialkylamino, halo, CF_3 or $-NR_{11}C(O)R_{10}$.

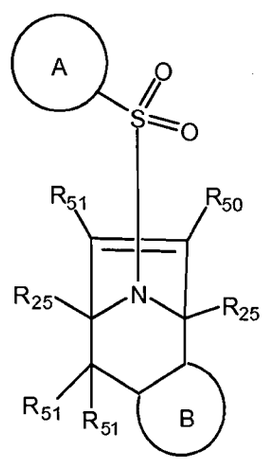
In another aspect, provided herein are compounds of Formulas 1b, 1c, 1d, 1e, 1f or 1g, *i.e.*, compounds of Formula 1 that have the following formulas:



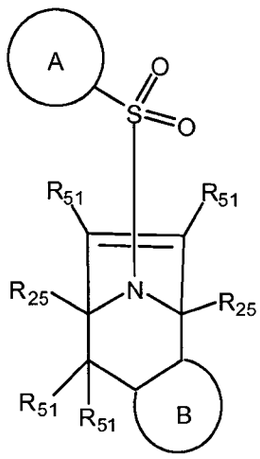
Formula 1b



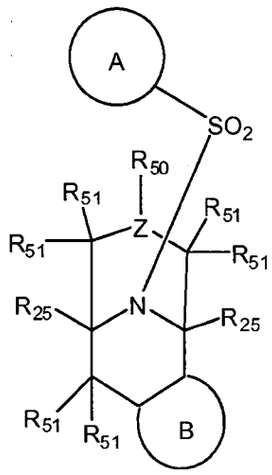
Formula 1c



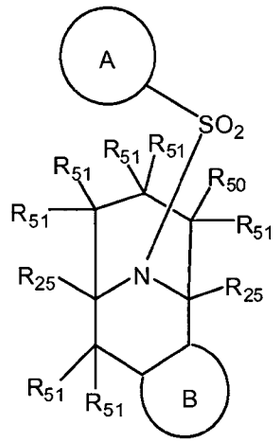
Formula 1d



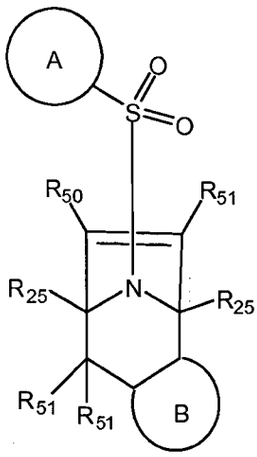
Formula 1e



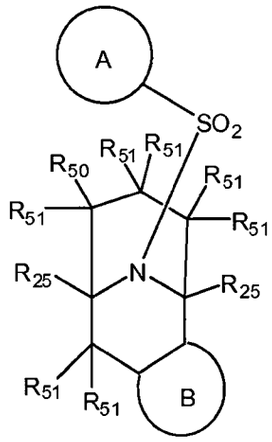
Formula 1f



Formula 1g



Formula 1h



Formula 1i

and enantiomers and/or pharmaceutically acceptable salts thereof, wherein the A-ring, B-ring, R_{25}, R_{50} and R_{51} are as defined above and where Z is N or CH.

In a first aspect, in the compounds of Formulas 1b, 1c, 1d, 1e, 1f, 1g, 1h, and 1i, the B-ring is pyrazolyl, dihydropyrazolyl, pyrazolonyl or pyrazolidinonyl, each of which is optionally substituted with $-NR_{11}$-C_2-C_6 alkanoyl, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxy, hydroxyalkyl, halo, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ or CN.

In an embodiment of this aspect, in the above Formulae, R_{50} is oxo, =N-NHR_{12} or =N-O-R_{13} (except in Formulas 2d, 2e, and 2f) or R_{50} is halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxy, hydroxy C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 haloalkyl, halo C_2-C_6 alkenyl, halo C_2-C_6 alkynyl, $-C(O)OR_{11}$, -(C_1-C_4 alkyl)-$C(O)OR_{11}$, $-CONR_{11}R_{11}$, $-OC(O)NR_{11}R_{11}$, $-NR_{11}C(O)OR_{10}$, $-NR_{11}S(O)_2R_{10}$, $-OS(O)_2R_{10}$, $-S(O)_2R_{10}$,

$-NR_{11}C(O)R_{10}$, CN, $-NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, heteroaryl that is selected from pyrazolyl, thiadiazolyl, triazolyl, isoxazolyl, isothiazolyl, imidazolyl, thiazolyl, oxadiazolyl, and pyridyl, heterocycloalkyl that is selected from tetrahydrofuranyl, pyrrolidinyl, piperidinyl, morpholinyl, and imidazolidinyl, C_3 –C_6 cycloalkyl, aryl that is selected from phenyl and naphthyl; wherein the aforementioned heteroaryl, heterocycloalkyl, cycloalkyl and aryl groups are optionally substituted with 1 or more groups that are independently halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxy, hydroxyC_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 haloalkyl, halo C_2-C_6 alkenyl, halo C_2-C_6 alkynyl, $-C(O)OR_{11}$, -(C_1-C_4 alkyl)-$C(O)OR_{11}$, $-CONR_{11}R_{11}$, $-OC(O)NR_{11}R_{11}$, $-NR_{11}C(O)OR_{10}$, $-NR_{11}S(O)_2R_{10}$, $-OS(O)_2R_{10}$, $-S(O)_2R_{10}$, $-NR_{11}C(O)R_{10}$, CN, $=N-NHR_{12}$, $-NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, heteroaryl that is selected from pyrazolyl, thiadiazolyl, triazolyl isoxazolyl, isothiazolyl, imidazolyl, thiazolyl, oxadiazolyl, oxazolyl, tetrazolyl, and pyridyl, heterocycloalkyl that is selected from tetrahydrofuranyl, pyrrolidinyl, piperidinyl, morpholinyl, and imidazolidinyl, C_3 –C_6 cycloalkyl, aryl that is selected from phenyl, benzo[d][1,3]dioxolyl, and naphthyl or $=N-O-R_{13}$; wherein the aforementioned heteroaryl, heterocycloalkyl, cycloalkyl and aryl substituents are optionally substituted with 1 or more groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkoxy or C_1-C_6 haloalkyl;

provided that in Formulas 1d and 1h, R_{50} is not oxo, $=N-O-R_{13}$ or $=N-NHR_{12}$;

each R_{51} is independently absent, H, C_1-C_4 alkyl, halogen (*e.g.*, F, Cl or Br), CN, amino, mono alkylamino, dialkylamino, OH, C_1-C_4 haloalkoxy (*e.g.*, OCF_3) or C_1-C_4 haloalkyl (*e.g.*, CF_3); or when there are two R_{51} groups on a carbon atom, the two R_{51} groups and the carbon to which they are attached may form a 3- to 6-membered cycloalkyl or heterocycloalkyl ring; or when there are two R_{51} groups on a carbon, the two R_{51} groups may form an oxo group; or when there are two R_{51} groups on a carbon, the two R_{51} groups may form an alkene group; or when there are two R_{51} groups on a carbon, the two R_{51} groups may form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime);

R_{10} and R_{11} at each occurrence are independently C_1-C_6 alkyl, heteroaryl that is selected from pyrazolyl, thiadiazolyl, triazolyl, isoxazolyl, isothiazolyl, imidazolyl, thiazolyl, oxadiazolyl, and pyridyl or aryl that is selected from phenyl and naphthyl, where the heteroaryl and aryl groups are optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2; or if two R_{11} groups are on a nitrogen, then the two R_{11} groups together with the nitrogen to which they are attached,

may form a 3-8 membered ring optionally including an additional heteroatom such as NH, NR_{12}, NR_{13}, O or S; and additionally R_{11} may be H;

R_{12} is H, C_1-C_6 alkyl, aryl or $-SO_2$-aryl (*e.g.*, phenyl or naphthyl, where phenyl is preferred), where each aryl group is optionally substituted with 1 to 5 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2;

R_{13} is H, aryl or C_1-C_6 alkyl optionally substituted with aryl (such as phenyl or naphthyl, more preferably, phenyl), hydroxyl or halogen, where each aryl group is optionally substituted with 1 to 5 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2. In a further embodiment of this aspect, R_{50} is oxo, =N-NHR_{12} or =N-O-R_{13}, (provided that R_{51} is absent, and R_{50} is not attached to a carbon-carbon double bond) or R_{50} is C_2-C_8 alkenyl, C_2-C_8 alkynyl, halo C_2-C_8 alkenyl, halo C_2-C_8 alkynyl, C_2-C_6 alkanoyl, -C(O)OR_{11}, -OS(O)$_2R_{10}$, -S(O)$_2R_{10}$, -$NR_{11}R_{11}$,-$SO_2NR_{11}R_{11}$, heteroaryl, heterocycloalkyl, cycloalkyl or aryl, wherein the heteroaryl, heterocycloalkyl, cycloalkyl and aryl groups are optionally substituted *e.g.*, with 1 or more groups that are independently halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxy, hydroxyC_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 haloalkyl, halo C_2-C_6 alkenyl, halo C_2-C_6 alkynyl, -C(O)OR_{11}, -(C_1-C_4 alkyl)-C(O)OR_{11}, -CON$R_{11}R_{11}$, -OC(O)N$R_{11}R_{11}$, -NR_{11}C(O)OR_{10}, -NR_{11}S(O)$_2R_{10}$, -OS(O)$_2R_{10}$, -S(O)$_2R_{10}$, -NR_{11}C(O)R_{10}, CN, =N-NHR_{12}, -N$R_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, heteroaryl that is selected from pyrazolyl, thiadiazolyl, triazolyl isoxazolyl, isothiazolyl, imidazolyl, thiazolyl, oxadiazolyl, oxazolyl, tetrazolyl, and pyridyl, heterocycloalkyl that is selected from tetrahydrofuranyl, pyrrolidinyl, piperidinyl, morpholinyl, and imidazolidinyl, C_3 –C_6 cycloalkyl, aryl that is selected from phenyl, benzo[d][1,3]dioxolyl, and naphthyl or =N-O-R_{13}; wherein the aforementioned heteroaryl, heterocycloalkyl, cycloalkyl and aryl substituents are optionally substituted with 1 or more groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkoxy or C_1-C_6 haloalkyl. In a further embodiment, R_{50} is C_2-C_6 alkenyl, C_2-C_6 alkynyl, halo C_2-C_6 alkenyl, halo C_2-C_6 alkynyl, C_2-C_6 alkanoyl, OS(O)$_2R_{10}$, -S(O)$_2R_{10}$, -N$R_{11}R_{11}$, C(O)OR_{11} -$SO_2NR_{11}R_{11}$, heteroaryl that is selected from pyrazolyl, thiadiazolyl (*e.g.*, 1,2,4-thiadiazolyl or 1,3,4-thiadiazolyl), triazolyl (*e.g.*, 1,2,3-triazolyl or 1,2,4-triazolyl), isoxazolyl, isothiazolyl, imidazolyl, thiazolyl, oxadiazolyl (*e.g.*, 1,2,4-oxadiazolyl or 1,3,4-oxadiazolyl), oxazolyl, tetrazolyl, and pyridyl, heterocycloalkyl that is selected from tetrahydrofuranyl, pyrrolidinyl, piperidinyl, morpholinyl, and imidazolidinyl, C_3 –C_6 cycloalkyl, aryl that is selected from phenyl, benzo[d][1,3]dioxolyl, and naphthyl or =N-O-R_{13}; wherein the aforementioned heteroaryl, heterocycloalkyl, cycloalkyl and aryl

groups are optionally substituted with 1 or more groups that are independently halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxy, hydroxyC_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 haloalkyl, halo C_2-C_6 alkenyl, halo C_2-C_6 alkynyl, -C(O)OR_{11}, -(C_1-C_4 alkyl)-C(O)OR_{11}, -$CONR_{11}R_{11}$, -OC(O)$NR_{11}R_{11}$, -NR_{11}C(O)OR_{10}, -$NR_{11}S(O)_2R_{10}$, -$OS(O)_2R_{10}$, -$S(O)_2R_{10}$, -NR_{11}C(O)R_{10}, CN, =N-NHR_{12}, -$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, heteroaryl that is selected from pyrazolyl, thiadiazolyl, triazolyl isoxazolyl, isothiazolyl, imidazolyl, thiazolyl, oxadiazolyl, oxazolyl, tetrazolyl, and pyridyl, heterocycloalkyl that is selected from tetrahydrofuranyl, pyrrolidinyl, piperidinyl, morpholinyl, and imidazolidinyl, C_3 –C_6 cycloalkyl, aryl that is selected from phenyl, benzo[d][1,3]dioxolyl, and naphthyl or =N-O-R_{13}; wherein the aforementioned heteroaryl, heterocycloalkyl, cycloalkyl and aryl substituents are optionally substituted with 1 or more groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkoxy or C_1-C_6 haloalkyl;

In an aspect, provided herein are compounds of Formula 1b, 1c, 1d, 1e, 1f, 1g, 1h, and 1i, wherein the B-ring is pyrazolyl, dihydropyrazolyl, pyrazolonyl or pyrazolidinonyl, each of which is as defined in the first aspect, and R_{50} is halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxy C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_2-C_6 alkenyl, halo C_2-C_6 alkynyl, C_1-C_6 haloalkoxy or C_1-C_6 haloalkyl. In one embodiment, R_{50} is halogen, C_1-C_4 alkyl, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 alkoxy, halo C_2-C_4 alkenyl, halo C_2-C_4 alkynyl, C_1-C_4 haloalkoxy or C_1-C_4 haloalkyl. In another embodiment, R_{50} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, hydroxy C_1-C_4 alkyl or C_1-C_4 alkoxy. In still another embodiment, R_{50} is C_1-C_4 alkyl. In yet another embodiment, R_{50} is C_1-C_4 haloalkyl (*e.g.*, CF_3 or CH_2CF_3), hydroxy C_1-C_4 alkyl or C_1-C_4 alkoxy (*e.g.*, methoxy or ethoxy). In another embodiment, R_{50} is C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo C_2-C_4 alkenyl, halo C_2-C_4 alkynyl. In still another embodiment, R_{50} is halogen, hydroxy or hydroxy C_1-C_4 alkyl. In yet still another embodiment, R_{50} is halogen. In yet still another embodiment, R_{50} is hydroxy or hydroxy C_1-C_4 alkyl.

In another aspect, provided herein are compounds of Formula 1b, 1c, 1d, 1e, 1f, 1g, 1h, and 1i, wherein the B-ring is pyrazolyl, dihydropyrazolyl, pyrazolonyl or pyrazolidinonyl, each of which is as defined above and wherein R_{50} is -C(O)OR_{11}, -(C_1-C_4 alkyl)-C(O)OR_{11}, -$CONR_{11}R_{11}$, -OC(O)$NR_{11}R_{11}$, -NR_{11}C(O)OR_{11}, -$NR_{11}S(O)_2R_{10}$, -$OS(O)_2R_{10}$, -$S(O)_2R_{10}$, -NR_{11}C(O)R_{10}, CN, =N-NHR_{12}, =N-O-R_{13}, $NR_{11}R_{11}$ or -$SO_2NR_{11}R_{11}$;

R_{10} and R_{11} at each occurrence are independently C_1-C_6 alkyl, heteroaryl that is selected from pyrazolyl, thiadiazolyl, triazolyl, isoxazolyl, isothiazolyl, imidazolyl, thiazolyl, oxadiazolyl, and pyridyl or aryl that is selected from phenyl and naphthyl, where the heteroaryl and aryl groups are optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, CN or NO_2; and additionally R_{11} may be H; or if two R_{11} groups are on a nitrogen, then the two R_{11} groups together with the nitrogen to which they are attached, may form a 3-8 membered ring optionally including an additional heteroatom such as NH, NR_{12}, NR_{13}, O or S;

R_{12} is H, C_1-C_6 alkyl, aryl or $-SO_2$-aryl (*e.g.*, phenyl or naphthyl, where phenyl is preferred), where each aryl group is optionally substituted with 1 to 5 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2;

R_{13} is H, aryl or C_1-C_6 alkyl optionally substituted with aryl (such as phenyl or naphthyl, more preferably, phenyl), hydroxyl or halogen, where each aryl group is optionally substituted with 1 to 5 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2.

In an embodiment of this aspect, R_{10} is C_1-C_4 alkyl and R_{11} is independently hydrogen or C_1-C_4 alkyl.

In still another embodiment of this aspect, R_{11} is H.

In still another embodiment of this aspect, one of R_{10} and R_{11} is CH_3.

In another embodiment of this aspect, R_{10} and R_{11} together with the nitrogen to which they are attached may form a 3-8 membered ring, which optionally includes an additional heteroatom that is NH, NR_{12}, NR_{13}, O or S.

In still another embodiment of this aspect, R_{10} and R_{11} at each occurrence are independently phenyl optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, CN or NO_2; and additionally R_{11} may be H.

In another embodiment of this aspect, R_{10} and R_{11} at each occurrence are independently pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl or thiazolyl, each of which is optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, CN or NO_2; and additionally R_{11} may be H.

In another embodiment of this aspect, R_{10} and R_{11} at each occurrence are independently thiadiazolyl, triazolyl or oxadiazolyl, each of which is optionally substituted

with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, CN or NO_2; and additionally R_{11} may be H.

In yet still another embodiment of this aspect, R_{13} is H, C_1-C_4 alkyl or benzyl, where then phenyl portion is optionally substituted with halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, CF_3 or OCF_3. In another embodiment, R_{13} is C_1-C_4 alkyl or benzyl.

In another aspect, provided herein are compounds of Formula 1b, 1c, 1d, 1e, 1f, 1g, 1h, and 1i, wherein the B-ring is pyrazolyl, dihydropyrazolyl, pyrazolonyl or pyrazolidinonyl, each of which is as defined above, and wherein R_{50} is $-C(O)OR_{11}$, $-CONR_{11}R_{11}$, $-OC(O)NR_{11}R_{11}$, $-NR_{11}C(O)OR_{10}$, $-NR_{11}S(O)_2R_{10}$, $-OS(O)_2R_{10}$, $-S(O)_2R_{10}$, $-NR_{11}C(O)R_{10}$, $NR_{11}R_{11}$ or $-SO_2NR_{11}R_{11}$, wherein R_{10} and R_{11} at each occurrence are independently C_1-C_6 alkyl, heteroaryl that is selected from pyrazolyl, thiadiazolyl, triazolyl, isoxazolyl, isothiazolyl, imidazolyl, thiazolyl, oxadiazolyl, and pyridyl or aryl that is selected from phenyl and naphthyl, where the heteroaryl and aryl groups are optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, CN or NO_2; or if two R_{11} groups are on a nitrogen, then the two R_{11} groups together with the nitrogen to which they are attached, may form a 3-8 membered ring optionally including an additional heteroatom such as NH, NR_{12}, NR_{13}, O or S, and additionally R_{11} may be H;

R_{12} is H, C_1-C_6 alkyl, aryl or $-SO_2$-aryl (*e.g.*, phenyl or naphthyl, where phenyl is preferred), where each aryl group is optionally substituted with 1 to 5 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2;

R_{13} is H, aryl or C_1-C_6 alkyl optionally substituted with aryl (such as phenyl or naphthyl, more preferably, phenyl), hydroxyl or halogen, where each aryl group is optionally substituted with 1 to 5 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2.

In an embodiment of this aspect, R_{10} is C_1-C_4 alkyl and R_{11} is independently hydrogen or C_1-C_4 alkyl.

In still another embodiment of this aspect, R_{11} is H.

In still another embodiment of this aspect, one of R_{10} and R_{11} is CH_3.

In another embodiment of this aspect, the two R_{11} groups together with the nitrogen to which they are attached form a 3-8 membered ring, which optionally includes an additional heteroatom that is NH, NR_{12}, NR_{13}, O or S.

In another embodiment of this aspect, R_{10} and R_{11} at each occurrence are independently phenyl optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, CN or NO_2; and additionally R_{11} may be H.

In another embodiment of this aspect, R_{10} and R_{11} at each occurrence are independently pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl or thiazolyl, each of which is optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, CN or NO_2; and additionally R_{11} may be H.

In another embodiment of this aspect, R_{10} and R_{11} at each occurrence are independently H, thiadiazolyl, triazolyl or oxadiazolyl, each of which is optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, CN or NO_2; and additionally R_{11} may be H.

In yet still another embodiment of this aspect, R_{13} is H, C_1-C_4 alkyl or benzyl, where then phenyl portion is optionally substituted with halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, CF_3 or OCF_3. In another embodiment, R_{13} is C_1-C_4 alkyl or benzyl.

In another aspect, provided herein are compounds of Formula 1b, 1c, 1d, 1e, 1f, 1g, 1h, and 1i, wherein the B-ring is pyrazolyl, dihydropyrazolyl, pyrazolonyl or pyrazolidinonyl, each of which is as defined above, and wherein R_{50} is heteroaryl that is selected from pyrazolyl, thiadiazolyl, triazolyl, isoxazolyl, isothiazolyl, imidazolyl, thiazolyl, oxadiazolyl, and pyridyl, heterocycloalkyl that is selected from tetrahydrofuranyl, pyrrolidinyl, piperidinyl, morpholinyl, and imidazolidinyl, each of which is optionally substituted with 1 or more groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkoxy or C_1-C_6 haloalkyl.

In an embodiment of this aspect, R_{50} is pyrazolyl or imidazolyl, each of which is optionally substituted with 1 or more groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkoxy (*e.g.*, OCF_3) or C_1-C_4 haloalkyl (*e.g.*, CF_3). In a further embodiment of this aspect, R_{50} is unsubstituted.

In an embodiment of this aspect, R_{50} is thiazolyl or oxadiazolyl each of which is optionally substituted with 1 or more groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkoxy (*e.g.*, OCF_3) or C_1-C_4 haloalkyl (*e.g.*, CF_3). In a further embodiment of this aspect, R_{50} is unsubstituted.

In an embodiment of this aspect, R_{50} is pyridyl, which is optionally substituted with 1 or more groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkoxy (*e.g.*, OCF_3) or C_1-C_4 haloalkyl (*e.g.*, CF_3). In a further embodiment of this aspect, R_{50} is unsubstituted.

In an embodiment of this aspect, R_{50} is thiadiazolyl, which is optionally substituted with 1 or more groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkoxy (*e.g.*, OCF_3) or C_1-C_4 haloalkyl (*e.g.*, CF_3). In a further embodiment of this aspect, R_{50} is unsubstituted.

In an embodiment of this aspect, R_{50} is triazolyl, which is optionally substituted with 1 or more groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkoxy (*e.g.*, OCF_3) or C_1-C_4 haloalkyl (*e.g.*, CF_3). In a further embodiment of this aspect, R_{50} is unsubstituted.

In an embodiment of this aspect, R_{50} is isoxazolyl, which is optionally substituted with 1 or more groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkoxy (*e.g.*, OCF_3) or C_1-C_4 haloalkyl (*e.g.*, CF_3). In a further embodiment of this aspect, R_{50} is unsubstituted.

In an embodiment of this aspect, R_{50} is isothiazolyl, which is optionally substituted with 1 or more groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkoxy (*e.g.*, OCF_3) or C_1-C_4 haloalkyl (*e.g.*, CF_3). In a further embodiment of this aspect, R_{50} is unsubstituted.

In an embodiment of this aspect, R_{50} is selected from tetrahydrofuranyl, pyrrolidinyl, and imidazolidinyl, each of which is optionally substituted with 1 or more groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkoxy (*e.g.*, OCF_3) or C_1-C_4 haloalkyl (*e.g.*, CF_3). In a further embodiment of this aspect, R_{50} is unsubstituted.

In an embodiment of this aspect, R_{50} is piperidinyl or morpholinyl, each of which is optionally substituted with 1 or more groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkoxy (*e.g.*, OCF_3) or C_1-C_4 haloalkyl (*e.g.*, CF_3). In a further embodiment of this aspect, R_{50} is unsubstituted.

In a further embodiment of this aspect, R_{50} is unsubstituted.

In a still further embodiment of this aspect, R_{50} is substituted with one group that is halogen, C_1-C_2 alkyl, C_1-C_2 alkoxy, hydroxy, C_1-C_2 hydroxyalkyl, C_1-C_2 haloalkoxy (*e.g.*, OCF_3) or C_1-C_2 haloalkyl (*e.g.*, CF_3).

In another aspect, provided herein are compounds of Formula 1b, 1c, 1d, 1e, 1f, 1g, 1h, and 1i, wherein the B-ring is pyrazolyl, dihydropyrazolyl, pyrazolonyl or pyrazolidinonyl, each of which is as defined above, and wherein R_{50} is C_3 –C_6 cycloalkyl, which is optionally substituted with 1 or more groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkoxy or C_1-C_6 haloalkyl.

In an embodiment of this aspect, R_{50} is unsubstituted C_3 –C_6 cycloalkyl. In a further embodiment, R_{50} is cyclopropyl.

In another embodiment of this aspect, R_{50} is C_3 –C_6 cycloalkyl substituted with one or two groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkoxy (*e.g.*, OCF_3) or C_1-C_4 haloalkyl (*e.g.*, CF_3).

In still another embodiment, R_{50} is cyclopropyl, cyclopentyl or cyclohexyl, each of which is optionally substituted with halogen, C_1-C_2 alkyl, C_1-C_2 alkoxy (*e.g.*, methoxy), hydroxy, C_1-C_2 hydroxyalkyl, C_1-C_2 haloalkoxy (*e.g.*, OCF_3) or C_1-C_2 haloalkyl (*e.g.*, CF_3).

In still another embodiment, R_{50} is cyclopropyl, substituted with one group that is halogen, C_1-C_2 alkyl, C_1-C_2 alkoxy (*e.g.*, methoxy), hydroxy or C_1-C_2 hydroxyalkyl.

In another aspect, provided herein are compounds of Formula 1b, 1c, 1d, 1e, 1f, 1g, 1h, and 1i, wherein the B-ring is pyrazolyl, dihydropyrazolyl, pyrazolonyl or pyrazolidinonyl, each of which is as defined above, and wherein R_{50} is aryl that is selected from phenyl, benzo[d][1,3]dioxolyl, and naphthyl, each of which is optionally substituted with one or more groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkoxy or C_1-C_6 haloalkyl.

In an embodiment of this aspect, R_{50} is phenyl, which is optionally substituted with one or more groups that are independently halogen (*e.g.*, F), C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkoxy (*e.g.*, OCF_3) or C_1-C_4 haloalkyl (*e.g.*, CF_3).

In another embodiment of this aspect, R_{50} is unsubstituted phenyl.

In still yet another embodiment of this aspect, R_{50} is phenyl, which is substituted with at least one group that is halogen (*e.g.*, F), C_1-C_2 alkyl, C_1-C_2 alkoxy, hydroxy, C_1-C_2 hydroxyalkyl, C_1-C_2 haloalkoxy (*e.g.*, OCF_3), C_1-C_2 haloalkyl (*e.g.*, CF_3) or –CN. In a further embodiment, the phenyl group is substituted with two independently selected groups.

In still yet another embodiment of this aspect, R_{50} is phenyl, which is substituted with at least one group that is halogen (*e.g.*, F), C_1-C_2 alkyl, C_1-C_2 alkoxy, hydroxy, C_1-C_2 hydroxyalkyl, C_1-C_2 haloalkoxy (*e.g.*, OCF_3), C_1-C_2 haloalkyl (*e.g.*, CF_3) or –CN. In a further embodiment, the phenyl group is substituted with two groups. In a still further

embodiment, the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In still yet another embodiment of this aspect, R_{50} is phenyl, which is substituted with one group that is halogen (*e.g.*, F), C_1-C_2 alkyl, C_1-C_2 alkoxy, hydroxy, C_1-C_2 hydroxyalkyl, C_1-C_2 haloalkoxy (*e.g.*, OCF_3) or C_1-C_2 haloalkyl (*e.g.*, CF_3).

In an embodiment of this aspect, R_{50} is benzo[d][1,3]dioxolyl, which is optionally substituted with one or more groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkoxy (*e.g.*, OCF_3) or C_1-C_4 haloalkyl (*e.g.*, CF_3). In a further embodiment, the methylene group of the benzo[d][1,3]dioxolyl group is substituted with one or two C_1-C_4 alkyl groups (such as, *e.g.*, one or two methyl groups).

In another embodiment of this aspect, R_{50} is benzo[d][1,3]dioxolyl, which is unsubstituted.

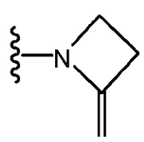
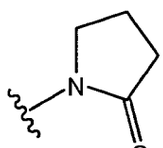
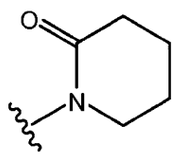
In still yet another embodiment of this aspect, R_{50} is benzo[d][1,3]dioxolyl, which is substituted with at least one group that is halogen, C_1-C_2 alkyl, C_1-C_2 alkoxy, hydroxy, C_1-C_2 hydroxyalkyl, C_1-C_2 haloalkoxy (*e.g.*, OCF_3), C_1-C_2 haloalkyl (*e.g.*, CF_3) or –CN.

In still yet another embodiment of this aspect, R_{50} is benzo[d][1,3]dioxolyl, which is substituted with one group that is halogen, C_1-C_2 alkyl, C_1-C_2 alkoxy, hydroxy, C_1-C_2 hydroxyalkyl, OCF_3 or CF_3.

In another aspect, provided herein are compounds of Formula 1b, 1c, 1d, 1e, 1f, 1g, 1h, and 1i, wherein the B-ring is pyrazolyl, dihydropyrazolyl, pyrazolonyl or pyrazolidinonyl, each of which is as defined above, and wherein R_{50} is C_1-C_4 alkyl and R_{51} H or C_1-C_4 alkyl. In a further embodiment, R_{50} and R_{51} are both methyl.

In one aspect of Formula 1f, Z is N. In a further embodiment of this aspect, R_{50} is $-C(O)OR_{11}$, C_2-C_6 alkanoyl, $-SO_2R_{10}$ or $-CONR_{11}R_{11}$; wherein R_{10} is C_1-C_4 alkyl or C_3-C_6 cycloalkyl; R_{11} is H or C_1-C_6 alkyl; and R_{13} is H or C_1-C_4 alkyl optionally substituted with C_1-C_4 alkoxy. In an embodiment of this aspect, R_{50} is $-C(O)OR_{11}$ and R_{13} is C_1-C_4 alkyl or C_1-C_4 alkyl substituted with C_1-C_4 alkoxy. In another embodiment of this aspect, R_{50} is C_2-C_4 alkanoyl. In an embodiment of this aspect, R_{50} is $-SO_2R_{10}$ and R_{10} is C_1-C_3 alkyl or cyclopropyl. In a further embodiment of this aspect, R_{50} is $-CONR_{11}R_{11}$ and each R_{11} is H or C_1-C_4 alkyl.

In a further embodiment of this aspect, all R_{51} groups are H and the B-ring is pyrazolyl, dihydropyrazolyl, pyrazolonyl or pyrazolidinonyl, each of which is as defined above.

In one aspect of Formula 1e (when Z is CH) and in an aspect of Formula 1a, wherein R_{50} is $NR_{11}R_{11}$, or $-SO_2NR_{11}R_{11}$, or $-S(O)_2R_{10}$, or oxadiazolyl, optionally substituted with C_1-C_4 alkyl, or C_3-C_6 cycloalkyl optionally substituted with C_1-C_4 alkyl or C_1-C_4 alkoxy, or phenyl optionally substituted with one or more groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, $-OCH_2O-$, $-OCH_2CH_2O-$, oxazolidinone (*e.g.*, oxazolidin-2-one), imidazolyl, thiazolyl, $-NR_{11}$-cyclohexyl, where the cyclohexyl is optionally substituted with $NR_{11}R_{11}$, C_1-C_4 alkyl or C_1-C_4 alkoxy; pyrazolyl, tetrazolyl, pyrrolidinonyl, $-NR_{11}R_{11}$, morpholinyl (*e.g.*, morpholin-2-onyl),  ,  ,  or C_2-C_6 alkanoyl; or

pyrazolyl optionally substituted with C_1-C_4 alkyl; or

thiazolyl optionally substituted with C_1-C_4 alkyl, C_1-C_4 haloalkyl (*e.g.*, CF_3 or CHF_2); or

oxazolyl optionally substituted with C_1-C_4 alkyl; or

benzimidazolyl optionally substituted with C_1-C_4 alkyl, C_1-C_4 alkoxy or halogen; or

C_2-C_6 alkenyl optionally substituted with a halogen (*e.g.*, Cl) or C_1-C_4 haloalkyl (*e.g.*, CF_3); or

triazolyl optionally substituted with one or two groups that are independently C_1-C_4 alkyl; or

C_2-C_6 alkynyl optionally substituted with a halogen (*e.g.*, Cl) or C_1-C_4 alkoxy; or

thiadiazolyl optionally substituted with C_1-C_4 alkyl, C_1-C_4 haloalkyl (*e.g.*, CF_3 or CHF_2); or

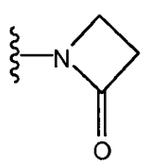
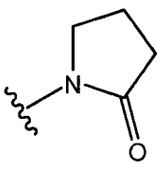
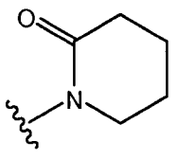
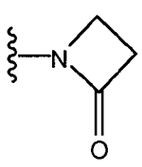
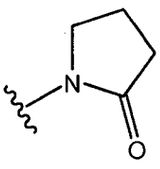
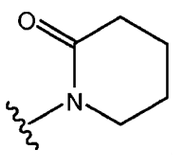
pyridyl optionally substituted with one or more groups that are independently C_1-C_4 alkyl, halogen or C_1-C_4 alkoxy; or

wherein R_{11} is H, C_1-C_6 alkyl or C_2-C_6 alkanoyl, where the alkyl portions of R_{11} are optionally substituted with one or two groups that are independently $-CO_2$-(C_1-C_6 alkyl), C_1-

C_6 alkyl-O-(C_1-C_6 alkyl), C_1-C_6 alkyl-O-(C_1-C_4 alkyl)-CO_2-(C_1-C_6 alkyl), C_1-C_6 alkyl-O-(C_1-C_4 alkyl)-CO_2H.

In an embodiment of this aspect, R_{50} is C_1-C_4 haloalkyl (*e.g.*, CF_3 or CHF_2), CN, C_1-C_4 alkoxy C_1-C_6 alkyl or $NR_{11}R_{11}$; where each R_{11} is independently H or C_1-C_4 alkyl. In a further embodiment, R_{50} is CN. In a still further embodiment, R_{50} is methoxymethyl, methoxyethy, ethoxymethyl or ethoxyethyl.

In an embodiment of this aspect, R_{50} is oxadiazolyl, substituted with a C_1-C_2 alkyl.

In an embodiment of this aspect, R_{50} is phenyl optionally substituted with one or more groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, -OCH_2O-, -OCH_2CH_2O-, oxazolidinone (*e.g.*, oxazolidin-2-one), imidazolyl, thiazolyl, -NR_{11}-cyclohexyl, where the cyclohexyl is optionally substituted with $NR_{11}R_{11}$, C_1-C_4 alkyl or C_1-C_4 alkoxy; pyrazolyl, tetrazolyl, pyrrolidinonyl, -$NR_{11}R_{11}$, morpholinyl (*e.g.*, morpholin-2-onyl),  ,  ,  or C_2-C_6 alkanoyl. In a further embodiment, R_{50} is unsubstituted phenyl. In another embodiment, R_{50} is phenyl substituted with one or more groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy or halogen (*e.g.*, F, Cl or Br). In a further embodiment, R_{50} is phenyl substituted with one group that is C_1-C_4 alkyl, C_1-C_4 alkoxy or halogen (*e.g.*, F, Cl or Br). In another embodiment, R_{50} is phenyl substituted with one group that is selected from oxazolidinonyl, imidazolyl, thiazolyl, pyrazolyl, tetrazolyl, morpholinyl and pyrrolidinonyl. In another embodiment, R_{50} is phenyl substituted with -$NR_{11}R_{11}$. In a further embodiment, the -$NR_{11}R_{11}$ group is -$NHC(O)CH_3$, -NH-(C_1-C_4 alkyl)-CO_2-(C_1-C_4 alkyl), -NH-(C_1-C_4 alkyl)-O-(C_1-C_4 alkyl)-CO_2-(C_1-C_4 alkyl) or -NH-(C_1-C_4 alkyl)-O-(C_1-C_4 alkyl)-CO_2H. In another embodiment, R_{50} is phenyl substituted with one group that is  ,  or  . In another embodiment, R_{50} is phenyl substituted with C_2-C_4 alkanoyl. In a further embodiment, the phenyl is substituted at the four-position.

In an embodiment of this aspect, R_{50} is pyrazolyl optionally substituted with C_1-C_4 alkyl; thiazolyl optionally substituted with C_1-C_4 alkyl (*e.g.*, methyl), C_1-C_4 haloalkyl (*e.g.*, CF_3 or CHF_2); oxazolyl optionally substituted with C_1-C_4 alkyl (*e.g.*, methyl); triazolyl

optionally substituted with one or two groups that are independently C_1-C_4 alkyl; or benzimidazolyl optionally substituted with C_1-C_4 alkyl (*e.g.*, methyl), C_1-C_4 alkoxy or halogen.

In an embodiment of this aspect, R_{50} is C_2-C_6 alkenyl optionally substituted with a halogen (*e.g.*, Cl) or C_1-C_4 haloalkyl (*e.g.*, CF_3).

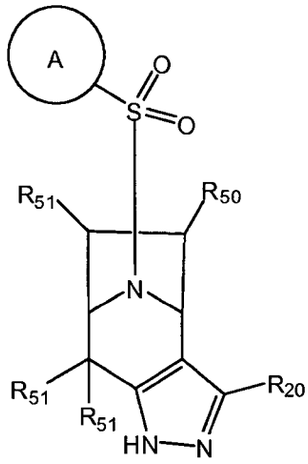
In an embodiment of this aspect, R_{50} is C_2-C_6 alkynyl optionally substituted with a halogen (*e.g.*, Cl) or C_1-C_4 alkoxy.

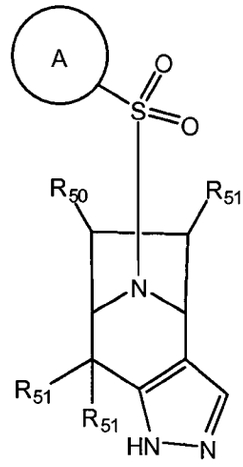
In an embodiment of this aspect, R_{50} is pyridyl optionally substituted with one or more groups that are independently C_1-C_4 alkyl, halogen or C_1-C_4 alkoxy.

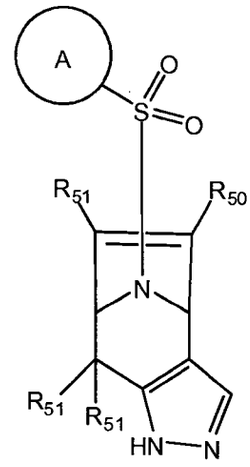
In an aspect of Formula 1f, all R_{51} groups are H and the B-ring is unsubstituted pyrazolyl. In an embodiment of this aspect, Z is CH and R_{50} is CHF_2, CN, -CH_2-O-(C_1-C_4 alkyl), oxadiazolyl optionally substituted with methyl, cyclopropyl, phenyl optionally substituted with one group that is halogen, C_1-C_4 alkyl, oxazolidinonyl, imidazolyl, thiazolyl, pyrazolyl, -$NR_{11}R_{11}$ or C_1-C_4 alkoxy, oxazolyl optionally substituted with C_1-C_4 alkyl, isoxazolyl optionally subsitted with C_1-C_4 alkyl, thiazolyl optionally substituted with CF_3, C_2-C_4 alkenyl optionally substituted with a halogen or a CF_3 group, C_2-C_4 alkynyl, thiadiazolyl, triazolyl optionally substituted with C_1-C_4 alkyl or pyridyl optionally substituted with C_1-C_4 alkyl or C_1-C_4 alkoxy.

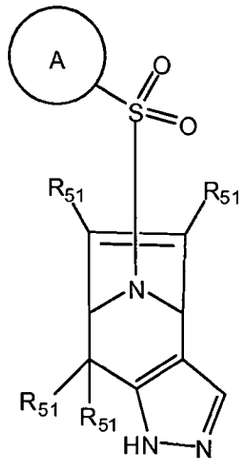
In one aspect of Formulas 1g and 1i, R_{50} is phenyl optionally substituted with one or more groups that are independently phenyl, optionally substituted with one group that is halogen, C_1-C_4 alkyl, oxazolidinonyl, imidazolyl, thiazolyl, pyrazolyl, -$NR_{11}R_{11}$ or C_1-C_4 alkoxy. In an embodiment of this aspect, R_{50} is unsubstituted phenyl.

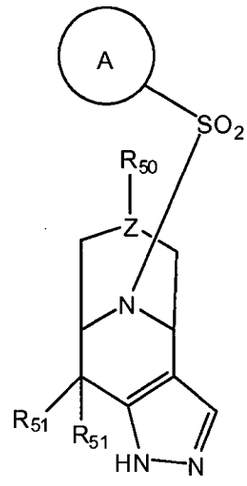
In one aspect, the compounds of 1b, 1c, 1d, 1e, 1f, 1g, 1h and 1i are of the following formulas, respectively:

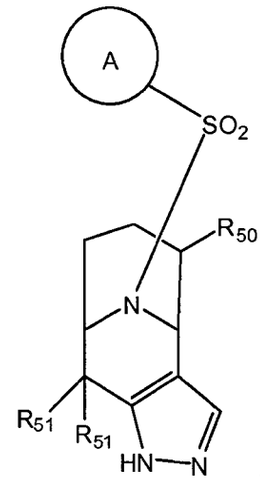












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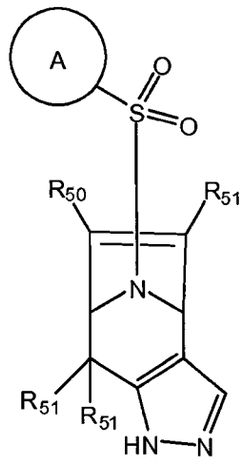
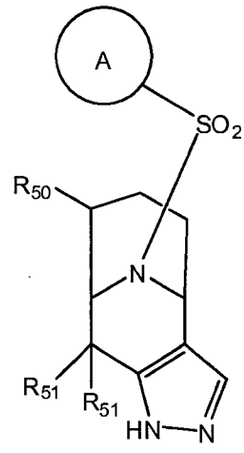




wherein R_{51} and R_{50} are as previously defined in any of the above aspects and/or embodiments.

In a still further embodiment, R_{13} is C_1-C_4 alkyl substituted with phenyl, hydroxyl, C_1-C_6 alkoxy or halogen, where the phenyl is optionally substituted *e.g.*, with 1 to 5 groups

that are independently halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl (*e.g.*, CF_3), C_1-C_4 haloalkoxy (*e.g.*, OCF_3), CN or NO_2. In a yet still further embodiment, R_{13} is C_1-C_4 alkyl substituted with an unsubstituted phenyl. In a still further embodiment, R_{13} is C_1-C_4 alkyl substituted with phenyl, which is substituted with at least one group that is independently halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, CN or NO_2.

In one aspect, the compounds of Formula 1 are the compounds of Formula 1b.

In one aspect, the compounds of Formula 1 are the compounds of Formula 1c.

In one aspect, the compounds of Formula 1 are the compounds of Formula 1d.

In one aspect, the compounds of Formula 1 are the compounds of Formula 1e.

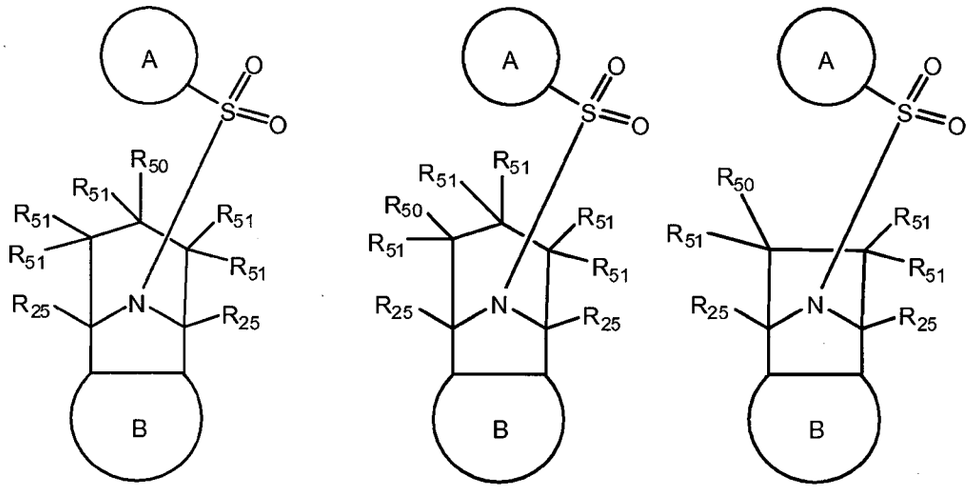
In one aspect, the compounds of Formula 1 are the compounds of Formula 1f.

In one aspect, the compounds of Formula 1 are the compounds of Formula 1g.

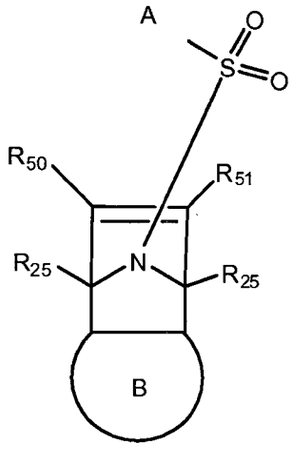
In one aspect, the compounds of Formula 1 are the compounds of Formula 1h.

In one aspect, the compounds of Formula 1 are the compounds of Formula 1i.

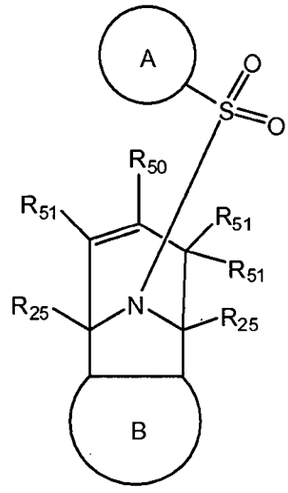
In one aspect, provided herein are compounds of Formulas 2a, 2b, 2c, 2d, 2e or 2f, *i.e.*, compounds of Formula 2 that have the following formulas:



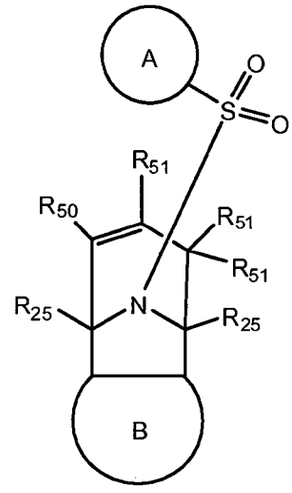
Formula 2a



Formula 2b



Formula 2c



Formula 2d Formula 2e Formula 2f

including enantiomers, pharmaceutically acceptable salts, and solvates thereof, wherein,

B-ring is pyrazolyl, dihydropyrazolyl, pyrazolonyl or pyrazolidinonyl, each of which is optionally substituted with $-NR_{11}$-C_2-C_6 alkanoyl, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxy, hydroxyalkyl, halo, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ or CN;

R_{50} is oxo, $=N-NHR_{12}$ or $=N-O-R_{13}$ (except in Formulas 2d, 2e, and 2f) or R_{50} is halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxy, hydroxy C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 haloalkyl, halo C_2-C_6 alkenyl, halo C_2-C_6 alkynyl, $--C(O)OR_{11}$, $-(C_1$-C_4 alkyl$)$-$C(O)OR_{11}$, $-CONR_{11}R_{11}$, $-OC(O)NR_{11}R_{11}$, $-NR_{11}C(O)OR_{10}$, $-NR_{11}S(O)_2R_{10}$, $-OS(O)_2R_{10}$, $-S(O)_2R_{10}$, $-NR_{11}C(O)R_{10}$, CN, $-NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, heteroaryl that is selected from pyrazolyl, thiadiazolyl, triazolyl, isoxazolyl, isothiazolyl, imidazolyl, thiazolyl, oxadiazolyl, and pyridyl, heterocycloalkyl that is selected from tetrahydrofuranyl, pyrrolidinyl, piperidinyl, morpholinyl, and imidazolidinyl, C_3 –C_6 cycloalkyl, aryl that is selected from phenyl and naphthyl; wherein the aforementioned heteroaryl, heterocycloalkyl, cycloalkyl and aryl groups are optionally substituted with 1 or more groups that are independently halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxy, hydroxyC_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 haloalkyl, halo C_2-C_6 alkenyl, halo C_2-C_6 alkynyl, $-C(O)OR_{11}$, $-(C_1$-C_4 alkyl$)$-$C(O)OR_{11}$, $-CONR_{11}R_{11}$, $-OC(O)NR_{11}R_{11}$, $-NR_{11}C(O)OR_{10}$, $-NR_{11}S(O)_2R_{10}$, $-OS(O)_2R_{10}$, $-S(O)_2R_{10}$, $-NR_{11}C(O)R_{10}$, CN, $=N-NHR_{12}$, $-NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, heteroaryl that is selected from pyrazolyl,

thiadiazolyl, triazolyl isoxazolyl, isothiazolyl, imidazolyl, thiazolyl, oxadiazolyl, oxazolyl, tetrazolyl, and pyridyl, heterocycloalkyl that is selected from tetrahydrofuranyl, pyrrolidinyl, piperidinyl, morpholinyl, and imidazolidinyl, C_3 –C_6 cycloalkyl, aryl that is selected from phenyl, benzo[d][1,3]dioxolyl, and naphthyl or =N-O-R_{13}; wherein the aforementioned heteroaryl, heterocycloalkyl, cycloalkyl and aryl substituents are optionally substituted with 1 or more groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkoxy or C_1-C_6 haloalkyl;

each R_{51} is independently absent, H, C_1-C_4 alkyl, halogen (*e.g.*, F, Cl or Br), CN, amino, mono alkylamino, dialkylamino, OH, C_1-C_4 haloalkoxy (*e.g.*, OCF_3) or C_1-C_4 haloalkyl (*e.g.*, CF_3); or when there are two R_{51} groups on a carbon atom, the two R_{51} groups and the carbon to which they are attached may form a 3- to 6-membered cycloalkyl or heterocycloalkyl ring; or when there are two R_{51} groups on a carbon, the two R_{51} groups may form an oxo group; or when there are two R_{51} groups on a carbon, the two R_{51} groups may form an alkene group; or when there are two R_{51} groups on a carbon, the two R_{51} groups may form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime);

a non-bridgehead carbon (and any substituent or substituents thereon) in the [3.3.1], [3.2.1] or [2.2.1] ring systems may be replaced with an NR_{15} group; provided that in Formulas 2d, 2e, and 2f, R_{50} is not oxo, =N-O-R_{13} or =N-NHR_{12};

R_{10} and R_{11} at each occurrence are independently C_1-C_6 alkyl, heteroaryl that is selected from pyrazolyl, thiadiazolyl, triazolyl, isoxazolyl, isothiazolyl, imidazolyl, thiazolyl, oxadiazolyl, and pyridyl or aryl that is selected from phenyl and naphthyl, where the heteroaryl and aryl groups are optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2; or if two R_{11} groups are on a nitrogen, then the two R_{11} groups together with the nitrogen to which they are attached, may form a 3-8 membered ring optionally including an additional heteroatom such as NH, NR_{12}, NR_{13}, O or S, and additionally R_{11} may be H;

R_{12} is H, C_1-C_6 alkyl, aryl or –SO_2-aryl (*e.g.*, phenyl or naphthyl, where phenyl is preferred), where each aryl group is optionally substituted with 1 to 5 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2;

R_{13} is H, aryl or C_1-C_6 alkyl optionally substituted with aryl (such as phenyl or naphthyl, more preferably, phenyl), hydroxyl or halogen, where each aryl group is optionally substituted with 1 to 5 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2. In a further embodiment, R_{50} is C_2-C_6 alkenyl, C_2-C_6 alkynyl, halo C_2-C_6 alkenyl, halo C_2-C_6 alkynyl, C_2-C_6 alkanoyl, $OS(O)_2R_{10}$, -$S(O)_2R_{10}$,

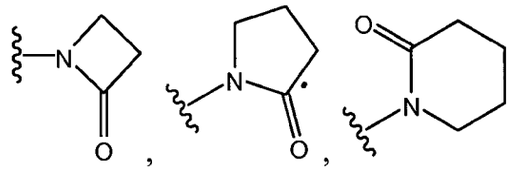
$-NR_{11}R_{11}$,$C(O)OR_{11}C(O)OR_{11}$ $-SO_2NR_{11}R_{11}$, heteroaryl that is selected from pyrazolyl, thiadiazolyl (*e.g.*, 1,2,4-thiadiazolyl or 1,3,4-thiadiazolyl), triazolyl (*e.g.*, 1,2,3-triazolyl or 1,2,4-triazolyl), isoxazolyl, isothiazolyl, imidazolyl, thiazolyl, oxadiazolyl (*e.g.*, 1,2,4-oxadiazolyl or 1,3,4-oxadiazolyl), oxazolyl, tetrazolyl, and pyridyl, heterocycloalkyl that is selected from tetrahydrofuranyl, pyrrolidinyl, piperidinyl, morpholinyl, and imidazolidinyl, C_3 –C_6 cycloalkyl, aryl that is selected from phenyl, benzo[d][1,3]dioxolyl, and naphthyl or $=N-O-R_{13}$; wherein the aforementioned heteroaryl, heterocycloalkyl, cycloalkyl and aryl groups are optionally substituted with 1 or more groups that are independently halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxy, hydroxyC_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 haloalkyl, halo C_2-C_6 alkenyl, halo C_2-C_6 alkynyl, $-C(O)OR_{11}$, -(C_1-C_4 alkyl)-$C(O)OR_{11}$, $-CONR_{11}R_{11}$, $-OC(O)NR_{11}R_{11}$, $-NR_{11}C(O)OR_{10}$, $-NR_{11}S(O)_2R_{10}$, $-OS(O)_2R_{10}$, $-S(O)_2R_{10}$, $-NR_{11}C(O)R_{10}$, CN, $=N-NHR_{12}$, $-NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, heteroaryl that is selected from pyrazolyl, thiadiazolyl, triazolyl isoxazolyl, isothiazolyl, imidazolyl, thiazolyl, oxadiazolyl, oxazolyl, tetrazolyl, and pyridyl, heterocycloalkyl that is selected from tetrahydrofuranyl, pyrrolidinyl, piperidinyl, morpholinyl, and imidazolidinyl, C_3 –C_6 cycloalkyl, aryl that is selected from phenyl, benzo[d][1,3]dioxolyl, and naphthyl or $=N-O-R_{13}$; wherein the aforementioned heteroaryl, heterocycloalkyl, cycloalkyl and aryl substituents are optionally substituted with 1 or more groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkoxy or C_1-C_6 haloalkyl.

In an aspect, provided herein are compounds of Formula 2a, 2b, 2c, 2d, 2e or 2f, wherein R_{50} is halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxy C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy or C_1-C_6 haloalkyl. In one embodiment, R_{50} is halogen, C_1-C_4 alkyl, hydroxy, hydroxy C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy or C_1-C_4 haloalkyl. In another embodiment, R_{50} is C_1-C_4 alkyl, C_1-C_4 haloalkyl, hydroxy C_1-C_4 alkyl or C_1-C_4 alkoxy. In still another embodiment, R_{50} is C_1-C_4 alkyl. In yet another embodiment, R_{50} is C_1-C_4 haloalkyl (*e.g.*, CF_3 or CH_2CF_3), hydroxy C_1-C_4 alkyl or C_1-C_4 alkoxy (*e.g.*, methoxy or ethoxy). In another embodiment, R_{50} is C_2-C_4 alkenyl or C_2-C_4 alkynyl. In still another embodiment, R_{50} is halogen, hydroxy or hydroxy C_1-C_4 alkyl. In yet still another embodiment, R_{50} is halogen. In yet still another embodiment, R_{50} is hydroxy or hydroxy C_1-C_4 alkyl.

In an aspect, provided herein are compounds of Formula 2a, 2b, 2c, 2d, 2e or 2f, wherein R_{50} is $NR_{11}R_{11}$, or $-SO_2NR_{11}R_{11}$, or $-S(O)_2R_{10}$, or

oxadiazolyl, optionally substituted with C_1-C_4 alkyl, or

C_3-C_6 cycloalkyl optionally substituted with C_1-C_4 alkyl or C_1-C_4 alkoxy, or

phenyl optionally substituted with one or more groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, $-OCH_2O-$, $-OCH_2CH_2O-$, oxazolidinone (*e.g.*, oxazolidin-2-one), imidazolyl, thiazolyl, $-NR_{11}$-cyclohexyl, where the cyclohexyl is optionally substituted with $NR_{11}R_{11}$, C_1-C_4 alkyl or C_1-C_4 alkoxy; pyrazolyl, tetrazolyl, pyrrolidinonyl, $-NR_{11}R_{11}$, morpholinyl (*e.g.*, morpholin-2-onyl),  , or C_2-C_6 alkanoyl; or

pyrazolyl optionally substituted with C_1-C_4 alkyl; or

thiazolyl optionally substituted with C_1-C_4 alkyl, C_1-C_4 haloalkyl (*e.g.*, CF_3 or CHF_2); or

oxazolyl optionally substituted with C_1-C_4 alkyl; or

benzimidazolyl optionally substituted with C_1-C_4 alkyl, C_1-C_4 alkoxy or halogen; or

C_2-C_6 alkenyl optionally substituted with a halogen (*e.g.*, Cl) or C_1-C_4 haloalkyl (*e.g.*, CF_3); or

triazolyl optionally substituted with one or two groups that are independently C_1-C_4 alkyl; or

C_2-C_6 alkynyl optionally substituted with a halogen (*e.g.*, Cl) or C_1-C_4 alkoxy; or

thiadiazolyl optionally substituted with C_1-C_4 alkyl, C_1-C_4 haloalkyl (*e.g.*, CF_3 or CHF_2); or

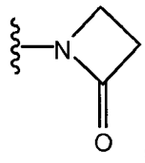
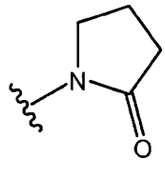
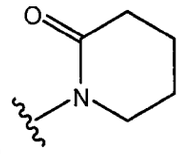
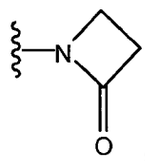
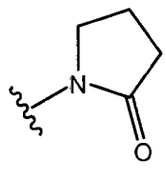
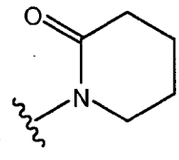
pyridyl optionally substituted with one or more groups that are independently C_1-C_4 alkyl, halogen or C_1-C_4 alkoxy; or

wherein R_{11} is H, C_1-C_6 alkyl or C_2-C_6 alkanoyl, where the alkyl portions of R_{11} are optionally substituted with one or two groups that are independently $-CO_2$-(C_1-C_6 alkyl), C_1-C_6 alkyl-O-(C_1-C_6 alkyl), C_1-C_6 alkyl-O-(C_1-C_4 alkyl)-CO_2-(C_1-C_6 alkyl), C_1-C_6 alkyl-O-(C_1-C_4 alkyl)-CO_2H.

In an embodiment of this aspect, R_{50} is C_1-C_4 haloalkyl (*e.g.*, CF_3 or CHF_2), CN, C_1-C_4 alkoxy C_1-C_6 alkyl or $NR_{11}R_{11}$; where each R_{11} is independently H or C_1-C_4 alkyl. In a

further embodiment, R_{50} is CN. In a still further embodiment, R_{50} is methoxymethyl, methoxyethy, ethoxymethyl or ethoxyethyl.

In an embodiment of this aspect, R_{50} is oxadiazolyl, substituted with a C_1-C_2 alkyl.

In an embodiment of this aspect, R_{50} is phenyl optionally substituted with one or more groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, $-OCH_2O-$, $-OCH_2CH_2O-$, oxazolidinone (*e.g.*, oxazolidin-2-one), imidazolyl, thiazolyl, $-NR_{11}$-cyclohexyl, where the cyclohexyl is optionally substituted with $NR_{11}R_{11}$, C_1-C_4 alkyl or C_1-C_4 alkoxy; pyrazolyl, tetrazolyl, pyrrolidinonyl, $-NR_{11}R_{11}$, morpholinyl (*e.g.*, morpholin-2-onyl),  ,  ,  or C_2-C_6 alkanoyl. In a further embodiment, R_{50} is unsubstituted phenyl. In another embodiment, R_{50} is phenyl substituted with one or more groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy or halogen (*e.g.*, F, Cl or Br). In a further embodiment, R_{50} is phenyl substituted with one group that is C_1-C_4 alkyl, C_1-C_4 alkoxy or halogen (*e.g.*, F, Cl or Br). In another embodiment, R_{50} is phenyl substituted with one group that is selected from oxazolidinonyl, imidazolyl, thiazolyl, pyrazolyl, tetrazolyl, morpholinyl and pyrrolidinonyl. In another embodiment, R_{50} is phenyl substituted with $-NR_{11}R_{11}$. In a further embodiment, the $-NR_{11}R_{11}$ group is $-NHC(O)CH_3$, $-NH-(C_1-C_4\ alkyl)-CO_2-(C_1-C_4\ alkyl)$, $-NH-(C_1-C_4\ alkyl)-O-(C_1-C_4\ alkyl)-CO_2-(C_1-C_4\ alkyl)$ or $-NH-(C_1-C_4\ alkyl)-O-(C_1-C_4\ alkyl)-CO_2H$. In another embodiment, R_{50} is phenyl substituted with one group that is  ,  or  . In another embodiment, R_{50} is phenyl substituted with C_2-C_4 alkanoyl. In a further embodiment, the phenyl is substituted at the four-position.

In an embodiment of this aspect, R_{50} is pyrazolyl optionally substituted with C_1-C_4 alkyl; thiazolyl optionally substituted with C_1-C_4 alkyl (*e.g.*, methyl), C_1-C_4 haloalkyl (*e.g.*, CF_3 or CHF_2); oxazolyl optionally substituted with C_1-C_4 alkyl (*e.g.*, methyl); triazolyl optionally substituted with one or two groups that are independently C_1-C_4 alkyl; or benzimidazolyl optionally substituted with C_1-C_4 alkyl (*e.g.*, methyl), C_1-C_4 alkoxy or halogen.

In an embodiment of this aspect, R_{50} is C_2-C_6 alkenyl optionally substituted with a halogen (*e.g.*, Cl) or C_1-C_4 haloalkyl (*e.g.*, CF_3).

In an embodiment of this aspect, R_{50} is C_2-C_6 alkynyl optionally substituted with a halogen (*e.g.*, Cl) or C_1-C_4 alkoxy.

In an embodiment of this aspect, R_{50} is pyridyl optionally substituted with one or more groups that are independently C_1-C_4 alkyl, halogen or C_1-C_4 alkoxy.

In another aspect, provided herein are compounds of Formula 2a, 2b, 2c, 2d, 2e or 2f, wherein R_{50} is $-C(O)OR_{11}OR_{11}$, $-(C_1\text{-}C_4\ \text{alkyl})\text{-}C(O)OR_{11}$, $-CONR_{11}R_{11}$, $-OC(O)NR_{11}R_{11}$, $-NR_{11}C(O)OR_{10}$, $-NR_{11}S(O)_2R_{10}$, $-OS(O)_2R_{10}$, $-S(O)_2R_{10}$, $-NR_{11}C(O)R_{10}$, CN, $=N\text{-}NHR_{12}$, $-NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, or $=N\text{-}O\text{-}R_{13}$;

R_{10} and R_{11} at each occurrence are independently C_1-C_6 alkyl, heteroaryl that is selected from pyrazolyl, thiadiazolyl, triazolyl, isoxazolyl, isothiazolyl, imidazolyl, thiazolyl, oxadiazolyl, and pyridyl or aryl that is selected from phenyl and naphthyl, where the heteroaryl and aryl groups are optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, CN or NO_2; and additionally R_{11} may be H; or if two R_{11} groups are on a nitrogen, then the two R_{11} groups together with the nitrogen to which they are attached, may form a 3-8 membered ring optionally including an additional heteroatom such as NH, NR_{12}, NR_{13}, O or S;

R_{12} is H, C_1-C_6 alkyl, aryl or $-SO_2$-aryl (*e.g.*, phenyl or naphthyl, where phenyl is preferred), where each aryl group is optionally substituted with 1 to 5 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2;

R_{13} is H, aryl or C_1-C_6 alkyl optionally substituted with aryl (such as phenyl or naphthyl, more preferably, phenyl), hydroxyl or halogen, where each aryl group is optionally substituted with 1 to 5 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2.

In an embodiment of this aspect, R_{10} is C_1-C_4 alkyl and R_{11} is independently hydrogen or C_1-C_4 alkyl.

In still another embodiment of this aspect, R_{11} is H.

In still another embodiment of this aspect, one of R_{10} and R_{11} is CH_3.

In another embodiment of this aspect, R_{11} and R_{11} together with the nitrogen to which they are attached may form a 3-8 membered ring, which optionally includes an additional heteroatom that is NH, NR_{12}, NR_{13}, O or S.

In still another embodiment of this aspect, R_{10} and R_{11} at each occurrence are independently phenyl optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, CN or NO_2, and additionally R_{11} may be H.

In another embodiment of this aspect, R_{10} and R_{11} at each occurrence are independently pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl or thiazolyl, each of which is optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, CN or NO_2, and additionally R_{11} may be H.

In another embodiment of this aspect, R_{10} and R_{11} at each occurrence are independently thiadiazolyl, triazolyl or oxadiazolyl, each of which is optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, CN or NO_2, and additionally R_{11} may be H.

In yet still another embodiment of this aspect, R_{13} is H, C_1-C_4 alkyl or benzyl, where then phenyl portion is optionally substituted with halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, CF_3 or OCF_3. In another embodiment, R_{13} is C_1-C_4 alkyl or benzyl.

In another aspect, provided herein are compounds of Formula 2a, 2b, 2c, 2d, 2e or 2f, wherein R_{50} is $-C(O)OR_{11}$, $-CONR_{11}R_{11}$, $-OC(O)NR_{11}R_{11}$, $-NR_{11}C(O)OR_{10}$, $-NR_{11}S(O)_2R_{10}$, $-OS(O)_2R_{10}$, $-S(O)_2R_{10}$ or $-NR_{11}C(O)R_{10}$; wherein R_{10} and R_{11} at each occurrence are independently C_1-C_6 alkyl, heteroaryl that is selected from pyrazolyl, thiadiazolyl, triazolyl, isoxazolyl, isothiazolyl, imidazolyl, thiazolyl, oxadiazolyl, and pyridyl or aryl that is selected from phenyl and naphthyl, where the heteroaryl and aryl groups are optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, CN or NO_2; and additionally R_{11} may be H ; or if two R_{11} groups are on a nitrogen, then the two R_{11} groups together with the nitrogen to which they are attached, may form a 3-8 membered ring optionally including an additional heteroatom such as NH, NR_{12}, NR_{13}, O or S;

R_{12} is H, C_1-C_6 alkyl, aryl or $-SO_2$-aryl (*e.g.*, phenyl or naphthyl, where phenyl is preferred), where each aryl group is optionally substituted with 1 to 5 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2;

R_{13} is H, aryl or C_1-C_6 alkyl optionally substituted with aryl (such as phenyl or naphthyl, more preferably, phenyl), hydroxyl or halogen, where each aryl group is optionally

substituted with 1 to 5 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2.

In an embodiment of this aspect, R_{10} is C_1-C_4 alkyl and R_{11} is independently hydrogen or C_1-C_4 alkyl.

In still another embodiment of this aspect, R_{11} is H.

In still another embodiment of this aspect, one of R_{10} and R_{11} is CH_3.

In another embodiment of this aspect, R_{11} and R_{11} together with the nitrogen to which they are attached form a 3-8 membered ring, which optionally includes an additional heteroatom that is NH, NR_{12}, NR_{13}, O or S.

In another embodiment of this aspect, R_{10} and R_{11} at each occurrence are independently phenyl optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, CN or NO_2, and additionally R_{11} may be H;.

In another embodiment of this aspect, R_{10} and R_{11} at each occurrence are independently pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl or thiazolyl, each of which is optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, CN or NO_2, and additionally R_{11} may be H.

In another embodiment of this aspect, R_{10} and R_{11} at each occurrence are independently thiadiazolyl, triazolyl or oxadiazolyl, each of which is optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, CN or NO_2, and additionally R_{11} may be H.

In yet still another embodiment of this aspect, R_{13} is H, C_1-C_4 alkyl or benzyl, where then phenyl portion is optionally substituted with halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, CF_3 or OCF_3. In another embodiment, R_{13} is C_1-C_4 alkyl or benzyl.

In another aspect, provided herein are compounds of Formula 2a, 2b, 2c, 2d, 2e or 2f, wherein R_{50} is heteroaryl that is selected from pyrazolyl, thiadiazolyl (*e.g.*, 1,2,4-thiadiazolyl or 1,3,4-thiadiazolyl), triazolyl (*e.g.*, 1,2,3-triazolyl or 1,2,4-triazolyl), isoxazolyl, isothiazolyl, imidazolyl, thiazolyl, oxadiazolyl (*e.g.*, 1,2,4-oxadiazolyl or 1,3,4-oxadiazolyl), oxazolyl, tetrazolyl, and pyridyl, heterocycloalkyl that is selected from tetrahydrofuranyl, pyrrolidinyl, piperidinyl, morpholinyl, and imidazolidinyl, heterocycloalkyl that is selected from tetrahydrofuranyl, pyrrolidinyl, piperidinyl, morpholinyl, and imidazolidinyl, each of

which is optionally substituted with 1 or more groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkoxy or C_1-C_6 haloalkyl.

In an embodiment of this aspect, R_{50} is pyrazolyl or imidazolyl, each of which is optionally substituted with 1 or more groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkoxy (*e.g.*, OCF_3) or C_1-C_4 haloalkyl (*e.g.*, CF_3).

In an embodiment of this aspect, R_{50} is thiazolyl or oxadiazolyl each of which is optionally substituted with 1 or more groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkoxy (*e.g.*, OCF_3) or C_1-C_4 haloalkyl (*e.g.*, CF_3).

In an embodiment of this aspect, R_{50} is pyridyl, which is optionally substituted with 1 or more groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkoxy (*e.g.*, OCF_3) or C_1-C_4 haloalkyl (*e.g.*, CF_3).

In an embodiment of this aspect, R_{50} is thiadiazolyl, which is optionally substituted with 1 or more groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkoxy (*e.g.*, OCF_3) or C_1-C_4 haloalkyl (*e.g.*, CF_3).

In an embodiment of this aspect, R_{50} is triazolyl, which is optionally substituted with 1 or more groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkoxy (*e.g.*, OCF_3) or C_1-C_4 haloalkyl (*e.g.*, CF_3).

In an embodiment of this aspect, R_{50} is isoxazolyl, which is optionally substituted with 1 or more groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkoxy (*e.g.*, OCF_3) or C_1-C_4 haloalkyl (*e.g.*, CF_3).

In an embodiment of this aspect, R_{50} is isothiazolyl, which is optionally substituted with 1 or more groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkoxy (*e.g.*, OCF_3) or C_1-C_4 haloalkyl (*e.g.*, CF_3).

In an embodiment of this aspect, R_{50} is selected from tetrahydrofuranyl, pyrrolidinyl, and imidazolidinyl, each of which is optionally substituted with 1 or more groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkoxy (*e.g.*, OCF_3) or C_1-C_4 haloalkyl (*e.g.*, CF_3).

In an embodiment of this aspect, R_{50} is piperidinyl or morpholinyl, each of which is optionally substituted with 1 or more groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkoxy (*e.g.*, OCF_3) or C_1-C_4 haloalkyl (*e.g.*, CF_3).

In a further embodiment of this aspect, R_{50} is unsubstituted.

In a still further embodiment of this aspect, R_{50} is substituted with one group that is halogen, C_1-C_2 alkyl, C_1-C_2 alkoxy, hydroxy, C_1-C_2 hydroxyalkyl, C_1-C_2 haloalkoxy (*e.g.*, OCF_3) or C_1-C_2 haloalkyl (*e.g.*, CF_3).

In another aspect, provided herein are compounds of Formula 2a, 2b, 2c, 2d, 2e or 2f, wherein R_{50} is C_3 –C_6 cycloalkyl, which is optionally substituted with 1 or more groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkoxy or C_1-C_6 haloalkyl.

In an embodiment of this aspect, R_{50} is unsubstituted C_3 –C_6 cycloalkyl.

In another embodiment of this aspect, R_{50} is C_3 –C_6 cycloalkyl substituted with one or two groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkoxy (*e.g.*, OCF_3) or C_1-C_4 haloalkyl (*e.g.*, CF_3).

In still another embodiment, R_{50} is cyclopropyl, cyclopentyl or cyclohexyl, each of which is optionally substituted with halogen, C_1-C_2 alkyl, C_1-C_2 alkoxy (*e.g.*, methoxy), hydroxy, C_1-C_2 hydroxyalkyl, C_1-C_2 haloalkoxy (*e.g.*, OCF_3) or C_1-C_2 haloalkyl (*e.g.*, CF_3).

In still another embodiment, R_{50} is cyclopropyl, substituted with one group that is halogen, C_1-C_2 alkyl, C_1-C_2 alkoxy (*e.g.*, methoxy), hydroxy or C_1-C_2 hydroxyalkyl.

In another aspect, provided herein are compounds of Formula 2a, 2b, 2c, 2d, 2e or 2f, wherein R_{50} is aryl that is selected from phenyl, benzo[d][1,3]dioxolyl, and naphthyl, each of which is optionally substituted with one or more groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkoxy or C_1-C_6 haloalkyl.

In an embodiment of this aspect, R_{50} is phenyl, which is optionally substituted with one or more groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkoxy (*e.g.*, OCF_3) or C_1-C_4 haloalkyl (*e.g.*, CF_3).

In another embodiment of this aspect, R_{50} is phenyl, which is unsubstituted.

In still yet another embodiment of this aspect, R_{50} is phenyl, which is substituted with at least one group that is halogen, C_1-C_2 alkyl, C_1-C_2 alkoxy, hydroxy, C_1-C_2 hydroxyalkyl, C_1-C_2 haloalkoxy (*e.g.*, OCF_3), C_1-C_2 haloalkyl (*e.g.*, CF_3) or –CN..

In still yet another embodiment of this aspect, R_{50} is phenyl, which is substituted with one group that is halogen, C_1-C_2 alkyl, C_1-C_2 alkoxy, hydroxy, C_1-C_2 hydroxyalkyl, C_1-C_2 haloalkoxy (*e.g.*, OCF_3) or C_1-C_2 haloalkyl (*e.g.*, CF_3).

In an embodiment of this aspect, R_{50} is benzo[d][1,3]dioxolyl, which is optionally substituted with one or more groups that are independently halogen, C_1-C_4 alkyl, C_1-C_4

alkoxy, hydroxy, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkoxy (*e.g.*, OCF_3) or C_1-C_4 haloalkyl (*e.g.*, CF_3). In a further embodiment, the methylene group of the benzo[d][1,3]dioxolyl group is substituted with one or two C_1-C_4 alkyl groups (such as, *e.g.*, one or two methyl groups).

In another embodiment of this aspect, R_{50} is benzo[d][1,3]dioxolyl, which is unsubstituted.

In still yet another embodiment of this aspect, R_{50} is benzo[d][1,3]dioxolyl, which is substituted with at least one group that is halogen, C_1-C_2 alkyl, C_1-C_2 alkoxy, hydroxy, C_1-C_2 hydroxyalkyl, C_1-C_2 haloalkoxy (*e.g.*, OCF_3), C_1-C_2 haloalkyl (*e.g.*, CF_3) or –CN..

In still yet another embodiment of this aspect, R_{50} is benzo[d][1,3]dioxolyl, which is substituted with one group that is halogen, C_1-C_2 alkyl, C_1-C_2 alkoxy, hydroxy, C_1-C_2 hydroxyalkyl, OCF_3 or CF_3.

In one aspect, the compounds of Formula 2 are the compounds of Formula 2a.

In one aspect, the compounds of Formula 2 are the compounds of Formula 2b.

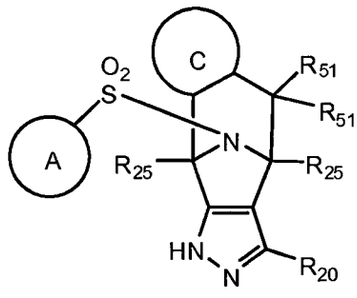
In one aspect, the compounds of Formula 2 are the compounds of Formula 2c.

In one aspect, the compounds of Formula 2 are the compounds of Formula 2d.

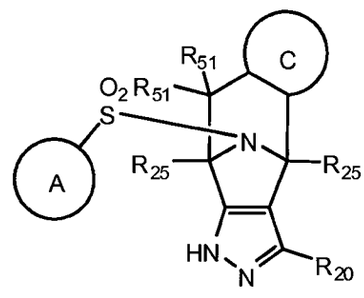
In one aspect, the compounds of Formula 2 are the compounds of Formula 2e.

In one aspect, the compounds of Formula 2 are the compounds of Formula 2f.

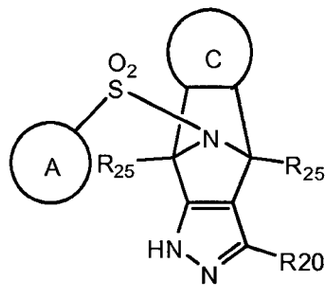
In one aspect, provided herein are compounds of Formulas 3a, 3b or 3c, *i.e.*, compounds of Formula 3 having the formulas:



Formula 3a

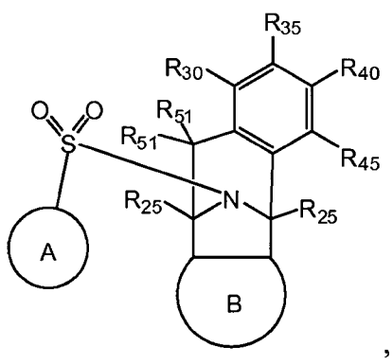


Formula 3b

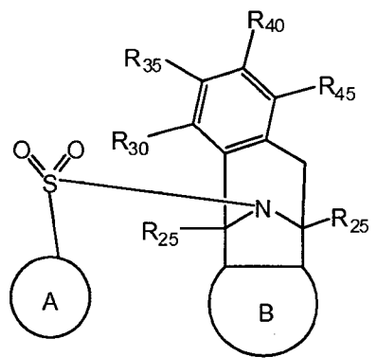
or 

Formula 3c

In one aspect, provided herein are compounds of Formulas 3d, 3e or 3f, *i.e.*, compounds of Formula 3 that have the following formulas:

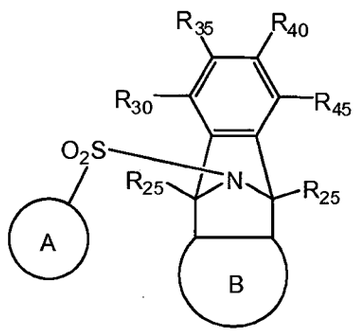


Formula 3d

, 

Formula 3e

or



Formula 3f

including enantiomers and/or pharmaceutically acceptable salts thereof, wherein, the A-ring is as defined below;

B-ring is pyrazolyl, dihydropyrazolyl, pyrazolonyl or pyrazolidinonyl, each of which is optionally substituted with $-NR_{11}$-C_2-C_6 alkanoyl, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxy, hydroxyalkyl, halo, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ or CN. where

R_{10} and R_{11} at each occurrence are independently C_1-C_6 alkyl, heteroaryl that is selected from pyrazolyl, thiadiazolyl, triazolyl, isoxazolyl, isothiazolyl, imidazolyl, thiazolyl, oxadiazolyl, and pyridyl or aryl that is selected from phenyl and naphthyl, where the heteroaryl and aryl groups are optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, CN or NO_2; and additionally R_{11} may be H; or if two R_{11} groups are on a nitrogen, then the two R_{11} groups together with the nitrogen to which they are attached, may form a 3-8 membered ring optionally including an additional heteroatom such as NH, NR_{12}, NR_{13}, O or S;

R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, -C(O)OR_{11}, -$SO_2NR_{11}R_{11}$, aryl C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, CN, NO_2, hydroxyl, C_1-C_6 alkoxy, -C_1-C_6 alkyl-OH, -C_1-C_6 alkyl-C_1-C_6 alkoxy, phenyloxy, -S(O_2)R_{10}, -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alkanoyl, heteroaryl C_1-C_6 alkyl, heteroaryl, where the heteroaryl groups are oxazolyl, oxadiazolyl pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl or thienyl, and wherein each heteroaryl group is optionally substituted with a C_1-C_6 alkyl group; heterocycloalkylalkyl, heterocycloalkyl, wherein the heterocycloalkyl groups are pyrrolidinyl, imidazolidinyl, piperidinyl or morpholinyl, wherein each heterocycloalkyl group is optionally substituted with one or two groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy or halogen, phenyl, naphthyl, phenyloxy, naphthyloxy or phenyl C_1-C_6 alkyl, where the phenyl portions of the above are optionally substituted with one to five groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, C_1-C_4 haloalky (*e.g.*, CF_3) or halogen; and wherein two adjacent carbons of the C-ring optionally form a heterocycloalkyl or a heteroaryl ring, each of which is optionally substituted with 1, 2, 3 or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen or C_2-C_4 alkanoyl wherein the alkanoyl group is optionally substituted with up to 3 halogen atoms; or

two adjacent carbons of the fused aryl ring form a benzo ring which is optionally substituted with 1 to 4 groups that are independently halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, CN or NO_2; and R_{51} is as previously defined. In a further embodiment of this aspect, R_{10} and R_{11} at each occurrence are independently C_1-C_6 alkyl, heteroaryl that is selected from pyrazolyl, thiadiazolyl, triazolyl, isoxazolyl, isothiazolyl, imidazolyl, thiazolyl, oxadiazolyl, and pyridyl or aryl that is selected from phenyl and naphthyl, where the heteroaryl and aryl groups are optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_4

alkyl, halo C_1-C_4 alkoxy, CN or NO_2; and additionally R_{11} may be H; or if two R_{11} groups are on a nitrogen, then the two R_{11} groups together with the nitrogen to which they are attached, may form a 3-8 membered ring optionally including an additional heteroatom such as NH, NR_{12}, NR_{13}, O or S;

R_{12} is H, C_1-C_6 alkyl, aryl or $-SO_2$-aryl (*e.g.*, phenyl or naphthyl, where phenyl is preferred), where each aryl group is optionally substituted with 1 to 5 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2;

R_{13} is H, aryl or C_1-C_6 alkyl optionally substituted with aryl (such as phenyl or naphthyl, more preferably, phenyl), hydroxyl or halogen, where each aryl group is optionally substituted with 1 to 5 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2.

In an embodiment of this aspect, R_{10} is C_1-C_4 alkyl and R_{11} is independently hydrogen or C_1-C_4 alkyl.

In still another embodiment of this aspect, R_{11} is H.

In still another embodiment of this aspect, one of R_{10} and R_{11} is CH_3.

In another embodiment of this aspect, R_{11} and R_{11} together with the nitrogen to which they are attached may form a 3-8 membered ring, which optionally includes an additional heteroatom that is NH, NR_{12}, NR_{13}, O or S.

In still another embodiment of this aspect, R_{10} and R_{11} at each occurrence are independently phenyl optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, CN or NO_2; and additionally R_{11} may be H.

In another embodiment of this aspect, R_{10} and R_{11} at each occurrence are independently pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl or thiazolyl, each of which is optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, CN or NO_2; and additionally R_{11} may be H.

In another embodiment of this aspect, R_{10} and R_{11} at each occurrence are independently thiadiazolyl, triazolyl or oxadiazolyl, each of which is optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, CN or NO_2; and additionally R_{11} may be H.

In yet still another embodiment of this aspect, R_{13} is H, C_1-C_4 alkyl or benzyl, where then phenyl portion is optionally substituted with halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, CF_3 or OCF_3. In another embodiment, R_{13} is C_1-C_4 alkyl or benzyl.

In another aspect, provided herein are compounds of Formulas 3a, 3b, and 3c (when the C-ring is benzo substituted with R_{30}, R_{35}, R_{40}, and R_{45}) 3d, 3e and/or 3f, wherein R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, -C(O)OR_{11}, -$SO_2NR_{11}R_{11}$, arylalkyl, cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, CN, NO_2, hydroxyl, C_1-C_6 alkoxy, -C_1-C_3 alkyl-OH, -C_1-C_3 alkyl- C_1-C_4 alkoxy, phenyloxy, -S(O_2)R_{10}, -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alkanoyl, oxazolyl, oxadiazolyl pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl or thienyl, wherein each heteroaryl group is optionally substituted with a C_1-C_6 alkyl group, phenyl or phenyl C_1-C_4 alkyl, where the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky (*e.g.* CF_3) or halogen.

In one embodiment of this aspect, R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen, C_1-C_6 alkyl, hydroxyl, C_1-C_6 alkoxy, -C_1-C_3 alkyl-OH or -C_1-C_3 alkyl-alkoxy.

In one embodiment of this aspect, R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen, C_1-C_4 alkyl, hydroxyl, C_1-C_4 alkoxy, -C_1-C_2 alkyl-OH or -C_1-C_2 alkyl- C_1-C_4 alkoxy.

In one embodiment of this aspect, R_{30}, R_{35}, R_{40}, and R_{45} are independently H, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkenyl or C_2-C_6 haloalkynyl. In one embodiment, the halo portion of the haloalkenyl or haloalkynyl group is F, Cl or Br.

In one embodiment of this aspect, R_{30}, R_{35}, R_{40}, and R_{45} are independently H, -C(O)OR_{11}, -S(O_2)R_{10}, -$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$ or C_2-C_6 alkanoyl.

In one embodiment of this aspect, R_{30} and R_{35} or R_{35} and R_{40} or R_{40} and R_{45} are -OCH_2O- or -OCH_2CH_2O- wherein each methylene of -OCH_2O- or -OCH_2CH_2O- is optionally substituted with one or two C_1-C_4 alkyl groups.

In still another embodiment of this aspect, R_{11} is H.

In still another embodiment of this aspect, one of R_{10} and R_{11} is CH_3.

In another embodiment of this aspect, R_{11} and R_{11} together with the nitrogen to which they are attached form a 3-8 membered ring, which optionally includes an additional heteroatom that is NH, NR_{12}, NR_{13}, O or S.

In still another embodiment of this aspect, R_{10} and R_{11} at each occurrence are independently phenyl optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, CN or NO_2; and additionally R_{11} may be H.

In another embodiment of this aspect, R_{10} and R_{11} at each occurrence are independently pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl or thiazolyl, each of which is optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, CN or NO_2; and additionally R_{11} may be H.

In another embodiment of this aspect, R_{10} and R_{11} at each occurrence are independently thiadiazolyl, triazolyl or oxadiazolyl, each of which is optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, CN or NO_2 and additionally R_{11} may be H.

In another aspect, provided herein are compounds of Formulas 3a, 3b, and 3c (when the C-ring is benzo substituted with R_{30}, R_{35}, R_{40}, and R_{45}), 3d, 3e and/or 3f, wherein R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen, C_1-C_4 alkyl, $-C(O)OR_{11}$, $-S(O_2)R_{10}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$ $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ or $-O-C(O)NR_{11}R_{11}$.

In an embodiment of this aspect, at least two of R_{30}, R_{35}, R_{40}, and R_{45} are H, while another is H, halogen or C1-C4 alkyl, and the other is $-C(O)OR_{11}$, $-S(O_2)R_{10}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ or $-O-C(O)NR_{11}R_{11}$.

In an embodiment of this aspect, three of R_{30}, R_{35}, R_{40}, and R_{45} are H, while the other is $-C(O)OR_{11}$, $-S(O_2)R_{10}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ or $-O-C(O)NR_{11}R_{11}$.

In yet another embodiment of this aspect, three of R_{30}, R_{35}, R_{40}, and R_{45} are H, while the other is $-NR_{11}R_{11}$.

In yet another embodiment of this aspect, three of R_{30}, R_{35}, R_{40}, and R_{45} are H, while the other is $-C(O)OR_{11}$.

In an embodiment of this aspect, three of R_{30}, R_{35}, R_{40}, and R_{45} are H, while the other is $-C(O)NR_{11}R_{11}$ or $-NR_{11}C(O)R_{10}$.

In still another embodiment of this aspect, three of R_{30}, R_{35}, R_{40}, and R_{45} are H, while the other is $-O-C(O)NR_{11}R_{11}$.

In still another embodiment of this aspect, two of R_{30}, R_{35}, R_{40}, and R_{45} are H, while one is methyl and the other is $-NR_{11}R_{11}$ or $-C(O)NR_{11}R_{11}$.

In still another embodiment of this aspect, at least two of R_{30}, R_{35}, R_{40}, and R_{45} are H, one of R_{30}, R_{35}, R_{40}, and R_{45} is H or methyl and the other is $-NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$ or $-NR_{11}SO_2R_{10}$.

In an embodiment of this aspect, three of R_{30}, R_{35}, R_{40}, and R_{45} are H, while the other is $-C(O)NR_{11}R_{11}$ or $-NR_{11}C(O)R_{10}$.

In still another embodiment of this aspect, three of R_{30}, R_{35}, R_{40}, and R_{45} are H, while the other is $-O-C(O)NR_{11}R_{11}$.

In still another embodiment of this aspect, two of R_{30}, R_{35}, R_{40}, and R_{45} are H, while one is methyl and the other is $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$ or $-NR_{11}C(O)R_{10}$.

In an embodiment of this aspect, three of R_{30}, R_{35}, R_{40}, and R_{45} are H, while the other is $-C(O)OR_{11}$. In a further embodiment, R_{11} is H or C_1-C_4 alkyl.

In another aspect, provided herein are compounds of Formulas 3a, 3b, and 3c (when the C-ring is benzo substituted with R_{30}, R_{35}, R_{40}, and R_{45}), 3d, 3e and/or 3f, wherein R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, phenyloxy, C_2-C_6 alkanoyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl, thienyl, phenyl or phenyl C_1-C_4 alkyl, where the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky (*e.g.* CF_3) or halogen.

In another embodiment of this aspect, at least two of R_{30}, R_{35}, R_{40}, and R_{45} are H.

In still another embodiment of this aspect, three of R_{30}, R_{35}, R_{40}, and R_{45} are H.

In a still another embodiment of this aspect, R_{30}, R_{35}, R_{40}, and R_{45} are H.

In another embodiment of this aspect, at least one of R_{30}, R_{35}, R_{40}, and R_{45} is a halogen (*e.g.*, F, Cl or Br). In a still another embodiment, at least two of R_{30}, R_{35}, R_{40}, and R_{45} is a halogen (*e.g.*, F, Cl or Br), where the halogens may be the same or different.

In yet still another embodiment of this aspect, R_{30} and R_{45} are H; and R_{35} and R_{40} are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy or C_2-C_6 alkanoyl.

In still another embodiment of this aspect, R_{30} and R_{45} are H; and R_{35} and R_{40} are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_2-C_6 alkanoyl, phenyloxy, phenyl or phenyl C_1-C_4 alkyl, where the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky (*e.g.* CF_3) or halogen.

In still another embodiment of this aspect, R_{30} and R_{45} are H; and R_{35} and R_{40} are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_2-C_6 alkanoyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl or thienyl.

In yet still another embodiment of this aspect, R_{35} and R_{40} are H; and R_{30} and R_{45} are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy or C_2-C_6 alkanoyl.

In still another embodiment of this aspect, R_{35} and R_{40} are H; and R_{30} and R_{45} are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_2-C_6 alkanoyl, phenyloxy, phenyl or phenyl C_1-C_4 alkyl, where the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky (*e.g.* CF_3) or halogen.

In still another embodiment of this aspect, R_{35} and R_{40} are H; and R_{30} and R_{45} are independently halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_2-C_6 alkanoyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl or thienyl.

In another aspect, provided herein are compounds of Formulas 3a, 3b, and 3c (when the C-ring is benzo substituted with R_{30}, R_{35}, R_{40}, and R_{45}), 3d, 3e and/or 3f, wherein R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_2-C_6 alkanoyl; provided that two adjacent carbons of the fused aryl ring (the ring to which the R_{30}, R_{35}, R_{40} and R_{45} groups are attached) optionally form a heterocycloalkyl or a heteroaryl ring, each of which is optionally substituted with 1, 2, 3 or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen or C_1-C_4 alkanoyl wherein the alkanoyl group is optionally substituted with up to 3 halogen atoms.

In one embodiment of this aspect, the heterocycloalkyl ring is piperidinyl, pyrrolidinyl or morpholinyl, and the heteroaryl ring is pyrazolyl, imidazolyl or pyridinyl, wherein each heterocycloalkyl or heteroaryl group is optionally substituted with 1, 2, 3 or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen or C_1-C_4 alkanoyl wherein the alkanoyl group is optionally substituted with up to 3 halogen atoms.

In one embodiment of this aspect, the heterocycloalkyl ring is piperidinyl or pyrrolidinyl, each of which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen or C_2-C_4 alkanoyl wherein the alkanoyl group is optionally substituted with up to 3 halogen atoms.

In one embodiment of this aspect, the heteroaryl ring is pyrazolyl, imidazolyl or pyridinyl, each of which is optionally substituted with 1 or 2 groups that are independently

C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen or C_2-C_4 alkanoyl wherein the alkanoyl group is optionally substituted with up to 3 halogen atoms.

In another aspect, provided herein are compounds of Formulas 3a, 3b, and 3c (when the C-ring is benzo substituted with R_{30}, R_{35}, R_{40}, and R_{45}), 3d, 3e and/or 3f, wherein R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_2-C_6 alkanoyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_2-C_8 haloalkenyl or C_2-C_8 haloalkynyl; provided that two adjacent carbons of the fused aryl ring form a benzo ring, which is optionally substituted with 1 to 4 groups that are independently halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, CN or NO_2. In a further aspect, the benzo ring is unsubstituted.

In one embodiment of this aspect, R_{30} and R_{45} are independently H, halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, and R_{35}, R_{40}, and the carbons to which they are attached form a benzo ring, which is optionally substituted with 1 to 4 groups that are independently halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, CN or NO_2. In a further embodiment, the benzo ring is unsubstituted.

In one embodiment of this aspect, R_{30} and R_{35} are independently H, halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, and R_{40}, R_{45}, and the carbons to which they are attached form a benzo ring, which is optionally substituted with 1 to 4 groups that are independently halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, CN or NO_2. In a further embodiment, the benzo ring is unsubstituted.

In one embodiment of this aspect, R_{40} and R_{45} are independently H, halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, and R_{30}, R_{35}, and the carbons to which they are attached form a benzo ring, which is optionally substituted with 1 to 4 groups that are independently halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, CN or NO_2. In a further embodiment, the benzo ring is unsubstituted.

In one aspect, provided herein are compounds of Formulas 3a, 3b, and/or 3c, wherein the C-ring is heteroaryl or heterocycloalkyl ring that is optionally substituted with one or more groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, $-C(O)OR_{11}$, CN, hydroxyl, C_1-C_6 alkoxy, $-C_1$-C_6 alkyl-OH, $-C_1$-C_6 alkyl-C_1-C_6 alkoxy, aryloxy (*e.g.*, phenyloxy), $-S(O_2)R_{10}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl, thienyl, phenyl or phenyl C_1-C_4 alkyl, wherein the

phenyl portions of the above are optionally substituted *e.g.*, with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalkyl (*e.g.* CF_3), C_1-C_4 haloalkoxy (*e.g.* OCF_3), hydroxyl, CN, NO_2 or halogen; wherein each R_{11} is independently C_1-C_6 alkyl, heteroaryl that is selected from pyrazolyl, thiadiazolyl, triazolyl, isoxazolyl, isothiazolyl, imidazolyl, thiazolyl, oxadiazolyl, and pyridyl or aryl that is selected from phenyl and naphthyl, where the heteroaryl and aryl groups are optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2; or if two R_{11} groups are on a nitrogen, then the two R_{11} groups together with the nitrogen to which they are attached, may form a 3-8 membered ring optionally including an additional heteroatom such as NH, NR_{12}, NR_{13}, O or S; and additionally R_{11} may be H.

In one embodiment of this aspect, the C-ring is heteroaryl or heterocycloalkyl ring that is optionally substituted with one or more groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, C_1-C_4 haloalkyl (*e.g.* CF_3) or C_1-C_4 haloalkoxy (*e.g.*, OCF_3); R_{51} is as previously defined, and n is 0 or 1.

In one embodiment of this aspect, the C-ring is heteroaryl or heterocycloalkyl ring that is optionally substituted with one or more groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, $-S(O_2)R_{10}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$ or $-C(O)OR_{11}$.

In one embodiment of this aspect, the C-ring is heteroaryl or heterocycloalkyl ring that is optionally substituted with one or more groups that are independently C_1-C_4 alkyl, halogen, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl or $-C(O)OR_{11}$.

In an embodiment of this aspect, the C-ring is a pyridyl ring optionally substituted with one or more groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, C_1-C_4 haloalkyl (*e.g.* CF_3) or C_1-C_4 haloalkoxy (*e.g.*, OCF_3). In a further embodiment, the C-ring is an unsubstituted pyridyl ring.

In an embodiment of this aspect, the C-ring is a pyridyl ring substituted with one or two groups that are independently C_1-C_4 alkyl, halogen, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl or $-C(O)OR_{11}$, where R_{11} is H or C_1-C_6 alkyl.

In an embodiment of this aspect, the C-ring is a thiazolyl ring optionally substituted with one or more groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, C_1-C_4 haloalkyl (*e.g.* CF_3) or C_1-C_4 haloalkoxy (*e.g.*, OCF_3). In a further embodiment, the C-ring is an unsubstituted thiazolyl ring.

In an embodiment of this aspect, the C-ring is a thiazolyl ring substituted with one group that is C_1-C_4 alkyl, halogen, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl or -C(O)OR_{11}, where R_{11} is H or C_1-C_6 alkyl.

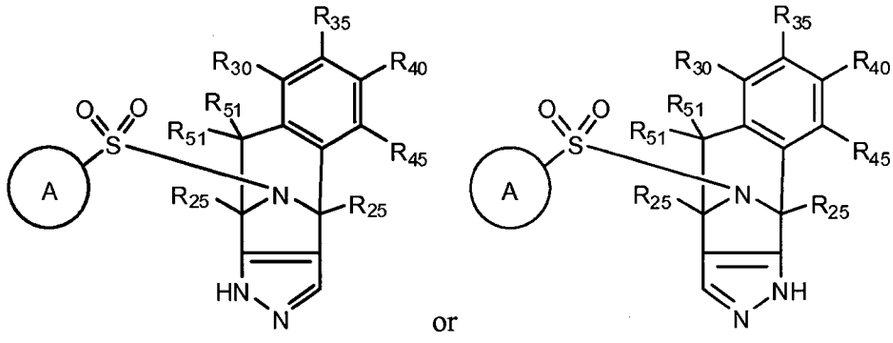
In an embodiment of this aspect, the C-ring is a pyrazolyl ring optionally substituted with one or more groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, C_1-C_4 haloalkyl (*e.g.* CF_3) or C_1-C_4 haloalkoxy (*e.g.*, OCF_3). In a further embodiment, the C-ring is an unsubstituted pyrazolyl ring.

In an embodiment of this aspect, the C-ring is a pyrazolyl ring substituted with one group that is C_1-C_4 alkyl, halogen, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl or -C(O)OR_{11}, where R_{11} is H or C_1-C_6 alkyl.

In an embodiment of this aspect, the C-ring is a thienyl ring optionally substituted with one or more groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, C_1-C_4 haloalkyl (*e.g.* CF_3) or C_1-C_4 haloalkoxy (*e.g.*, OCF_3). In a further embodiment, the C-ring is an unsubstituted thienyl ring.

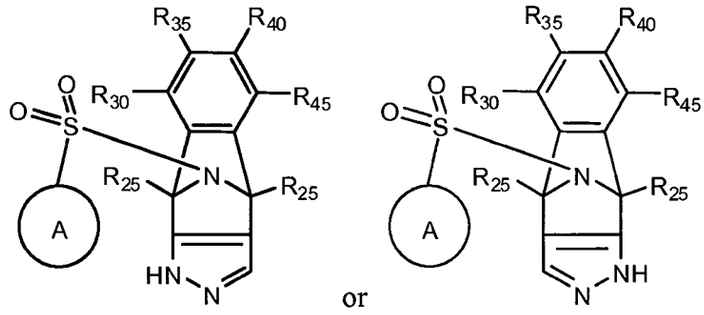
In an embodiment of this aspect, the C-ring is a thienyl ring substituted with one group that is C_1-C_4 alkyl, halogen, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl or -C(O)OR_{11}, where R_{11} is H or C_1-C_6 alkyl.

In one aspect, the compounds of Formula 3 are the compounds of Formula 3a. In a further embodiment, the compounds of Formula 3a are of the formula:



where R_{25}, R_{30}, R_{35}, R_{40}, R_{45}, R_{51} are as described above and the A-ring is as described herein.

In one aspect, the compounds of Formula 3 are the compounds of Formula 3b. In a further embodiment, the compounds of Formula 3a are of the formula:



where R_{25}, R_{30}, R_{35}, R_{40}, R_{45}, R_{51} are as described above and the A-ring is as described herein.

In one aspect, the compounds of Formula 3 are the compounds of Formula 3a.

In one aspect, the compounds of Formula 3 are the compounds of Formula 3b.

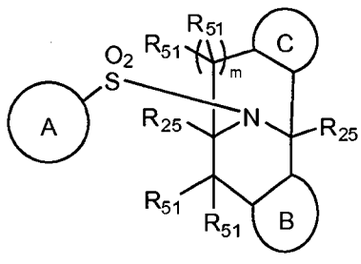
In one aspect, the compounds of Formula 3 are the compounds of Formula 3c.

In one aspect, the compounds of Formula 3 are the compounds of Formula 3d.

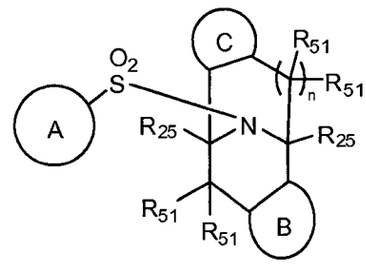
In one aspect, the compounds of Formula 3 are the compounds of Formula 3e.

In one aspect, the compounds of Formula 3 are the compounds of Formula 3f.

In one aspect, provided herein are compounds of Formulas 4a and/or 4b, *i.e.*, compounds of Formula 4 having the formulas:



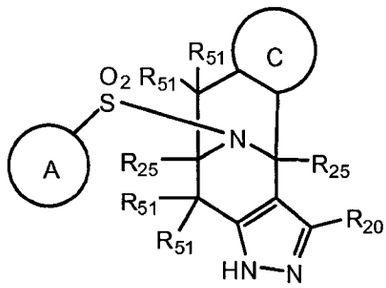
Formula 4a



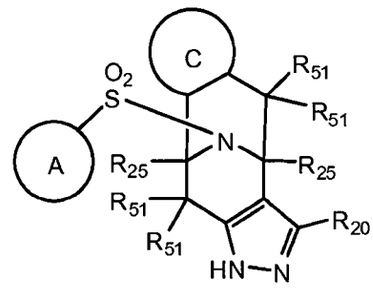
Formula 4b

Wherein the A-ring, B-ring, C-ring, R_{25}, R_{51}, m and n are as defined above for Formula 4.

In another aspect, provided herein are compounds of Formulas 4c and/or 4d, *i.e.*, compounds of Formula 4 having the formulas:



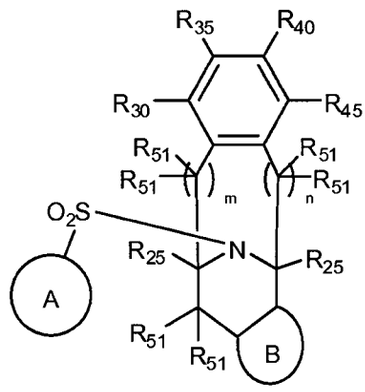
Formula 4c



Formula 4d

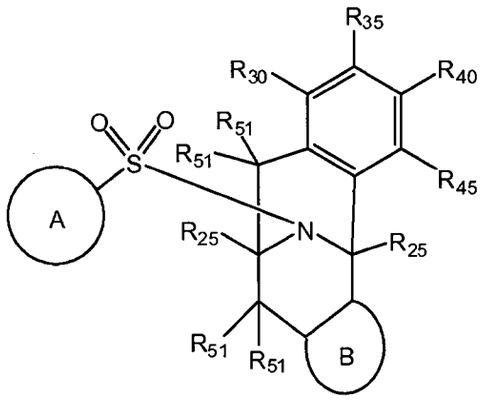
Wherein the A-ring, C-ring, R_{20}, R_{25}, and R_{51} are as defined above.

In one aspect, provided herein are compounds of Formulas 4e, *i.e.*, compounds of Formula 4 that have the following formula:

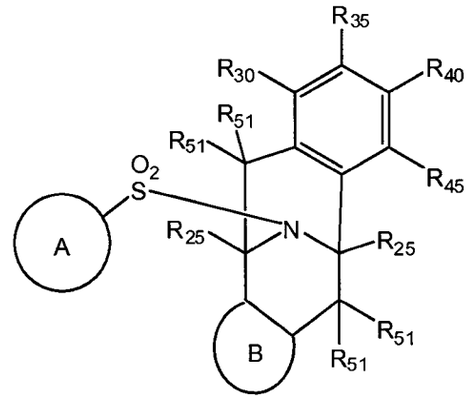


Wherein the A-ring, B-ring, R_{20}, R_{25}, R_{30}, R_{35}, R_{40}, R_{45}, R_{51}, m and n are as defined above.

In one aspect, provided herein are compounds of Formulas 4f and/or 4g, *i.e.*, compounds of Formula 4 that have the following formula:



Formula 4f



Formula 4g

including enantiomers and/or pharmaceutically acceptable salts thereof, wherein,

B-ring is pyrazolyl, dihydropyrazolyl, pyrazolonyl or pyrazolidinonyl, each of which is optionally substituted with $-NR_{11}$-C_2-C_6 alkanoyl, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxy, hydroxyalkyl, halo, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ or CN;

R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, $-C(O)OR_{11}$, $-SO_2NR_{11}R_{11}$, aryl C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, CN, NO_2, hydroxyl, C_1-C_6 alkoxy, -C_1-C_6 alkyl-OH, -C_1-C_6 alkyl-C_1-C_6 alkoxy, phenyloxy, $-S(O_2)R_{10}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, heteroaryl C_1-C_6 alkyl, heteroaryl, where the heteroaryl groups are oxazolyl, oxadiazolyl pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl or thienyl, and wherein each heteroaryl group is optionally substituted with a C_1-C_6 alkyl group; heterocycloalkylalkyl, heterocycloalkyl, wherein the heterocycloalkyl groups are pyrrolidinyl, imidazolidinyl, piperidinyl or morpholinyl, wherein each heterocycloalkyl group is optionally substituted with one or two groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy or halogen, phenyl, naphthyl, phenyloxy, naphthyloxy or phenyl C_1-C_6 alkyl, where the phenyl portions of the above are optionally substituted with one to five groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, C_1-C_4 haloalky (*e.g.*, CF_3) or halogen; and

wherein two adjacent carbons of the fused aryl ring optionally form a heterocycloalkyl (*e.g.*, $-OCH_2O-$ or $-OCH_2CH_2O-$) or a heteroaryl ring, each of which is optionally substituted with 1, 2, 3 or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen or C_2-C_4 alkanoyl wherein the alkanoyl group is optionally substituted with up to 3 halogen atoms; or

two adjacent carbons of the fused aryl ring form a benzo ring which is optionally substituted with 1 to 4 groups that are independently halogen, hydroxyl, C_1-C_4alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, CN or NO_2;

each R_{51} is independently absent, H, C_1-C_4 alkyl, halogen (*e.g.*, F, Cl or Br), CN, amino, mono alkylamino, dialkylamino, OH, C_1-C_4 haloalkoxy (*e.g.*, OCF_3) or C_1-C_4 haloalkyl (*e.g.*, CF_3); or when there are two R_{51} groups on a carbon atom, the two R_{51} groups and the carbon to which they are attached may form a 3- to 6-membered cycloalkyl or heterocycloalkyl ring; or when there are two R_{51} groups on a carbon, the two R_{51} groups may form an oxo group; or when there are two R_{51} groups on a carbon, the two R_{51} groups may form an alkene group; or when there are two R_{51} groups on a carbon, the two R_{51} groups may form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime);

a non-bridgehead carbon (and any substituent or substituents thereon) in the [3.3.1], [3.2.1] or [2.2.1] ring systems may be replaced with an NR_{15} group;

R_{10} and R_{11} at each occurrence are independently C_1-C_6 alkyl, heteroaryl that is selected from pyrazolyl, thiadiazolyl, triazolyl, isoxazolyl, isothiazolyl, imidazolyl, thiazolyl, oxadiazolyl, and pyridyl or aryl that is selected from phenyl and naphthyl, where the heteroaryl and aryl groups are optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, CN or NO_2; and additionally R_{11} may be H; or if two R_{11} groups are on a nitrogen, then the two R_{11} groups together with the nitrogen to which they are attached, may form a 3-8 membered ring optionally including an additional heteroatom such as NH, NR_{12}, NR_{13}, O or S. In one embodiment of this aspect, the B-ring is pyrazolyl, which is optionally substituted with C_1-C_4 –NR_{11}-C_2-C_6 alkanoyl (*e.g.*, -NR_{11}-C_2 alkanoyl, where R_{11} is H or C_1-C_4 alkyl), alkyl, C_3-C_6 cycloalkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxy C_1-C_4 alkyl, halo, CF_3, OCF_3 or CN;

R_{12} is H, C_1-C_6 alkyl, aryl or –SO_2-aryl (*e.g.*, phenyl or naphthyl, where phenyl is preferred), where each aryl group is optionally substituted with 1 to 5 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2; and

R_{13} is H, aryl or C_1-C_6 alkyl optionally substituted with aryl (such as phenyl or naphthyl, more preferably, phenyl), hydroxyl or halogen, where each aryl group is optionally substituted with 1 to 5 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2.

In another aspect, provided herein are compounds of Formulas 4a, 4b, 4c, 4d (when the C-ring is benzo substituted with R_{30}, R_{35}, R_{40}, and R_{45}), 4e, 4f and/or 4g, wherein R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, CN, hydroxyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, -C_1-C_3 alkyl-OH, -C_1-C_3 alkyl-alkoxy, phenyloxy, -C(O)OR_{11}, -S(O_2)R_{10}, -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alkanoyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl, thienyl, phenyl or phenyl C_1-C_4 alkyl, where the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky (*e.g.* CF_3) or halogen. In an embodiment of this aspect, the geminal R_{51} groups that are alpha to the B-ring are both hydrogen. In another further embodiment, at least one of the geminal R_{51} groups that are alpha to the B-ring is halogen. In another further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both halogen. In still another further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In one embodiment of this aspect, R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen (*e.g.*, F), C_1-C_6 alkyl, hydroxyl, C_1-C_4 haloalkyl (*e.g.*, CF_3), C_1-C_4 haloalkoxy (*e.g.*, OCF_3), C_1-C_6 alkoxy, -C_1-C_3 alkyl-OH, CN or -C_1-C_3 alkyl-alkoxy.

In one embodiment of this aspect, R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen, C_1-C_4 alkyl, CF_3, OCF_3, hydroxyl, C_1-C_4 alkoxy, -C_1-C_2 alkyl-OH, CN or -C_1-C_2 alkyl- C_1-C_4 alkoxy.

In one embodiment of this aspect, R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen, methyl, ethyl, hydroxyl, CF_3, OCF_3. In a further embodiment, at least two of R_{30}, R_{35}, R_{40}, and R_{45} are hydrogen. In a further embodiment, R_{40} is CF_3. In a still further embodiment, R_{35} is CF_3. In a further embodiment, R_{40} is CN. In a still further embodiment, R_{35} is CN. In a further embodiment, R_{35} or R_{40} is hydroxyl.

In one embodiment of this aspect, R_{30}, R_{35}, R_{40}, and R_{45} are independently H, -C(O)OR_{11}, -S(O_2)R_{10}, -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$ or C_2-C_6 alkanoyl.

In one embodiment of this aspect, R_{30} and R_{35} or R_{35} and R_{40} or R_{40} and R_{45} are -OCH_2O- or -OCH_2CH_2O- wherein each methylene of -OCH_2O- or -OCH_2CH_2O- is optionally substituted with one or two C_1-C_4 alkyl groups.

In still another embodiment of this aspect, R_{11} is H.

In still another embodiment of this aspect, one of R_{10} and R_{11} is CH_3.

In another embodiment of this aspect, R_{11} and R_{11} together with the nitrogen to which they are attached form a 3-8 membered ring, which optionally includes an additional heteroatom that is NH, NR_{12}, NR_{13}, O or S.

In still another embodiment of this aspect, R_{10} and R_{11} at each occurrence are independently phenyl optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, CN or NO_2; and additionally R_{11} may be H.

In another embodiment of this aspect, R_{10} and R_{11} at each occurrence are independently pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl or thiazolyl, each of which is optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, CN or NO_2; and additionally R_{11} may be H.

In another embodiment of this aspect, R_{10} and R_{11} at each occurrence are independently thiadiazolyl, triazolyl or oxadiazolyl, each of which is optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, CN or NO_2 and additionally R_{11} may be H.

In another aspect, provided herein are compounds of Formulas 4a, 4b, 4c, 4d (when the C-ring is benzo substituted with R_{30}, R_{35}, R_{40}, and R_{45}), 4e, 4f and/or 4g, wherein R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen (*e.g.*, F), C_1-C_4 alkyl, $-C(O)OR_{11}$, $-S(O_2)R_{10}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ or $-O-C(O)NR_{11}R_{11}$.

In an embodiment of this aspect, at least two of R_{30}, R_{35}, R_{40}, and R_{45} are H, while another is H, halogen or C1-C4 alkyl, and the other is $-C(O)OR_{11}$, $-S(O_2)R_{10}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ or $-O-C(O)NR_{11}R_{11}$. In a further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both hydrogen. In another further embodiment, at least one of the geminal R_{51} groups that are alpha to the B-ring is halogen. In another further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both halogen. In still another further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In an embodiment of this aspect, three of R_{30}, R_{35}, R_{40}, and R_{45} are H, while the other is $-C(O)OR_{11}$, $-S(O_2)R_{10}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ or $-O-C(O)NR_{11}R_{11}$. In a further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both hydrogen. In another further embodiment, at least one of the geminal R_{51} groups that are alpha to the B-ring is halogen. In another further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both halogen. In still another further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In yet another embodiment of this aspect, three of R_{30}, R_{35}, R_{40}, and R_{45} are H, while the other is $-NR_{11}R_{11}$. In a further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both hydrogen. In another further embodiment, at least one of the geminal R_{51} groups that are alpha to the B-ring is halogen. In another further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both halogen. In still another further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In yet another embodiment of this aspect, three of R_{30}, R_{35}, R_{40}, and R_{45} are H, while the other is $-SO_2NR_{11}R_{11}$ or $-NR_{11}SO_2R_{10}$. In a further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both hydrogen. In another further embodiment, at least one of the geminal R_{51} groups that are alpha to the B-ring is halogen. In another further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both halogen. In still another further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In an embodiment of this aspect, three of R_{30}, R_{35}, R_{40}, and R_{45} are H, while the other is $-C(O)NR_{11}R_{11}$ or $-NR_{11}C(O)R_{10}$. In a further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both hydrogen. In another further embodiment, at least one of the geminal R_{51} groups that are alpha to the B-ring is halogen. In another further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both halogen. In still another further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still

further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In still another embodiment of this aspect, three of R_{30}, R_{35}, R_{40}, and R_{45} are H, while the other is -O-C(O)$NR_{11}R_{11}$. In a further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both hydrogen. In another further embodiment, at least one of the geminal R_{51} groups that are alpha to the B-ring is halogen. In another further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both halogen. In still another further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In still another embodiment of this aspect, two of R_{30}, R_{35}, R_{40}, and R_{45} are H, while one is methyl and the other is -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$ or -NR_{11}C(O)R_{10}. In a further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both hydrogen. In another further embodiment, at least one of the geminal R_{51} groups that are alpha to the B-ring is halogen. In another further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both halogen. In still another further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In an embodiment of this aspect, three of R_{30}, R_{35}, R_{40}, and R_{45} are H, while the other is -C(O)OR_{11}. In a further embodiment, R_{11} is H or C_1-C_4 alkyl. In a further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both hydrogen. In another further embodiment, at least one of the geminal R_{51} groups that are alpha to the B-ring is halogen. In another further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both halogen. In still another further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In another aspect, provided herein are compounds of Formulas 4a, 4b, 4c, 4d (when the C-ring is benzo substituted with R_{30}, R_{35}, R_{40}, and R_{45}), 4e, 4f and/or 4g, wherein R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_3-C_6 cycloalkyl, phenyloxy, C_2-C_6 alkanoyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl, thienyl, phenyl or phenyl C_1-C_4 alkyl where the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky (*e.g.* CF_3) or halogen.

In another embodiment of this aspect, at least two of R_{30}, R_{35}, R_{40}, and R_{45} are H.

In still another embodiment of this aspect, three of R_{30}, R_{35}, R_{40}, and R_{45} are H.

In still another embodiment of this aspect, R_{30}, R_{35}, R_{40}, and R_{45} are H.

In another embodiment of this aspect, at least one of R_{30}, R_{35}, R_{40}, and R_{45} is a halogen (*e.g.*, F, Cl or Br). In a still another embodiment, at least two of R_{30}, R_{35}, R_{40}, and R_{45} is a halogen (*e.g.*, F, Cl or Br), where the halogens may be the same or different.

In still another embodiment of this aspect, R_{30}, R_{35}, R_{40}, and R_{45} are H; and the B-ring is unsubstituted pyrazolyl.

In yet still another embodiment of this aspect, R_{30} and R_{45} are H; and R_{35} and R_{40} are independently halogen (*e.g.*, F, Cl or Br), C_1-C_4 alkyl, C_1-C_4 alkoxy or C_2-C_6 alkanoyl.

In yet still another embodiment of this aspect, R_{30} and R_{45} are H; and R_{35} and R_{40} and the carbons to which they are attached form a heterocycloalkyl ring. In a further embodiment, the heterocycloalkyl ring is $-OCH_2O-$, $-OCH_2CH_2O-$ or $-OC(O)O-$. In a further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both hydrogen. In another further embodiment, at least one of the geminal R_{51} groups that are alpha to the B-ring is halogen. In another further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both halogen. In still another further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In yet still another embodiment of this aspect, R_{30} and R_{45} are H; and R_{35} and R_{40} are independently halogen (*e.g.*, F, Cl or Br), C_1-C_4 alkyl, C_1-C_4 alkoxy or C_2-C_6 alkanoyl. In a further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both hydrogen. In another further embodiment, at least one of the geminal R_{51} groups that are alpha to the B-ring is halogen. In another further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both halogen (*e.g.*, F). In still another further embodiment, the geminal R_{51} groups

that are alpha to the B-ring form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In yet still another embodiment of this aspect, R_{30} and R_{45} are H; and R_{35} and R_{40} are independently halogen (*e.g.*, F, Cl or Br), and the geminal R_{51} groups that are alpha to the B-ring are both halogens.

In still another embodiment of this aspect, R_{30} and R_{45} are H; and R_{35} and R_{40} are independently halogen (*e.g.*, F, Cl or Br), hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_2-C_6 alkanoyl, phenyloxy, phenyl or phenyl C_1-C_4 alkyl, where the phenyl portions are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky (*e.g.* CF_3) or halogen.

In still another embodiment of this aspect, R_{30} and R_{45} are H; and R_{35} and R_{40} are independently halogen (*e.g.*, F, Cl or Br), C_1-C_4 alkyl, C_1-C_4 alkoxy, C_2-C_6 alkanoyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl or thienyl.

In yet still another embodiment of this aspect, R_{35} and R_{40} are H; and R_{30} and R_{45} are independently halogen (*e.g.*, F, Cl or Br), hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy or C_2-C_6 alkanoyl.

In yet still another embodiment of this aspect, R_{35} and R_{40} are H; and R_{30} and R_{45} are independently halogen (*e.g.*, F, Cl or Br), hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, cyclopropyl or C_2-C_6 alkanoyl; and the geminal R_{51} groups that are alpha to the B-ring form an oxo group, an C_2-C_4 alkenyl group, an oxime, a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime), are both H or are both halogens *(e.g.*, F). In a further embodiment, one of R_{30} or R_{45} is H, while the other is F or Cl.

In yet still another embodiment of this aspect, R_{35} and R_{40} are H; and R_{30} and R_{45} are independently H, halogen (*e.g.*, F, Cl or Br), C_1-C_4 alkyl, C_1-C_4 alkoxy, cyclopropyl or C_2-C_6 alkanoyl; and the geminal R_{51} groups that are alpha to the B-ring are both halogens, provided that atleast one of R_{30} and R_{45} is not H. In another embodiment, both R_{51} groups that are alpha to the B-ring are F. In a further embodiment, R_{30} is halogen while R_{45} is H. In another further embodiment, R_{30} is H while R_{45} is halogen. In another further embodiment, R_{30} is cyclopropyl, while R_{45} is H. In another further embodiment, R_{30} is H while R_{45} is cyclopropyl. In a further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both hydrogen. In another further embodiment, at least one of the geminal R_{51} groups that are alpha to the B-ring is halogen. In another further embodiment, the geminal R_{51} groups

that are alpha to the B-ring are both halogen. In still another further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In yet still another embodiment of this aspect, R_{35} and R_{40} are H; and R_{30} and R_{45} are independently halogen (*e.g.*, F, Cl or Br), methyl or methoxy. In a further embodiment, R_{30} is halogen. In another further embodiment, R_{45} is halogen. In a further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both hydrogen. In another further embodiment, at least one of the geminal R_{51} groups that are alpha to the B-ring is halogen. In another further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both halogen (*e.g.*, F). In still another further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In still another embodiment of this aspect, R_{35} and R_{40} are H; and R_{30} and R_{45} are independently halogen (*e.g.*, F, Cl or Br), hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_2-C_6 alkanoyl, phenyloxy, phenyl or phenyl C_1-C_4 alkyl. In a further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both hydrogen. In another further embodiment, at least one of the geminal R_{51} groups that are alpha to the B-ring is halogen. In another further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both halogen (*e.g.*, F). In still another further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In still another embodiment of this aspect, R_{35} and R_{40} are H; and R_{30} and R_{45} are independently halogen (*e.g.*, F, Cl or Br), hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_2-C_6 alkanoyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl or thienyl. In a further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both hydrogen. In another further embodiment, at least one of the geminal R_{51} groups that are alpha to the B-ring is halogen. In another further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both halogen (*e.g.*, F). In still another further embodiment, the

geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In still another embodiment of this aspect, R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen (*e.g.*, F, Cl or Br), C_1-C_4 alkyl or C_1-C_4 alkoxy; and one R_{51} group is halogen or OH, while the other R_{51} group is H. In a still further embodiment, the B-ring is unsubstituted. In a further embodiment, at least two of R_{30}, R_{35}, R_{40}, and R_{45} are H. In a still further embodiment, R_{30}, R_{35}, R_{40}, and R_{45} are H.

In still another embodiment of this aspect, R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen (*e.g.*, F, Cl or Br), C_1-C_4 alkyl or C_1-C_4 alkoxy; and one R_{51} group is halogen or OH, while the other R_{51} group is H. In a still further embodiment, the B-ring is unsubstituted. In a further embodiment, at least one of R_{30}, R_{35}, R_{40}, and R_{45} is halogen (*e.g.*, F, Cl or Br), C_1-C_4 alkyl or C_1-C_4 alkoxy. In a still further embodiment, two of R_{30}, R_{35}, R_{40}, and R_{45} are H.

In another aspect, provided herein are compounds of Formulas 4a, 4b, 4c, 4d (when the C-ring is benzo substituted with R_{30}, R_{35}, R_{40}, and R_{45}), 4e, 4f and/or 4g, wherein R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_2-C_6 alkanoyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_2-C_8 haloalkenyl or C_2-C_8 haloalkynyl; provided that two adjacent carbons of the fused aryl ring (the ring to which the R_{30}, R_{35}, R_{40} and R_{45} groups are attached) optionally form a heterocycloalkyl or a heteroaryl ring, each of which is optionally substituted with 1, 2, 3 or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen or C_1-C_4 alkanoyl wherein the alkanoyl group is optionally substituted with up to 3 halogen atoms. In a further embodiment, the heterocycloalkyl ring is piperidinyl, pyrrolidinyl or morpholinyl, and the heteroaryl ring is pyrazolyl, imidazolyl or pyridinyl, wherein each heterocycloalkyl or heteroaryl group is optionally substituted with 1, 2, 3 or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen or C_1-C_4 alkanoyl wherein the alkanoyl group is optionally substituted with up to 3 halogen atoms. In a further embodiment, the heterocycloalkyl ring is piperidinyl or pyrrolidinyl, each of which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen or C_2-C_4 alkanoyl wherein the alkanoyl group is optionally substituted with up to 3 halogen atoms. In a further embodiment, the heteroaryl ring is pyrazolyl, imidazolyl or pyridinyl, each of which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4

alkoxy, halogen or C_2-C_4 alkanoyl wherein the alkanoyl group is optionally substituted with up to 3 halogen atoms.

In another aspect, provided herein are compounds of Formulas 4a, 4b, 4c, 4d (when the C-ring is benzo substituted with R_{30}, R_{35}, R_{40}, and R_{45}), 4e, 4f and/or 4g, wherein R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_2-C_6 alkanoyl; provided that two adjacent carbons of the fused aryl ring form a benzo ring, which is optionally substituted with 1 to 4 groups that are independently halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, CN or NO_2.

In one embodiment of this aspect, R_{30} and R_{45} are independently H, halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, and R_{35}, R_{40}, and the carbons to which they are attached form a benzo ring, which is optionally substituted with 1 to 4 groups that are independently halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, CN or NO_2. In a further embodiment, the benzo ring is unsubstituted.

In one embodiment of this aspect, R_{30} and R_{35} are independently H, halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, and R_{40}, R_{45}, and the carbons to which they are attached form a benzo ring, which is optionally substituted with 1 to 4 groups that are independently halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, CN or NO_2. In a further embodiment, the benzo ring is unsubstituted.

In one embodiment of this aspect, R_{40} and R_{45} are independently H, halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, and R_{30}, R_{35}, and the carbons to which they are attached form a benzo ring, which is optionally substituted with 1 to 4 groups that are independently halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, CN or NO_2. In a further embodiment, the benzo ring is unsubstituted.

In one aspect, the compounds of Formula 4 are the compounds of Formula 4a.

In one aspect, the compounds of Formula 4 are the compounds of Formula 4b.

In one aspect, the compounds of Formula 4 are the compounds of Formula 4c.

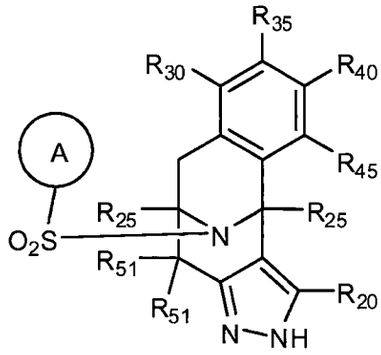
In one aspect, the compounds of Formula 4 are the compounds of Formula 4d.

In one aspect, the compounds of Formula 4 are the compounds of Formula 4e.

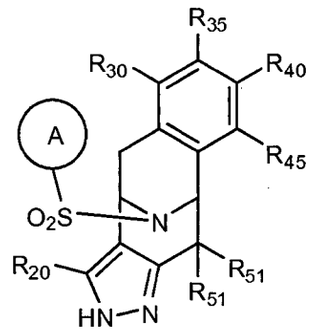
In one aspect, the compounds of Formula 4 are the compounds of Formula 4f.

In one aspect, the compounds of Formula 4 are the compounds of Formula 4g.

In one aspect, the compounds of Formula 4 have the Formulas 4f1 and 4g1:



Formula 4f1



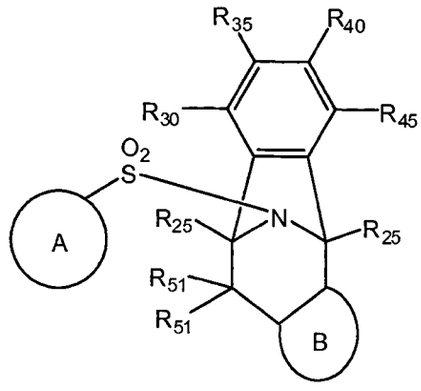
Formula 4g1

including stereoisomers, tautomers and mixtures of steroisomers and/or tautomers, and/or pharmaceutical salts thereof, wherein R_{30}, R_{35}, R_{40}, R_{45}, and the A-ring are as previously defined; R_{20} is H, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, C_1-C_6 alkylamino, C_1-C_6 dialkylamino, halo, CF_3 or $-NHC(O)CH_3$; and R_{51} is H, C_1-C_4 alkyl, F, Cl, Br, CN, amino, mono alkylamino, dialkylamino, OH, oxo, $=CH_2$, =NOH, $=NOCH_3$, $=NOCH_2CH_3$, or CF_3. In one embodiment, R_{20} is H. In another embodiment, R_{20} is methyl. In another embodiment, R_{51} is H. In another embodiment, R_{51} is F. In another embodiment, R_{51} is OH. In another embodiment, R_{51} is CF_3. In still another embodiment, R_{51} is H and R_{51} is F or Cl. In another embodiment, R_{51} is OH. In another embodiment, R_{51} is H. In another embodiment, R_{20} is H and R_{51} is F. In another embodiment, R_{20} is H and R_{51} is OH. In another embodiment, R_{20} is H and the geminal R_{51} groups form an oxo group. In another embodiment, R_{20} is methyl and the geminal R_{51} groups form an oxo group. In another embodiment, R_{20} is H and the geminal R_{51} groups form an $=CH_2$, group. In another embodiment, R_{20} is methyl and the geminal R_{51} groups form an $=CH_2$, group. In another embodiment, R_{20} is H and the geminal R_{51} groups form =NOH, $=NOCH_3$, or $=NOCH_2CH_3$. In another embodiment, R_{20} is methyl and the geminal R_{51} groups form an =NOH, $=NOCH_3$, or $=NOCH_2CH_3$.

In one aspect, the compounds of Formula 4 are the compounds of Formula 4f1.

In another aspect, the compounds of Formula 4 are the compounds of Formula 4g1.

In one aspect, provided herein are compounds of Formula 4h, *i.e.*, compounds of Formula 4 having the formula



including enantiomers and/or pharmaceutically acceptable salts thereof, wherein,

B-ring is pyrazolyl, dihydropyrazolyl, pyrazolonyl or pyrazolidinonyl, each of which is optionally substituted with $-NR_{11}$-C_2-C_6 alkanoyl, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxy, hydroxyalkyl, halo, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ or CN;

R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen, C_1-C_6 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, $-C(O)OR_{11}$, $-SO_2NR_{11}R_{11}$, aryl C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, CN, NO_2, hydroxyl, C_1-C_6 alkoxy, -C_1-C_6 alkyl-OH, -C_1-C_6 alkyl-C_1-C_6 alkoxy, phenyloxy, $-S(O_2)R_{10}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, heteroaryl C_1-C_6 alkyl, heteroaryl, where the heteroaryl groups are oxazolyl, oxadiazolyl pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl or thienyl, and wherein each heteroaryl group is optionally substituted with a C_1-C_6 alkyl group; heterocycloalkylalkyl, heterocycloalkyl, wherein the heterocycloalkyl groups are pyrrolidinyl, imidazolidinyl, piperidinyl or morpholinyl, wherein each heterocycloalkyl group is optionally substituted with one or two groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy or halogen, phenyl, naphthyl, phenyloxy, naphthyloxy or phenyl C_1-C_6 alkyl, where the phenyl portions of the above are optionally substituted with one to five groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, C_1-C_4 haloalky (*e.g.*, CF_3) or halogen; and

wherein two adjacent carbons and of the fused aryl ring optionally form a heterocycloalkyl (*e.g.*, $-OCH_2O-$ or $-OCH_2CH_2O-$) or a heteroaryl ring, each of which is optionally substituted with 1, 2, 3 or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen or C_2-C_4 alkanoyl wherein the alkanoyl group is optionally substituted with up to 3 halogen atoms; or

two adjacent carbons of the fused aryl ring form a benzo ring which is optionally substituted with 1 to 4 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2;

each R_{51} is independently absent, H, C_1-C_4 alkyl, halogen (*e.g.*, F, Cl or Br), CN, amino, mono alkylamino, dialkylamino, OH, C_1-C_4 haloalkoxy (*e.g.*, OCF_3), C_1-C_4 haloalkyl (*e.g.*, CF_3) or –CN; or when there are two R_{51} groups on a carbon atom, the two R_{51} groups and the carbon to which they are attached may form a 3- to 6-membered cycloalkyl or heterocycloalkyl ring; or when there are two R_{51} groups on a carbon, the two R_{51} groups may form an oxo group; or when there are two R_{51} groups on a carbon, the two R_{51} groups may form an alkene group; or when there are two R_{51} groups on a carbon, the two R_{51} groups may form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime);

a non-bridgehead carbon (and any substituent or substituents thereon) in the [3.3.1], [3.2.1] or [2.2.1] ring systems may be replaced with an NR_{15} group. In a further embodiment, R_{10} and R_{11} at each occurrence are independently C_1-C_6 alkyl, heteroaryl that is selected from pyrazolyl, thiadiazolyl, triazolyl, isoxazolyl, isothiazolyl, imidazolyl, thiazolyl, oxadiazolyl, and pyridyl or aryl that is selected from phenyl and naphthyl, where the heteroaryl and aryl groups are optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2; and additionally R_{11} may be H;

or if two R_{11} groups are on a nitrogen, then the two R_{11} groups together with the nitrogen to which they are attached, may form a 3-8 membered ring optionally including an additional heteroatom such as NH, NR_{12}, NR_{13}, O or S;

R_{12} is H, C_1-C_6 alkyl, aryl or $-SO_2$-aryl (*e.g.*, phenyl or naphthyl, where phenyl is preferred), where each aryl group is optionally substituted with 1 to 5 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2;

R_{13} is H, aryl or C_1-C_6 alkyl optionally substituted with aryl (such as phenyl or naphthyl, more preferably, phenyl), hydroxyl or halogen, where each aryl group is optionally substituted with 1 to 5 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2. In a further embodiment the B-ring is pyrazolyl, which is optionally substituted with $-NR_{11}$-C_2-C_6 alkanoyl, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_2-C_4

alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxy C_1-C_4 alkyl, halo, CF_3, OCF_3 or CN.

In another aspect, provided herein are compounds of Formula 4h, wherein R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, CN, hydroxyl, C_1-C_6 alkoxy, -C_1-C_3 alkyl-OH, -C_1-C_3 alkyl-alkoxy, phenyloxy, -C(O)OR_{11}, -S(O_2)R_{10}, -$NR_{11}R_{11}$, --C(O)$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alkanoyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl, thienyl, phenyl or phenyl C_1-C_4 alkyl, where the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy or halogen. In an embodiment of this aspect, the geminal R_{51} groups that are alpha to the B-ring are both hydrogen. In another further embodiment, at least one of the geminal R_{51} groups that are alpha to the B-ring is halogen. In another further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both halogen. In still another further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In one embodiment of this aspect, R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen (*e.g.*, F), C_1-C_6 alkyl, hydroxyl, C_1-C_4 haloalkyl (*e.g.*, CF_3), C_1-C_4 haloalkoxy (*e.g.*, OCF_3), C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, C_1-C_6 alkoxy, -C_1-C_3 alkyl-OH, CN or -C_1-C_3 alkyl-alkoxy.

In one embodiment of this aspect, R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen, C_1-C_4 alkyl, CF_3, OCF_3, hydroxyl, C_1-C_4 alkoxy, -C_1-C_2 alkyl-OH, CN or -C_1-C_2 alkyl- C_1-C_4 alkoxy.

In one embodiment of this aspect, R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl or -C(O)OR_{11}. In a further embodiment, the halo portion of the haloalkenyl and haloalkynyl groups is F, Cl or Br.

In one embodiment of this aspect, two of R_{30}, R_{35}, R_{40}, and R_{45} are H, while at least one of the other groups is halogen, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl or -C(O)OR_{11}. In a further embodiment, the halo portion of the haloalkenyl and haloalkynyl groups is F, Cl or Br.

In one embodiment of this aspect, R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen, methyl, ethyl, hydroxyl, CF_3 or OCF_3. In a further embodiment, at least two of R_{30}, R_{35}, R_{40}, and R_{45} are hydrogen. In a further embodiment, R_{40} is CF_3. In a still further embodiment, R_{35} is CF_3. In a further embodiment, R_{40} is CN. In a still further embodiment, R_{35} is CN. In a further embodiment, R_{35} or R_{40} is hydroxyl.

In one embodiment of this aspect, R_{30}, R_{35}, R_{40}, and R_{45} are independently H, $-C(O)OR_{11}$, $-S(O_2)R_{10}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$ or C_2-C_6 alkanoyl.

In one embodiment of this aspect, R_{30} and R_{35} or R_{35} and R_{40} or R_{40} and R_{45} are $-OCH_2O-$ or $-OCH_2CH_2O-$ wherein each methylene of $-OCH_2O-$ or $-OCH_2CH_2O-$ is optionally substituted with one or two C_1-C_4 alkyl groups.

In still another embodiment of this aspect, R_{11} is H.

In still another embodiment of this aspect, one of R_{10} and R_{11} is CH_3.

In another embodiment of this aspect, R_{11} and R_{11} together with the nitrogen to which they are attached may form a 3-8 membered ring, which optionally includes an additional heteroatom that is NH, NR_{12}, NR_{13}, O or S.

In still another embodiment of this aspect, R_{10} and R_{11} at each occurrence are independently phenyl optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, CN or NO_2; and additionally R_{11} may be H.

In another embodiment of this aspect, R_{10} and R_{11} at each occurrence are independently pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl or thiazolyl, each of which is optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, CN or NO_2; and additionally R_{11} may be H.

In another embodiment of this aspect, R_{10} and R_{11} at each occurrence are independently thiadiazolyl, triazolyl or oxadiazolyl, each of which is optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, halo C_1-C_4 alkyl, halo C_1-C_4 alkoxy, CN or NO_2 and additionally R_{11} may be H.

In another aspect, provided herein are compounds of Formula 4h, wherein R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen (*e.g.*, F), C_1-C_4 alkyl, $-C(O)OR_{11}$, $-S(O_2)R_{10}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ or $-O-C(O)NR_{11}R_{11}$.

In an embodiment of this aspect, at least two of R_{30}, R_{35}, R_{40}, and R_{45} are H, while another is H, halogen or C1-C4 alkyl, and the other is $-C(O)OR_{11}$, $-S(O_2)R_{10}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ or $-O-C(O)NR_{11}R_{11}$. In a further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both hydrogen. In another further embodiment, at least one of the geminal R_{51} groups that are alpha to the B-ring is halogen. In another further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both halogen. In still another further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In an embodiment of this aspect, three of R_{30}, R_{35}, R_{40}, and R_{45} are H, while the other is $-C(O)OR_{11}$, $-S(O_2)R_{10}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ or $-O-C(O)NR_{11}R_{11}$. In a further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both hydrogen. In another further embodiment, at least one of the geminal R_{51} groups that are alpha to the B-ring is halogen. In another further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both halogen. In still another further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In yet another embodiment of this aspect, three of R_{30}, R_{35}, R_{40}, and R_{45} are H, while the other is $-NR_{11}R_{11}$. In a further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both hydrogen. In another further embodiment, at least one of the geminal R_{51} groups that are alpha to the B-ring is halogen. In another further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both halogen. In still another further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In yet another embodiment of this aspect, three of R_{30}, R_{35}, R_{40}, and R_{45} are H, while the other is $-SO_2NR_{11}R_{11}$ or $-NR_{11}SO_2R_{10}$. In a further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both hydrogen. In another further embodiment, at least one of the geminal R_{51} groups that are alpha to the B-ring is halogen. In another further

embodiment, the geminal R_{51} groups that are alpha to the B-ring are both halogen. In still another further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In an embodiment of this aspect, three of R_{30}, R_{35}, R_{40}, and R_{45} are H, while the other is -C(O)$NR_{11}R_{11}$ or -NR_{11}C(O)R_{10}. In a further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both hydrogen. In another further embodiment, at least one of the geminal R_{51} groups that are alpha to the B-ring is halogen. In another further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both halogen. In still another further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In still another embodiment of this aspect, three of R_{30}, R_{35}, R_{40}, and R_{45} are H, while the other is -O-C(O)$NR_{11}R_{11}$. In a further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both hydrogen. In another further embodiment, at least one of the geminal R_{51} groups that are alpha to the B-ring is halogen. In another further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both halogen. In still another further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In still another embodiment of this aspect, two of R_{30}, R_{35}, R_{40}, and R_{45} are H, while one is methyl and the other is -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$ or -NR_{11}C(O)R_{10}. In a further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both hydrogen. In another further embodiment, at least one of the geminal R_{51} groups that are alpha to the B-ring is halogen. In another further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both halogen. In still another further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In an embodiment of this aspect, three of R_{30}, R_{35}, R_{40}, and R_{45} are H, while the other is -C(O)OR_{11}. In a further embodiment, R_{11} is H or C_1-C_4 alkyl. In a further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both hydrogen. In another further embodiment, at least one of the geminal R_{51} groups that are alpha to the B-ring is halogen. In another further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both halogen. In still another further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In another aspect, provided herein are compounds of Formula 4h, wherein R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, phenyloxy, C_2-C_6 alkanoyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl, thienyl, phenyl or phenyl C_1-C_4 alkyl where the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky (*e.g.* CF_3) or halogen.

In another embodiment of this aspect, at least two of R_{30}, R_{35}, R_{40}, and R_{45} are H.

In still another embodiment of this aspect, three of R_{30}, R_{35}, R_{40}, and R_{45} are H.

In still another embodiment of this aspect, R_{30}, R_{35}, R_{40}, and R_{45} are H.

In still another embodiment of this aspect, R_{30}, R_{35}, R_{40}, and R_{45} are H; and the B-ring is unsubstituted pyrazolyl.

In still another embodiment of this aspect, R_{30}, R_{35}, R_{40}, and R_{45} are H; the B-ring is unsubstituted pyrazolyl; and the geminal R_{51} groups that are alpha to the B-ring form an oxo group.

In still another embodiment of this aspect, R_{30}, R_{35}, R_{40}, and R_{45} are H; the B-ring is unsubstituted pyrazolyl; and the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group.

In still another embodiment of this aspect, R_{30}, R_{35}, R_{40}, and R_{45} are H; the B-ring is unsubstituted pyrazolyl; and the geminal R_{51} groups that are alpha to the B-ring form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In still another embodiment of this aspect, R_{30}, R_{35}, R_{40}, and R_{45} are H; the B-ring is unsubstituted pyrazolyl; and the geminal R_{51} groups that are alpha to the B-ring are both H or one is H and the other is F or OH.

In yet still another embodiment of this aspect, R_{30} and R_{45} are H; and R_{35} and R_{40} are independently halogen (*e.g.*, F, Cl or Br), C_1-C_4 alkyl, C_1-C_4 alkoxy or C_2-C_6 alkanoyl.

In yet still another embodiment of this aspect, R_{30} and R_{45} are H; and R_{35} and R_{40} and the carbons to which they are attached form a heterocycloalkyl ring. In a further embodiment, the heterocycloalkyl ring is $-OCH_2O-$, $-OCH_2CH_2O-$ or $-OC(O)O-$. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both H.

In yet still another embodiment of this aspect, R_{30} and R_{45} are H; and R_{35} and R_{40} are independently halogen (*e.g.*, F, Cl or Br), C_1-C_4 alkyl, C_1-C_4 alkoxy or C_2-C_6 alkanoyl; and the geminal R_{51} groups that are alpha to the B-ring form an oxo group.

In yet still another embodiment of this aspect, R_{30} and R_{45} are H; and R_{35} and R_{40} are independently halogen (*e.g.*, F, Cl or Br), C_1-C_4 alkyl, C_1-C_4 alkoxy or C_2-C_6 alkanoyl; and the geminal R_{51} groups that are alpha to the B-ring are both H.

In yet still another embodiment of this aspect, R_{30} and R_{45} are H; and R_{35} and R_{40} are independently halogen (*e.g.*, F, Cl or Br), C_1-C_4 alkyl, C_1-C_4 alkoxy or C_2-C_6 alkanoyl; and the geminal R_{51} groups that are alpha to the B-ring are both halogens. In another embodiment, both R_{51} groups that are alpha to the B-ring are F.

In yet still another embodiment of this aspect, R_{30} and R_{45} are H; and R_{35} and R_{40} are independently halogen (*e.g.*, F, Cl or Br), and the geminal R_{51} groups that are alpha to the B-ring are both halogens.

In yet still another embodiment of this aspect, R_{30} and R_{45} are H; and R_{35} and R_{40} are independently halogen (*e.g.*, F, Cl or Br), and the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group.

In yet still another embodiment of this aspect, R_{30} and R_{45} are H; and R_{35} and R_{40} are independently halogen (*e.g.*, F, Cl or Br), and the geminal R_{51} groups that are alpha to the B-ring form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In still another embodiment of this aspect, R_{30} and R_{45} are H; and R_{35} and R_{40} are independently halogen (*e.g.*, F, Cl or Br), hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_2-C_6 alkanoyl, phenyloxy, phenyl or phenyl C_1-C_4 alkyl, where the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky (*e.g.* CF_3) or halogen.

In still another embodiment of this aspect, R_{30} and R_{45} are H; and R_{35} and R_{40} are independently halogen (*e.g.*, F, Cl or Br), C_1-C_4 alkyl, C_1-C_4 alkoxy, C_2-C_6 alkanoyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl or thienyl.

In yet still another embodiment of this aspect, R_{35} and R_{40} are H; and R_{30} and R_{45} are independently halogen (*e.g.*, F, Cl or Br), hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy or C_2-C_6 alkanoyl.

In yet still another embodiment of this aspect, R_{35} and R_{40} are H; and R_{30} and R_{45} are independently halogen (*e.g.*, F, Cl or Br), hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy or C_2-C_6 alkanoyl; and the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a further embodiment, one of R_{30} or R_{45} is H, while the other is F or Cl.

In yet still another embodiment of this aspect, R_{35} and R_{40} are H; and R_{30} and R_{45} are independently halogen (*e.g.*, F, Cl or Br), hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy or C_2-C_6 alkanoyl; and the geminal R_{51} groups that are alpha to the B-ring are both hydrogen. In a further embodiment, one of R_{30} or R_{45} is H, while the other is F or Cl.

In yet still another embodiment of this aspect, R_{35} and R_{40} are H; and R_{30} and R_{45} are independently halogen (*e.g.*, F, Cl or Br), hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy or C_2-C_6 alkanoyl; and the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group.

In yet still another embodiment of this aspect, R_{35} and R_{40} are H; and R_{30} and R_{45} are independently halogen (*e.g.*, F, Cl or Br), hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy or C_2-C_6 alkanoyl; and the geminal R_{51} groups that are alpha to the B-ring form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In yet still another embodiment of this aspect, R_{35} and R_{40} are H; and R_{30} and R_{45} are independently H, halogen (*e.g.*, F, Cl or Br), C_1-C_4 alkyl, C_1-C_4 alkoxy or C_2-C_6 alkanoyl; provided that atleast one of R_{30} and R_{45} is not H. In another embodiment, both R_{51} groups that are alpha to the B-ring are F. In a further embodiment, R_{30} is halogen while R_{45} is H. In another further embodiment, R_{30} is H while R_{45} is halogen. In a further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both hydrogen. In another further embodiment, at least one of the geminal R_{51} groups that are alpha to the B-ring is halogen. In another further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both halogen . In still another further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In yet still another embodiment of this aspect, R_{35} and R_{40} are H; and R_{30} and R_{45} are independently halogen (*e.g.*, F, Cl or Br), methyl or methoxy. In another embodiment, both

R_{51} groups that are alpha to the B-ring are F. In a further embodiment, R_{30} is halogen. In another further embodiment, R_{45} is halogen. In a further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both hydrogen. In another further embodiment, at least one of the geminal R_{51} groups that are alpha to the B-ring is halogen. In another further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both halogen. In still another further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In still another embodiment of this aspect, R_{35} and R_{40} are H; and R_{30} and R_{45} are independently halogen (*e.g.*, F, Cl or Br), hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_2-C_6 alkanoyl, phenyloxy, phenyl or phenyl C_1-C_4 alkyl. In a further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both hydrogen. In another further embodiment, at least one of the geminal R_{51} groups that are alpha to the B-ring is halogen. In another further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both halogen. In still another further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In still another embodiment of this aspect, R_{35} and R_{40} are H; and R_{30} and R_{45} are independently halogen (*e.g.*, F, Cl or Br), hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_2-C_6 alkanoyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl or thienyl.

In still another embodiment of this aspect, R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen (*e.g.*, F, Cl or Br), C_1-C_4 alkyl or C_1-C_4 alkoxy; and one R_{51} group is halogen or OH, while the other R_{51} group is H. In a still further embodiment, the B-ring is unsubstituted. In a further embodiment, at least two of R_{30}, R_{35}, R_{40}, and R_{45} are H. In a still further embodiment, R_{30}, R_{35}, R_{40}, and R_{45} are H.

In still another embodiment of this aspect, R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen (*e.g.*, F, Cl or Br), C_1-C_4 alkyl or C_1-C_4 alkoxy; and one R_{51} group is halogen or OH, while the other R_{51} group is H. In a still further embodiment, the B-ring is unsubstituted. In a further embodiment, at least one of R_{30}, R_{35}, R_{40}, and R_{45} is halogen (*e.g.*, F, Cl or Br), C_1-C_4 alkyl or C_1-C_4 alkoxy. In a still further embodiment, two of R_{30}, R_{35}, R_{40}, and R_{45} are H.

In another aspect, provided herein are compounds of Formula 4h, wherein R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_2-C_6 alkanoyl; provided that two adjacent carbons of the fused aryl ring (the ring to which the R_{30}, R_{35}, R_{40} and R_{45} groups are attached) optionally form a heterocycloalkyl or a heteroaryl ring, which is optionally substituted with 1, 2, 3 or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen or C_1-C_4 alkanoyl wherein the alkanoyl group is optionally substituted with up to 3 halogen atoms. In a further embodiment, the heterocycloalkyl ring is piperidinyl, pyrrolidinyl or morpholinyl, and the heteroaryl ring is pyrazolyl, imidazolyl or pyridinyl, wherein each heterocycloalkyl or heteroaryl group is optionally substituted with 1, 2, 3 or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen or C_2-C_4 alkanoyl wherein the alkanoyl group is optionally substituted with up to 3 halogen atoms. In a further embodiment, the heterocycloalkyl ring is piperidinyl or pyrrolidinyl, each of which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen or C_2-C_4 alkanoyl wherein the alkanoyl group is optionally substituted with up to 3 halogen atoms. In a further embodiment, , the heteroaryl ring is pyrazolyl, imidazolyl or pyridinyl, each of which is optionally substituted with 1 or 2 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen or C_2-C_4 alkanoyl wherein the alkanoyl group is optionally substituted with up to 3 halogen atoms.

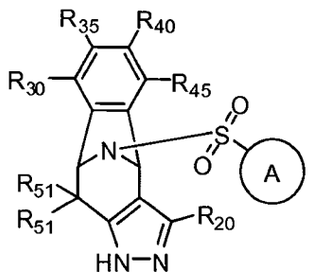
In another aspect, provided herein are compounds of Formula 4h, wherein R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_2-C_6 alkanoyl; provided that two adjacent carbons of the fused aryl ring form a benzo ring, which is optionally substituted with 1 to 4 groups that are independently halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, CN or NO_2.

In one embodiment of this aspect, R_{30} and R_{45} are independently H, halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, and R_{35}, R_{40}, and the carbons to which they are attached form a benzo ring, which is optionally substituted with 1 to 4 groups that are independently halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, CN or NO_2. In a further embodiment, the benzo ring is unsubstituted.

In one embodiment of this aspect, R_{30} and R_{35} are independently H, halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, and R_{40}, R_{45}, and the carbons to which they are attached form a benzo ring, which is optionally substituted with 1 to 4 groups that are independently halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, CN or NO_2. In a further embodiment, the benzo ring is unsubstituted.

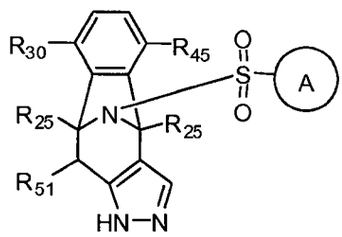
In one embodiment of this aspect, R_{40} and R_{45} are independently H, halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, and R_{30}, R_{35}, and the carbons to which they are attached form a benzo ring, which is optionally substituted with 1 to 4 groups that are independently halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, CN or NO_2. In a further embodiment, the benzo ring is unsubstituted.

In another aspect, provided herein are compounds or salts of Formula 4i, *i.e.*, compounds and/or salts of Formula 4h having the formula:



or pharmaceutically acceptable solvates, salts or mixtures thereof, wherein the A-ring is as defined below and R_{30}, R_{35}, R_{40}, R_{45} and R_{51} are as previously defined, and R_{20} is H, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-NR_{11}C(O)CH_3$, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, halo, CF_3, CN or $-NHC(O)CH_3$; where R_{11} is H or C_1-C_6 alkyl. In a further embodiment, R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, CN, hydroxyl, C_1-C_6 alkoxy, $-C_1$-C_3 alkyl-OH, $-C_1$-C_3 alkyl-alkoxy, phenyloxy, $-S(O_2)R_{10}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl, thienyl, phenyl or phenyl C_1-C_4 alkyl, where the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy or halogen.

In another aspect, the compounds of Formula 4i are compounds or salts of Formula 4i1:



including stereoisomers, tautomers and mixtures of steroisomers and/or tautomers, and/or pharmaceutical salts thereof, wherein

R_{30} ane R_{45} are independently H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, CN, hydroxyl, C_1-C_6 alkoxy, -C_1-C_3 alkyl-OH, -C_1-C_3 alkyl-alkoxy, phenyloxy, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -C(O)OR_{11}, -S(O_2)R_{10}, -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alkanoyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl, thienyl, phenyl or phenyl C_1-C_4 alkyl, where the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky (*e.g.*, CF_3) or halogen; and

R_{51} is H, C_1-C_4 alkyl, F, Cl, Br, CN, amino, mono alkylamino, dialkylamino, OH or CF_3.

In one embodiment of this aspect, R_{30} ane R_{45} are independently H, halogen, C_1-C_6 alkyl, hydroxyl, C_1-C_6 alkoxy, -C_1-C_3 alkyl-OH or -C_1-C_3 alkyl-alkoxy; and R_{51} is H, methyl, ethyl, F, Cl, Br or CF_3.

In one embodiment of this aspect, R_{30} ane R_{45} are independently H, halogen, C_1-C_6 alkyl, hydroxyl, C_1-C_6 alkoxy, -C_1-C_3 alkyl-OH or -C_1-C_3 alkyl-alkoxy; and R_{51} is CN, amino, mono alkylamino, dialkylamino.

In one embodiment of this aspect, at least one of R_{30} ane R_{45} is C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl or -C(O)OR_{11}; and R_{51} is H, methyl, ethyl, F, Cl, Br or CF_3. In a further embodiment, R_{11} is H or C_1-C_4 alkyl.

In one embodiment of this aspect, R_{30} ane R_{45} are independently H, halogen, C_1-C_4 alkyl, hydroxyl, C_1-C_4 alkoxy, -C_1-C_2 alkyl-OH or -C_1-C_2 alkyl- C_1-C_4 alkoxy; and R_{51} is H, methyl, ethyl, F, Cl or CF_3.

In one embodiment of this aspect, R_{30} ane R_{45} are independently H, F or Cl; and R_{51} is H, F, Cl or Br.

In still another embodiment of this aspect, at least one of R_{30} and R_{45} is F; and R_{51} is H, F or OH.

In yet another embodiment of this aspect, only one of R_{30} and R_{45} is F, while the other is H; and R_{51} is H, F or OH.

In another embodiment of this aspect, R_{30} and R_{45} are both H; and R_{51} is H or F.

In yet another embodiment of this aspect, R_{30} and R_{45} are both H; and R_{51} is F.

In yet another embodiment of this aspect, R_{30} and R_{45} are both H; and R_{51} is OH.

In yet another embodiment of this aspect, one of R_{30} and R_{45} is H, while the other is F, and R_{51} is OH.

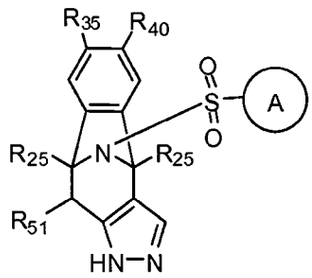
In another embodiment of this aspect, R_{30}, R_{45}, and R_{51} are H.

In still another embodiment of this aspect, only one of R_{30}, R_{45}, and R_{51} is F.

In still another embodiment of this aspect, R_{30}, R_{45}, and R_{51} are F.

In one embodiment of this aspect, R_{30} and R_{45} are independently H, $-C(O)OR_{11}$, $-S(O_2)R_{10}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$ or C_2-C_6 alkanoyl; where each R_{11} is independently H or C_1-C_4 alkyl.

In another aspect, the compounds of Formula 4i are compounds of Formulas 4i2:



including stereoisomers, tautomers and mixtures of steroisomers and/or tautomers, and/or pharmaceutical salts thereof, wherein

R_{35} ane R_{40} are independently H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, CN, hydroxyl, C_1-C_6 alkoxy, $-C_1$-C_3 alkyl-OH, $-C_1$-C_3 alkyl-alkoxy, phenyloxy, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, $-C(O)OR_{11}$, $-S(O_2)R_{10}$, $--NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl, thienyl, phenyl or phenyl C_1-C_4 alkyl, wherein the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky (*e.g.* CF_3) or halogen; and

R_{51} is H, C_1-C_4 alkyl, F, Cl, Br, CN, CN, amino, mono alkylamino, dialkylamino, OH or CF_3.

In one embodiment of this aspect, R_{35} ane R_{40} are independently H, halogen, C_1-C_6 alkyl, hydroxyl, C_1-C_6 alkoxy, $-C_1$-C_3 alkyl-OH or $-C_1$-C_3 alkyl-alkoxy; and R_{51} is H, methyl, ethyl, F, Cl or CF_3.

In one embodiment of this aspect, R_{35} ane R_{40} are independently H, halogen, C_1-C_6 alkyl, hydroxyl, C_1-C_6 alkoxy, $-C_1$-C_3 alkyl-OH or $-C_1$-C_3 alkyl-alkoxy; and R_{51} is CN, amino, mono alkylamino, dialkylamino.

In one embodiment of this aspect, at least one of R_{35} ane R_{40} is C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl or -C(O)OR_{11}; and R_{51} is H, methyl, ethyl, F, Cl, Br or CF_3. In a further embodiment, R_{11} is H or C_1-C_4 alkyl.

In one embodiment of this aspect, R_{35} ane R_{40} are independently H, halogen, C_1-C_4 alkyl, hydroxyl, C_1-C_4 alkoxy, -C_1-C_2 alkyl-OH or -C_1-C_2 alkyl- C_1-C_4 alkoxy; and R_{51} is H, methyl, ethyl, F, Cl or CF_3.

In one embodiment of this aspect, R_{35} ane R_{40} are independently H, F or Cl; and R_{51} is H, F or Cl.

In still another embodiment of this aspect, at least one of R_{35} and R_{40} is F; and R_{51} is H, F or OH.

In yet another embodiment of this aspect, only one of R_{35} and R_{40} is F, while the other is H; and R_{51} is H, F or OH.

In another embodiment of this aspect, R_{35} and R_{40} are both H; and R_{51} is H, F, Cl or Br.

In another embodiment of this aspect, R_{35} and R_{40} are both H; and R_{51} is CN, amino, mono alkylamino or dialkylamino.

In yet another embodiment of this aspect, R_{35} and R_{40} are both H; and R_{51} is F.

In yet another embodiment of this aspect, R_{35} and R_{40} are both H; and R_{51} is OH.

In yet another embodiment of this aspect, one of R_{35} and R_{40} is H, while the other is F, and R_{51} is OH.

In another embodiment of this aspect, R_{35}, R_{40}, and R_{51} are H.

In still another embodiment of this aspect, only one of R_{35}, R_{40}, and R_{51} is F.

In still another embodiment of this aspect, R_{35}, R_{40}, and R_{51} are F.

In one embodiment of this aspect, R_{35} and R_{40} are independently H, -C(O)OR_{11}, -S(O_2)R_{10}, -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$ or C_2-C_6 alkanoyl; where each R_{11} is independently H or C_1-C_4 alkyl.

In another aspect, provided herein are compounds wherein the C-ring is phenyl substituted with R_{30}, R_{35}, R_{40}, and R_{45}; or heteroaryl, wherein the heteroaryl, group is optionally substituted with H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, CN, hydroxyl, C_1-C_6 alkoxy, -C_1-C_3 alkyl-OH, -C_1-C_3 alkyl-alkoxy, phenyloxy, -S(O_2)R_{10}, -$SO_2NR_{11}R_{11}$, -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alkanoyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl,

thienyl, phenyl or phenyl C_1-C_4 alkyl, wherein the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky or halogen;

R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, $-SO_2NR_{11}R_{11}$, arylalkyl, cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, CN, NO_2, hydroxyl, C_1-C_6 alkoxy, -C_1-C_6 alkyl-OH, -C_1-C_6 alkyl-C_1-C_6 alkoxy, aryloxy, $-S(O_2)R_{10}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, heteroarylalkyl, heteroaryl, wherein each heteroaryl group is optionally substituted with a C_1-C_6 alkyl group, heterocycloalkylalkyl, heterocycloalkyl, wherein each heterocycloalkyl group is optionally substituted *e.g.*, with one or two groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy or halogen, aryl, aryloxy or arylalkyl, where the aryl portions of the above are optionally substituted *e.g.*, with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, C_1-C_4 haloalky or halogen; and

wherein when the C-ring is aryl or heteroaryl, two adjacent carbons of the C-ring optionally form a heterocycloalkyl or a heteroaryl ring, each of which is optionally substituted with one or more groups that are independently alkyl, alkoxy, halogen or C_2-C_4 alkanoyl wherein the alkanoyl group is optionally further substituted with up to 3 halogen atoms; or two adjacent carbons of the C-ring optionally form a benzo ring which is optionally substituted *e.g.*, with 1 to 4 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2.

In another aspect, provided herein are compounds of Formulas 4j, *i.e.*, compounds of Formulas 4, 4a, 4b, 4c, and/or 4d, wherein the C-ring is a heteroaryl or heterocycloalkyl ring that is optionally substituted with one or more groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, $-C(O)OR_{11}$, CN, hydroxyl, C_1-C_6 alkoxy, -C_1-C_3 alkyl-OH, -C_1-C_3 alkyl-alkoxy, phenyloxy, $-S(O_2)R_{10}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl, thienyl, phenyl or phenyl C_1-C_4 alkyl, wherein the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky (*e.g.* CF_3) or halogen. In a further embodiment, the C-ring is optionally substituted with C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, C_1-C_4 haloalkyl (*e.g.* CF_3) or C_1-C_4 haloalkoxy (*e.g.*, OCF_3). In a still further embodiment, the

C-ring is unsubstituted. In one embodiment, each R_{10} and R_{11} is independently C_1-C_6 alkyl or phenyl; and additionally R_{11} may be H.

In a further embodiment of this aspect, the C-ring is a heteroaryl substituted with at least one group that is halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl.

In a further embodiment of this aspect, the C-ring is a heteroaryl substituted with at least one group that is $-C(O)OR_{11}$, CN, hydroxyl, C_1-C_6 alkoxy, $-C_1$-C_3 alkyl-OH, $-C_1$-C_3 alkyl-alkoxy, phenyloxy, $-S(O_2)R_{10}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$ or C_2-C_6 alkanoyl.

In a further embodiment of this aspect, the C-ring is a heteroaryl substituted with at least one group that is oxazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl, thienyl, phenyl or phenyl C_1-C_4 alkyl, wherein the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky (*e.g.* CF_3) or halogen.

In a further embodiment of this aspect, the C-ring is a heterocycloalkyl substituted with at least one group that is halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_2-C_8 haloalkenyl or C_2-C_8 haloalkynyl.

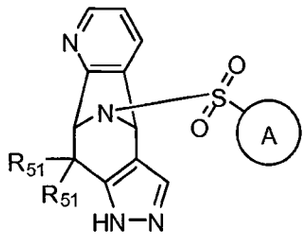
In a further embodiment of this aspect, the C-ring is a heterocycloalkyl substituted with at least one group that is $-C(O)OR_{11}$, CN, hydroxyl, C_1-C_6 alkoxy, $-C_1$-C_3 alkyl-OH, $-C_1$-C_3 alkyl-alkoxy, phenyloxy, $-S(O_2)R_{10}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$ or C_2-C_6 alkanoyl.

In a further embodiment of this aspect, the C-ring is a heterocycloalkyl substituted with at least one group that is oxazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl, thienyl, phenyl or phenyl C_1-C_4 alkyl, wherein the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky (*e.g.* CF_3) or halogen.

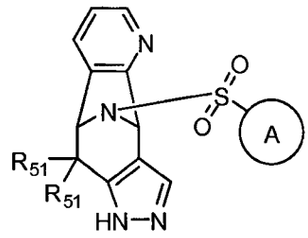
In an embodiment of this aspect, the C-ring is an optionally substituted (as described above) pyridyl ring. In a further embodiment, the C-ring is an unsubstituted pyridyl ring. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both H. In a yet further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both halogens. In another embodiment, both R_{51} groups that are alpha to the B-ring are F. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring

form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

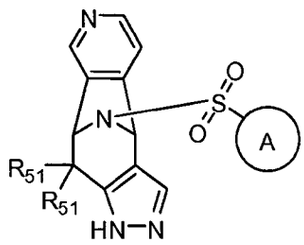
In another embodiment of this aspect, the compounds of Formula 4j have the Formulas:



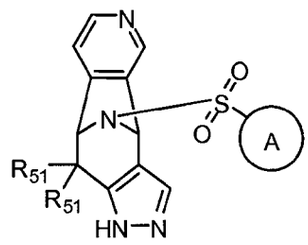
Formula 4k1



Formula 4k2



Formula 4k3

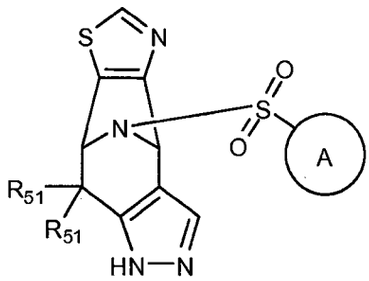


Formula 4k4

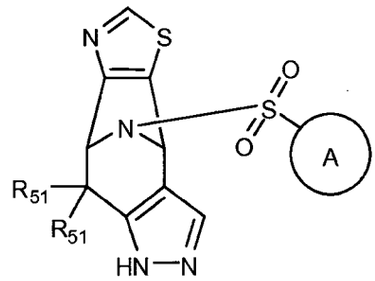
wherein each R_{51} is H, C_1-C_4 alkyl, F, Cl, Br, CN, amino, mono alkylamino or dialkylamino, OH, CF_3 or both R_{51} groups form an oxo group. In one embodiment, at least one R_{51} is H. In another embodiment, one R_{51} is H while the other is R_{51} is F or Cl. In another embodiment, one R_{51} is H, while the other R_{51} is OH. In still another embodiment, both R_{51} groups are halogen (*e.g.*, F). In still another embodiment, both R_{51} groups form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In an embodiment of this aspect, the C-ring is an optionally substituted (as described above) thiazolyl ring. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both H. In a yet further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both halogens. In another embodiment, both R_{51} groups that are alpha to the B-ring are F. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In another embodiment of this aspect, the compounds of Formula 4j have the formulas:



Formula 411

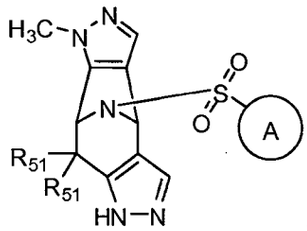


Formula 412

wherein each R_{51} is H, C_1-C_4 alkyl, F, Cl, Br, CN, amino, mono alkylamino or dialkylamino, OH, CF_3 or both R_{51} groups form an oxo group. In one embodiment, at least one R_{51} is H. In another embodiment, one R_{51} is H while the other is R_{51} is F or Cl. In another embodiment, one R_{51} is H, while the other R_{51} is OH. In still another embodiment, both R_{51} groups are halogen (*e.g.*, F). In still another embodiment, both R_{51} groups form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In an embodiment of this aspect, the C-ring is an optionally substituted (as described above) pyrazolyl ring. In a further embodiment, the C-ring is an unsubstituted pyrazolyl ring. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both H. In a yet further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both halogens. In another embodiment, both R_{51} groups that are alpha to the B-ring are F. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still further embodiment, the C-ring is substituted with C_1-C_4 alkyl. In another embodiment of this aspect, one of the R_{51} groups is H, while the other is halogen or OH.

In another embodiment of this aspect, the compounds of Formula 4j have the formula:



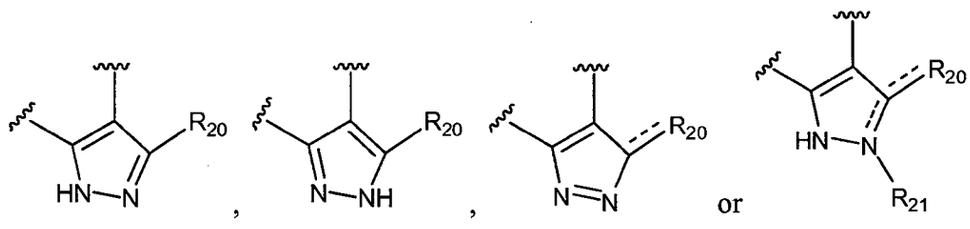
Formula 4m

wherein each R_{51} is H, C_1-C_4 alkyl, F, Cl, Br, CN, amino, mono alkylamino or dialkylamino, OH, CF_3 or both R_{51} groups form an oxo group. In one embodiment, at least one R_{51} is H. In

another embodiment, one R_{51} is H while the other is R_{51} is F or Cl. In another embodiment, one R_{51} is H, while the other R_{51} is OH. In still another embodiment, both R_{51} groups are halogen (*e.g.*, F). In still another embodiment, both R_{51} groups form an oxo group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an C_2-C_4 alkenyl group. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form form an oxime or a C_1-C_4 alkylated oxime (*e.g.*, O-methyl oxime).

In an embodiment of this aspect, the C-ring is an optionally substituted (as described above) thienyl ring. In a further embodiment, the C-ring is an unsubstituted thienyl ring. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both H. In a yet further embodiment, the geminal R_{51} groups that are alpha to the B-ring are both halogens. In another embodiment, both R_{51} groups that are alpha to the B-ring are F. In a still further embodiment, the geminal R_{51} groups that are alpha to the B-ring form an oxo group. In a still further embodiment, the C-ring is substituted with C_1-C_4 alkyl. In another embodiment of this aspect, one of the R_{51} groups is H, while the other is halogen or OH.

In another aspect, provided herein are compounds of Formulas 1 (and aspects and embodiments thereof), 2 (and aspects and embodiments thereof), 3 (and aspects and embodiments thereof), and 4 (and aspects and embodiments thereof), (provided that the B-ring is not otherwise defined) wherein the B-ring is

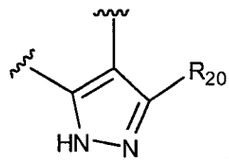


wherein the dashed bond represents an optional second bond;

R_{20} is H, oxo (only when there is a double bond to R_{20}) C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, C_1-C_6 alkylamino, C_1-C_6 dialkylamino, $-NR_{11}C(O)R_{10}$, halo, CF_3 or $-NHC(O)CH_3$;

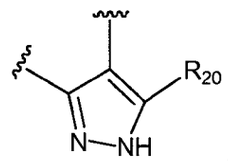
R_{21} is absent or hydrogen; provided that when there are two dashed bonds in the ring formula only one may form a double bond; still further, R_{21} is absent when the dashed bond to the nitrogen is a bond, and thereby forms a double bond.

In another embodiment of this aspect, the B-ring has the formula:



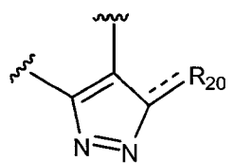
wherein R_{20} is H, C_1-C_4 alkyl, C_1-C_4 alkoxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, $-NR_{11}C(O)R_{10}$, halo or CF_3. In a further embodiment, R_{20} is H, C_1-C_4 alkyl, C_1-C_4 alkoxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, halo or CF_3. In a further embodiment, R_{20} is H.

In another embodiment of this aspect, the B-ring has the formula:



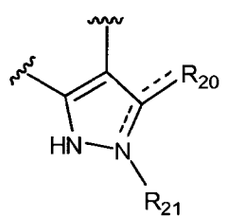
wherein R_{20} is H, C_1-C_4 alkyl, C_1-C_4 alkoxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, $-NR_{11}C(O)R_{10}$, halo or CF_3. In a further embodiment, R_{20} is H.

In another embodiment of this aspect, the B-ring has the formula:



wherein R_{20} is H, oxo (only if there is a double bond to the R_{20} group), C_1-C_4 alkyl, C_1-C_4 alkoxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, $-NR_{11}C(O)R_{10}$, halo or CF_3; where the dashed bond represents an optional second bond. In a further embodiment, R_{20} is oxo and the dashed line is a bond. In another embodiment, R_{20} is H.

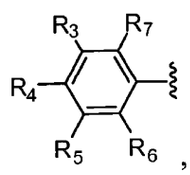
In another embodiment of this aspect, the B-ring has the formula:



R_{20} is H, oxo (only if there is a double bond to the R_{20} group), C_1-C_4 alkyl, C_1-C_4 alkoxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, $-NR_{11}C(O)R_{10}$, halo or CF_3; and R_{21} is absent or hydrogen; and where the dashed bond represents an optional second bond; provided that only one of the two dashed bonds may be a second bond, and thereby form a double bond; still further, R_{21} is absent when the dashed bond to the nitrogen is a bond, and thereby forms a double bond to the nitrogen.

In another aspect, in the compounds of Formulas 1 (and aspects and embodiments thereof), 2 (and aspects and embodiments thereof), 3 (and aspects and embodiments thereof), and 4 (and aspects and embodiments thereof), the A-ring is phenyl or naphthyl (preferably phenyl), 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, haloalkyl, haloalkoxy, hydroxyl, hydroxyalkyl, CN, phenyloxy, -$S(O)_{0-2}$-(C_1-C_6 alkyl), -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, C_0-C_3alkylCO_2R_{10}, pyridyl, thienyl, furanyl, pyrrolyl, pyrrolidinyl, piperidinyl, piperazinyl, phenyl, phenyl C_1-C_4 alkyl, -OCH_2O-, -OCH_2CH_2O- or -$SO_2NR_{11}R_{11}$, wherein each methylene of -OCH_2O- or -OCH_2CH_2O- is optionally substituted with one or two C_1-C_4 alkyl groups.

In an embodiment of this aspect, the A-ring is phenyl, and has the following formula:



wherein,

R_3, R_4, R_5, R_6, R_7 are independently of each other H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, CN, hydroxyl, C_1-C_6 alkoxy, -C_1-C_3 alkyl-OH, -C_1-C_3 alkyl-alkoxy, phenyloxy, -$S(O_2)R_{10}$, -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl, thienyl, phenyl or phenyl C_1-C_4 alkyl, where the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky (*e.g.* CF_3) or halogen; or

R_4 and R_5 or R_5 and R_6 and the carbons to which they are attached form a heterocycloalkyl or a heteroaryl ring which is optionally substituted with 1, 2, 3 or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen or C_1-C_4 alkanoyl wherein the alkanoyl group is optionally substituted with up to 3 halogen atoms; or

R_4 and R_5 or R_5 and R_6 and the carbons to which they are attached form a benzo ring which is optionally substituted with optionally substituted with 1 to 5 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2.

In an embodiment of this aspect, R_3 is H, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, haloalkyl or CN; R_4 is H, halogen; C_1-C_6 alkyl; C_1-C_6 alkoxy; C_1-C_6 haloalkyl; haloalkoxy, CN, phenyloxy, -SO_2-(C_1-C_6 alkyl), -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$,

$-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl or phenyl; and R_5 is H, C_1-C_6 alkyl, $-SO_2-NR_{11}R_{11}$ or halogen.

In an embodiment of this aspect, R_3, R_4, R_5, R_6, R_7 are independently of each other H, halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl (*e.g.*, CF_3), C_1-C_4 haloalkoxy (*e.g.*, OCF_3), CN, hydroxyl, C_1-C_4 alkoxy, $-C_1$-C_3 alkyl-OH, $-C_1$-C_3 alkyl-C_1-C_4 alkoxy, phenyloxy, $-S(O_2)R_{10}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$ or C_2-C_4 alkanoyl. In a further embodiment, each R_{10} and R_{11} is independently C_1-C_6 alkyl or phenyl; and additionally R_{11} may be H.

In an embodiment of this aspect, R_3, R_4, R_5, R_6, R_7 are independently of each other H, halogen, C_1-C_4 alkyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl, thienyl, phenyl or phenyl C_1-C_4 alkyl, where the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky (*e.g.* CF_3) or halogen.

In an embodiment of this aspect, R_6 and R_7 are independently H or methyl.

In an embodiment of this aspect, R_3 and R_5 are independently H, halo, CF_3, CHF_2 or methyl.

In an embodiment of this aspect, R_4, R_6 and R_7 are independently H, halo, CF_3, CHF_2 or methyl.

In an embodiment of this aspect, R_4 is H, halogen (in one aspect, I, Br, F or Cl), C_1-C_6 alkyl optionally substituted with halogen or hydroxyl, C_1-C_6 alkoxy, OCF_3 or CN.

In an embodiment of this aspect, R_4 is phenyloxy, $-SO_2-(C_1$-C_6 alkyl), $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl or phenyl.

In an embodiment of this aspect, R_4 is $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$ or $-O-C(O)NR_{11}R_{11}$.

In an embodiment of this aspect, R_4 is $-SO_2NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$ or $-NR_{11}SO_2R_{10}$.

In an embodiment of this aspect, R_4 is $-SO_2NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$ or $-NR_{11}SO_2R_{10}$ and R_3, R_5, R_6, and R_7 are H.

In an embodiment of this aspect, R_4 is $-C(O)NR_{11}R_{11}$.

In an embodiment of this aspect, R_4 is $-C(O)NR_{11}R_{11}$, and R_3, R_5, R_6, and R_7 are H.

In an embodiment of this aspect, R_4 is $-O-C(O)NR_{11}R_{11}$.

In an embodiment of this aspect, R_4 is $-O-C(O)NR_{11}R_{11}$, and R_3, R_5, R_6, and R_7 are H.

In an embodiment of this aspect, R_4 is $-NR_{11}R_{11}$.

In an embodiment of this aspect, R_4 is $-NR_{11}R_{11}$, and R_3, R_5, R_6, and R_7 are H.

In an embodiment of this aspect, R_3, R_4, R_5, R_6, and R_7 are H, halo, CF_3, CHF_2 or methyl.

In an embodiment of this aspect, R_3, R_5, R_6, and R_7 are H.

In an embodiment of this aspect, R_4 is chloro.

In an embodiment of this aspect, R_4 is chloro, and R_3, R_5, R_6, and R_7 are H.

In an embodiment of this aspect, R_4 is trihalomethyl, and R_3, R_5, R_6, and R_7 are H. In one embodiment, R_4 is CCl_3 or CF_3. In another embodiment, R_4 is CF_3.

In an embodiment of this aspect, at least one of R_3, R_4 or R_5 is chloro, and R_6 and R_7 are H.

In an embodiment of this aspect, R_3 is hydrogen, halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, CF_3 or CN; R_4 is hydrogen, halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3, CN, phenyloxy, --SO_2-(C_1-C_4 alkyl), -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$ or C_1-C_4 alkanoyl, and R_5 is hydrogen, C_1-C_4 alkyl, -$SO_2NR_{11}R_{11}$ or halogen. In one embodiment, R_6 and R_7 are H.

In an embodiment of this aspect, R_4 is halogen (in one aspect, F or Cl), C_1-C_4 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3 or CN. In a further embodiment, R_3, R_5 R_6, and R_7 are hydrogen.

In an embodiment of this aspect, R_4, R_5 R_6, and R_7 are hydrogen.

In an embodiment of this aspect, R_3 is hydrogen, halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, CF_3 or CN; R_4 is oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl, thienyl or phenyl; and R_5 is hydrogen, C_1-C_4 alkyl, -$SO_2NR_{11}R_{11}$ or halogen. In one embodiment of this aspect, R_6 and R_7 are H.

In an embodiment of this aspect, R_3 is -C(O)$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$ or -O-C(O)$NR_{11}R_{11}$, R_4 is H, C_1-C_4 alkyl or halogen, and R_5, R_6, and R_7 are H.

In an embodiment of this aspect, R_4 is halogen (in one aspect, F or Cl), CH_3, OCH_3, CF_3 or OCF_3.

In an embodiment of this aspect, R_3 is hydrogen, halogen, C_1-C_2 alkyl, C_1-C_2 alkoxy, CF_3 or CN; R_4 is hydrogen, halogen, C_1-C_2 alkyl, C_1-C_2 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, CN, -$NR_{11}R_{11}$, C_2-C_3 alkanoyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, furanyl or thienyl; R_5 is hydrogen, CH_3 or F; and R_6 and R_7 are independently hydrogen or halogen.

In an embodiment of this aspect, R_4 is CF_3 or OCF_3. In one embodiment, R_6 and R_7 are H. In a further embodiment, R_3 and R_5 are also H.

In an embodiment of this aspect, R_4 and R_5 or R_5 and R_6 and the carbons to which they are attached form a benzo ring which is optionally substituted with optionally substituted

with 1 or 2 groups that are independently halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_3 haloalkyl, C_1-C_3 haloalkoxy, CN or NO_2.

In an embodiment of this aspect, R_4 and R_5 or R_5 and R_6 and the carbons to which they are attached form a pyridyl, pyrrolyl, thienyl, furanyl, pyrrolidinyl, piperidinyl ring, each of which is optionally substituted with 1, 2 or 3 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen or C_1-C_4 alkanoyl wherein the alkanoyl group is optionally substituted with up to 3 halogen atoms (*e.g.*, F).

In an embodiment of this aspect, R_6 and R_7 are independently hydrogen or methyl.

In an embodiment of this aspect, R_3 and R_5 are independently hydrogen, halo or methyl.

In an embodiment of this aspect, R_3 and R_4 or R_5 and R_6 are $-OCH_2O-$, $-OCH_2CH_2O-$, wherein each methylene of $-OCH_2O-$ or $-OCH_2CH_2O-$ is optionally substituted with one or two C_1-C_4 alkyl groups. In one embodiment, each methylene is unsubstituted. In another embodiment, at least one methylene is substituted with at least one C_1-C_4 alkyl group.

In an embodiment of this aspect, R_{11} at each occurrence is independently H or C_1-C_5 alkyl. In a further embodiment, R_{10} is C_1-C_4 alkyl or phenyl.

In another aspect, in the compounds of Formulas 1 (and aspects and embodiments thereof), 2 (and aspects and embodiments thereof), 3 (and aspects and embodiments thereof), and 4 (and aspects and embodiments thereof), 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, haloalkyl, haloalkoxy, hydroxyl, hydroxyalkyl, CN, phenyloxy, $-S(O)_{0-2}-(C_1$-C_6 alkyl), $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, C_0-C_3alkylCO_2R_{10}, pyridyl, thienyl, furanyl, pyrrolyl, pyrrolidinyl, piperidinyl, piperazinyl, phenyl, phenyl C_1-C_4 alkyl or $-SO_2NR_{11}R_{11}$, where the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky (*e.g.* CF_3) or halogen.

In an embodiment of this aspect, the C_3-C_8 cycloalkyl is optionally substituted at a substitutable position with halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, hydroxyl or C_1-C_4hydroxyalkyl. In one embodiment, the C_3-C_8 cycloalkyl group is substituted with one group. In one embodiment, the C_3-C_8 cycloalkyl group is substituted with one group that is $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ or $-O-C(O)NR_{11}R_{11}$, where R_{10} and R_{11} are independently C_1-C_4 alkyl or phenyl; and additionally R_{11} may be H.

In yet still another embodiment of this aspect, the C_3-C_8 cycloalkyl is substituted with one or two groups that are independently methoxy, ethoxy, methyl, ethyl or halogen.

In an embodiment of this aspect, the A-ring is unsubstituted cyclopropyl.

In an embodiment of this aspect, the A-ring is unsubstituted cyclobutyl.

In an embodiment of this aspect, the A-ring is unsubstituted cyclopentyl.

In an embodiment of this aspect, the A-ring is unsubstituted cyclohexyl.

In an embodiment of this aspect, the A-ring is unsubstituted cycloheptyl.

In an embodiment of this aspect, the A-ring is unsubstituted cyclooctyl.

In another aspect, in the compounds of Formulas 1 (and aspects and embodiments thereof), 2 (and aspects and embodiments thereof), 3 (and aspects and embodiments thereof), and 4 (and aspects and embodiments thereof), the A-ring is heteroaryl, for instance, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, thienyl, furanyl, pyrrolyl, pyrazolyl or imidazolyl, each of which is optionally substituted at one or more substitutable positions with halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, haloalkyl, haloalkoxy, hydroxyl, hydroxyalkyl, CN, phenyloxy, $-S(O)_{0-2}-(C_1-C_6$ alkyl), $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, C_0-C_3alkylCO_2R_{10}, pyridyl, thienyl, furanyl, pyrrolyl, pyrrolidinyl, piperidinyl, piperazinyl, phenyl, phenyl C_1-C_4 alkyl or $-SO_2NR_{11}R_{11}$, where the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky (*e.g.* CF_3) or halogen.

In an embodiment of this aspect, the heteroaryl group is pyridyl, which is optionally substituted at one or more substitutable positions with groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, CF_3, OCF_3, hydroxyl, CN, phenyloxy, $-SO_2-(C_1-C_6$ alkyl), $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, pyridyl, phenyl or $-SO_2NR_{11}R_{11}$, where each R_{10} and R_{11} is independently C_1-C_6 alkyl or phenyl; and additionally R_{11} may be H. In some embodiments the pyridyl group is substituted with one halogen, *e.g.* chloro. In an embodiment of this aspect, the pyridyl group is substituted with one C_1-C_4 haloalkyl group (*e.g.*, CF_3). In a further embodiment of this aspect, the pyridyl group is 5-(trifluoromethyl)pyridin-2-yl or 6-(trifluoromethyl)pyridin-3-yl. In a still further embodiment of this aspect, the pyridyl group is 6-(trifluoromethyl)pyridin-3-yl. In another embodiment, the pyridyl group is substituted with one or two groups that are independently halogen, C_1-C_4 alkyl or C_1-C_4 alkoxy. In still another embodiment, the pyridyl group is substituted with one group that is $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$ or -O-

$C(O)NR_{11}R_{11}$. In yet another embodiment, the pyridyl group is substituted with one group that is $-SO_2-(C_1-C_6$ alkyl) or $-SO_2NR_{11}R_{11}$. In still another embodiment, the pyridyl group is substituted with one or two groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy or hydroxyl. In a further embodiment, the pyridyl group is unsubstituted.

In an embodiment of this aspect, the heteroaryl group is pyrimidyl, which is optionally substituted at one or more substitutable positions with groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, CF_3, OCF_3, hydroxyl, CN, phenyloxy, $-SO_2-(C_1-C_6$ alkyl), $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, pyridyl, phenyl or $-SO_2NR_{11}R_{11}$, where each R_{10} and R_{11} is independently C_1-C_6 alkyl or phenyl; and additionally R_{11} may be H. In some embodiments the pyrimidyl group is substituted with one halogen, *e.g.* chloro. In another embodiment, the pyrimidyl group is substituted with one or two groups that are independently halogen, C_1-C_4 alkyl or C_1-C_4 alkoxy. In still another embodiment, the pyrimidyl group is substituted with one group that is $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, or $-O-C(O)NR_{11}R_{11}$. In yet another embodiment, the pyrimidyl group is substituted with one group that is $-SO_2-(C_1-C_6$ alkyl) or $-SO_2NR_{11}R_{11}$. In still another embodiment, the pyrimidyl group is substituted with one or two groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy or hydroxyl. In a further embodiment, the pyrimidyl group is unsubstituted.

In an embodiment of this aspect, the heteroaryl group is pyridazinyl, which is optionally substituted at one or more substitutable positions with groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, CF_3, OCF_3, hydroxyl, CN, phenyloxy, $-SO_2-(C_1-C_6$ alkyl), $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, pyridyl, phenyl or $-SO_2NR_{11}R_{11}$, where each R_{10} and R_{11} is independently C_1-C_6 alkyl or phenyl; and additionally R_{11} may be H. In some embodiments the pyridazinyl group is substituted with one halogen, *e.g.* chloro. In another embodiment, the pyridazinyl group is substituted with one or two groups that are independently halogen, C_1-C_4 alkyl or C_1-C_4 alkoxy. In still another embodiment, the pyridazinyl group is substituted with one group that is $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$ or $-O-C(O)NR_{11}R_{11}$. In yet another embodiment, the pyridazinyl group is substituted with one group that is $-SO_2-(C_1-C_6$ alkyl) or $-SO_2NR_{11}R_{11}$. In still another embodiment, the pyridazinyl group is substituted with one or two groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy or hydroxyl. In a further embodiment, the pyridazinyl group is unsubstituted.

In an embodiment of this aspect, the heteroaryl group is pyrazinyl, which is optionally substituted at one or more substitutable positions with groups that are

independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, CF_3, OCF_3, hydroxyl, CN, phenyloxy, -SO_2-(C_1-C_6 alkyl), -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alkanoyl, pyridyl, phenyl or -$SO_2NR_{11}R_{11}$, where each R_{10} and R_{11} is independently C_1-C_6 alkyl or phenyl; and additionally R_{11} may be H. In some embodiments the pyrazinyl group is substituted with one halogen, *e.g.* chloro. In another embodiment, the pyrazinyl group is substituted with one or two groups that are independently halogen, C_1-C_4 alkyl or C_1-C_4 alkoxy. In still another embodiment, the pyrazinyl group is substituted with one group that is -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, or -O-C(O)$NR_{11}R_{11}$. In yet another embodiment, the pyrazinyl group is substituted with one group that is -SO_2-(C_1-C_6 alkyl) or -$SO_2NR_{11}R_{11}$. In still another embodiment, the pyrazinyl group is substituted with one or two groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy or hydroxyl. In a further embodiment, the pyrazinyl group is unsubstituted.

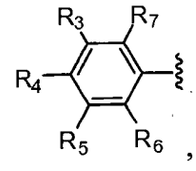
In an embodiment of this aspect, the heteroaryl group is thienyl, which is optionally substituted at one or more substitutable positions with groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, CF_3, OCF_3, hydroxyl, CN, phenyloxy, -SO_2-(C_1-C_6 alkyl), -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alkanoyl, pyridyl, phenyl or -$SO_2NR_{11}R_{11}$, where each R_{10} and R_{11} is independently C_1-C_6 alkyl or phenyl; and additionally R_{11} may be H. In some embodiments the thienyl group is substituted with one halogen, *e.g.* chloro. In one embodiment, the thienyl group is substituted at the 5-position with a Cl. In another embodiment, the heteroaryl group is 5-chlorothiophen-2-yl. In another embodiment, the thienyl group is substituted with one or two groups that are independently halogen, C_1-C_4 alkyl or C_1-C_4 alkoxy. In still another embodiment, the thienyl group is substituted with one group that is -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10} or -O-C(O)$NR_{11}R_{11}$. In yet another embodiment, the thienyl group is substituted with one group that is -SO_2-(C_1-C_6 alkyl) or -$SO_2NR_{11}R_{11}$. In still another embodiment, the thienyl group is substituted with one or two groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy or hydroxyl. In a further embodiment, the thienyl group is unsubstituted.

In an embodiment of this aspect, the heteroaryl group is furanyl, which is optionally substituted at one or more substitutable positions with groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, CF_3, OCF_3, hydroxyl, CN, phenyloxy, -SO_2-(C_1-C_6 alkyl), -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alkanoyl, pyridyl, phenyl or -$SO_2NR_{11}R_{11}$, where each R_{10} and R_{11} is independently C_1-C_6 alkyl or phenyl; and additionally R_{11} may be H. In some embodiments the furanyl group is substituted with one halogen, *e.g.* chloro. In another embodiment, the furanyl group is

substituted with one or two groups that are independently halogen, C_1-C_4 alkyl or C_1-C_4 alkoxy. In still another embodiment, the furanyl group is substituted with one group that is -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, or -O-$C(O)NR_{11}R_{11}$. In yet another embodiment, the furanyl group is substituted with one group that is -SO_2-(C_1-C_6 alkyl) or -$SO_2NR_{11}R_{11}$. In still another embodiment, the furanyl group is substituted with one or two groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy or hydroxyl. In a further embodiment, the furanyl group is unsubstituted.

In an embodiment of this aspect, the heteroaryl group is pyrrolyl, which is optionally substituted at one or more substitutable positions with groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, CF_3, OCF_3, hydroxyl, CN, phenyloxy, -SO_2-(C_1-C_6 alkyl), -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, pyridyl, phenyl or -$SO_2NR_{11}R_{11}$, where each R_{10} and R_{11} is independently C_1-C_6 alkyl or phenyl; and additionally R_{11} may be H. In some embodiments the pyrrolyl group is substituted with one halogen, *e.g.* chloro. In another embodiment, the pyrrolyl group is substituted with one or two groups that are independently halogen, C_1-C_4 alkyl or C_1-C_4 alkoxy. In still another embodiment, the pyrrolyl group is substituted with one group that is -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, or -O-$C(O)NR_{11}R_{11}$. In yet another embodiment, the pyrrolyl group is substituted with one group that is -SO_2-(C_1-C_6 alkyl) or -$SO_2NR_{11}R_{11}$. In still another embodiment, the pyrrolyl group is substituted with one or two groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy or hydroxyl. In a further embodiment, the pyrrolyl group is unsubstituted.

In another aspect, in the compounds of Formulas 1 (and aspects and embodiments thereof), 2 (and aspects and embodiments thereof), 3 (and aspects and embodiments thereof), and 4 (and aspects and embodiments thereof), the A-ring is:



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wherein,

R_3, R_4, R_5, R_6, R_7 are independently of each other H, halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, CN, hydroxyl, C_1-C_4 alkoxy, -C_1-C_3 alkyl-OH, -C_1-C_3 alkyl-C_1-C_4 alkoxy, phenyloxy, -$S(O_2)R_{10}$, -$SO_2NR_{11}R_{11}$, -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$ or C_2-C_4 alkanoyl; or

the A-ring is pyridyl, which is optionally substituted at one or more substitutable positions with groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, CF_3, OCF_3, hydroxyl, CN, phenyloxy, -SO_2-(C_1-C_6 alkyl), -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alkanoyl, pyridyl, phenyl or -$SO_2NR_{11}R_{11}$, where each R_{10} and R_{11} is independently C_1-C_6 alkyl or phenyl; and additionally R_{11} may be H.

In a further embodiment of this aspect, the A-ring is phenyl or pyridyl, each of which is optionally substituted with halogen or C_1-C_4 haloalkyl (*e.g.*, CF_3 or CHF_2).

In a further embodiment of this aspect, the A-ring is phenyl substituted with R_3, R_4, R_5, R_6 and R_7, wherein R_4 is halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3 or CN; and R_3, R_5 R_6, and R_7 are hydrogen.

In a further embodiment of this aspect, the A-ring is pyridyl, optionally substituted with one halogen or CF_3.

In another aspect, in the compounds of Formulas 1 (and aspects and embodiments thereof), 2 (and aspects and embodiments thereof), 3 (and aspects and embodiments thereof), and 4 (and aspects and embodiments thereof), the A-ring is heterocycloalkyl that is pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl or thiomorpholinyl-S,S-dioxide, where each of the above rings 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, haloalkyl, haloalkoxy, hydroxyl, hydroxyalkyl, CN, phenyloxy, -S(O)$_{0-2}$-(C_1-C_6 alkyl), -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alkanoyl, C_0-C_3alkylCO_2R_{10}, pyridyl, thienyl, furanyl, pyrrolyl, pyrrolidinyl, piperidinyl, piperazinyl, phenyl, phenyl C_1-C_4 alkyl or -$SO_2NR_{11}R_{11}$, where the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky (*e.g.* CF_3) or halogen.

In an embodiment of this aspect, the heterocycloalkyl group is pyrrolidinyl, which is optionally substituted at one or more substitutable positions with groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, CF_3, OCF_3, hydroxyl, CN, phenyloxy, -SO_2-(C_1-C_6 alkyl), -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alkanoyl, pyridyl, phenyl or -$SO_2NR_{11}R_{11}$, where each R_{10} and R_{11} is independently C_1-C_6 alkyl or phenyl; and additionally R_{11} may be H. In some embodiments the pyrrolidinyl group is substituted with one halogen, *e.g.* chloro. In another embodiment,

the pyrrolidinyl group is substituted with one or two groups that are independently halogen, C_1-C_4 alkyl or C_1-C_4 alkoxy. In still another embodiment, the pyrrolidinyl group is substituted with one group that is $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, or $-O-C(O)NR_{11}R_{11}$. In yet another embodiment, the pyrrolidinyl group is substituted with one group that is $-SO_2-(C_1-C_6$ alkyl) or $-SO_2NR_{11}R_{11}$. In still another embodiment, the pyrrolidinyl group is substituted with one or two groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy or hydroxyl. In a further embodiment, the pyrrolidinyl group is unsubstituted.

In an embodiment of this aspect, the heterocycloalkyl group is piperidinyl, which is optionally substituted at one or more substitutable positions with groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, CF_3, OCF_3, hydroxyl, CN, phenyloxy, $-SO_2-(C_1-C_6$ alkyl), $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, pyridyl, phenyl or $-SO_2NR_{11}R_{11}$, where each R_{10} and R_{11} is independently C_1-C_6 alkyl or phenyl; and additionally R_{11} may be H. In some embodiments the pyrrolidinyl group is substituted with one halogen, *e.g.* chloro. In another embodiment, the pyrrolidinyl group is substituted with one or two groups that are independently halogen, C_1-C_4 alkyl or C_1-C_4 alkoxy. In still another embodiment, the pyrrolidinyl group is substituted with one group that is $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, or $-O-C(O)NR_{11}R_{11}$. In yet another embodiment, the pyrrolidinyl group is substituted with one group that is $-SO_2-(C_1-C_6$ alkyl) or $-SO_2NR_{11}R_{11}$. In still another embodiment, the pyrrolidinyl group is substituted with one or two groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy or hydroxyl. In a further embodiment, the pyrrolidinyl group is unsubstituted.

In an embodiment of this aspect, the heterocycloalkyl group is piperazinyl, which is optionally substituted at one or more substitutable positions with groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, CF_3, OCF_3, hydroxyl, CN, phenyloxy, $-SO_2-(C_1-C_6$ alkyl), $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, pyridyl, phenyl or $-SO_2NR_{11}R_{11}$, where each R_{10} and R_{11} is independently C_1-C_6 alkyl or phenyl; and additionally R_{11} may be H. In some embodiments the pyrrolidinyl group is substituted with one halogen, *e.g.* chloro. In another embodiment, the pyrrolidinyl group is substituted with one or two groups that are independently halogen, C_1-C_4 alkyl or C_1-C_4 alkoxy. In still another embodiment, the pyrrolidinyl group is substituted with one group that is $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, or $-O-C(O)NR_{11}R_{11}$. In yet another embodiment, the pyrrolidinyl group is substituted with one group that is $-SO_2-(C_1-C_6$ alkyl), $-NR_{11}SO_2R_{10}$ or $-SO_2NR_{11}R_{11}$. In still another embodiment, the pyrrolidinyl group is substituted with one or two groups that are independently C_1-C_4

alkyl, C_1-C_4 alkoxy or hydroxyl. In a further embodiment, the pyrrolidinyl group is unsubstituted.

In an embodiment of this aspect, the heterocycloalkyl group is morpholinyl, which is optionally substituted at one or more substitutable positions with groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, CF_3, OCF_3, hydroxyl, CN, phenyloxy, -SO_2-(C_1-C_6 alkyl), -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alkanoyl, pyridyl, phenyl or -$SO_2NR_{11}R_{11}$, where each R_{10} and R_{11} is independently C_1-C_6 alkyl or phenyl; and additionally R_{11} may be H. In some embodiments the pyrrolidinyl group is substituted with one halogen, *e.g.* chloro. In another embodiment, the pyrrolidinyl group is substituted with one or two groups that are independently halogen, C_1-C_4 alkyl or C_1-C_4 alkoxy. In still another embodiment, the pyrrolidinyl group is substituted with one group that is -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$ -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, or -O-C(O)$NR_{11}R_{11}$. In yet another embodiment, the pyrrolidinyl group is substituted with one group that is -SO_2-(C_1-C_6 alkyl) or -$SO_2NR_{11}R_{11}$. In still another embodiment, the pyrrolidinyl group is substituted with one or two groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy or hydroxyl. In a further embodiment, the pyrrolidinyl group is unsubstituted.

In an embodiment of this aspect, the heterocycloalkyl group is thiomorpholinyl, which is optionally substituted at one or more substitutable positions with groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, CF_3, OCF_3, hydroxyl, CN, phenyloxy, -SO_2-(C_1-C_6 alkyl), -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alkanoyl, pyridyl, phenyl or -$SO_2NR_{11}R_{11}$, where each R_{10} and R_{11} is independently C_1-C_6 alkyl or phenyl; and additionally R_{11} may be H. In some embodiments the pyrrolidinyl group is substituted with one halogen, *e.g.* chloro. In another embodiment, the pyrrolidinyl group is substituted with one or two groups that are independently halogen, C_1-C_4 alkyl or C_1-C_4 alkoxy. In still another embodiment, the pyrrolidinyl group is substituted with one group that is -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, or -O-C(O)$NR_{11}R_{11}$. In yet another embodiment, the pyrrolidinyl group is substituted with one group that is -SO_2-(C_1-C_6 alkyl) or -$SO_2NR_{11}R_{11}$. In still another embodiment, the pyrrolidinyl group is substituted with one or two groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy or hydroxyl. In a further embodiment, the pyrrolidinyl group is unsubstituted.

In an embodiment of this aspect, the heterocycloalkyl group is thiomorpholinyl-S,S-dioxide, which is optionally substituted at one or more substitutable positions with groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, CF_3, OCF_3, hydroxyl, CN, phenyloxy, -SO_2-(C_1-C_6 alkyl), -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-

$C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, pyridyl, phenyl or $-SO_2NR_{11}R_{11}$, where each R_{10} and R_{11} is independently C_1-C_6 alkyl or phenyl; and additionally R_{11} may be H. In some embodiments the pyrrolidinyl group is substituted with one halogen, *e.g.* chloro. In another embodiment, the pyrrolidinyl group is substituted with one or two groups that are independently halogen, C_1-C_4 alkyl or C_1-C_4 alkoxy. In still another embodiment, the pyrrolidinyl group is substituted with one group that is $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, or $-O-C(O)NR_{11}R_{11}$. In yet another embodiment, the pyrrolidinyl group is substituted with one group that is $-SO_2$-(C_1-C_6 alkyl) or $-SO_2NR_{11}R_{11}$. In still another embodiment, the pyrrolidinyl group is substituted with one or two groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy or hydroxyl. In a further embodiment, the pyrrolidinyl group is unsubstituted.

In another aspect, provided herein are compounds of Formulas 1, 2, 3, and 4, as well as all aspects and embodiments thereof, wherein each R_{25} is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-C(O)OR_{11}$, $-C(O)NR_{11}R_{11}$, -(C_1-C_6 alkyl)-$C(O)OR_{11}$, C_1-C_6 alkoxy C_1-C_6 alkyl, $-CONR_{11}R_{11}$, CN, C_1-C_6 alkyl-CN or hydroxy C_1-C_6 alkyl. In an embodiment, the two R_{25} groups are the same. In another embodiment, the two R_{25} groups are different.

In an embodiment of this aspect, each R_{25} is independently H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, hydroxy C_1-C_4 alkyl or C_1-C_4 alkoxyalkyl. In a further embodiment, R_{25} is H or unsubstituted C_1-C_4 alkyl (*e.g.*, CH_3). In a further embodiment, R_{25} is H or hydroxy C_1-C_4 alkyl (*e.g.*, hydroxymethyl). In a further embodiment, R_{25} is H or C_1-C_4 alkoxy C_1-C_4 alkyl. In a further embodiment, R_{25} is H or C_1-C_4 haloalkyl (*e.g.*, CF_3, CHF_2, CH_2F, CH_2Cl). In a further embodiment, R_{25} is C_1-C_4 alkyl or C_1-C_4 haloalkyl (*e.g.*, CF_3, CHF_2, CH_2F, CH_2Cl). In a further embodiment, R_{25} is C_1-C_4 alkyl or hydroxy C_1-C_4 alkyl (*e.g.*, hydroxymethyl). In a further embodiment, R_{25} is C_1-C_4 alkyl or C_1-C_4 alkoxy C_1-C_4 alkyl.

In an embodiment of this aspect, each R_{25} is independently H, $-C(O)OR_{11}$, -(C_1-C_6 alkyl)-$C(O)OR_{11}$. In a further embodiment, R_{25} is H or $-C(O)OR_{11}$, -(C_1-C_6 alkyl)-$C(O)OR_{11}$. In a further embodiment, R_{13} is H or unsubstituted C_1-C_4 alkyl. In a further embodiment, R_{13} is H. In a still further embodiment, R_{13} is C_1-C_4 alkyl substituted with at least one group that is phenyl, naphthyl, hydroxyl, C_1-C_6 alkoxy or halogen, where the phenyl and naphthyl groups are unsubstituted. In a further embodiment, R_{13} is C_1-C_4 alkyl substituted with phenyl, wherein the phenyl is substituted with 1 to 5 groups that are independently halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl (*e.g.*, CF_3), C_1-C_4 haloalkoxy (*e.g.*, OCF_3), CN or NO_2.

In an embodiment of this aspect, each R_{25} is independently H, C_1-C_6 alkyl-CN or CN.

In a further embodiment of this aspect, R_{25} is H, -C(O)OR_{11} or -CON$R_{11}R_{11}$. In a still further embodiment, each R_{11} is independently H, C_3-C_6 cycloalkyl, heteroaryl that is pyrazolyl, thiadiazolyl (*e.g.*, 1,2,4-thiadiazolyl or 1,3,4-thiadiazolyl), triazolyl (*e.g.*, 1,2,3-triazolyl or 1,2,4-triazolyl), isoxazolyl, isothiazolyl, imidazolyl, thiazolyl, oxadiazolyl (*e.g.*, 1,2,4-oxadiazolyl or 1,3,4-oxadiazolyl), oxazolyl, tetrazolyl or pyridyl, heterocycloalkyl that is selected from tetrahydrofuranyl, pyrrolidinyl, piperidinyl, morpholinyl, and imidazolidinyl, phenyl, C_2-C_6 alkanoyl or C_1-C_6 alkyl optionally substituted *e.g.*, with -C(O)OR_{11} or alkoxy, where the alkoxy group is optionally further substituted with -C(O)OR_{11}, and where the heteroaryl and aryl groups are optionally substituted *e.g.*, with 1 to 3 groups that are independently halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, CN or NO_2; or the two R_{11} groups together with the nitrogen to which they are attached, form a 3-8 membered ring that optionally contains an additional heteroatom such as *e.g.*, NH, NR_{12}, NR_{13}, O or S, and R_{13} is H or C_1-C_6 alkyl.

In another embodiment of this aspect, each R_{25} is independently H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, hydroxy C_1-C_4 alkyl, C_1-C_4 alkoxyalkyl, -C(O)OR_{11} or -C(O)N$R_{11}R_{11}$.

In another embodiment of this aspect, each R_{11} is independently H or C_1-C_4 alkyl optionally substituted with -C(O)OR_{11} or alkoxy, where R_{11} is H or C_1-C_4 alkyl.

In another embodiment of this aspect, each R_{25} is independently H, hydroxymethyl, methyl or -CO_2CH_3.

In another embodiment of this aspect, each R_{25} is H.

The compounds of Formulas 1, 2, 3, and 4 encompass the sulfonamido derivatives of the invention as disclosed, and/or the pharmaceutically acceptable salts, solvates or polymorphs of such compounds. In addition, the compounds of this invention include the individual stereochemical and geometrical isomers, tautomers, and mixtures thereof, arising from the selection of substituent groups. Certain compounds of this invention may exist in isomeric forms. The invention contemplates all such stereoisomers both in pure form and in admixture, as well as racemic mixtures.

Definitions

The definitions and explanations below are for the terms as used throughout this entire document including both the specification and the claims. Throughout the specification and the appended claims, a given formula or name shall encompass all isomers thereof, such as stereoisomers, geometrical isomers, optical isomers, tautomers, and mixtures

thereof where such isomers exist, as well as pharmaceutically acceptable salts and solvates therof, such as for instance hydrates.

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, *e.g.*, 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 to be understood that the substituents can be the same or different. Thus *e.g.* "R_m optionally substituted with 1, 2, 3 or 4 R_q groups" indicates that R_m is substituted with 1, 2, 3 or 4 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, *e.g.*, 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 "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.

The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain hydrocarbon radical, which can include di- and multivalent radicals, having the number of carbon atoms designated (*e.g.*, C_1-C_{10} means one to ten carbon atoms). Typically, an alkyl group will have from 1 to 10 carbon atoms, with those groups having from 1 to 8 carbon atoms, from 1 to 6 carbon atoms or from 1 to 4 carbon atoms being preferred. A "lower alkyl" group is an alkyl group having from 1 to 4

carbon atoms. The term "alkyl" includes "alkylene" wherever appropriate, *e.g.*, when the formula indicates that the alkyl group is divalent or when substituents are joined to form a ring. Examples of alkyl radicals include, but are not limited to methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *tert*-butyl, *iso*-butyl and *sec*-butyl, as well as homologs and isomers of, *e.g.*, *n*-pentyl, *n*-hexyl, *n*-heptyl and *n*-octyl.

The term "alkylene" by itself or as part of another substituent means a divalent (diradical) alkyl group, wherein alkyl is defined herein. "Alkylene" is exemplified, but not limited, by $-CH_2CH_2CH_2CH_2-$. Typically, an "alkylene" group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms (*e.g.*, 1 to 8 or 1 to 6 carbon atoms) being preferred in the present invention. A "lower alkylene" is an alkylene group having from 1 to 4 carbon atoms.

By "aryl" is meant an aromatic carbocyclic group having a single ring or multiple condensed rings in which at least one is an aromatic hydrocarbon, (*e.g.*, 1,2,3,4-tetrahydronaphthyl, naphthyl). When the "aryl" group includes a non-aromatic ring (such as in 1,2,3,4-tetrahydronaphthyl) or heteroaryl group then the "aryl" group is linked to the core/remainder of the molecule via the aromatic, hydrocarbon ring. Non-limiting examples of aryl groups include phenyl, 1-naphthyl, 2-naphthyl, qinoline, indanyl, indenyl, dihydronaphthyl, fluorenyl, tetralinyl, benzo[d][1,3]dioxolyl or 6,7,8,9-tetrahydro-5H-benzo[a]cycloheptenyl. Preferred "aryl" groups include phenyl, benzo[d][1,3]dioxolyl and naphthyl. Particularly preferred is phenyl.

By "aryloxy" is meant the group -O-aryl, where aryl is as defined herein. More preferably the aryl portion of the aryloxy group is phenyl or naphthyl, still more preferably, phenyl.

By "arylalkyl" is meant the group -alkyl-aryl, wherein alkyl and aryl are defined herein.

By the term "halogen" in the present invention is meant fluorine, bromine, chlorine, and/or iodine.

The term "alkenyl" by itself or as part of another substituent refers to a straight or branched chain hydrocarbon radical having from 2 to 12 carbon atoms and at least one carbon-carbon double bond. A typical alkenyl group has from 2 to 10 carbon atoms and at least one double bond. Preferred alkenyl groups have from 2 to 8 carbon atoms or from 2 to 6 carbon atoms and from 1 to 3 double bonds. Exemplary "alkenyl" groups include vinyl, 2-propenyl, 1-but-3-enyl, crotyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), 2-isopentenyl, 1-pent-3-enyl, 1-hex-5-enyl and the like.

The term "alkynyl" by itself or as part of another substituent refers to a straight or branched chain, unsaturated or polyunsaturated hydrocarbon radical having from 2 to 12 carbon atoms and at least one triple bond. A typical "alkynyl" group has from 2 to 10 carbon atoms and at least one triple bond. Preferred "alkynyl" groups have from 2 to 6 carbon atoms and at least one triple bond. Exemplary "alkynyl" groups include prop-1-ynyl, prop-2-ynyl (i.e., propargyl), ethynyl and 3-butynyl.

The term "cycloalkyl" by itself or in combination with other terms, represents a saturated carbocyclic radical having from 3 to 8 carbon atoms, with those groups having from 3 to 6 carbon atoms (*e.g.*, C_3-C_6 cycloalkyl) being preferred. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cycloheptyl and the like. The term "cycloalkyl" also includes bridged, polycyclic (*e.g.*, bicyclic) structures, such as norbornyl, adamantyl and bicyclo[2.2.1]heptyl. The "cycloalkyl" group can be fused to at least one (*e.g.*, 1 to 3) other rings selected from aromatic (*e.g.*, phenyl), heteroaromatic (*e.g.*, pyridyl) or non-aromatic (*e.g.*, heterocyclic) rings. When the "cycloalkyl" group is fused to an aryl, heteroaryl or heterocyclic ring, then the "cycloalkyl" portion of the fused ring system is attached to the core/remainder of the molecule.

By "oxo" is meant the group =O.

By "halogen" 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.

The term "heteroaryl" or "heteroaromatic" refers to a polyunsaturated, 5-, 6- or 7-membered aromatic moiety containing at least one heteroatom (*e.g.*, 1 to 5 heteroatoms, and preferably 1-3 heteroatoms) selected from N, O, S, Si and B (preferably N, O and S), wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. The "heteroaryl" group can be a single ring or be fused to other aryl, heteroaryl, cycloalkyl or heterocycloalkyl rings (*e.g.*, from 1 to 3 other rings). When the "heteroaryl" group includes a fused aryl, cycloalkyl or heterocycloalkyl ring, then the "heteroaryl" group is attached to the core/remainder of the molecule via the heteroaryl ring. A heteroaryl group can be attached to the remainder of the molecule through a carbon- or heteroatom. Non-limiting examples of heteroaryl groups 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 imidazolyl, pyrazolyl, thiadiazolyl, triazolyl, isoxazolyl, isothiazolyl, imidazolyl, thiazolyl, oxadiazolyl, and pyridyl. Other exemplary heteroaryl groups include 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, pyridin-4-yl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl.

The term “heterocycloalkyl", “heterocyclic”, “heterocycle" or “heterocyclyl", by itself or in combination with other terms, represents is a carbocyclic, non-aromatic ring (*e.g.*, 3- to 8-membered ring and preferably 4-, 5-, 6- or 7-membered ring) containing at least one and up to 5 heteroatoms (*e.g.*, from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur) or a fused ring system of 4- to 8-membered rings, containing at least one and up to 10 heteroatoms (*e.g.*, from 1 to 5 heteroatoms selected from nitrogen, oxygen and sulfur) in stable combinations known to those of skill in the art. The “heterocyclic” group may be fused to one ore more aryl, heteroaryl or cycloalkyl rings. In such fused ring systems, the “heterocyclic” group is attached to the core/remainder of the molecule via the saturated,

heterocyclic ring. A heteroatom can occupy the position at which the heterocycle is attached to the core/remainder of the molecule. Exemplary heterocycloalkyl or heterocyclic groups of the present invention include morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, piperazinyl, homopiperazinyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, tetrahydropyranyl, piperidinyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, homopiperidinyl, homomorpholinyl, homothiomorpholinyl, dioxanyl, dioxolanyl, dioxolan-2-onyl, dihydrodioxinyl, dioxol-2-onyl, dioxolyl, homothiomorpholinyl S,S-dioxide, oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl, dihydropyrazolyl, dihydropyridyl, dihydropyrimidinyl, dihydrofuryl, dihydropyranyl, tetrahydrothienyl S-oxide, tetrahydrothienyl S,S-dioxide, homothiomorpholinyl S-oxide, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like.

The term "hydrogen" or "H" is understood to also encompass the isotopes deuterium and tritium. Hydrogen (rather than deuterium or tritium) is preferred.

The term "neurodegenerative diseases" includes any disease or condition characterized by problems with movements, such as ataxia, and conditions affecting cognitive abilities (*e.g.*, memory) as well as conditions generally related to all types of dementia. "Neurodegenerative diseases" may be associated with impairment or loss of cognitive abilities, potential loss of cognitive abilities and/or impairment or loss of brain cells. Exemplary "neurodegenerative diseases" include Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), Down syndrome, dementia, multi-infarct dementia, mild cognitive impairment (MCI), epilepsy, seizures, Huntington's disease, neurodegeneration induced by viral infection (*e.g.* AIDS, encephalopathies), traumatic brain injuries, as well as ischemia and stroke.

Most compounds were named using Autonom 2000 4.01.305, which is available from Beilstein Information Systems, Inc, Englewood, Colorado, ChemDraw v.10.0, (available from Cambridgesoft at 100 Cambridge Park Drive, Cambridge, MA 02140) or ACD Name pro (*e.g.*, version 12), which is available from Advanced Chemistry Development, Inc., at 110 Yonge Street, 14th floor, Toronto, Ontario, Canada M5c 1T4. Alternatively, the names were generated based on the IUPAC rules or were derived from names originally generated using the aforementioned nomenclature programs.

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,

e.g., 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, *e.g.*, by conventional methods such as crystallization in the presence of a resolving agent; chromatography, using, *e.g.* 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 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 Formulas 1, 2, 3 and 4.

Provided herein are also the acylated prodrugs of the compounds of Formulas 1, 2, 3 and 4. 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 Formulas 1, 2, 3 and 4.

The term "acid prodrug group" denotes a moiety that is converted in vivo into an active carboxylic acid compound of Formulas 1, 2, 3 and 4. 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.

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 invention also encompasses the prodrugs of the compounds of Formulas 1, 2, 3 and 4. 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 Formulas 1, 2, 3, and 4. 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.

Pharmaceutical Compositions

In one embodiment, the invention provides a pharmaceutical composition comprising at least one compound of the invention (*e.g.*, those of Formula 1, Formula 2, Formula 3, Formula 4 or any aspects and embodiments thereof) and at least one pharmaceutically acceptable carrier. The term "pharmaceutically acceptable carrier" includes all pharmaceutically acceptable ingredients known to those of skill in the art and includes solvents, solid or liquid diluents, vehicles, adjuvants, excipients, glidants, binders, granulating agents, dispersing agents, suspending agents, wetting agents, lubricating agents, disintegrants, solubilizers, stabilizers, emulsifiers, fillers, preservatives (*e.g.*, anti-oxidants), flavoring agents, sweetening agents, thickening agents, buffering agents, coloring agents and the like, as well as any mixtures thereof. Exemplary carriers (*i.e.*, excipients) are described in, *e.g.*, *Handbook of Pharmaceutical Manufacturing Formulations*, Volumes 1-6, Niazi, Sarfaraz K., Taylor & Francis Group 2005, which is incorporated herein by reference in its entirety.

In one embodiment, the invention provides a pharmaceutical composition comprising at least one compound Formulas1-5, and aspects and embodiments of each of the above, and at least one pharmaceutically acceptable solvent, adjuvant, excipient, carrier, glidant, binder and/or disintegrant.

The compounds or compositions of the invention 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 Formulas 1, 2, 3, and 4 and a pharmaceutically acceptable carrier. One or more compounds of general Formulas 1, 2, 3, and 4 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 Formulas 1, 2, 3 and 4 may be in a form suitable for oral use, *e.g.*, 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 *e.g.*, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, *e.g.*, corn starch or alginic acid; binding agents, *e.g.* starch, gelatin or acacia, and lubricating agents, *e.g.* 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. *E.g.*, 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, *e.g.*, calcium carbonate, calcium phosphate or kaolin or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, *e.g.* 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, *e.g.* sodium carboxymethylcellulose, methylcellulose, hydropropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, *e.g.*, lecithin or condensation products of an alkylene oxide with fatty acids, *e.g.* polyoxyethylene stearate or condensation products of ethylene oxide with long chain aliphatic alcohols, *e.g.* 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, *e.g.* polyethylene

sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, *e.g.* 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, *e.g.* 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, *e.g.* 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, *e.g.* 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, *e.g.* gum acacia or gum tragacanth, naturally-occurring phosphatides, *e.g.* soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, *e.g.* sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, *e.g.* polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, *e.g.* 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, *e.g.* 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 Formulas 1, 2, 3, and 4 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 Formulas 1, 2, 3, and 4 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, *e.g.*, 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, *e.g.* 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.

Formulations suitable for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable aqueous or organic solvents or mixtures therof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as describe above. The compositions may be administered by oral or nasal respiratory route for local or systemic effect. Compositions may be nebulized by use of inert gases or vaporized, and breathed directly from the nebulizing/vaporizing device or the nebulizing device may be attached to a facemask tent or intermittent positive pressure-breathing machine.

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.

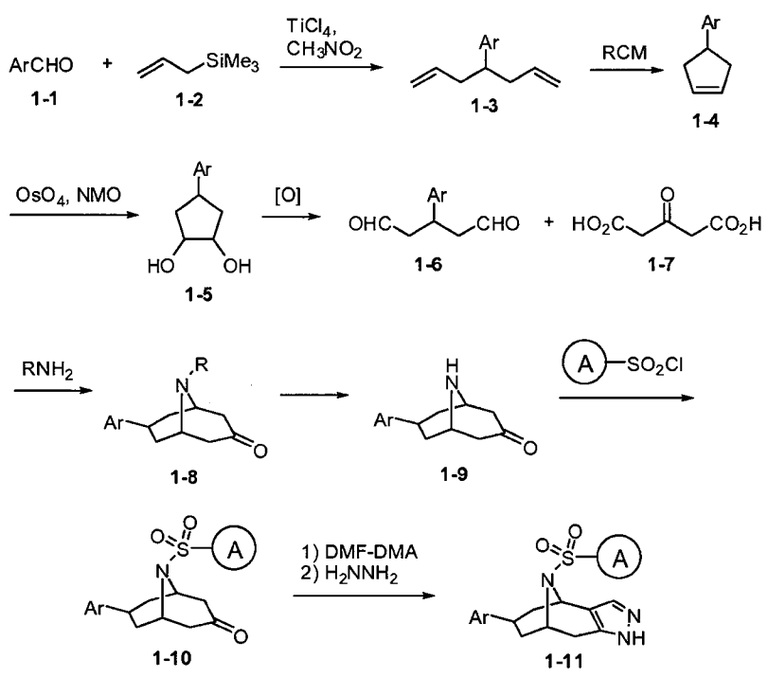
General Synthetic Procedures

The starting materials and various intermediates may be obtained from commercial sources, prepared from commercially available compounds, and/or prepared using known synthetic methods.

The compounds of the invention can be prepared using methods known in the art of organic synthesis. *E.g.*, 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. *E.g.*, 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.

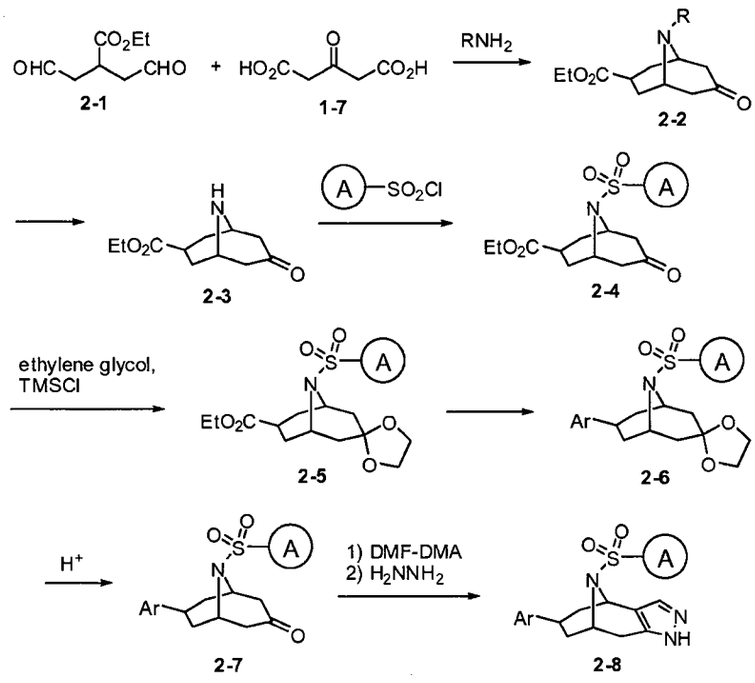
Scheme 1



In the above scheme, the A-ring is defined as described above, R is an amino protecting group, and Ar is an aryl group.

One method for obtaining compounds of Formula 1 may be to couple aldehyde **1-1** with allylsilane **1-2** in the presence of titanium tetrachloride to afford the double allylation product, **1-3**. Ring-closing metathesis of **1-3** may afford cyclopentene **1-4** (see: Durand, A-C; et al. *Synth. Commun.* **2005**, *35*(13), 1825). Treatment of **1-4** with OsO_4/NMO may afford diol **1-5**. Oxidative cleavage of the diol may afford dialdehyde **1-6**. Mannich condensation of **1-6** with acetone-1,3-dicarboxylic acid (**1-7**) and an amine may afford bicyclic ketone **1-8** (see: Mach, R.H.; et al. *J. Med. Chem.* **1993**, *36*(23), 3707). Conversion of **1-8** to **1-9** may be effected by using conditions familiar to one of ordinary skill in the art and the conditions may vary depending on the nature of R. Sulfonylation of **1-9** with a sulfonylchloride of formula A-SO_2Cl, wherein A is as defined above, in the presence of a base may give compound **1-10**. Treatment of **1-10** with an acylating agent such as DMF-DMA followed by cyclization with hydrazine may give compounds of formula **1-11**.

Scheme 2

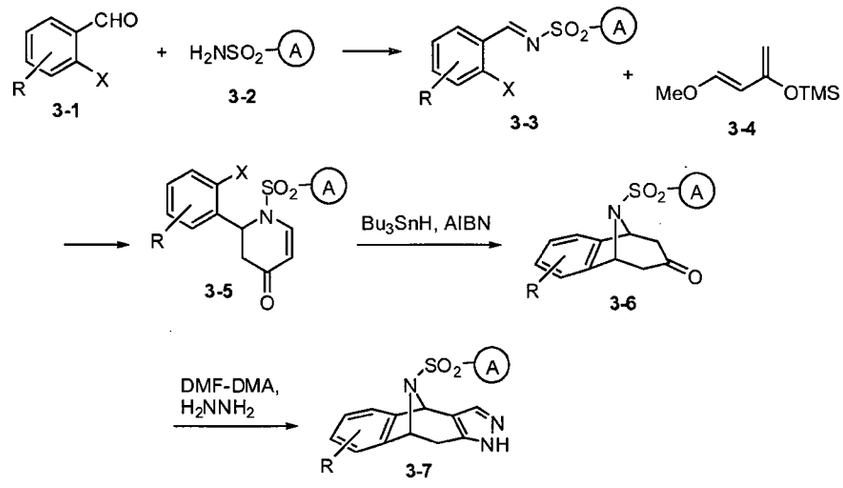


In the above scheme, the A-ring is defined as described above and R is a protecting group, and Ar is an aryl group.

Another method for obtaining compounds of Formula 1 is to prepare an azabicylo[3.2.1]nonane containing an alkoxycarbonyl group that may be elaborated to a heteroaromatic group as shown in the scheme above. Mannich condensation of dialdehyde **2-1** with acetonedicarboxylic acid (**1-7**) and an amine may afford bicyclic ketone **2-2**.

Conversion of **2-2** to **2-3** may be effected by using conditions familiar to one of ordinary skill in the art and the conditions may vary depending on the nature of R. Sulfonylation of **2-3** with a sulfonylchloride of formula A-SO_2Cl, wherein A is as defined above, in the presence of a base may give compound **2-4**. Protection of the ketone may be accomplished using ethylene glycol in the presence of a Lewis acid to give **2-5**. Conversion of the alkoxycarbonyl group to a heteroaryl ring may be accomplished by numerous methods familiar to one skilled in the art (see: Gupta, R.R.; Kumar, M.; Gupta, V. *Heterocyclic Chemistry* Vol .I – Vol.III, Springer-Verlag: Berlin, 1999) to give compound **2-6**. Deprotection of the ketone followed by treatment with an acylating agent such as DMF-DMA and cyclization with hydrazine may give compounds of formula **2-8**.

Scheme 3



In the above scheme, the A-ring is defined as described above and R equivalent to R_{30}, R_{35}, R_{40} and/or R_{45}, and X is a halogen.

One method for obtaining compounds of the invention is to couple a 2-halobenzaldehyde such as **3-1** with sulfonamide **3-2** to afford sulfonimine **3-3** (see *e.g.*: Castellano, S.; et al. *J. Am. Chem. Soc.* **2007**, *129*(18), 5843). Cycloaddition of **3-3** with a diene such as **3-4** may form dihydropyridinone **3-5**. Radical cyclization of 3-5 with a reagent such as Bu_3SnH/AIBN may give nortropanone 3-6. Treatment of **3-6** with an acylating agent such as DMF-DMA followed by cyclization with hydrazine may give compounds of formula **3-7**.

Certain compounds of this invention are prepared from other compounds of this invention via known reactions and functional group transformations. Examples of such transformations are ester hydrolysis, amide formation, and reductive alkylation; with

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.

Methods

Method of Treatment

In one embodiment, provided herein is a method of treating a neurodegenerative disease comprising administering to a mammalian subject (e.g., a human subject) in need thereof a pharmaceutically effective amount of a compound or salt of Formulas 1, 2, 3 or 4 (or any embodiment thereof) or a pharmaceutical composition comprising at least one compound of Formulas 1, 2, 3 or 4 (or any embodiment thereof). In one example, the neurodegenerative disease is a member selected from Alzheimer's Disease, diffuse Lewy body type of Alzheimer's disease, Parkinson's disease, Down syndrome, dementia, mild cognitive impairment (MCI), amyotrophic lateral sclerosis (ALS), traumatic brain injuries, cerebral ischemic brain damage, ischemic or hemorrhaging stroke, hereditary cerebral hemorrhage with amyloidosis of the dutch-type and cerebral amyloid angiopathy. In a particular example, the neurodegenerative disease is Alzheimer's disease or diffuse Lewy body type of Alzheimer's disease. Thus, in one example, the invention provides a method of treating Alzheimer's disease or diffuse Lewy body type of Alzheimer's disease comprising administering a therapeutically effective amount of a compound or salt of Formulas 1, 2, 3 or 4 to a patient in need of such treatment.

In another embodiment, the invention provides a method of treating a disease selected from epilepsy, seizures, Huntington's disease, multiple sclerosis, cancer, age-related macular degeneration, diabetic retinopathy and retinal neurodegeneration related to glaucoma or ocular trauma, the method comprising administering to a mammalian subject (e.g., a human subject) in need thereof a pharmaceutically effective amount of a compound or salt of Formulas 1, 2, 3 or 4 (or any embodiment thereof) or a pharmaceutical composition comprising at least one compound of Formulas 1, 2, 3 or 4 (or any embodiment thereof). In a particular example, the invention provides a method of treating cancer selected from medulloblastoma (e.g., with high levels of the Notch2 gene), colorectal cancers (treated with compounds of the invention alone or in conjuction with taxanes), lung cancers, acute lymphoblastic leukemia and other hematologic cancers, Kaposi's sarcoma, breast cancer and melanoma, the method comprising administering to a mammalian subject (e.g., a human subject) in need thereof a pharmaceutically effective amount of a compound or salt of

Formulas 1, 2, 3 or 4 (or any embodiment thereof) or a pharmaceutical composition comprising at least one compound of Formulas 1, 2, 3 or 4 (or any embodiment thereof).

The invention further provides a method of treating a disease state in a cell, a group of cells (*e.g.* mammalian tissue) or an organism (*e.g.*, human), comprising: administering a compound and/or salts of Formulas 1, 2, 3, and/or 4, to the cell, group of cells or organism, wherein the disease is selected from the group consisting of cancer, intraocular disorders (*e.g.* age related macular degeneration), protein deposition-related diseases, Down's syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, cerebral amyloid angiopathy, Parkinson's disease, progressive supranuclear palsy, dementia associated with cortical basal degeneration, and diffuse Lewy body type of Alzheimer's disease.

Still further, the invention provides a method of inhibiting angiogenesis in a mammalian tissue or an organism (*e.g.*, human), comprising administering a pharmaceutically effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof, to the tissue or the organism.

Further still, provided herein is a method of inhibiting angiogenesis in a mammalian tissue or organism, comprising administering a pharmaceutically effective amount of a compound of Formulas 1, 2, 3, and/or 4 or pharmaceutically acceptable salt(s) thereof, to the tissue or the organism, wherein the compound (or pharmaceutical composition) is administered to prevent, treat or cure a condition treatable by inhibiting angiogenesis.

In vitro Methods

In one embodiment, the compounds and compositions of the invention can be used in an *in vitro* assay measuring gamma-secretase activity. In one example, the gamma-secretase activity is measured by detecting cleavage of a gamma-secretase substrate (e.g., APP or Notch). In another example, the compounds and compositions of the invention can be used in an *in vitro* assay for identifying candidate compounds that are capable of inhibiting gamma-secretase activity.

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.

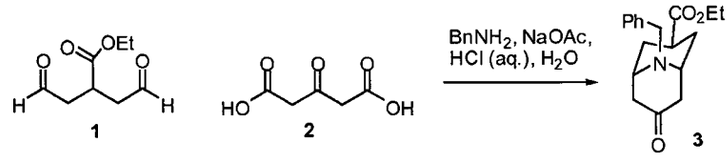
EXAMPLES

General

Reagents and solvents obtained from commercial suppliers were used without further purification unless otherwise stated. Thin layer chromatography was performed on percolated 0.25 mm silica gel plates (E. Merck, silica gel 60, F254). 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.

Example 1

Synthesis of 9-benzyl-7-oxo-9-aza-bicyclo[3.3.1]nonane-3-carboxylic acid ethyl ester (3)

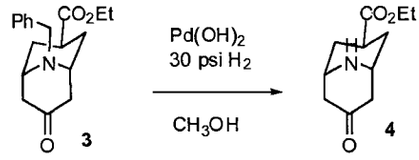


Acetone-1,3-dicarboxylic acid (**2**) (8.81 g, 60.36 mmol) and sodium acetate (5.04 g, 61.5 mmol) were added to a solution of 4-oxo-2-(2-oxo-ethyl)-butyric acid ethyl ester (**1**) (European Patent EP 0330788A1) (10.3 g, 60.36 mmol) in H_2O (75 mL). Benzylamine (6.59 mL, 60.36 mmol) was dissolved in aqueous HCl (3 N, 41 mL) and was subsequently added to the stirring solution of the dialdehyde and the dicarboxylic acid over a 15 minute period. The reaction mixture was stirred for 3 days at room temperature after which the pH was adjusted to 8 by the addition of potassium carbonate. The resulting solution was extracted with CH_2Cl_2 (4 × 50 mL), the organic extracts dried (Na_2SO_4), filtered and concentrated under vacuum. The resulting residue was purified by silica gel chromatography, (eluant hexane/EtOAc 9/1 to 1/1, v/v) to give 7.43 g (40%) of 9-benzyl-7-oxo-9-aza-bicyclo[3.3.1]nonane-3-carboxylic acid ethyl ester (**3**) as a brown oil. Retention time (min) = 0.963, method [1], MS(ESI) 302.2 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.10 (m, 5H), 4.10 (q, J = 7.1 Hz, 2H), 3.91 (s,

2H), 3.41-3.38 (m, 2H), 2.74 (dd, J = 16.5, 6.6 Hz, 2H), 2.61-2.48 (m, 1H), 2.30 (d, J = 16.5 Hz, 2H), 2.08 (dt, J = 3.8 Hz, J = 13.2 Hz, 2H), 1.81-1.72 (m, 2H), 1.22 (t, J = 7.1 Hz, 3H).

Example 2

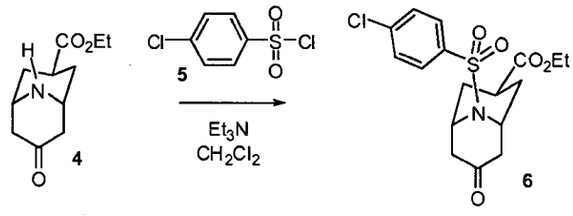
Synthesis of 7-oxo-9-aza-bicyclo[3.3.1]nonane-3-carboxylic acid ethyl ester (4)



9-Benzyl-7-oxo-9-aza-bicyclo[3.3.1]nonane-3-carboxylic acid ethyl ester (**3**) (11.1 g, 36.8 mmol) was dissolved in MeOH (30 mL) and added to a suspension of palladium hydroxide (1 g) in MeOH (10 mL) in a Parr bottle. The Parr bottle was filled with hydrogen (30 psi) and evacuated three times. The Parr bottle was refilled with hydrogen (30 psi) and shook for 12 h. The suspension was filtered through Celite and concentrated under vacuum to give 7.81 g (quantitative yield) of 7-oxo-9-aza-bicyclo[3.3.1]nonane-3-carboxylic acid ethyl ester as a yellow oil. Retention time (min) = 0.369, method [1], MS(ESI) 212.1 (M+H).

Example 3

Synthesis of 9-(4-chloro-benzenesulfonyl)-7-oxo-9-aza-bicyclo[3.3.1]nonane-3-carboxylic acid ethyl ester (6)

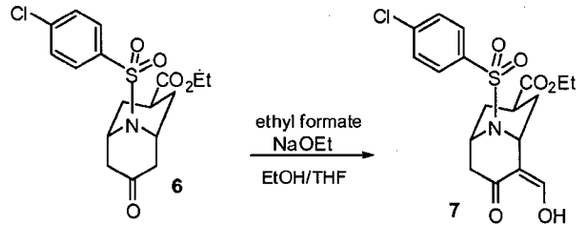


7-Oxo-9-aza-bicyclo[3.3.1]nonane-3-carboxylic acid ethyl ester (**4**) (5.91 g, 27.9 mmol) was dissolved in CH_2Cl_2 (60 mL). Et_3N (7.76 mL, 55.9 mmol) and 4-chlorobenzenesulfonyl chloride (**5**) (7.08 g, 33.6 mmol) were added and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with saturated $NaHCO_3$ (50 mL). The aqueous phase was separated and extracted once with CH_2Cl_2 (50 mL). The combined organic phases were then dried (Na_2SO_4), filtered, concentrated under vacuum and the residue was purified on a silica gel column (eluant hexane/EtOAc, 9/1 to 1/1) to give 9.52 g (88%) of 9-(4-chloro-benzenesulfonyl)-7-oxo-9-aza-bicyclo[3.3.1]nonane-3-carboxylic acid ethyl ester (**6**). Retention time (min) = 2.100, method [1], MS(ESI) 408.1 (M+Na); ^{1}H NMR ($CDCl_3$) δ 7.81 (d, J= 8.2 Hz, 2H), 7.51 (d, J = 8.2 Hz, 2H), 4.61-4.57 (m, 2H), 4.09 (q, J = 7.1 Hz, 2H), 2.80 (dd, J = 17.0, 7.1 Hz, 2H),

2.67-2.51 (m, 1H), 2.41 (d, J = 16.4 Hz, 2H), 1.99-1.90 (m, 2H), 1.80 (dt, J = 13.2, 4.4 Hz, 2H), 1.20 (t, J = 7.1 Hz, 3H).

Example 4

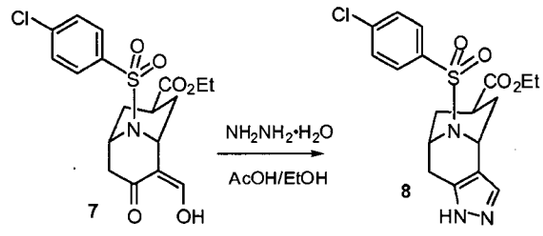
Synthesis of 9-(4-chloro-benzenesulfonyl)-6-hydroxymethylene-7-oxo-9-aza-bicyclo[3.3.1]nonane-3-carboxylic acid ethyl ester (7)



9-(4-Chloro-benzenesulfonyl)-7-oxo-9-aza-bicyclo[3.3.1]nonane-3-carboxylic acid ethyl ester (**6**) (2.49 g, 6.45 mmol) was dissolved in THF/ethanol (14 mL, 1/1, v/v). Ethyl formate (5.19 mL, 64.53 mmol) was added followed by sodium ethoxide (6.2 mL of 21% solution in ethanol). The resulting mixture was heated to 60 °C for 30 minutes after which the solution was cooled to room temperature and quenched by the addition of saturated aqueous NH_4Cl (10 mL). The resulting mixture was extracted with EtOAc (2 × 20 mL) and the combined organic phases were dried (Na_2SO_4), filtered and concentrated under vacuum to yield 2.51 g (94%) of 9-(4-chloro-benzenesulfonyl)-6-hydroxymethylene-7-oxo-9-aza-bicyclo[3.3.1]nonane-3-carboxylic acid ethyl ester (**7**) as a yellow oil. Retention time (min) = 2.017, method [1], MS(ESI) 414.0 (M+H).

Example 5

Synthesis of 12-(4-chloro-benzenesulfonyl)-4,5,12-triaza-tricyclo[6.3.1.0$_{2,6}$]dodeca-2(6),3-diene-10-carboxylic acid ethyl ester (8)

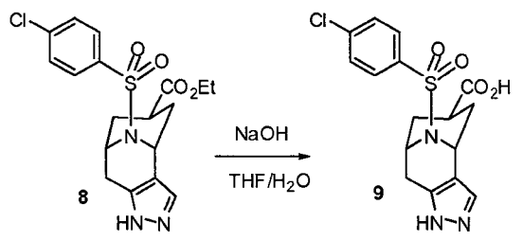


To a solution of 9-(4-chloro-benzenesulfonyl)-6-hydroxymethylene-7-oxo-9-aza-bicyclo[3.3.1]nonane-3-carboxylic acid ethyl ester (**7**) (2.48 g, 5.99 mmol) in ethanol (10 mL) was added glacial acetic acid (0.2 mL) followed by hydrazine monohydrate (2.9 mL, 59.9 mmol). The reaction mixture was stirred at room temperature for 1 h after which saturated $NaHCO_3$ (10 mL) was added. The resulting solution was extracted with EtOAc (3 × 20 mL), the organic extracts were combined, dried (Na_2SO_4), filtered, concentrated and

purified by silica gel column chromatography (eluant hexane/EtOAc, 9/1 to 1/1) and preparative HPLC to give 12-(4-chloro-benzenesulfonyl)-4,5,12-triaza-tricyclo[6.3.1.$0_{2,6}$]dodeca-2(6),3-diene-10-carboxylic acid ethyl ester (**8**) as a white solid. Retention time (min) = 1.739, method [1],MS(ESI) 410.1 (M+H); ^{1}H NMR ($CDCl_3$) δ 7.66 (d, J = 8.2 Hz, 2H), 7.51 (s, 1H), 7.38 (d, J = 8.2 Hz, 2H), 5.37 (bs, 1H), 4.61-4.55 (m, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.04 (dd, J = 17.6, 7.1 Hz, 1H), 2.67 (d, J = 17.6 Hz, 1H), 2.48-2.31 (m, 1H), 2.11-1.91 (m, 4H), 1.20 (t, J = 7.1 Hz, 3H).

Example 6

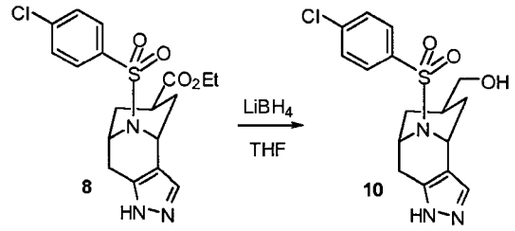
Synthesis of 12-(4-Chloro-benzenesulfonyl)-4,5,12-triaza-tricyclo[6.3.1.$0_{2,6}$]dodeca-2(6),3-diene-10-carboxylic acid (9)



Sodium hydroxide (0.5 mL, 3 N solution) was added to a solution 12-(4-chloro-benzenesulfonyl)-4,5,12-triaza-tricyclo[6.3.1.$0_{2,6}$]dodeca-2(6),3-diene-10-carboxylic acid ethyl ester (**8**) (321 mg, 0.783 mmol) in THF (2 mL). The resulting mixture was stirred at room temperature for 4 h. The reaction mixture was extracted with EtOAc (2 × 5 mL) and the combined organic phases were dried (Na_2SO_4), filtered, concentrated and purified by preparative HPLC to give 12-(4-chloro-benzenesulfonyl)-4,5,12-triaza-tricyclo[6.3.1.$0_{2,6}$]dodeca-2(6),3-diene-10-carboxylic acid (**9**) as a white solid. Retention time (min) = 1.316, method [1], MS(ESI) 382.0 (M+H); ^{1}H NMR ($CDCl_3$) δ 7.56 (d, J = 8.7 Hz, 2H), 7.30-7.22 (m, 3H), 5.30-5.25 (m, 1H), 4.54-4.45 (m, 1H), 2.80 (dd, J = 17.0, J = 7.7 Hz, 1H), 2.50 (d, J = 17.0 Hz, 1H), 2.42-2.30 (m, 1H), 2.24-1.85 (m, 4H).

Example 7

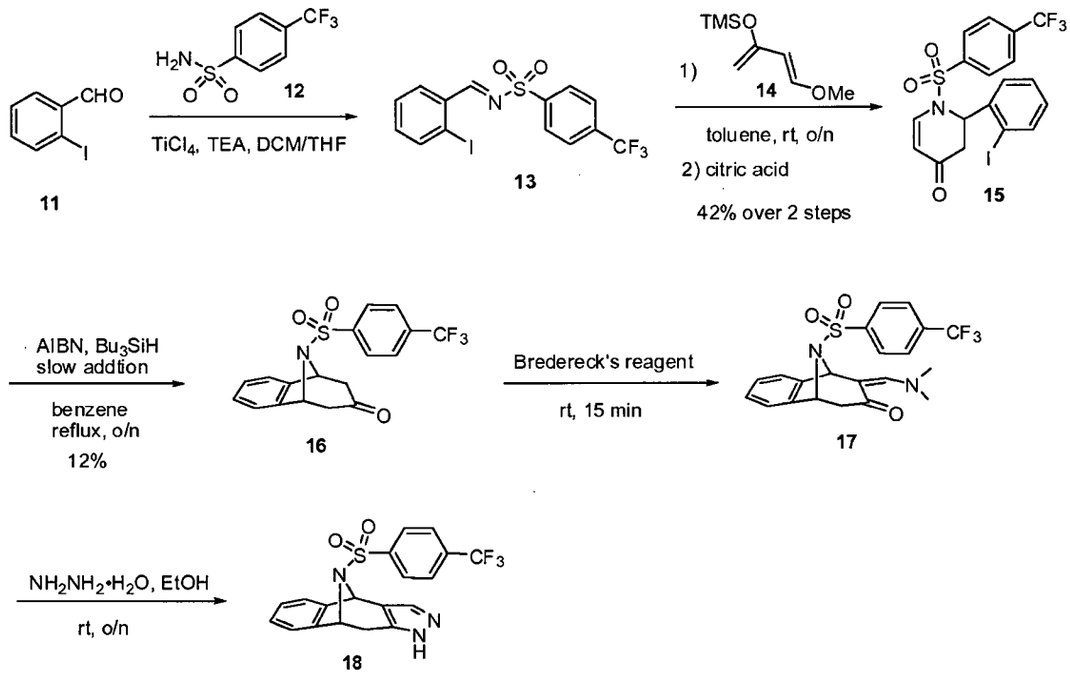
[12-(4-Chloro-benzenesulfonyl)-4,5,12-triaza-tricyclo[6.3.1.$0_{2,6}$]dodeca-2,5-dien-10-yl]-methanol (10)



Lithium borohydride (17 mg, 0.80 mmol) was added to a solution of 12-(4-chloro-benzenesulfonyl)-4,5,12-triaza-tricyclo[6.3.1.$0_{2,6}$]dodeca-2(6),3-diene-10-carboxylic acid ethyl ester (**8**) (328 mg, 0.80 mmol) in THF (3 mL). The resulting solution was stirred at room temperature for 18 h then heated to 60 °C for 2 h. The reaction was quenched by the addition of water (5 mL) and the resulting mixture was extracted with EtOAc (3 × 5 mL). The combined organic phases were dried (Na_2SO_4), filtered, concentrated and purified by silica gel column chromatography (eluant hexane/EtOAc, 9/1 to 1/1) and preparative HPLC to give [12-(4-chloro-benzenesulfonyl)-4,5,12-triaza-tricyclo[6.3.1.$0_{2,6}$]dodeca-2,5-dien-10-yl]-methanol (**10**) as a white solid. Retention time (min) = 1.242, method [1], MS(ESI) 368.0 (M+H); ^{1}H NMR ($CDCl_3$) δ 7.73 (d, J = 8.2 Hz, 2H), 7.58 (s, 1H), 7.38 (d, J = 8.2 Hz, 2H), 5.33 (s, 1H), 4.48 (d, J = 7.1 Hz, 1H), 3.41 (d, J = 2.7 Hz, 2H), 3.08 (dd, J = 17.6, 7.7 Hz, 1H), 2.62 (d, J = 17.6 Hz, 1H), 1.81-1.54 (m, 5H).

Example 8

Synthesis of (11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazole) (18)



8.1. (*E*)-*N*-(2-Iodobenzylidene)-4-(trifluoromethyl)benzene-sulfonamide (13)

To the mixture of 2-iodobenzaldehyde (**11**) (12.3 g, 53 mmol) and 4-trifluoromethylbenzenesulfonamide (**12**) (12.15 g, 54 mmol) in CH_2Cl_2 (110 mL) and THF (27 mL) was added triethylamine (22.5 mL) and titanium(IV) chloride (3 mL) at 0 °C. After stirring at 0 °C for 2h, the solid was separated via Celite filtration. The filtrate was

concentrated under reduced pressure to dryness, triturated with toluene to give 27 g of a yellow solid as the crude product (**3**) which was used without further purification.

8.2. 2-(2-Iodophenyl)-1-(4-(trifluoromethyl)phenylsulfonyl)-2,3-dihydropyridin-4(1H)-one (15)

To the suspension of 27 g of (**3**) from step 1 in toluene (250 mL) was added Danishefsky's diene (**14**) (10 g) at room temperature. The suspension was stirred at room temperature (became clear in a few minutes) for 2 hours. 2 N citric acid (40 mL) was added and the mixture was stirred at room temperature overnight. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 50 mL). The organic layers were combined and concentrated under reduced pressure to give a reddish oil. After flash chromatography on silica gel, a sticky yellow gel was isolated as the product (**15**) (11g, 42% in two steps). ^{1}H NMR ($CDCl_3$) δ 7.98 (d, J = 8.1 Hz, 1H), 7.77-7.71 (m, 3H), 7.56 (d, J = 8.7 Hz, 2H), 6.84-6.77 (m, 3H), 5.81 (d, J = 8.1 Hz, 1H), 5.47 (d, J = 8.1 Hz, 1H), 3.04 (dd, J = 8.1, 16.5 Hz, 1H), 2.61 (d, J = 16.5 Hz, 1H).

8.3. (10-{[4-(Trifluoromethyl)phenyl]sulfonyl}-5,6,8,9-tetrahydro-7*H*-5,9-epiminobenzo[7]annulen-7-one) (16)

To a solution of compound **15** (1.65 g, 3.25 mmol) in benzene (300 mL) at 80 °C was added a solution of AIBN (105 mg, 20% mol) and tri(*n*-butyl)tin hydride (0.86 mL, 3.25 mmol) in benzene (20 mL) over a 2 hour period. The mixture was heated at reflux for 48 h. After evaporation of the solvent, the residue was purified via flash chromatography on silica gel to give a white solid as the product (**16**) (150 mg, 12%). ^{1}H NMR ($CDCl_3$) δ 7.66 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.0-6.9 (m, 4H), 5.25 (dd, J = 3.3 Hz, 2H), 3.14 (dd, J = 4.5, 16.8 Hz, 2H), 2.58 (d, J = 16 Hz, 2H).

8.4. (6-[(Dimethylamino)methylidene]-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-5,6,8,9-tetrahydro-7*H*-5,9-epiminobenzo[7]annulen-7-one) (17)

Compound **16** (15 mg, 0.04 mmol) was mixed with 0.3 mL of Bredereck's reagent and the mixture was stirred at room temperature for 30 min. The reaction was quenched with water (1 mL) and extracted with EtOAc. After evaporation of the solvent, the crude product was obtained as a yellow oil and used without further purification.

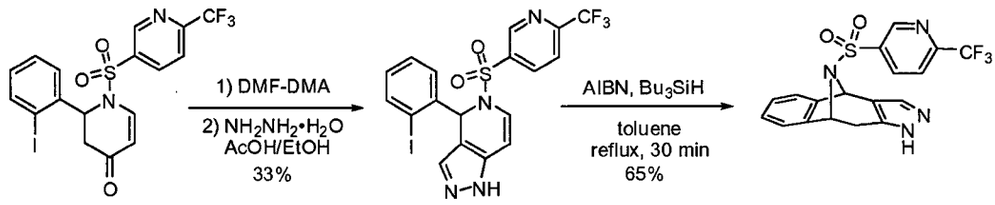
8.5. (11-{[4-(Trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazole) (18)

Compound **17** was dissolved in EtOH (0.5 mL) and hydrazine monohydrate (6 L) was then added. The mixture was stirred at room temperature overnight. Solvent was removed under

reduced pressure and the crude product was purified by HPLC to give a white solid as the pure product (**18**) (8 mg, 50% in two steps). ^{1}H NMR ($CDCl_3$) δ 7.71 (d, J = 8.7 Hz, 2H), 7.45 (d, J = 8.7 Hz, 2H), 7.07-7.04 (m, 1H), 6.99-6.93 (m, 3H), 5.83 (s, 1H), 5.38 (d, J = 5.1 Hz, 1H), 3.53 (dd, J = 5.1, 16.2 Hz, 1H), 2.85 (d, J = 16.2 Hz, 1H).

Example 9

Synthesis of (11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazole) (21)



9.1. (4-(2-Iodophenyl)-5-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]pyridine) (20)

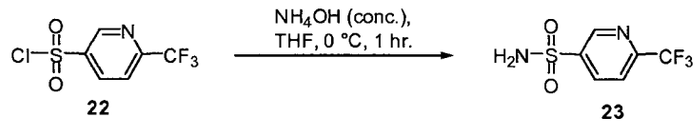
Compound **19** (200 mg, 0.39 mmol), similarly prepared as described for compound **15** in Example 8 using compound **23** in place of compound **12**, was mixed with DMF-DMA complex (1.7 mL) and the mixture was heated at 75 °C for 30 min. After evaporation of the excess DMF-DMA, the residue was dissolved in AcOH/EtOH (2 mL, 1:1) and hydrazine monohydrate (0.11 mL) was added. The mixture was stirred at room temperature for 2 hours and concentrated under reduced pressure to dryness. The crude product was purified by flash chromatography on silica gel to give a white solid as the pure product (**20**) (69 mg, 33%). ^{1}H NMR ($CDCl_3$) δ 8.95 (d, J = 2.4 Hz, 1H), 8.06 (dd, J = 2.1, 8.1 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.50 (s, 1H), 7.20 (dd, J = 1.8, 7.8 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 6.96 (t, J = 7.8 Hz, 1H), 6.84-6.79 (m, 2H), 6.09 (d, J = 8.1 Hz, 1H).

9.2. (11-{[6-(Trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazole) (21)

Compound **20** (62 mg, 0.12 mmol) was dissolved in toluene (10 mL) and treated with AIBN (8 mg) and Bu_3SnH (55 μL) sequentially at 120 °C. The mixture was stirred at 120 °C for 30 minutes. After evaporation of the solvent, the residue was purified by flash chromatography on silica gel to give a white solid as the pure product (**21**) (31 mg, 65%). ^{1}H NMR ($CDCl_3$) δ 8.86 (d, J = 1.5 Hz, 1H), 8.01 (dd, J = 1.5, 7.5 Hz, 1H), 7.44 (d, J = 8.1 Hz, 1H), 7.35 (s, 1H), 7.09-7.07 (m, 1H), 6.97-6.85 (m, 3H), 5.86 (s, 1H), 5.38 (d, J = 5.4 Hz, 1H), 3.45 (dd, J = 5.4, 16.5 Hz, 1H), 2.84 (d, J = 16.5 Hz, 1H).

Example 10

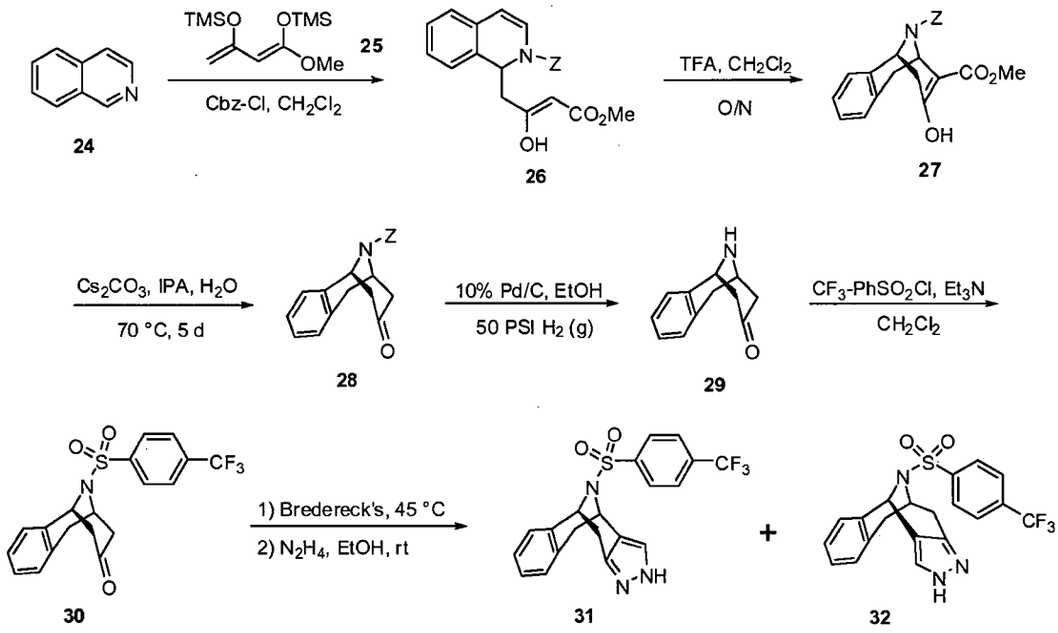
Synthesis of 6-(trifluoromethyl)pyridine-3-sulfonamide (23)



A two neck, 2L round bottom flask, containing a magnetic stirbar and fitted with an addition funnel was charged with concentrated aqueous ammonium hydroxide (600 mL). The solution was cooled to 0_oC. The sulfonyl chloride, **22**, (54.4 g, 221 mmol) was dissolved in THF (300 mL) and placed in the addition funnel. The sulfonyl chloride solution was added to the cold ammonium hydroxide solution at 0 °C over 15-20 minutes. The reaction was stirred at 0 °C for 1 hr. The reaction solution was partially concentrated under vacuum with a cold water bath to provide temperature regulation of the evaporation flask during 3 hours. *(Attention – the excess ammonia is evaporated under vacuum and on large scale the vapor should be trapped by bubbling the rotary evaporator exhaust through an aqueous acid solution.)* Once the reaction solution volume was reduced to approximately half the starting volume, a white solid formed in the aqueous solution. The slurry was extracted with EtOAc (500 mL) and the organic solution was washed with bicarbonate solution ($NaHCO_3$ aq., 300 mL) and brine (300 mL). The organic solution was dried over $MgSO_4$, filtered through a small pad of basic alumina (200 mL), and concentrated under vacuum. The white solid was dried under vacuum over night to yield 43.9 g of compound **23** (194 mmol, 87.8% yield, m.p. 192-193 °C). ^{1}H NMR (DMSO-d_6) δ 9.16 (d, J =1.6 Hz, 1H), 8.48 (dd, J = 8.3, 1.6 Hz, 1H), 8.18 (d, J = 8.3 Hz, 1H), 7.88 (s, 2H).

Example 11

Synthesis of 12-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,10,11-tetrahydro-2*H*-4,10-epiminobenzo[5,6]cycloocta[1,2-*c*]pyrazole (31) and 12-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,11-tetrahydro-2*H*-5,11-epiminobenzo[4,5]cycloocta[1,2-*c*]pyrazole (32)



11.1. Benzyl 1-(4-methoxy-2,4-dioxobutyl)isoquinoline-2(1*H*)-carboxylate (26)

To the mixture of isoquinoline (**24**) (2.05 g, 15.9 mmol) in 150 mL of CH_2Cl_2 at 0 °C was added (*Z*)-4-methoxy-2,2,8,8-tetramethyl-6-methylene-3,7-dioxa-2,8-disilanon-4-ene (**25**) (8.29 g, 31.8 mmol), followed by benzyl chloroformate (2.7 mL, 19.1 mmol). After stirring at room temperature overnight, 100 mL of NH_4Cl (aq) was added to the mixture. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were dried over Na_2SO_4. After the desiccant was filtered off, the organic extracts were concentrated under reduced pressure to provide (**26**) as a yellow oil (6.73 g). ^{1}H NMR indicated about a 1:2 ratio of keto:enol tautomers. This crude oil was used in the next reaction without further purification.

11.2. 11-Benzyl 8-methyl-7-hydroxy-5,6,9,10-tetrahydro-5,9-epiminobenzo[8]annulene-8,11-dicarboxylate (27)

To a mixture of ester (**26**) (6.73 g, 17.7 mmol) in 60 mL of CH_2Cl_2 at room temperature was added trifluoroacetic acid (2.6 mL, 35.5 mmol). This mixture was stirred at room temperature overnight. Additional trifluoroacetic acid (2.6 mL, 35.5 mmol) was added and the mixture for stirred overnight at room temperature. To this mixture were carefully added

40 mL of sat. $NaHCO_3$ (aq). After the effervescence had subsided, the layers were separated; and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried over Na_2SO_4. After the desiccant was filtered off, the organic extracts were concentrated under reduced pressure to provide (**27**) as a yellow liquid (2.79 g). This crude liquid was used in the next reaction without further purification.

11.3. Benzyl-7-oxo-5,6,7,8,9,10-hexahydro-5,9-epiminobenzo[8]annulene-11-carboxylate (28)

To a mixture of ester (**27**) (2.79 mg, 7.35 mmol) in 60 mL of isopropanol and 20 mL of water was added Cs_2CO_3 (47.9 g, 147 mmol) The slurry was heated at 90 °C for 20 h. Additional Cs_2CO_3 (47.9 g, 147 mmol) was added and the mixture was stirred at 90 °C for 20 h. Additional Cs_2CO_3 (47.9 g, 147 mmol) was added and the mixture was stirred at 90 °C for another two days. The mixture was carefully quenched with 100 mL of 6 N HCl. The aqueous solution was extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with 10% NaCl (aq) (250 mL) and dried over Na_2SO_4. After the desiccant was filtered off, the organic extracts were concentrated under reduced pressure to provide a crude oil. After flash chromatography on silica gel, a thick light yellow oil (**28**) (1.13 g) was obtained.

11.4. 5,8,9,10-Tetrahydro-5,9-epiminobenzo[8]annulen-7(6*H*)-one (29)

To a mixture of carbamate (**28**) (1.13 g) in 100 mL of MeOH in a Parr bottle was added 500 mg of 10% Pd/C. This slurry was shaken under 50 psi of H_2 (g) at room temperature overnight. The mixture was filtered through a pad of Celite and rinsed with CH_2Cl_2 (2 x 100 mL). The solution was concentrated to a crude yellow oil (**29**) (130 mg) and used in the next reaction without further purification.

11.5. 11-{[4-(Trifluoromethyl)phenyl]sulfonyl}-5,8,9,10-tetrahydro-5,9-epiminobenzo[8]annulen-7(6*H*)-one (30)

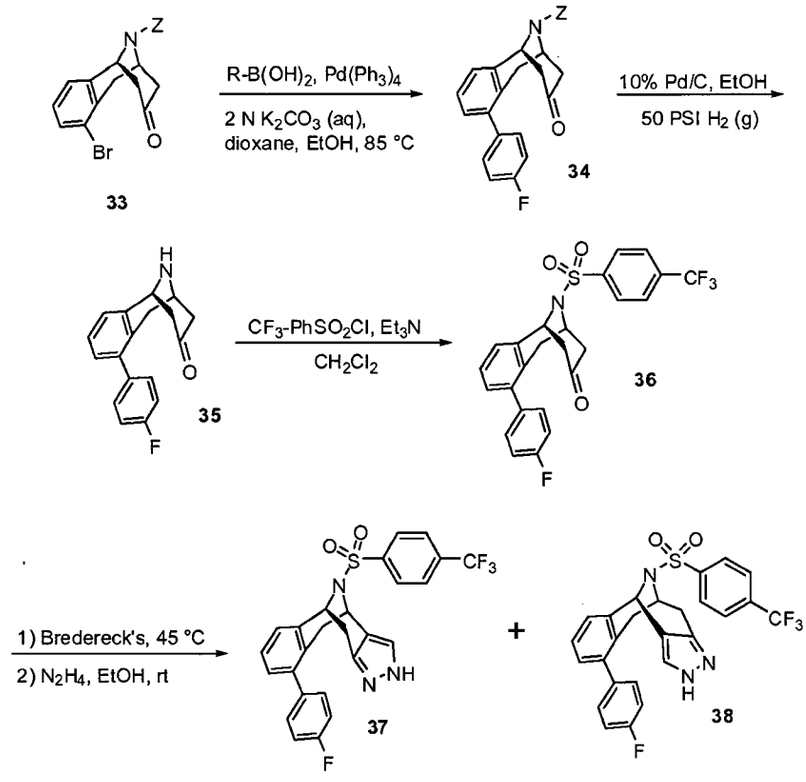
To a mixture of amine (130 mg, 0.69 mmol) (**29**) in 7 mL of CH_2Cl_2 at room temperature was added triethylamine (0.2 mL), followed by 4-trifluoromethylbenzenesulfonyl chloride (204 mg, 0.83 mmol). This mixture was stirred at room temperature overnight. The mixture was concentrated under reduced pressure to a crude oil. After flash chromatography on silica gel, a white solid (**30**) (290 mg) was obtained.

11.6. 12-{[4-(Trifluoromethyl)phenyl]sulfonyl}-4,5,10,11-tetrahydro-2*H*-4,10-epiminobenzo[5,6]cycloocta[1,2-*c*]pyrazole (31) and 12-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,11-tetrahydro-2*H*-5,11-epiminobenzo[4,5]cycloocta[1,2-*c*]pyrazole (32)

To ketone **30** (290 mg, 0.73 mmol) was added *tert*-butoxybis(dimethylamino)methane (2.56 g, 14.67 mmol). This mixture was heated at 45 °C for 1 h. The mixture was diluted with 50 mL of H_2O and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4. After the desiccant was filtered off, the organic extracts were concentrated under reduced pressure to provide a crude oil. This crude oil was suspended in 7 mL of EtOH. To this solution was added hydrazine hydrate (73.4 mg, 1.47 mmol). This mixture was stirred at room temperature overnight. The mixture was diluted with water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with 10% NaCl (aq) (100 mL) and dried over Na_2SO_4. After the desiccant was filtered off, the organic extracts were concentrated under reduced pressure to provide a crude oil. After flash chromatography on silica gel, a yellow solid (**31**) (32.1 mg) ^{1}H NMR ($CDCl_3$) δ 7.90 (d, J = 8.1 Hz, 2H), 7.64 (d, J = 8.2 Hz, 2H), 7.40 (s, 1H), 7.19-7.09 (m, 3H), 6.93 (d, J = 7.7 Hz, 1H), 5.53 (d, J = 5.3 Hz, 1H), 5.49 (d, J = 5.2 Hz, 1H), 3.32 (dd, J = 16.5, 6.1 Hz, 1H), 3.16 (dd, J = 15.9, 5.7 Hz, 1H), 2.85 (d, J = 16.3 Hz, 1H), 2.73 (d, J = 16.4 Hz, 1H); and a yellow solid (**32**) (35.8 mg) ^{1}H NMR ($CDCl_3$) δ 7.62 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.3 Hz, 2H), 7.33 (s, 1H), 7.15 (d, J = 7.4 Hz, 1H), 7.06 (d, J = 7.4 Hz, 1H), 6.95 (dt, J = 1.5, 7.5 Hz, 1H), 6.59 (d, J = 7.6 Hz, 1H), 6.01 (s, 1H), 4.88-4.84 (m, 1H), 3.24 (dd, J = 16.1, 6.1 Hz, 1H), 3.08 (d, J = 17.9, 9.6 Hz, 1H), 2.75 (dd, J = 17.3, 1.1 Hz, 1H); 2.46 (d, J = 17.9 Hz, 1H) were obtained.

Example 12

Synthesis of 6-(4-fluorophenyl)-12-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,10,11-tetrahydro-2*H*-4,10-epiminobenzo[5,6]cycloocta[1,2-*c*]pyrazole (37) and 7-(4-fluorophenyl)-12-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,11-tetrahydro-2*H*-5,11-epiminobenzo[4,5]cycloocta[1,2-*c*]pyrazole (38)



12.1 Benzyl-1-(4-fluorophenyl)-7-oxo-5,6,7,8,9,10-hexahydro-5,9-epiminobenzo[8]annulene-11-carboxylate (34)

To a mixture of ketone **33** (243 mg, 0.61 mmol), prepared as described for compound **28** in Example 11 using 5-bromoisoquinoline, in 2M K_2CO_3 (aq) (6 mL), dioxane (6 mL), and EtOH (1.2 mL) was added 4-fluorophenyl boronic acid (102 mg, 0.73 mmol), followed by palladium tetrakis(triphenylphosphine) (35 mg, 0.03 mmol). This mixture was stirred at 85 °C overnight. The mixture was filtered through a pad of Celite and rinsed with EtOAc (20 mL). The solution was diluted with 30 mL of H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with 10% NaCl (aq) (150 mL) and dried over Na_2SO_4. After the desiccant was filtered off, the organic extracts were concentrated under reduced pressure to provide a crude oil. After flash chromatography on silica gel, a yellow foam (**34**) (148 mg) was obtained.

12.2. 1-(4-Fluorophenyl)-5,8,9,10-tetrahydro-5,9-epiminobenzo[8]annulen-7(6*H*)-one (35)

To a mixture of carbamate (**34**) (144 mg) in 100 mL of MeOH in a Parr bottle was added 35 mg of 10% Pd/C. This slurry was shaken under 50 psi of H_2 (gas) at room temperature overnight. The mixture was filtered through a pad of Celite and rinsed with CH_2Cl_2 (2 x 100 mL). The solution was concentrated to a crude yellow oil (**35**) (110 mg) and used in the next reaction without further purification.

12.3. (5*S*)-1-(4-Fluorophenyl)-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-5,8,9,10-tetrahydro-5,9-epiminobenzo[8]annulen-7(6*H*)-one (36)

To a mixture of crude amine (110 mg) (**35**) in 4 mL of CH_2Cl_2 at room temperature was added triethylamine (0.1 mL) followed by 4-trifluoromethylbenzenesulfonyl chloride (101 mg, 0.42 mmol). This mixture was stirred at room temperature overnight. The mixture was concentrated under reduced pressure to a crude oil. After flash chromatography on silica gel, a white waxy solid (**36**) (119 mg) was obtained.

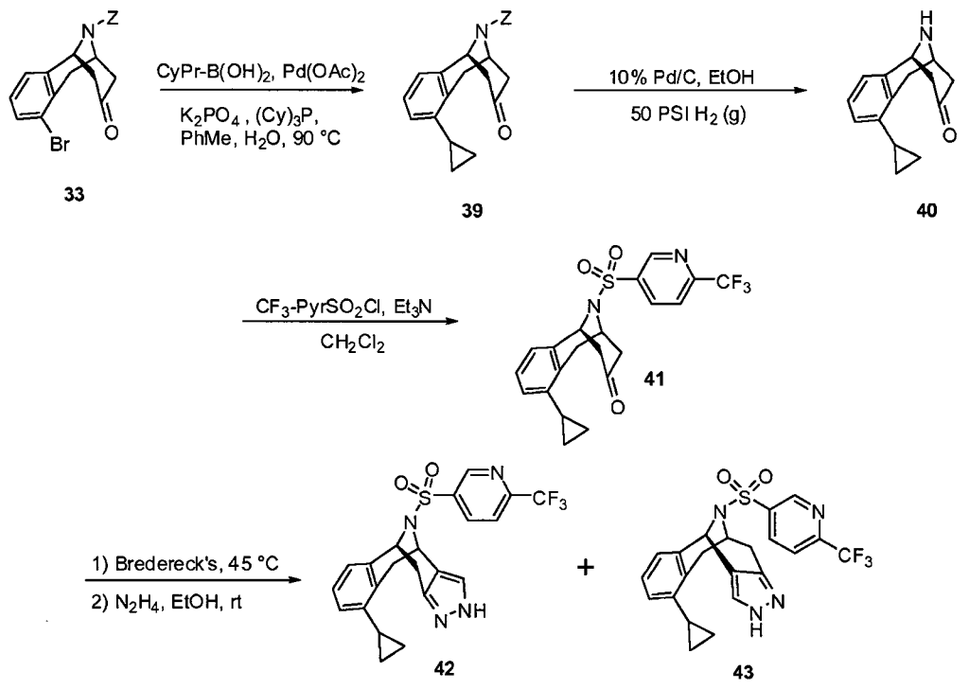
12.4. 6-(4-Fluorophenyl)-12-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,10,11-tetrahydro-2*H*-4,10-epiminobenzo[5,6]cycloocta[1,2-*c*]pyrazole (37) and 7-(4-fluorophenyl)-12-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,11-tetrahydro-2*H*-5,11-epiminobenzo[4,5]cycloocta[1,2-*c*]pyrazole (38)

To ketone (119 mg, 0.24 mmol) (**36**) was added *tert*-butoxybis(dimethylamino)methane (1 mL, 4.86 mmol). This mixture was heated at 45 °C for 1 h. The mixture was diluted with 50 mL of H_2O and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4. After the desiccant was filtered off, the organic extracts were concentrated under reduced pressure to provide a crude oil. This crude oil was suspended in 2 mL of EtOH. To this solution was added hydrazine hydrate (24.3 mg, 0.49 mmol). This mixture was stirred at room temperature overnight. The mixture was diluted with water (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with 10% NaCl (aq) (100 mL) and dried over Na_2SO_4. After the desiccant was filtered off, the organic extracts were concentrated under reduced pressure to provide a crude oil. After flash chromatography on silica gel, a yellow solid (**37**) (19.8 mg) ^{1}H NMR ($CDCl_3$) δ 7.90 (d, J = 8.2 Hz, 2H), 7.65 (d, J = 8.2 Hz, 2H), 7.30 (s, 1H), 7.25-7.18 (m, 2H), 7.08-6.93 (m, 5H), 5.59 (d, J = 5.3 Hz, 1H), 5.44 (d, J = 5.5 Hz, 1H), 3.20 (dd, J = 5.7, 16.0 Hz, 1H), 3.04 (dd, J = 5.4, 16.3 Hz, 1H), 2.92 (d, J = 16.8 Hz, 1H), 2.42 (d, J = 15.7 Hz, 1H); and a yellow solid (**38**) (16.4 mg) ^{1}H NMR ($CDCl_3$) δ 7.61 (d, J = 7.9 Hz, 2H), 7.46 (d, J = 8.3 Hz, 2H), 7.41 (s,

1H), 7.25 (dd, J = 1.2, 7.6 Hz, 1H), 7.17 (t, J = 7.4 Hz,1H), 7.02 (t, J = 8.7 Hz, 2H), 6.89 (dd, J = 1.4, 7.5 Hz, 1H), 6.83-6.79 (m, 2H), 6.12 (s, 1H), 4.77-4.72 (m, 1H), 3.26 (dd, J = 5.6, 15.9 Hz, 1H), 2.87-2.81 (m, 1H), 2.75 (d, J = 16.9 Hz, 1H), 2.28 (d, J = 18.6 Hz, 1H) were obtained.

Example 13

Synthesis of 6-cyclopropyl-12-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,10,11-tetrahydro-2*H*-4,10-epiminobenzo[5,6]cycloocta[1,2-*c*]pyrazole (42) and 7-cyclopropyl-12-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,11-tetrahydro-2*H*-5,11-epiminobenzo[4,5]cycloocta[1,2-*c*]pyrazole (43)



13.1. Benzyl 1-cyclopropyl-7-oxo-5,6,7,8,9,10-hexahydro-5,9-epiminobenzo[8]annulene-11-carboxylate (39)

To a mixture of ketone (**33**) (400 mg, 1 mmol) in toluene (4.5 mL), and H_2O (0.2 mL) was added cyclopropylboronic acid (112 mg, 1.3 mmol), potassium phosphate (743 mg, 3.5 mmol), tricyclohexylphosphine (28 mg, 0.1 mmol), and palladium acetate (11 mg, 0.05 mmol). This mixture was stirred at 90 °C overnight. The mixture was filtered through a pad of Celite and rinsed with EtOAc (20 mL). The solution was diluted with 30 mL of H_2O, and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with 10% NaCl (aq) (150 mL) and dried over Na_2SO_4. After the desiccant was filtered off, the organic extracts were concentrated under

reduced pressure to provide a crude oil. After flash chromatography on silica gel, a yellow oil (**39**) (330 mg) was obtained.

13.2. 1-Cyclopropyl-5,8,9,10-tetrahydro-5,9-epiminobenzo[8]annulen-7(6*H*)-one (40)

To a mixture of carbamate (**39**) (330 mg) in 100 mL of MeOH in a Parr bottle was added 50 mg of 10% Pd/C. This slurry was shaken under 50 psi of H_2 (gas) at room temperature overnight. The mixture was filtered through a pad of Celite and rinsed with CH_2Cl_2 (2 x 100 mL). The solution was concentrated to a crude tan solid (**40**) (192 mg) and used in the next reaction without further purification.

13.3. 1-Cyclopropyl-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-5,8,9,10-tetrahydro-5,9-epiminobenzo[8]annulen-7(6*H*)-one (41)

To a mixture of crude amine (192 mg) (**40**) in 8 mL of CH_2Cl_2 at room temperature was added triethylamine (0.23 mL), followed by 6-(trifluoromethyl)pyridine-3-sulfonyl chloride (244 mg, 0.99 mmol). This mixture was stirred at room temperature overnight. The mixture was concentrated under reduced pressure. After flash chromatography on silica gel, a white solid (**41**) (281 mg) was obtained.

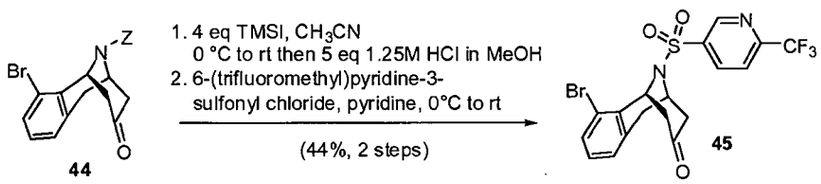
13.4. 6-Cyclopropyl-12-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,10,11-tetrahydro-2*H*-4,10-epiminobenzo[5,6]cycloocta[1,2-*c*]pyrazole (42) and 7-Cyclopropyl-12-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,11-tetrahydro-2*H*-5,11-epiminobenzo[4,5]cycloocta[1,2-*c*]pyrazole (43)

To ketone (278 mg, 0.64 mmol) (**41**) was added *tert*-butoxybis(dimethylamino)methane (2.22 g, 12.74 mmol). This mixture was heated at 45 °C for 1.5 h. The mixture was diluted with 50 mL of H_2O and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4. After the dessicant was filtered off, the organic extracts were concentrated under reduced pressure to provide a crude oil. This crude oil was resuspended in 6 mL of EtOH. To this solution was added hydrazine-hydrate (61 mg, 1.22 mmol). This mixture was stirred at room temperature overnight. The mixture was diluted with water (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with 10% NaCl (aq) (100 mL) and dried over Na_2SO_4. After the desiccant was filtered off, the organic extracts were concentrated under reduced pressure to provide a crude oil. After HPLC, a white solid (**42**) (17.9 mg) ^{1}H NMR ($CDCl_3$) δ 9.07 (d, J = 2.0 Hz, 1H), 8.20 (dd, J = 1.9, 8.2 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.54 (s, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.02 (d, J = 7.5 Hz, 1H), 6.88 (d, J = 7.6 Hz, 1H), 5.64 (d, J = 5.7 Hz, 1H), 5.53 (d, J = 5.1 Hz, 1H), 3.35 (dd, J = 6.3, 16.5 Hz, 1H), 3.16 (dd, J = 5.8, 17 Hz, 1H), 3.00 (d, J = 11.1 Hz, 1H), 2.94 (d, J

= 11.4 Hz, 1H); 1.58-1.49 (m, 1H); 0.91-0.77 (m, 2H); 0.51-0.35 (m, 2H); and a white solid (**43**) (23.8 mg) ^{1}H NMR ($CDCl_3$) δ 8.88 (d, J = 1.9 Hz, 1H), 7.87 (dd, J = 1.9, 8.2 Hz, 1H), 7.50 (s, 1H), 7.38 (d, J = 8.2 Hz, 1H), 7.06 (t, J = 4.4 Hz, 1H), 6.76-6.71 (m, 1H), 6.06 (s, 1H), 5.05-5.00 (m, 1H), 3.42 (dd, J = 5.6, 16.5 Hz, 1H), 3.30 (dd, J = 9.9, 18.5 Hz, 1H), 2.95 (d, J = 16.5 Hz, 1H), 2.38 (d, J = 18.6 Hz, 1H); 1.32-1.23 (m, 1H); 0.84-0.72 (m, 2H), 0.46-0.37 (m, 1H), 0.30-0.24 (m, 1H) were obtained.

Example 14

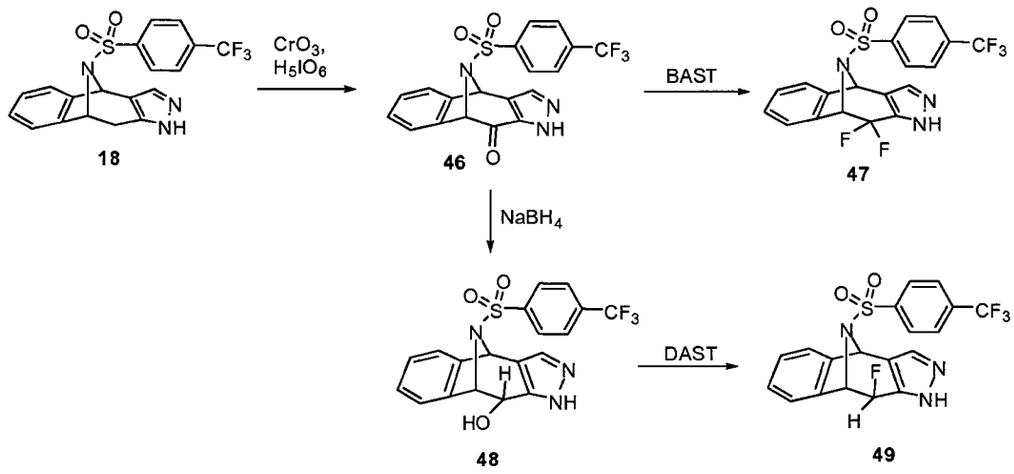
Synthesis of 4-bromo-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-5,8,9,10-tetrahydro-5,9-epiminobenzo[8]annulen-7(6*H*)-one (45)



To an ice chilled solution of ketone **44** (706 mg, 1.76 mmol), prepared as described for compound **28** in Example 11 using 8-bromoisoquinoline, in acetonitrile (17 mL) was added TMSI (960 μL, 7.05 mmol). The reaction mixture was allowed to warm to room temperature over two hours at which time LC/MC analysis determined no starting material remained. The reaction mixture was chilled to 0 °C and treated with 1.25 M HCl in MeOH (7 ml, 8.80 mmol) and allowed to warm to room temperature over 1.5 hours. Concentration yielded 530 mg of a thick brown residue which was dissolved in pyridine (9 mL), chilled to 0 °C, and treated with 6-(trifluoromethyl)pyridine-3-sulfonyl chloride (1.07g, 4.37 mmol). After stirring over night at room temperature, LC/MS analysis revealed the presence of starting material so the reaction mixture was treated with 6-(trifluoromethyl)pyridine-3-sulfonyl chloride (644 mg, 2.65 mmol) and stirred at room temperature for five days. The reaction mixture was then diluted with EtOAc and water (20 mL each). The organic portion was washed with 0.2 N citric acid (6 x 35 mL), water (1 x 20 mL), 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 silica gel chromatography to yield 366 mg (44%) of compound **45**. ^{1}H NMR ($CDCl_3$) δ 9.05 (d, J = 2.1 Hz, 1H), 8.16 (dd, J = 8.0,1.0 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.39 (d, J = 8.4 Hz), 6.97 (t, J = 7.8 Hz, 1H), 6.77 (d, J = 7.2 Hz, 1H), 5.79 - 5.75 (m, 1H), 4.98 (t, J = 7.8 Hz, 1H), 3.07-2.93 (m, 3H), 2.78-2.64 (m, 2H), 2.46 (d, J = 15.0 Hz, 1H).

Example 15

Synthesis of 10-fluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazole (49)



15.1. 11-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazol-10(1*H*)-one (46)

To a solution of periodic acid (532 mg, 2.33 mmol) in acetonitrile (6 mL) was added chromium(VI) oxide (9 mg, 0.09 mmol). After stirring for 5 minutes, compound **18** (200 mg, 0.49 mmol) in acetonitrile (6 mL) was added. The resulting solution was stirred at room temperature overnight. TLC analysis (1:1 EtOAc: hexanes) and LC/MS indicated completion of reaction. The reaction was then quenched with water (20 mL) and extracted with CH_2Cl_2 (30 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. Purification by flash chromatography over silica gel, eluting with 0 to 60% EtOAc in hexanes, gave the title compound (162 mg, 78% yield). ^{1}H NMR ($CDCl_3$) δ 7.77 (d, J = 8.3 Hz, 2H), 7.62 (s, 1H), 7.53 (d, J = 8.3 Hz, 2H), 7.25-7.28 (m, 1H), 7.11-7.02 (m, 3H), 6.18 (s, 1H), 5.44 (s, 1H).

15.2. 10,10-difluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazole (47)

Compound **46** (36 mg, 0.09 mmol) was dissolved in bis(2-methoxyethyl)aminosulfur trifluoride (BAST) (0.5 mL) and heated at 80 °C for 30 minutes. LC/MS showed no starting material. The reaction mixture was cooled to room temperature and added dropwise to a cold saturated aqueous sodium bicarbonate solution. After stirring for 10 minutes, the mixture was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. Purification by preparative HPLC gave the title compound (12 mg, 25% yield) as a TFA salt. ^{1}H NMR ($CDCl_3$) δ 7.79 (d, 2H, J = 8.2 Hz), 7.52 (d, 2H,

J = 8.3 Hz), 7.45 (s, 1H), 7.25-7.29 (m, 1H), 6.94-7.06 (m, 3H), 6.00 (s, 1H), 5.47 (d, 1H, J = 10.6 Hz).

15.3. 11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazol-10-ol (48)

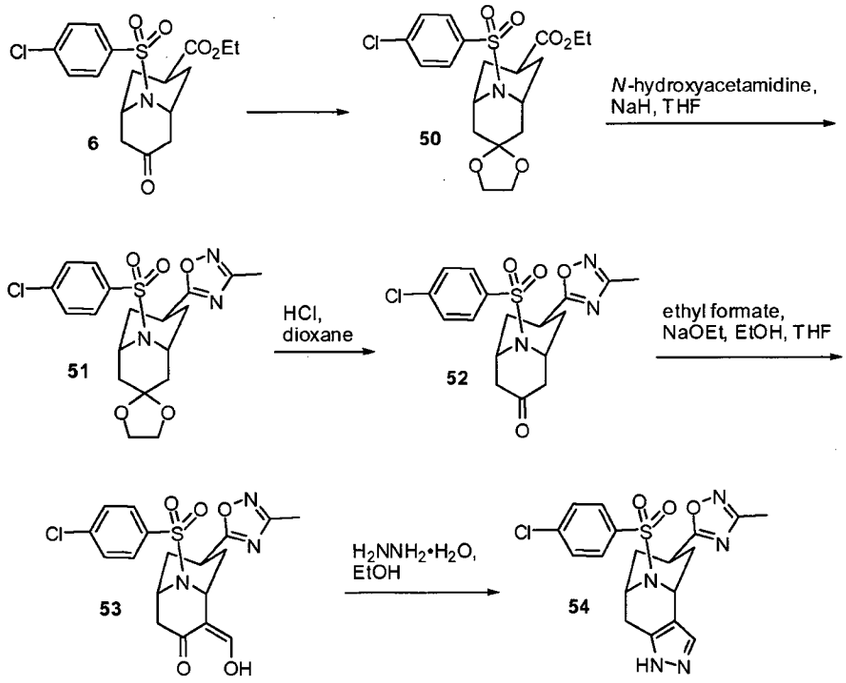
To a suspension of compound **46** (158 mg, 0.38 mmol) in MeOH (7 mL) was added sodium borohydride (29 mg, 0.75 mmol). The mixture was stirred at room temperature for 30 minutes. TLC analysis (1:1 EtOAc: hexanes) indicated completion of reaction. The reaction was then quenched with water (20 mL) and extracted with CH_2Cl_2 (30 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. Purification by flash chromatography over silica gel, eluting with 0 to 80% EtOAc in hexanes, gave the title compound (137 mg, 86% yield). ^{1}H NMR ($CDCl_3$) δ 7.82 (d, J = 8.3 Hz, 2H), 7.53 (d, J = 8.3 Hz, 2H), 7.48 (s, 1H), 7.10-7.07 (m, 1H), 6.93-6.86 (m, 3H), 5.91 (s, 1H), 5.30-5.23 (m, 2H).

15.4. 10-fluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazole (49)

To a solution of (diethylamino)sulfur trifluoride (DAST) (14 mg, 0.09 mmol) in CH_2Cl_2 (4 mL) at -78 °C was added a solution of compound **48** (21 mg, 0.05 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at this temperature for 6h, at 4h more DAST (14 mg, 0.09 mmol) was added. The reaction was quenched with saturated aqueous sodium bicarbonate (10 mL) and extracted with CH_2Cl_2 (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. Purification by flash chromatography over silica gel, eluting with 0 to 70% EtOAc in hexanes, gave the title compound (8.5 mg, 40% yield). ^{1}H NMR ($CDCl_3$) δ 7.80 (d, J = 8.3 Hz, 2H), 7.49 (d, J = 8.3 Hz, 2H), 7.40 (s, 1H), 7.19-7.16 (m, 1H), 7.03-6.94 (m, 3H), 6.01 (s, 1H), 5.61-5.44 (m, 2H).

Example 16

Synthesis of 10-[(4-chlorophenyl)sulfonyl]-6-(3-methyl-1,2,4-oxadiazol-5-yl)-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole (54)



16.1. Ethyl 9-[(4-chlorophenyl)sulfonyl]spiro[9-azabicyclo[3.3.1]nonane-3,2'-[1,3]dioxolane]-7-carboxylate (50)

To a solution of 9-(4-chloro-benzenesulfonyl)-7-oxo-9-aza-bicyclo[3.3.1]nonane-3-carboxylic acid ethyl ester (**6**) (1.62 g, 4.19 mmol) in CH_2Cl_2 (14 mL) was added ethylene glycol (0.94 mL, 16.7 mmol) and TMSCl (1.06 mL, 8.39 mmol). The resulting solution was heated to reflux for 48 h and was subsequently washed with saturated aqueous $NaHCO_3$ (10 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated under vacuum to yield 1.62 g (90%) of compound **50**. MS(ESI) 430.1 (M+H).

16.2. 9-[(4-Chlorophenyl)sulfonyl]-7-(3-methyl-1,2,4-oxadiazol-5-yl)spiro[9-azabicyclo[3.3.1]nonane-3,2'-[1,3]dioxolane] (51)

Sodium hydride (60% dispersion, 43 mg, 1.09 mmol) was added to a solution of *N*-hydroxyacetamidine (81 mg, 1.09 mmol) in THF (2 mL) and the resulting mixture was stirred at 50 °C for 15 minutes. Ethyl 9-[(4-chlorophenyl)sulfonyl]spiro[9-azabicyclo[3.3.1]nonane-3,2'-[1,3]dioxolane]-7-carboxylate (**50**) (0.394 g, 0.916 mmol) in THF (2 mL) was added to the reaction mixture and the resulting solution was stirred at room temperature for 1 hour. The mixture was diluted with EtOAc and washed with H_2O. The organic phase was dried

(Na_2SO_4), filtered and concentrated under vacuum to yield 0.40 g (quant.) of compound **51**. MS(ESI) 440.1 (M+H).

16.3. 9-[(4-Chlorophenyl)sulfonyl]-7-(3-methyl-1,2,4-oxadiazol-5-yl)-9-azabicyclo[3.3.1]nonan-3-one (52)

9-[(4-Chlorophenyl)sulfonyl]-7-(3-methyl-1,2,4-oxadiazol-5-yl)spiro[9-azabicyclo[3.3.1]nonane-3,2'-[1,3]dioxolane] (**51**) (0.40 g, 0.916 mmol) was covered with HCl in dioxane (4 N, 2 mL). The reaction mixture was stirred at room temperature for 2 h after which it was diluted with EtOAc and washed with aqueous sodium hydroxide (1 N). The organic phase was dried (Na_2SO_4), filtered and concentrated under vacuum to yield 0.36 g (quant.) of 9-[(4-chlorophenyl)sulfonyl]-7-(3-methyl-1,2,4-oxadiazol-5-yl)-9-azabicyclo[3.3.1]nonan-3-one (**52**). MS(ESI) 396.1 (M+H).

16.4. 9-[(4-Chlorophenyl)sulfonyl]-2-(hydroxymethylidene)-7-(3-methyl-1,2,4-oxadiazol-5-yl)-9-azabicyclo[3.3.1]nonan-3-one (53)

9-[(4-Chlorophenyl)sulfonyl]-7-(3-methyl-1,2,4-oxadiazol-5-yl)-9-azabicyclo[3.3.1]nonan-3-one (**52**) (0.357 g, 0.902 mmol) was dissolved in THF/EtOH (2 mL, 1/1, v/v). Ethyl formate (0.725 mL, 9.02 mmol) was added followed by sodium ethoxide (1.01 mL of 21% solution in EtOH). The resulting mixture was stirred at 50 °C for 1 hour after which the solution was cooled back to room temperature and quenched by the addition of saturated aqueous NH_4Cl. The resulting mixture was extracted with EtOAc and the combined organic phases were dried (Na_2SO_4), filtered and concentrated under vacuum to give 9-[(4-chlorophenyl)sulfonyl]-2-(hydroxymethylidene)-7-(3-methyl-1,2,4-oxadiazol-5-yl)-9-azabicyclo[3.3.1]nonan-3-one (**53**). MS(ESI) 424.0 (M+H).

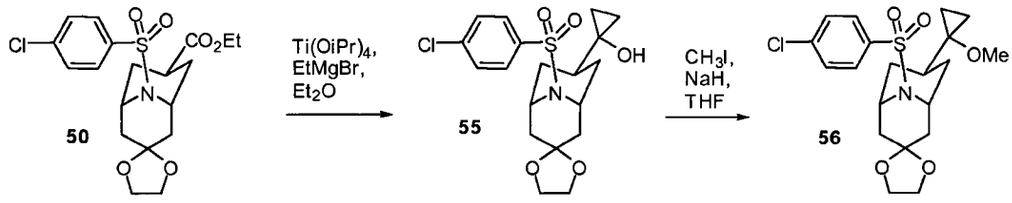
16.5. 10-[(4-Chlorophenyl)sulfonyl]-6-(3-methyl-1,2,4-oxadiazol-5-yl)-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole (54)

To a solution of 9-[(4-chlorophenyl)sulfonyl]-2-(hydroxymethylidene)-7-(3-methyl-1,2,4-oxadiazol-5-yl)-9-azabicyclo[3.3.1]nonan-3-one (**53**) (0.38 g, 0.902 mmol) in EtOH (5 mL) was added glacial acetic acid (0.1 mL) followed by hydrazine monohydrate (0.44 mL, 9.02 mmol). The reaction mixture was stirred at room temperature for 2 h and then at 50 °C for a further 2 h. The resulting solution was diluted with EtOAc and washed with H_2O. The organic phase was dried (Na_2SO_4), filtered, concentrated and purified by silica gel column chromatography (eluant hexane/EtOAc, 9/1 to 2/8) and preparative HPLC to give 10-[(4-chlorophenyl)sulfonyl]-6-(3-methyl-1,2,4-oxadiazol-5-yl)-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole (**54**). MS(ESI) 420.1 (M+H). ^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.67 (d, J = 8.8 Hz, 2H), 7.52 (s, 1H), 7.39 (d, J = 8.8 Hz, 2H), 5.43 (bs, 1H), 4.66 (bs, 1H), 3.06 (m, 1H), 2.72 (d, J = 17.6 Hz, 1H), 2.34 (s, 3H), 2.32-2.09 (m, 4H).

Example 17

Synthesis of 9-[(4-Chlorophenyl)sulfonyl]-7-(1-methoxycyclopropyl)spiro[9-azabicyclo[3.3.1]nonane-3,2'-[1,3]dioxolane] (56)



17.1. 1-{9-[(4-Chlorophenyl)sulfonyl]spiro[9-azabicyclo[3.3.1]nonane-3,2'-[1,3]dioxolan]-7-yl}cyclopropanol (55)

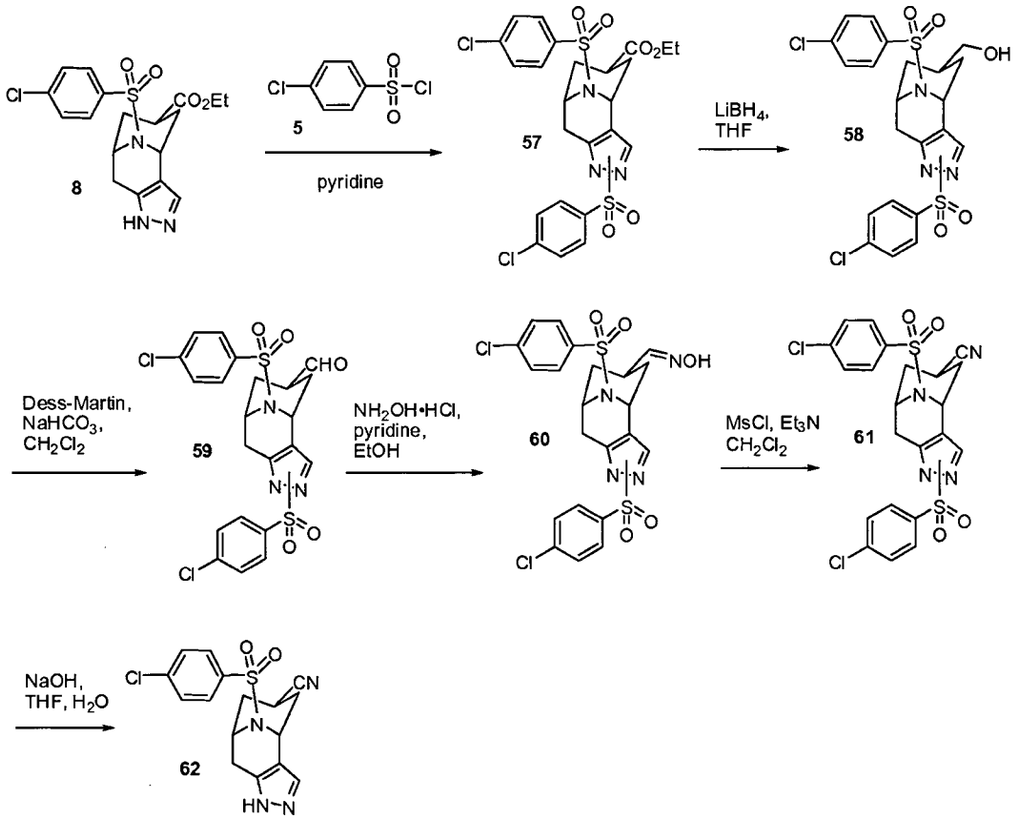
Ethyl 9-[(4-chlorophenyl)sulfonyl]spiro[9-azabicyclo[3.3.1]nonane-3,2'-[1,3]dioxolane]-7-carboxylate (**50**) (395 mg, 0.918 mmol) was dissolved in Et_2O (2 mL) and the resulting solution was cooled to -78 °C. Ti(O-*i*-Pr)$_4$ was added followed by EtMgBr dropwise over 10 minutes. The reaction mixture was warmed to room temperature and stirred for 18 h. The resulting solution was diluted with EtOAc and washed with saturated aqueous NH_4Cl. The organic phase was dried (Na_2SO_4), filtered, and concentrated to give 1-{9-[(4-chlorophenyl)sulfonyl]spiro[9-azabicyclo[3.3.1]nonane-3,2'-[1,3]dioxolan]-7-yl}cyclopropanol (**55**). MS(ESI) 414.1 (M+H).

17.2. 9-[(4-Chlorophenyl)sulfonyl]-7-(1-methoxycyclopropyl)spiro[9-azabicyclo[3.3.1]nonane-3,2'-[1,3]dioxolane] (56)

Sodium hydride (60% dispersion in mineral oil, 46 mg, 1.16 mol) was added to a solution of 1-{9-[(4-chlorophenyl)sulfonyl]spiro[9-azabicyclo[3.3.1]nonane-3,2'-[1,3]dioxolan]-7-yl}cyclopropanol (**55**) (321 mg, 0.775 mmol) in THF (2 mL). The resulting solution was stirred for 10 minutes, after which iodomethane (72 μL, 1.16 mmol) was added. The reaction mixture was stirred at room temperature for 18 h and was subsequently diluted with EtOAc and washed with brine. The organic phase was dried (Na_2SO_4), filtered, and concentrated to give 9-[(4-chlorophenyl)sulfonyl]-7-(1-methoxycyclopropyl)spiro[9-azabicyclo[3.3.1]nonane-3,2'-[1,3]dioxolane] (**56**). MS(ESI) 428.1 (M+H).

Example 18

Synthesis of 10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole-6-carbonitrile (62)



18.1. Ethyl 1,10-bis[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole-6-carboxylate and ethyl 2,10-bis[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-2*H*-4,8-epiminocycloocta[*c*]pyrazole-6-carboxylate (57)

4-Chlorobenzenesulfonyl chloride (0.315 g, 1.49 mmol) was added to a solution of ethyl 10-(4-chlorophenyl)sulfonyl-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole-6-carboxylate (**8**) (0.51 g, 1.24 mmol) in pyridine (5 mL) and the resulting mixture was stirred at room temperature for 1 h. The resulting solution was diluted with CH_2Cl_2 and washed with aqueous 1N HCl then saturated aqueous $NaHCO_3$. The organic phase was dried (Na_2SO_4), filtered, concentrated and purified by silica gel column chromatography (eluant hexane/EtOAc, 20/1 to 1/1) to give ethyl 1,10-bis[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole-6-carboxylate and ethyl 2,10-bis[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-2*H*-4,8-epiminocycloocta[*c*]pyrazole-6-carboxylate (**57**) (0.721 mmol, 1.23 mmol, quant). MS(ESI) 584.0 (M+H).

18.2. {1,10-Bis[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazol-6-yl}methanol and {2,10-bis[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-2*H*-4,8-epiminocycloocta[*c*]pyrazol-6-yl}methanol (58)

Lithium borohydride (10 mg, 0.516 mmol) was added to a solution of ethyl 1,10-bis[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole-6-carboxylate and ethyl 2,10-bis[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-2*H*-4,8-epiminocycloocta[*c*]pyrazole-6-carboxylate (**57**) (0.151 mg, 0.258 mmol) in THF (1 mL) and the resulting solution was stirred at room temperature for 2 h. The reaction mixture was diluted with EtOAc and washed with water. The organic phase was dried (Na_2SO_4), filtered and concentrated to give {1,10-bis[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazol-6-yl}methanol and {2,10-Bis[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-2*H*-4,8-epiminocycloocta[*c*]pyrazol-6-yl}methanol (**58**). MS(ESI) 542.0 (M+H).

18.3. 1,10-Bis[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole-6-carbaldehyde and 2,10-bis[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-2*H*-4,8-epiminocycloocta[*c*]pyrazole-6-carbaldehyde (59)

Dess-Martin periodinane (128 mg, 0.304 mmol) was added to a solution of {1,10-bis[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazol-6-yl}methanol and {2,10-Bis[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-2*H*-4,8-epiminocycloocta[*c*]pyrazol-6-yl}methanol (**58**) (110 mg, 0.202 mmol) containing sodium bicarbonate (76 mg, 0.912 mmol). The resulting suspension was stirred at room temperature for 2 h after which a mixture of saturated aqueous $NaHCO_3$ and saturated aqueous Na_2SO_4 (1/1, v/v) was added. The organic phase was dried (Na_2SO_4), filtered, concentrated and purified by silica gel column chromatography (eluant hexane/EtOAc, 4/1 to 1/1) to give 1,10-bis[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole-6-carbaldehyde and 2,10-bis[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-2*H*-4,8-epiminocycloocta[*c*]pyrazole-6-carbaldehyde (**59**) (95 mg, 0.175 mmol, 87%). MS(ESI) 540.0 (M+H).

18.4. 1-{1,10-Bis[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazol-6-yl}-*N*-hydroxymethanimine and 1-{2,10-Bis[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazol-6-yl}-*N*-hydroxymethanimine (60)

Hydroxylamine hydrochloride (18 mg, 0.252 mmol) was added to a solution of 1,10-bis[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole-6-

carbaldehyde and 2,10-bis[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-2*H*-4,8-epiminocycloocta[*c*]pyrazole-6-carbaldehyde (**59**) (91 mg, 0.168 mmol) in EtOH/pyridine (2 ml, 1/1, v/v) and the resulting solution was stirred at room temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic phase was dried (Na_2SO_4), filtered and concentrated to give 1-{1,10-bis[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazol-6-yl}-*N*-hydroxymethanimine and 1-{2,10-bis[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazol-6-yl}-*N*-hydroxymethanimine (**60**). MS(ESI) 555.0 (M+H).

18.5. 1,10-Bis[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole-6-carbonitrile and 2,10-Bis[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-2*H*-4,8-epiminocycloocta[*c*]pyrazole-6-carbonitrile (61)

Methanesulfonyl chloride (30 μL, 0.390 mmol) and triethylamine (162 μL, 1.17 mmol) were added to a solution of 1-{1,10-bis[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazol-6-yl}-*N*-hydroxymethanimine and 1-{2,10-bis[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazol-6-yl}-*N*-hydroxymethanimine (**60**) (73 mg, 0.130 mmol) in CH_2Cl_2 (1 mL) and the resulting solution was stirred at room temperature for 0.5 h. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic phase was dried (Na_2SO_4), filtered, and concentrated to give 1,10-bis[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole-6-carbonitrile and 2,10-bis[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-2*H*-4,8-epiminocycloocta[*c*]pyrazole-6-carbonitrile (**61**). MS(ESI) 537.0 (M+H).

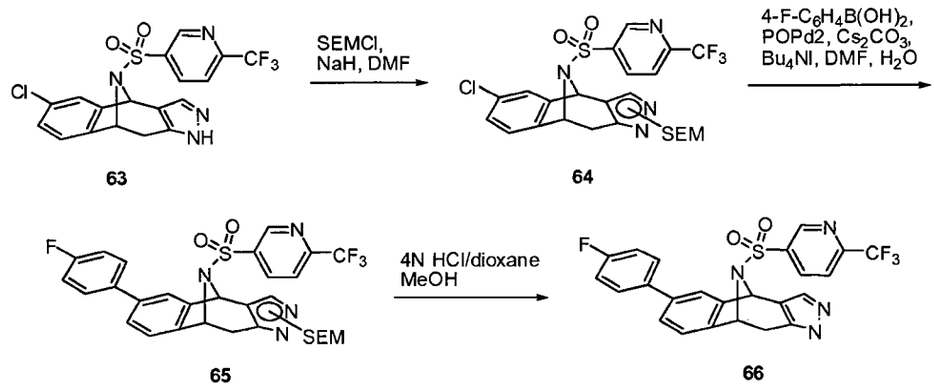
18.6. 10-[(4-Chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole-6-carbonitrile (62)

Sodium hydroxide (130 μL of a 3N aqueous solution) was added to a solution of 1,10-bis[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole-6-carbonitrile and 2,10-bis[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-2*H*-4,8-epiminocycloocta[*c*]pyrazole-6-carbonitrile (**61**) (69 mg, 0.13 mmol) in THF (0.5 mL) and the resulting solution was stirred at room temperature for 5 h. The reaction mixture was diluted with EtOAc and washed with brine. The organic phase was dried (Na_2SO_4), filtered, concentrated and purified by preparative HPLC to give 10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole-6-carbonitrile (**62**). MS(ESI) 363.1 (M+H). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, J = 8.8 Hz, 2H), 7.43 (s, 1H), 7.35 (d, J

= 8.8 Hz, 2H), 5.38 (bs, 1H), 4.61-4.52 (m, 1H), 2.93 (dd, J = 17.0, 6.6 Hz, 1H), 2.71-2.52 (m, 2H), 2.32-1.98 (m, 4H).

Example 19

Synthesis of 6-(4-fluorophenyl)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazole (66)



19.1. 6-Chloro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazole and 6-Chloro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-2-[2-(trimethylsilyl)ethoxy]-2,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazole (64)

To a suspension of NaH (4.21 mmol, 0.17 g) in DMF (10 mL) at 0 °C was added compound **63** (1.40 mmol, 0.62 g). The reaction mixture was stirred for 10 minutes prior to the addition of 2-(trimethylsilyl)ethoxymethyl chloride (4.21 mmol, 0.70 g). The reaction mixture was stirred for 2 h at 0 °C, and then quenched with saturated aqueous NH_4Cl (10 mL). The reaction mixture was diluted with EtOAc (25 mL). The two layers were separated. The organic layer was dried with $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography (30% EtOAc in hexanes) to afford compound **64** (0.57 g, 72%) as a regioisomeric mixture of alkylated pyrazoles.

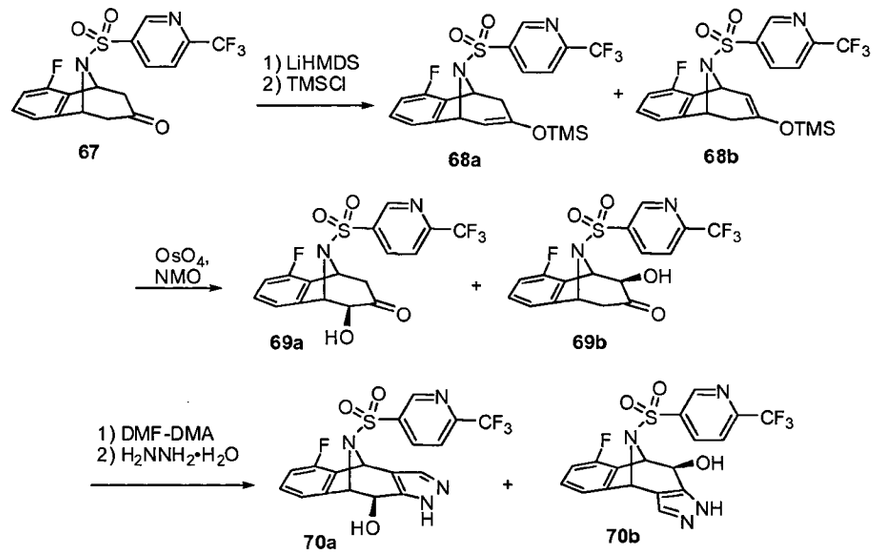
19.2. 6-(4-Fluorophenyl)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazole (66)

To a solution of **64** (0.26 mmol, 0.15 g) and 4-fluorophenylboronic acid (1.31 mmol, 0.18 g) in THF (3mL) was added dihydrogen di-ε-chlorodichlorobis(di-tert-butylphosphinito-kP)dipalladate(2-) (0.008 mmol, 0.005 g), and Cs_2CO_3 (1.31 mmol, 0.43 g). The reaction mixture was irradiated in the microwave for 60 minutes at 145 °C (300W). The reaction mixture was diluted with MeOH (5 mL) and filtered through a pad of Celite. The filtrate was concentrated, and the resulting residue was dissolved in MeOH (2 mL). The temperature was

decreased to 0 °C and 4N HCl in dioxane (5 mL) was added. The reaction mixture was warmed to room temperature and then plunged into a preheated 60 °C oil bath and stirred for 18 h. The reaction mixture was cooled to room temperature and concentrated. The resulting residue was dissolved in CH_2Cl_2 (5 mL) and the temperature was decreased to 0 °C. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (5 mL) and stirred for 5 minutes. The two layers were then separated, and the organic layer was dried with $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography (70% EtOAc in hexanes) to afford compound **66** (0.07 g, 54%).

Example 20

Synthesis of (10*S*)-5-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazol-10-ol and (4*R*,10*R*)-8-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazol-10-ol (70a and 70b)



20.1. 4-Fluoro-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-7-[(trimethylsilyl)oxy]-6,9-dihydro-5*H*-5,9-epiminobenzo[7]annulene and 1-Fluoro-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-7-[(trimethylsilyl)oxy]-6,9-dihydro-5*H*-5,9-epiminobenzo[7]annulene (68a and 68b)

To a solution of **67** (525 mg, 1.31 mmol) in THF (10 mL) at -78 °C was added LiHMDS (1.0M in THF, 1.97 mL, 1.97 mmol) over 5 minutes. After the mixture was stirred at -78 °C for 30 min, chlorotrimethylsilane (500 μL, 3.94 mmol) was added dropwise and stirred at this temperature for 60 minutes. The reaction was quenched with sat. aq. $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic layers were combined, dried over Na_2SO_4,

filtered, and concentrated under reduced pressure to give a mixture of regioisomers (577 mg) consisting of racemates **68a** and **68b**.

20.2. (6*S*)-1-Fluoro-6-hydroxy-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-5,6,8,9-tetrahydro-7*H*-5,9-epiminobenzo[7]annulen-7-one and (8*R*)-1-Fluoro-8-hydroxy-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-5,6,8,9-tetrahydro-7*H*-5,9-epiminobenzo[7]annulen-7-one (69a and 69b)

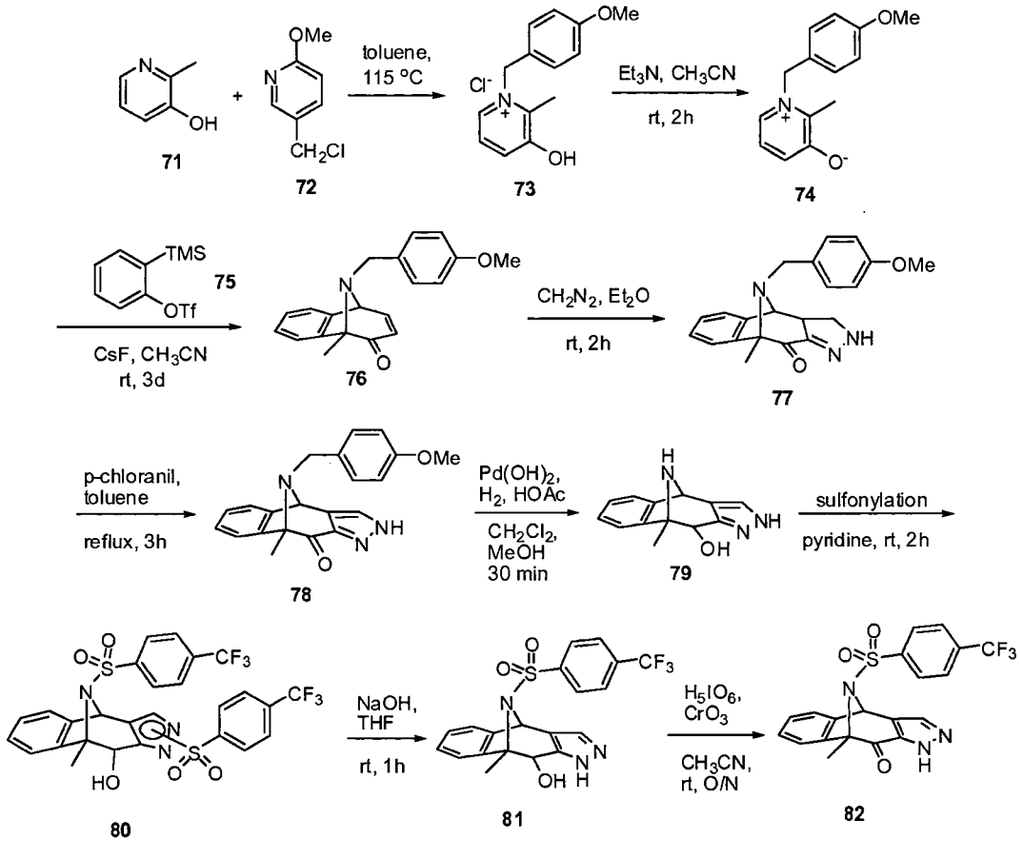
To a solution of **68a** and **68b** (1.31 mmol) in THF (9 mL) was added 4-methylmorpholine *N*-oxide (198 mg, 1.31 mmol), water (4 mL), and osmium tetroxide (4 wt.% in water, 253 μL, 0.04 mmol). The mixture was stirred at room temperature overnight, quenched with a 10% aqueous solution of $Na_2S_2O_3$ (15 mL), and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were concentrated under reduced pressure and the material was purified by flash chromatography (eluting with 0 to 50% EtOAc in hexane) to give a mixture of regioisomers consisting of racemates **69a** and **69b** (57 mg, 10% yield).

20.3. (10*S*)-5-Fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazol-10-ol and (4*R*,10*R*)-8-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazol-10-ol (70a and 70b)

The above mixture (**69a** and **69b**) (0.14 mmol) was heated with neat DMF-DMA (2 mL) at 100 °C for 60 min. The reaction mixture was concentrated under reduced pressure, dried on high vacuum and dissolved in acetic acid (3 mL). The solution was cooled in an ice bath and treated with hydrazine hydrate (15 μL, 0.31 mmol). The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure. The residue was purified by flash chromatography (solid load, 0 to 100% EtOAc in hexane) to give a mixture of regioisomers consisting of racemates **70a** and **70b**. Individual stereoisomers were isolated by chiral HPLC.

Example 21

Synthesis of (+/-)-9-methyl-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazol-10(1*H*)-one (82)



21.1. 3-Hydroxy-1-(4-methoxybenzyl)-2-methylpyridinium chloride (73)

To a suspension of 2-methyl-3-hydroxypyridine (**71**) (10g, 91.6 mmol) in toluene (45 mL) was added 4-methyoxybenzyl chloride (**72**) (12.4 mL, 1eq). The mixture was refluxed overnight. The solvent was concentrated to about 1/3 of the volume. After cooling, the solid was isolated via filtration and washed with a small amount of toluene to give the desired product, which was used without further purification. ^{1}H NMR (d_6-DMSO) δ 8.61 (d, 1H, J = 6 Hz), 8.16 (d, 1H, J = 8.4 Hz), 7.85 (t, 1H, J = 6.9 Hz), 7.28 (d, 2H, J = 8.1 Hz), 7.02 (d, 2H, J = 8.4 Hz), 5.82 (s, 2H), 3.79 (s 3H), 2.59 (s, 3H).

21.2. 1-(4-Methoxybenzyl)-2-methylpyridinium-3-olate (74)

To a suspension of compound **73** (23g) in CH_3CN (200 mL) was added triethylamine (15 mL) and the mixture was stirred at room temperature for 1.5 hours. The solvent was concentrated to about 1/4 of the volume. The solid was isolated via filtration and washed with a small amount of CH_3CN to give the desired product, which was used without further purification. ^{1}H NMR (d_6-DMSO) δ 8.57 (d, 1H, J = 6 Hz), 8.08 (d, 1H, J = 8.1 Hz), 7.82 (t,

1H, J = 7.5 Hz), 7.25 (d, 2H, J = 8.7 Hz), 6.99 (d, 2H, J = 8.4 Hz), 5.78 (s, 2H), 3.74 (s 3H), 2.51 (s, 3H).

21.3. (+/-)-10-(4-Methoxybenzyl)-5-methyl-5,9-dihydro-6*H*-5,9-epiminobenzo[7]annulen-6-one (76)

To a suspension of compound **73** (11.97g) in CH_3CN (125 mL) was added 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**75**) (30g) and CsF (20g). The mixture was stirred at room temperature for 3 days. Water was added to quench the reaction and most of the CH_3CN was removed via rotavaporator. The residue was extracted with EtOAc, washed with water and brine, and dried over $MgSO_4$. After concentration of the solvent, the crude product was purified by silica gel chromatography, eluting with a gradient of 100% hexane to 80% EtOAc/hexane over 30 min. The pure product was isolated as a brown oil. ^{1}H NMR ($CDCl_3$) δ 7.30-7.24 (m 3H), 7.21-7.15 (m, 3H), 7.01 (dd, 1H, J = 5.1, 9.6 Hz), 6.87 (d, 2H, J = 8.7 Hz), 5.62 (d, 2H, J = 9.6 Hz), 4.31 (d, 1H, J = 5.1 Hz), 3.81 (s 3H), 1.65 (s, 3H).

21.4. (+/-)-11-(4-Methoxybenzyl)-9-methyl-3,3a,4,9-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazol-10(2*H*)-one (77)

Diazomethane in ether (75 mL) (prepared from 2.5g NMMG) was added with caution to compound **75** (2.6g) and the solution was stirred at room temperature for 2 hours. The excess diazomethane was quenched by adding HOAc. The solvent was removed to afford the desired product as a yellow solid consisting of a mixture of the two regioisomers. The product was used without further purification.

21.5. (+/-)-11-(4-Methoxybenzyl)-9-methyl-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazol-10(2*H*)-one (78)

To a solution of compound **77** (3.6g) in toluene (300 mL) was added p-chloranil (7.66g) and the mixture was refluxed for 3 hours. The solvent was removed and the residue was purified by silica gel chromatography, eluted with 100% hexane to 50% EtOAc/hexane over 30 min.

21.6. (+/-)-9-Methyl-2,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazol-10-ol (79)

To a solution of compound **78** (104 mg) in $MeOH/CH_2Cl_2$ (2:1, 10 mL) were added a few drops of 3N HCl and Pd/C (10%, 40 mg). Hydrogenation was carried out on a Parr shaker at 50 psi of H_2 for 30 minutes. The catalyst was filtered off and the solvent was removed. The crude material was purified by preparative HPLC to afford the product as a white solid. ^{1}H NMR (CD_3OD) δ 7.73 (s 1H), 7.48-7.37 (m, 4H), 5.94 (s, 1H), 5.17 (s 1H), 2.00 (s, 3H).

21.7. (+/-)-9-Methyl-1,11-bis{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazol-10-ol and (+/-)-9-Methyl-2,11-bis{[4-(trifluoromethyl)phenyl]sulfonyl}-2,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazol-10-ol (80)

To a solution of compound **79** (34.2 mg) in pyridine (0.6 mL) was added 4-trifluoromethylbenzenesulfonyl chloride (147.3 mg). The mixture was stirred at room temperature for 2 hours. The reaction was quenched with water and extracted with EtOAc. The organic layers were combined and washed with water, sat. aq. $NaHCO_3$, HCl, brine and dried over $MgSO_4$. After removal of the solvent, the bis-sulfonylated mixture of regioisomers was isolated as a yellow oil.

21.8. (+/-)-9-methyl-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazol-10-ol (81)

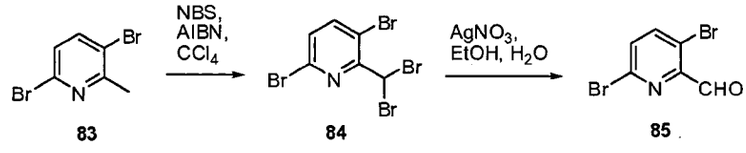
To a solution of compound **80** (61 mg) in THF (3 mL) was added 0.5 N NaOH (3 mL). The resulting mixture was stirred at room temperature for 1 hour and concentrated *in vacuo*. The aqueous mixture was then extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered and the solvent was removed to afford the product as an off-white solid.

21.9. (+/-)-9-methyl-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazol-10(1*H*)-one (82)

H_5IO_6 (153 mg) was suspended in CH_3CN (3.1 mL) and CrO_3 (6.1 mg) was added to the mixture. The resulting mixture was stirred at room temperature for 15 min at which point the mixture became a homogeneous solution. To this solution was added a solution of the compound **8b** (34 mg) in CH_3CN (5 mL) and a yellow precipitate formed. The mixture was stirred at room temperature overnight. Water and sat. aq. $NaHCO_3$ were added to quench the reaction and the solvent was concentrated to remove most of the CH_3CN. EtOAc was added and the organic layer was washed with water, brine and dried over $MgSO_4$. After evaporation of the solvent, an off-white solid was afforded as the pure product. ^{1}H NMR ($CDCl_3$) δ 7.83 (d, 2H, J = 8.4 Hz), 7.67 (s, 1H), 7.63 (d, 2H, J = 8.4 Hz), 7.29-7.17 (m, 4H), 6.28 (s, 1H), 1.92 (s, 3H).

Example 22

Synthesis of 3,6-Dibromopicolinaldehyde (85)



22.1. 3,6-Dibromo-2-(dibromomethyl)pyridine (84)

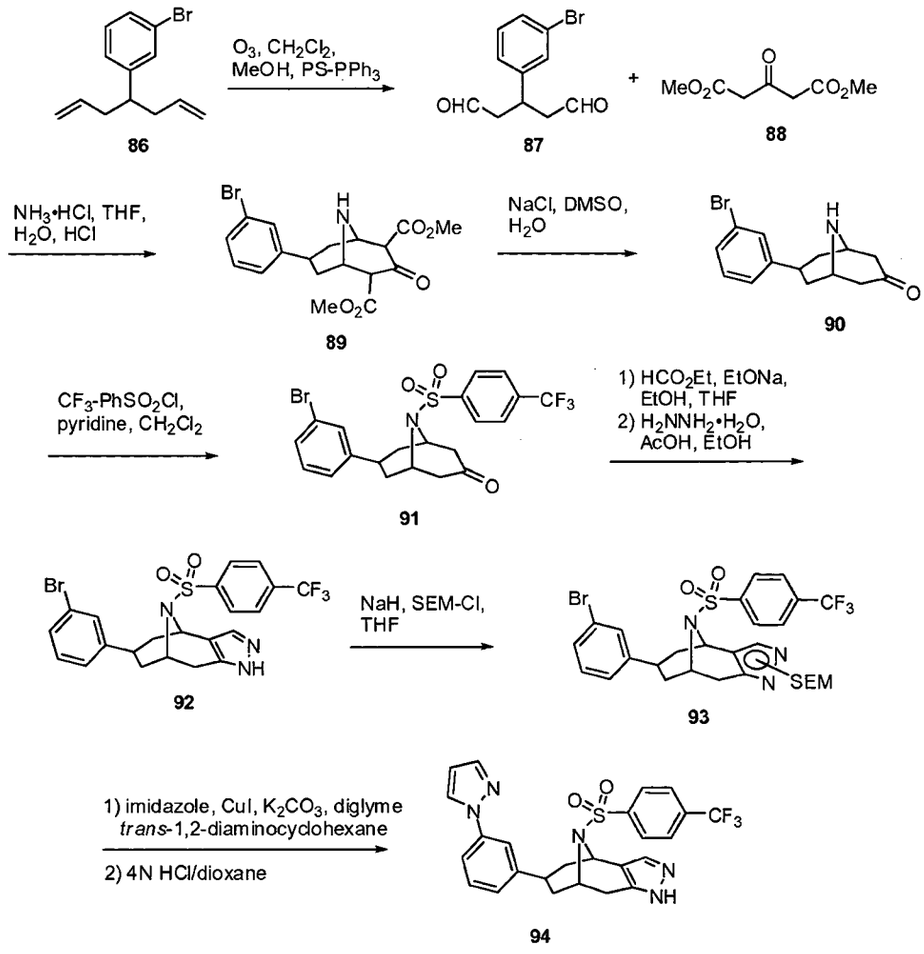
To a solution of 3,6-dibromo-2-methylpyridine (5.34 g, 21 mmol) in CCl_4 (50 mL) was added *N*-bromosuccinimide (7.57 g, 42 mmol) and 2,2'-azobis(2-methylpropionitrile) (0.70 g, 4.3 mmol). The mixture was heated at 70 °C overnight and cooled to room temperature. The solid was removed by filtration and the filtrate was concentrated under reduced pressure. The product was obtained after flash chromatography eluting with 0-10% EtOAc in hexane (8.17 g).

22.2. 3,6-Dibromopicolinaldehyde (85)

A solution of silver nitrate (8.5 g, 50 mmol) in water (26 mL) was added dropwise to a solution of compound **84** (8.17 g, 20 mmol) in refluxing EtOH (100 mL). The mixture was stirred at 80 °C for 5 hours. After the mixture was cooled to room temperature, it was diluted with water (100 mL), extracted with EtOAc (3 x), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The product was obtained after silica gel chromatography eluting with 0-40% EtOAc in hexane (2.85 g, 51% over two steps).

Example 23

Synthesis of 6-[3-(1*H*-Imidazol-1-yl)phenyl]-10-{[4-(trifluoromethyl)-phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole (94)



23.1. 3-(3-Bromophenyl)pentanedial (87)

Ozone was bubbled through a solution of 1-bromo-3-(hepta-1,6-dien-4-yl)benzene (6.14g, 24.4 mmol) in CH_3OH (10 ml) and CH_2Cl_2 (90 ml) at -78 °C for 30 min at which time the solution was pale blue. Nitrogen was then bubbled through the solution for 5 min and the solution became clear. Polymer support triphenylphosphine (20 g, 60.0 mmol) was added and the solution stirred at -78 °C for 30 min. The dry ice/acetone bath was removed and the heterogeneous mixture was stirred for 1 h. The heterogeneous mixture was filtered through Celite and the filtrate was concentrated to afford compound **87**.

23.2. Dimethyl 7-(3-bromophenyl)-3-oxo-9-azabicyclo[3.3.1]nonane-2,4-dicarboxylate (89)

3-(3-Bromophenyl)pentanedial (**87**), dimethyl 3-oxopentanedioate (**88**) (5.78 g, 33.2 mmol), ammonium chloride (14.42 g, 270 mmol) in THF (100 ml), 10% aqueous HCl (100 ml), and

water (100 ml) was stirred for 18 h. Sodium acetate was then added until the pH was 4-5. After stirring for 6 h, the solution was extracted with EtOAc. The combined organic extracts were washed with saturated aqueous Na_2CO_3, dried over $MgSO_4$, filtered and concentrated to afford compound **89**.

23.3. 7-(3-Bromophenyl)-9-azabicyclo[3.3.1]nonan-3-one (90)

Dimethyl 7-(3-bromophenyl)-3-oxo-9-azabicyclo[3.3.1]nonane-2,4-dicarboxylate (**89**) and NaCl (61.22 g, 1.05 mol) in DMSO (200 ml) and water (10 ml) was placed into a preheated oil bath at 160 °C. After stirring for 14 h, the solution was cooled to ambient temperature and exhaustively extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to afford compound **90**.

23.4. 7-(3-Bromophenyl)-9-{[4-(trifluoromethyl)phenyl]sulfonyl}-9-azabicyclo[3.3.1]nonan-3-one (91)

7-(3-Bromophenyl)-9-azabicyclo[3.3.1]nonan-3-one (**90**) and 4-(trifluoromethyl)benzene-1-sulfonyl chloride (12.25 g, 50.1 mmol) in pyridine (100 ml) and CH_2Cl_2 (100 ml) was stirred for 24 h. The solution was concentrated and flash chromatographed with CH_2Cl_2 as the eluant to yield 2.29 g (19% yield over 4 steps) of compound **91** as a pink solid.

23.5. 6-(3-Bromophenyl)-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole (92)

21% NaOEt (6 ml, 16.1 mmol) was added to a solution of 7-(3-Bromophenyl)-9-(4-(trifluoromethyl)phenylsulfonyl)-9-azabicyclo[3.3.1]nonan-3-one (**90**) (2.28 g, 4.54 mmol) and ethyl formate (6 ml, 74.5 mmol) in THF (20 ml). The solution was placed into a preheated oil bath at 60°C. After stirring for 30 min, the solution was cooled to ambient temperature, diluted with saturated aqueous NH_4Cl, and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to afford 7-(3-bromophenyl)-2-(hydroxymethylene)-9-(4-(trifluoromethyl)phenylsulfonyl)-9-azabicyclo[3.3.1]nonan-3-one. Hydrazine monohydrate (3 ml) was added to a solution of 7-(3-bromophenyl)-2-(hydroxymethylene)-9-(4-(trifluoromethyl)phenylsulfonyl)-9-azabicyclo[3.3.1]nonan-3-one and glacial acetic acid (1 ml) in EtOH (20 ml). After stirring for 18 h, the solution was concentrated to afford compound **92**.

23.6. 6-(3-Bromophenyl)-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-1-{[2-(trimethylsilyl)ethoxy]methyl}-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta-[*c*]pyrazole and 6-(3-Bromophenyl)-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-2-{[2-(trimethylsilyl)ethoxy]methyl}-4,5,6,7,8,9-hexahydro-2*H*-4,8-epiminocycloocta[*c*]-pyrazole (93)

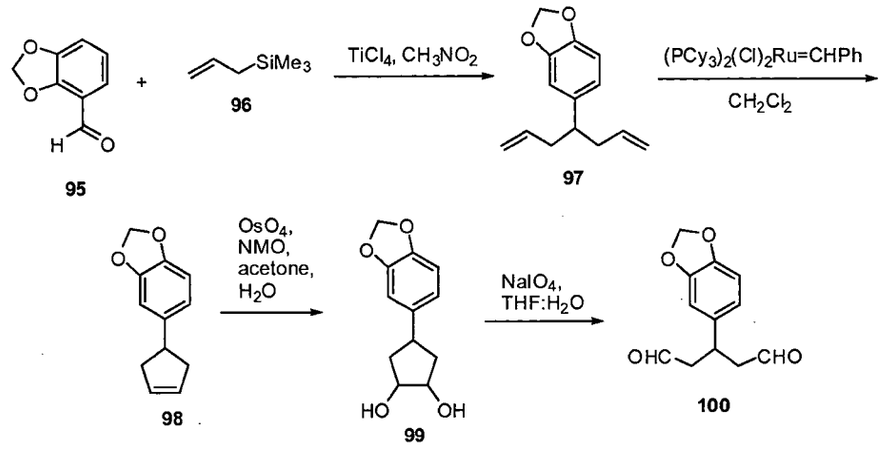
60% Sodium hydride (0.41 g, 10.3 mmol) was added to a solution of compound **92** in THF (50 mL). After stirring for 1 h, SEM-Cl (3.0 ml, 17.0 mmol) was added. After stirring for 1 h, the solution was diluted with saturated aqueous NH_4Cl, and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was flash chromatographed with 9:1, 4:1, 7:3, 3:2, 1:1, and 2:3 hexanes:EtOAc as the eluant to yield 2.06 g (69% yield over 3 steps) of the product as a orange oil.

23.7. 6-[3-(1*H*-Imidazol-1-yl)phenyl]-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole (94)

To a solution of compound **93** (0.07 mmol, 0.05 g) and pyrazole (1.52 mmol, 0.10 g) in dimethoxyethane (1 mL) was added copper iodide (0.02 mmol, 0.004 g), *trans*-1,2-diaminocyclohexane (0.02 mmol, 0.002 g), and potassium carbonate (0.76 mmol, 0.11 g). The reaction mixture was irradiated in a microwave for 35 minutes at 220 °C (300W). The reaction mixture was diluted with MeOH (5 mL) and filtered through a pad of Celite. The filtrate was concentrated, and the resulting residue was dissolved in MeOH (2 mL). The temperature was decreased to 0 °C and 4N HCl in dioxane (3 mL) was added. The reaction mixture was warmed to room temperature and then plunged into a preheated 60 °C oil bath and stirred for 18 h. The reaction mixture was cooled to room temperature and concentrated. The resulting residue was dissolved in CH_2Cl_2 (5 mL) and the temperature was decreased to 0 °C. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (5 mL) and stirred for 5 minutes. The two layers were then separated, and the organic layer was dried with $MgSO_4$, filtered and concentrated. The resulting residue was purified by silica gel chromatography (5% MeOH in CH_2Cl_2) to afford compound **94** (0.04 g, 56%).

Example 24

Synthesis of 3-(benzo[d][1,3]dioxol-5-yl)pentanedial (100)



24.1. 5-(Hepta-1,6-dien-4-yl)benzo[d][1,3]dioxole (97)

To a solution of nitromethane (133.2 mmol, 7.15 g) and CH_2Cl_2 (100 mL) at -78 °C was added $TiCl_4$ (56.61 mmol, 10.73 g) and aldehyde **95** (33.10 mmol, 5.00 g). The reaction mixture was stirred for 20 minutes prior to the dropwise addition of allyltrimethylsilane (**96**) (66.61 mmol, 7.61 g). The reaction mixture was stirred at -78 °C for 18 h. The reaction mixture was poured directly into a solution of saturated aqueous NaCl and warmed to room temperature. The two layers were separated and the organic layer was dried with $MgSO_4$, filtered and concentrated. The resulting residue was purified by silica gel chromatography (10% EtOAc in hexanes) to afford compound **97** (1.49 g, 21%).

24.2. 5-(Cyclopent-3-enyl)benzo[d][1,3]dioxole (98)

To a solution of Grubbs I (0.345 mmol, 0.284 g) in CH_2Cl_2 was added diene **97** (6.91 mmol, 1.49 g). The reaction mixture was stirred at room temperature for 48 h. The reaction mixture was purified by flash chromatography (hexanes) to afford compound **98** (0.42 g, 32%).

24.3. 4-(Benzo[d][1,3]dioxol-5-yl)cyclopentane-1,2-diol (99)

To a solution of 4-methylmorpholine *N*-oxide (2.89 mmol, 0.339 g) and OsO_4 (0.013 mmol, 0.081 mL) in acetone (5 mL) and H_2O (1.5 mL) at 0 °C was added cyclopentene **98** (2.22 mmol, 0.42 g). The reaction mixture was stirred for 18 h at room temperature. The temperature was then decreased to 0 °C and the reaction mixture was quenched with saturated aqueous Na_2SO_3. The reaction mixture was stirred for 3 h while warming to room temperature. The acetone was removed by rotary evaporation and the temperature was again decreased to 0 °C. The pH was adjusted to pH 2 through the addition of concentrated H_2SO_4. The reaction mixture was washed with EtOAc (3X, 25 mL). The combined organic layers

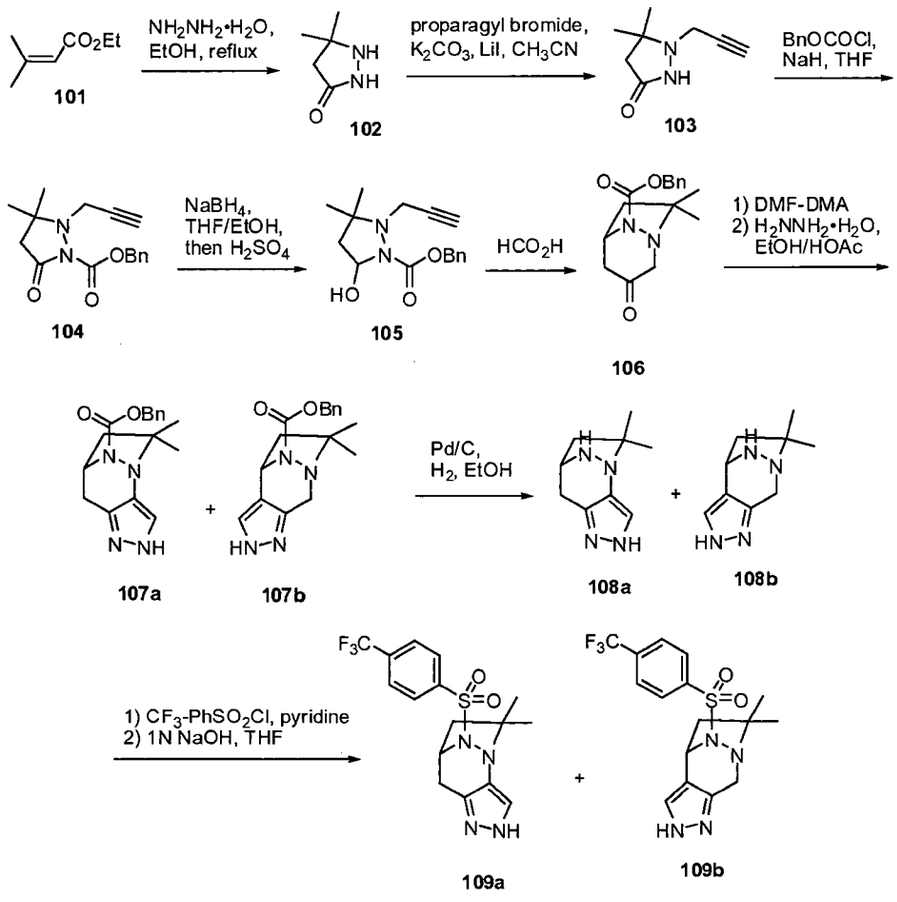
were dried with $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash chromatography (EtOAc) to afford compound **99** (0.42 g, 86%).

24.4. 3-(Benzo[d][1,3]dioxol-5-yl)pentanedial (100)

To a solution of sodium periodate (1.91 mmol, 0.41 g) in THF (3 mL) and H_2O (2 mL) at 0 °C was added diol **99** (1.91 mmol, 0.42 g). The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was filtered, and the resulting dialdehyde **100** was used as is, as an aqueous solution.

Example 25

Synthesis of 5,5-dimethyl-9-{[4-(trifluoromethyl)phenyl]sulfonyl}-5,6,7,8-tetrahydro-2*H*-4,7-epiminopyrazolo[4,3-*b*]azepine and 6,6-dimethyl-9-{[4-(trifluoromethyl)phenyl]sulfonyl}-2,5,6,8-tetrahydro-4*H*-4,7-epiminopyrazolo[3,4-*c*]azepine (109a and 109b)



25.1. 5,5-Dimethylpyrazolidin-3-one (102)

To a solution of hydrazine hydrate (4.4 g, 88 mmol) in EtOH (50 ml) was added ethyl 3,3-dimethylacrylate (**101**) (10.0 g, 78 mmol) in EtOH (40 mL) dropwise at room temperature over 1 h. The resulting reaction mixture was stirred at room temperature for 1 h and then

heated to reflux for 4 hrs. Progress of the reaction was monitored through TLC. Upon complete consumption of starting material, solvent was evaporated and the crude material was purified through column chromatography eluting with MeOH/ CH_2Cl_2 (1:25) to provide **2** (7.0 g) in 78 % yield as colorless liquid, which slowly converted to solid upon long standing. ^{1}H NMR ($CDCl_3$) δ 6.95 (bs, 1H), 4.09 (bs, 1H), 2.33 (s, 2H), 1.31 (s, 6H).

25.2. 5,5-Dimethyl-1-(prop-2-ynyl)pyrazolidin-3-one (103)

To a solution of **102** (10.0 g, 87.7 mmol) in acetonitrile (100 mL) was added K_2CO_3 (12.7 g, 92 mmol), LiI (0.59 g, 4.4 mmol) and propargyl bromide (11.0 g, 92 mmol). The resulting reaction mixture was refluxed for 24 h. Progress of the reaction was monitored using TLC. Upon completion of the starting material, the crude reaction mixture was filtered in a small pad of Celite and the solvent was evaporated under vacuum at room temperature. The crude material was passed through column eluting with EtOAc/hexane (3:7) to afford **103** (5.9 g) in 45% yield as a crystalline, pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.45 (bs, 1H), 3.53 (d, J = 2.2 Hz, 2H), 2.46 (s, 2H), 2.29 (t, J = 2.6 Hz, 1H), 1.35 (s, 6H).

25.3. Benzyl 3,3-dimethyl-5-oxo-2-(prop-2-ynyl)pyrazolidine-1-carboxylate (104) To a suspension of NaH (1.7 g, 71 mmol) in THF was added **103** (9.0 g, 59.2 mmol) dropwise at 0 °C. The resulting slurry was stirred for additional 1 h at 0 °C followed by introduction of benzyl chloroformate (30.4 g, 177.7 mmol) at the same temperature. The resulting reaction mixture was slowly warmed up to room temperature and stirred for another 2 h. Upon complete consumption of starting material, monitored through TLC, the reaction mixture was quenched with saturated NH_4Cl. The reaction mixture was extracted with EtOAc (50 × 2 mL), washed with water (30 mL), brine and dried over Na_2SO_4. Solvent was evaporated under vacuum at room temperature and the crude residue was purified by column chromatography eluting with EtOAc/hexanes (1:10) to afford **104** (8.8 g) in 52% yield as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.48-7.27 (m, 5H), 5.35 (s, 2H), 3.85 (s, 2H), 2.79 (bs, 2H), 2.29 (s, 1H), 1.38 (s, 6H).

25.4. Benzyl 5-hydroxy-3,3-dimethyl-2-(prop-2-ynyl)pyrazolidine-1-carboxylate (105)

To a stirred solution of **104** (3.0 g, 10.48 mmol) in THF (75 mL) and EtOH (50 mL), sodium borohydride (2.6 g, 68.1 mmol) was added at -20 °C followed by few drops of conc. H_2SO_4 and stirred for 3 h at -20 °C. The reaction mixture was quenched with sat. $NaHCO_3$ solution at -20 °C and allowed to reach room temperature. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc. The organic layer was washed with water, dried over Na_2SO_4 and concentrated under reduced pressure to get crude

compound which was purified through silica gel column chromatography, eluted with 15% EtOAc/hexanes to get **105** (2.3 g, 76%). ^{1}H NMR ($CDCl_3$) δ 7.26-7.37 (m, 5H), 5.76 (m, 1H), 5.25 (s, 2H), 3.80-3.60 (m, 3H), 2.48-2.38 (m, 1H), 2.22 (m, 2H), 1.38 (s, 3H), 1.18 (s, 3H).

25.5. Benzyl 7,7-dimethyl-3-oxo-1,8-diazabicyclo[3.2.1]octane-8-carboxylate (106)

A stirred solution of **105** (2.5 g, 8.6 mmol) in formic acid (10 mL) was heated at 100 °C for 5 h. After complete consumption of **105** (as monitored by TLC), formic acid was evaporated under reduced pressure. The residue was dissolved in EtOAc (100 mL) and washed with saturated with $NaHCO_3$ solution (2 × 50 mL), water (50 mL) and brine solution (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude compound which was purified through preparative HPLC to afford **106** (0.52 g, 18%). ^{1}H NMR ($CDCl_3$) δ 7.30-7.40 (m, 5H), 5.25 (s, 2H), 3.62 (m, 1H), 2.76 (m, 1H), 2.42 (m, 1H), 2.20 (m, 1H), 2.09 (s, 1H), 1.65 (m, 1H), 1.22 (s, 3H), 1.13 (s, 3H).

25.6. Benzyl 5,5-dimethyl-5,6,7,8-tetrahydro-2*H*-4,7-epiminopyrazolo[4,3-*b*]azepine-9-carboxylate and Benzyl 6,6-dimethyl-2,5,6,8-tetrahydro-4*H*-4,7-epiminopyrazolo[3,4-*c*]azepine-9-carboxylate (107a and 107b)

A DMF-DMA solution(700 μL) of **106** (53 mg, 0.18 mmol) was heated at 100 °C for 2 hours at which time LC/MS analysis determined no starting material remained. The reaction mixture was cooled and diluted with water and EtOAc. The separated organic phase was washed with water (2 x 20 mL), brine (1 x 20 mL), dried ($MgSO_4$) and filtered. Concentration yielded 62 mg (0.18 mmol) of an oil which was dissolved in 25:1 EtOH/glacial HOAc (1 mL) and treated with hydrazine hydrate (43 μL, 0.90 mmol). After a few hours additional hydrazine hydrate was added (84 μL, 1.8 mmol) and the reaction mixture was allowed to stir overnight at room temperature. The reaction was then concentrated and the residue was dissolved in EtOAc and washed with sat $NaHCO_3$ (2 x 20mL), brine (1 x 20 mL), dried ($MgSO_4$), filtered and concentrated to give 34 mg of a golden oil which was purified by preparative HPLC to give **107a** and **107b** as approximately a 4:1 mixture of pyrazole regioisomers as determined by HPLC analysis.

25.7. 5,5-Dimethyl-5,6,7,8-tetrahydro-2*H*-4,7-epiminopyrazolo[4,3-*b*]azepine and 6,6-Dimethyl-2,5,6,8-tetrahydro-4*H*-4,7-epiminopyrazolo[3,4-*c*]azepine (108a and 108b)

A Parr bottle was charged with **107** (132mg, 0.42 mmol) 10 wt% Pd/C (13 mg), and absolute EtOH (5 mL) and placed under 35 psi H_2. After shaking overnight, the reaction mixture was

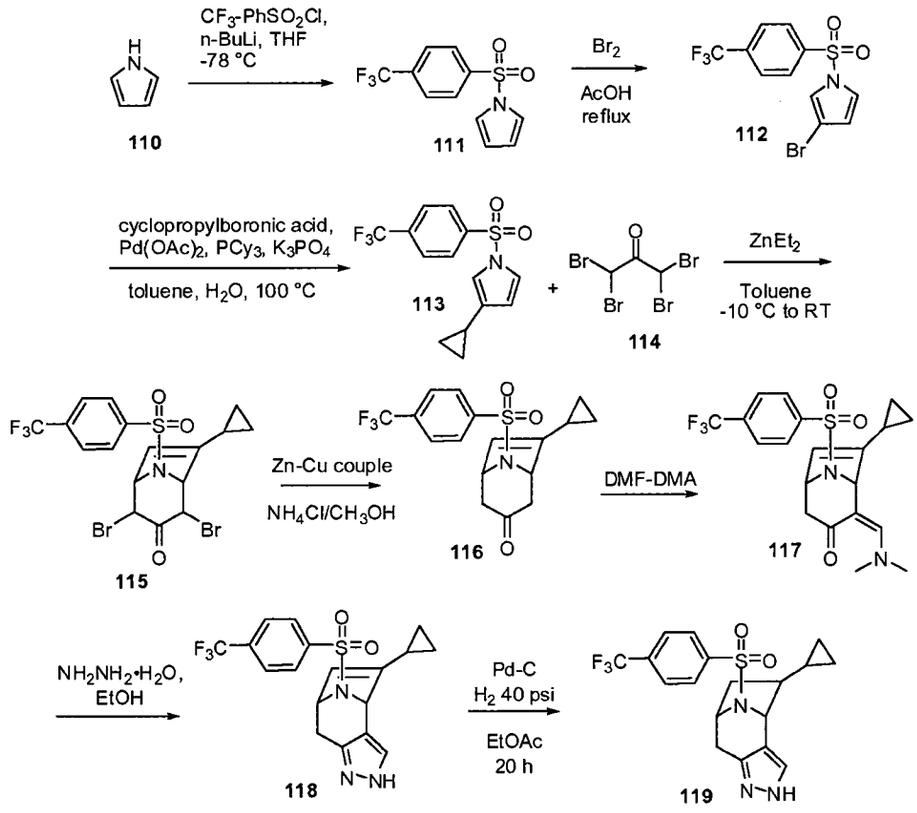
filtered through a pad of Celite and concentrated to give 81 mg (100%) of **108a** and **108b** as an oil which was used without purification.

25.8. 5,5-dimethyl-9-{[4-(trifluoromethyl)phenyl]sulfonyl}-5,6,7,8-tetrahydro-2*H*-4,7-epiminopyrazolo[4,3-*b*]azepine and 6,6-dimethyl-9-{[4-(trifluoromethyl)phenyl]sulfonyl}-2,5,6,8-tetrahydro-4*H*-4,7-epiminopyrazolo[3,4-*c*]azepine (109a and 109b)

The regioisomeric mixture of pyrazoles **108a** and **108b** (81mg, 0.45 mmol) was dissolved in pyridine (4.5 mL) and chilled to 0 °C in an ice bath to which was added 4-(trifluoromethyl)benzenesulfonyl chloride (1.1 g, 4.54 mmol). The reaction was warmed to room temperature and stirred overnight. Additional 4-(trifluoromethyl)benzenesulfonyl chloride (444 mg, 1.82 mmol) was added to the reaction and stirring was continued for 48 hours. The reaction mixture was then diluted with EtOAc and water. The organic portion was washed with water (1 x 20 mL), 0.5 N HCL (3 x 15 mL), water (1 x 10 mL), sat $NaHCO_3$ (3 x 20 mL) brine (1 x 20 mL), dried ($MgSO_4$), filtered and concentrated to a thick yellow oil. The crude product was purified by preparative thin later chromatography eluting with 3:1 hexanes/EtOAc to give the bis-sulfonylated pyrazoles as a thick clear oil: $(MH)^+ = 595.1$. The purified product was dissolved in THF (3 mL) to which was added 1N NaOH (1mL). The two phase solution was rigorously stirred overnight at which time LC/MS analysis determined no starting material remained. The reaction mixture was concentrated and the residue was dissolved in EtOAc and washed with water (3 x 15), brine (1 x 10), dried ($MgSO_4$) filtered and concentrated to give 82 mg (85%) of **109a** and **109b** as a 5:1 mixture of pyrazoles. ^{1}H-NMR (Major pyrazole regioisomer) ($CDCl_3$) δ 7.92 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.28 (s, 1H), 4.87(m, 1H), 3.09 (dd, J = 16.5, 4.8 Hz, 1H), 2.51 (d, J = 16.2 Hz, 1H), 2.40 (m, 1H), 1.55 (d, J = 12.0 Hz, 1H), 1.28 (s, 3H), 1.02 (s, 3H).

Example 26

Synthesis of 5-cyclopropyl-9-{[4-(trifluoromethyl)phenyl]sulfonyl}-2,4,5,6,7,8-hexahydro-4,7-epiminocyclohepta[*c*]pyrazole (119).



26.1. 1-(4-(Trifluoromethyl)phenylsulfonyl)-1*H*-pyrrole (111)

n-BuLi (56 mL, 89.7 mmol) was added to a solution of 1*H*-pyrrole (6.02 g, 89.7 mmol) in THF (179 mL) at -78 °C over 10 minutes. 4-(trifluoromethyl)benzene-1-sulfonyl chloride (26.3 g, 107.6 mmol) was dissolved in THF (20 mL) and added to the reaction mixture over 30 minutes. The reaction was stirred for 30 minutes then allowed to warm to room temperature and stirred for a further 18 h. The solution was diluted with EtOAc washed with brine and the organic phase was separated, dried (Na_2SO_4), filtered and concentrated under vacuum and purified on a silica gel column (eluant hexane/EtOAc 99/1 to 4/1, v/v) to give compound **111** (21.4 g, 77.7 mmol, 87%). MS(ESI) 276.1 (M+H).

26.2. 3-Bromo-1-(4-(trifluoromethyl)phenylsulfonyl)-1*H*-pyrrole (112)

Bromine (4.12 mL, 80.1 mmol) was added to a solution of 1-(4-(trifluoromethyl)phenylsulfonyl)-1*H*-pyrrole (**111**) (21 g, 76.2 mmol) in acetic acid (254 mL) and the resulting solution was heated to 100 °C for 1 h. The mixture was diluted with CH_2Cl_2 and poured slowly into ice cold aqueous sodium hydroxide (3 N). The solution was adjusted

to pH 7 with aqueous sodium hydroxide (3 N), extracted with CH_2Cl_2. The organic phase was separated, dried (Na_2SO_4), filtered and concentrated under vacuum and purified on a silica gel column (eluant hexane/EtOAc, 4/1, v/v) to give compound **112** (20.4 g, 57.6 mmol, 75%). MS(ESI) 354.0 (M+H).

26.3. 3-Cyclopropyl-1-(4-(trifluoromethyl)phenylsulfonyl)-1*H*-pyrrole (113)

Cyclopropyl boronic acid (1.6 g, 18.7 mmol), palladium (II)acetate (323 mg, 1.44 mmol), tricyclohexylphosphine (808 mg, 2.88 mmol) and potassium phosphate (10.7 g, 50.5 mmol) were added to a solution of 3-bromo-1-(4-(trifluoromethyl)phenylsulfonyl)-1*H*-pyrrole (5.11 g, 14.4 mmol) in toluene/H_2O (75 mL, 19/1). The resulting suspension was evacuated and purged with nitrogen three times and then placed in an oil bath pre-heated to 100 °C. The reaction was stirred for 6 h and was subsequently concentrated under vacuum. The residue was purified on a silica gel column (eluant hexane/EtOAc, 9/1, v/v) to give compound **113** (3.21 g, 10.1 mmol, 71%). MS(ESI) 316.1 (M+H).

26.4. 2,4-Dibromo-6-cyclopropyl-8-(4-(trifluoromethyl)phenylsulfonyl)-8-azabicyclo[3.2.1]oct-6-en-3-one (115)

Diethyl zinc (18.1 mL, 18.1 mmol of a 1M solution in hexane) was added to a solution of 3-cyclopropyl-1-(4-(trifluoromethyl)phenylsulfonyl)-1*H*-pyrrole (3.18 g, 10.1 mmol) and tetrabromoacetone (7.53 g, 20.1 mmol) in toluene at -10 °C. The reaction mixture was stirred at room temperature for 17 h and was subsequently diluted with EtOAc and washed with saturated aqueous Na_2CO_3. The organic phase was separated, dried (Na_2SO_4), filtered, concentrated under vacuum and purified on a silica gel column (eluant hexane/EtOAc, 9/1 to 7/3, v/v) to give compound **115** (3.31 g, 6.25 mmol, 62%). MS(ESI) 530.0 (M+H).

26.5. 6-cyclopropyl-8-{[4-(trifluoromethyl)phenyl]sulfonyl}-8-azabicyclo[3.2.1]oct-6-en-3-one (116)

Zinc-copper couple (3.21 g, 24.8 mmol) was added to a solution of 2,4-dibromo-6-cyclopropyl-8-(4-(trifluoromethyl)phenylsulfonyl)-8-azabicyclo[3.2.1]oct-6-en-3-one (3.29 g, 6.21 mmol) in a saturated methanolic solution of NH_4Cl (24 mL). The reaction mixture was stirred at room temperature for 4 h and was subsequently filtered though Celite. The filtrate was concentrated under vacuum, re-dissolved in CH_2Cl_2 and washed with saturated aqueous Na_2CO_3. The organic phase was separated, dried (Na_2SO_4), filtered, concentrated under vacuum and purified on a silica gel column (eluant hexane/EtOAc, 9/1 to 1/1, v/v) to give compound **116** (1.68 g, 4.52 mmol, 73%). MS(ESI) 372.1 (M+H).

26.6. 7-cyclopropyl-2-[(dimethylamino)methylidene]-8-{[4-(trifluoromethyl)phenyl]sulfonyl}-8-azabicyclo[3.2.1]oct-6-en-3-one (117)

6-Cyclopropyl-8-(4-(trifluoromethyl)phenylsulfonyl)-8-azabicyclo[3.2.1]oct-6-en-3-one (1.02 g, 2.74 mmol), was dissolved in DMF-DMA (6 mL) and heated to 100 °C for 4 h. The reaction mixture was concentrated under vacuum to give compound **117**. MS(ESI) 427.1 (M+H).

26.7. 5-cyclopropyl-9-{[4-(trifluoromethyl)phenyl]sulfonyl}-2,4,7,8-tetrahydro-4,7-epiminocyclohepta[*c*]pyrazole (118)

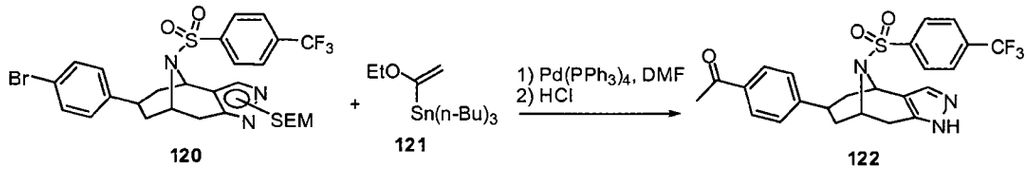
7-Cyclopropyl-2-((dimethylamino)methylene)-8-(4-(trifluoromethyl)phenylsulfonyl)-8-azabicyclo[3.2.1]oct-6-en-3-one (1.16 g, 2.74 mmol) was dissolved in ethanol (13 mL) and hydrazine monohydrate (1.3 mL, 27.4 mmol) was added. The resulting solution was stirred at room temperature for 1 h after which EtOAc was added. The solution was washed with brine, dried (Na_2SO_4), filtered, concentrated under vacuum and purified on a silica gel column (eluant hexane/EtOAc, 3/1 to 1/1) to give compound **118** as a mixture of regioisomers. MS(ESI) 395.1 (M+H).

26.8. 5-cyclopropyl-9-{[4-(trifluoromethyl)phenyl]sulfonyl}-2,4,5,6,7,8-hexahydro-4,7-epiminocyclohepta[*c*]pyrazole (119)

A suspension of 7-cyclopropyl-2-((dimethylamino)methylene)-8-(4-(trifluoromethyl)phenylsulfonyl)-8-azabicyclo[3.2.1]oct-6-en-3-one (107 mg, 0.27 mmol) and Pd/C (20 mg) in EtOAc (2 mL) was stirred under an atmosphere of hydrogen (30 psi) for 18 h. The resulting suspension was filtered through Celite and concentrated under vacuum. The residue was purified by preparative HPLC to give compound **119**. MS(ESI) 398.1 (M+H).

Example 27

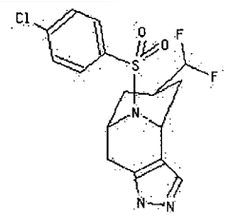
Synthesis of 1-[4-(10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazol-6-yl)phenyl]ethanone (122)

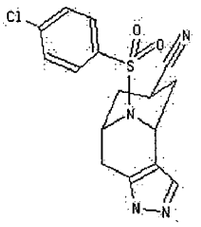
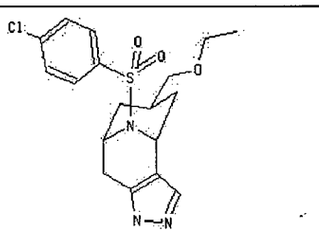


Tetrakis(triphenylphosphine)palladium (200 mg, 173 umol) was added to a solution of compound **120** (170 mg, 324 umol) and tributyl-(1-ethoxy-vinyl)-stannane (**121**) (610 mg, 1.69 mmol) in DMF (5 ml) and placed into a preheated oil bath at 90°C. After stirring for 18 h, the solution was cooled to ambient temperature and 10% aqueous HCl was added. After

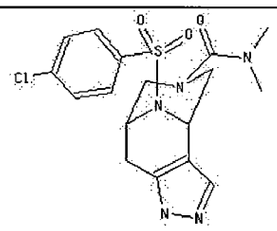
stirring for another 18 h, the solution was filtered and the crude product was purified by HPLC to afford the title compound **122**.

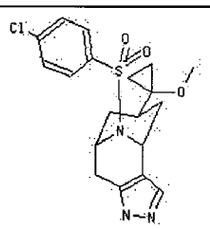
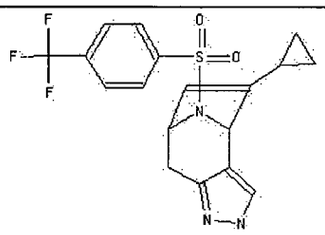
The compounds in Table 1 were prepared essentially according to the methods and procedures described above.

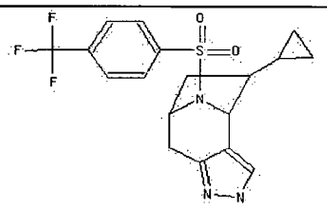
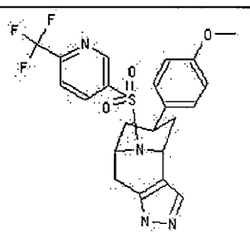
Ex. No.	**Structure / Compound Name / Mass Spec** (M+H) / **^{1}H-NMR** (300 MHz) **/ Experimental Procedures**	**γAPP IC_{50}** (nM)
28	ethyl 10-[(4-chlorophenyl)sulfonyl]-1,4,5,7,8,9-hexahydro-6H-4,8-epiminopyrazolo[4,3-d]azocine-6-carboxylate; MS 411.0. Prepared by treatment of 10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminopyrazolo[4,3-d]azocine (WO2007/022502) with ethyl chloroformate followed by hydrolysis of the N-ethylcarbamoylpyrazole with NaOH.	C
29	 10-[(4-chlorophenyl)sulfonyl]-6-(difluoromethyl)-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 388.0. Prepared by sulfonylation of ethyl 10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole-6-carboxylate (WO2007/022502) with 4-chlorobenzenesulfonyl chloride followed by reduction of the ester with $LiBH_4$, oxidation with Dess-Martin periodinane, and treatment DAST. The N-sulfonylpyrazole was then hydrolyzed with NaOH.	D
30	1-{10-[(4-chlorophenyl)sulfonyl]-1,4,5,7,8,9-hexahydro-6H-4,8-epiminopyrazolo[4,3-d]azocin-6-yl}propan-1-one; MS 395.0. Prepared from 10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminopyrazolo[4,3-d]azocine (WO2007/022502) and propionic anhydride, and hydrolysis of the N-propionoylpyrazole with NaOH.	B

31	 (±)-10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole-6-carbonitrile; MS 363.1. ^{1}H NMR ($CDCl_3$) δ 7.62 (d, J = 8.8 Hz, 2H), 7.43 (s, 1H), 7.35 (d, J = 8.8 Hz, 2H), 5.38 (bs, 1H), 4.61-4.52 (m, 1H), 2.93 (dd, J = 17.0, 6.6 Hz, 1H), 2.71-2.52 (m, 2H), 2.32-1.98 (m, 4H). Prepared as described in Example 18.	D
32	2-methoxyethyl 10-[(4-chlorophenyl)sulfonyl]-1,4,5,7,8,9-hexahydro-6H-4,8-epiminopyrazolo[4,3-d]azocine-6-carboxylate; MS 441.0. Prepared by treatment of 10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminopyrazolo[4,3-d]azocine (WO2007/022502) with 2-methoxyethyl chloroformate followed by hydrolysis of the N-methoxyethylcarbamoyl-pyrazole with NaOH.	B
33	 10-[(4-chlorophenyl)sulfonyl]-6-(ethoxymethyl)-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 396.1. Prepared by protection of ethyl 10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole-6-carboxylate (WO2007/022502) with SEM-Cl followed by reduction of the ester with LiBH4, and alkylation with ethyl iodide and treatment with 4N HCl in dioxane.	D
34	10-[(4-chlorophenyl)sulfonyl]-6-(methoxymethyl)-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 382.1. Prepared by protection of ethyl 10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole-6-carboxylate (WO2007/022502) with SEM-Cl followed by reduction of the ester with LiBH4, and alkylation with methyl iodide and treatment with 4N HCl in dioxane.	D

35	propan-2-yl 10-[(4-chlorophenyl)sulfonyl]-1,4,5,7,8,9-hexahydro-6H-4,8-epiminopyrazolo[4,3-d]azocine-6-carboxylate; MS 425.0. Prepared by treatment of 10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminopyrazolo[4,3-d]azocine (WO2007/022502) with isopropyl chloroformate followed by hydrolysis of the N-isopropylcarbamoylpyrazole with NaOH.	A
36	10-[(4-chlorophenyl)sulfonyl]-6-(methylsulfonyl)-4,5,6,7,8,9-hexahydro-1H-4,8-epiminopyrazolo[4,3-d]azocine; MS 417.0. Prepared by treatment of 10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminopyrazolo-[4,3-d]azocine (WO2007/022502) with methanesulfonyl-chloride followed by hydrolysis of the resulting N-sulfonylpyrazole with NaOH.	A
37	(±)-10-[(4-chlorophenyl)sulfonyl]-6-(3-methyl-1,2,4-oxadiazol-5-yl)-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 420.1. ^{1}H NMR ($CDCl_3$) δ 7.67 (d, J = 8.8 Hz, 2H), 7.52 (s, 1H), 7.39 (d, J = 8.8 Hz, 2H), 5.43 (bs, 1H), 4.66 (bs, 1H), 3.06 (m, 1H), 2.72 (d, J = 17.6 Hz, 1H), 2.34 (s, 3H), 2.32-2.09 (m, 4H). Prepared as described in Example 16.	D
38	10-[(4-chlorophenyl)sulfonyl]-6-(cyclopropylsulfonyl)-4,5,6,7,8,9-hexahydro-1H-4,8-epiminopyrazolo[4,3-d]azocine; MS 453.0. Prepared by treatment of 10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1H-4,8-epimino-pyrazolo[4,3-d]azocine (WO2007/022502) with cyclopropanesulfonylchloride followed by hydrolysis of the resulting N-sulfonylpyrazole with NaOH.	A

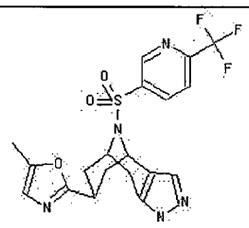
39	 10-[(4-chlorophenyl)sulfonyl]-N,N-dimethyl-1,4,5,7,8,9-hexahydro-6H-4,8-epiminopyrazolo[4,3-d]azocine-6-carboxamide; MS 410.1. ^{1}H NMR (CDCl3) δ 7.63 (d, J = 8.8 Hz, 2H), 7.36 (s, 1H), 7.34 (d, J = 8.8 Hz, 2H), 5.18 (s, 1H), 4.34 (s, 1H), 2.82 (d, J = 13.2 Hz, 1H), 3.46-3.33 (m, 2H), 3.21 (dd, J = 13, 3.2 Hz, 1H), 2.93-2.78 (m, 2H), 2.51 (s, 6H). Prepared by treatment of 10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminopyrazolo[4,3-d]azocine (WO2007/022502) with N,N-dimethylcarbamoylchloride followed by hydrolysis of the resulting N,N-dimethylcarbamoylpyrazole with NaOH.	C
40	10-[(4-chlorophenyl)sulfonyl]-6-(ethylsulfonyl)-4,5,6,7,8,9-hexahydro-1H-4,8-epiminopyrazolo[4,3-d]azocine; MS 431.0. Prepared by treatment of 10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminopyrazolo-[4,3-d]azocine (WO2007/022502) with ethanesulfonylchloride followed by hydrolysis of the resulting N-sulfonylpyrazole with NaOH.	A
41	(-)-10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole-6-carbonitrile; MS 363.1. ^{1}H NMR ($CDCl_3$) δ 7.62 (d, J = 8.8 Hz, 2H), 7.43 (s, 1H), 7.35 (d, J = 8.8 Hz, 2H), 5.38 (bs, 1H), 4.61-4.52 (m, 1H), 2.93 (dd, J = 17.0, 6.6 Hz, 1H), 2.71-2.52 (m, 2H), 2.32-1.98 (m, 4H). Prepared as described in Example 18 followed by chiral chromatographic separation of stereoisomers.	A
42	(+)-10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole-6-carbonitrile; MS 363.1. ^{1}H NMR ($CDCl_3$) δ 7.62 (d, J = 8.8 Hz, 2H), 7.43 (s, 1H), 7.35 (d, J = 8.8 Hz, 2H), 5.38 (bs, 1H), 4.61-4.52 (m, 1H), 2.93 (dd, J = 17.0, 6.6 Hz, 1H), 2.71-2.52 (m, 2H), 2.32-1.98 (m, 4H). Prepared as described in Example 18 followed by chiral chromatographic separation of stereoisomers.	D

43	 (±)-10-[(4-chlorophenyl)sulfonyl]-6-(1-methoxycyclopropyl)-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 408.1. ^{1}H NMR ($CDCl_3$) δ 7.62 (d, J = 8.6 Hz, 2H), 7.34 (s, 1H), 7.32 (d, J = 8.8 Hz, 2H), 5.35 (bs, 1H), 4.57 (d, J = 7.9 Hz, 1H)), 3.05 (s, 3H), 2.86 (dd, J = 17.1, 6.6 Hz, 1H), 2.51 (d J = 17.1, 1H), 1.75-1.61 (m, 5H), 0.66-0.63 (m, 2H), 0.33-0.29 (m, 2H). Prepared as described in Example 16 using compound **56** of Example 17.	C
44	 5-cyclopropyl-9-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,7,8-tetrahydro-4,7-epiminocyclohepta[c]pyrazole; MS 396.1. Major isomer: ^{1}H NMR ($CDCl_3$) δ 8.01 (d, J = 8.7 Hz, 2H), 7.75 (d, J = 8.7 Hz, 2H), 7.49 (s, 1H), 5.36-5.31 (m, 1H), 5.05 (s, 1H), 4.94-4.92 (m, 1H), 3.24-3.21 (m, 1H), 2.65 (d, J = 16.5 Hz, 1H), 1.16-1.11 (m, 1H), 0.66-0.59 (m, 2H), 0.17-0.65 (m, 2H). Minor isomer: ^{1}H NMR ($CDCl_3$) δ 8.01 (d, J = 8.7 Hz, 2H), 7.75 (d, J = 8.7 Hz, 2H), 7.42 (s, 1H), 5.53-5.52 (m, 1H), 5.07-5.05 (m, 1H), 4.70 (d, J = 5.4 Hz,1H), 3.30-3.28 (m, 1H), 2.86 (d, J = 16.5 Hz, 1H), 1.16-1.11 (m, 1H), 0.66-0.59 (m, 2H), 0.17-0.65 (m, 2H). Prepared as described in Example 26.	D

45	 5-cyclopropyl-9-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,5,6,7,8-hexahydro-4,7-epiminocyclohepta[c]pyrazole; MS 398.1. Major isomer: ^{1}H NMR ($CDCl_3$) δ 7.91 (d, J = 8.0 Hz, 2H), 7.68 (d, J = 8.0 Hz, 2H), 7.56 (s, 1H), 4.95 (d, J = 5.5 Hz,1H), 4.56-4.53 (m, 1H), 3.09 (dd, J = 16.7, 4.4 Hz, 1H), 2.65 (d, J = 16.7 Hz, 1H), 1.82-1.77 (m, 2H), 1.64-1.62 (m, 1H), 0.58-0.42 (m, 2H), 0.27-0.35 (m, 3H). Minor isomer: ^{1}H NMR ($CDCl_3$) δ 7.91 (d, J = 8.0 Hz, 2H), 7.68 (d, J = 8.0 Hz, 2H), 7.42 (s, 1H), 5.13 (d, J = 6.4 Hz,1H), 4.65-4.58 (m, 1H), 3.23 (d, J = 16.7, 1H), 2.52-2.46 (m, 1H), 1.82-1.77 (m, 2H), 1.64-1.62 (m, 1H), 0.58-0.42 (m, 2H), 0.27-0.35 (m, 3H). Prepared as described in Example 26.	D
46	 (±)-6-(4-methoxyphenyl)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 479.1 ^{1}H NMR ($CDCl_3$) δ 8.95 (s, 1H), 8.15 (d, J = 7.6 Hz, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.26 (d, J = 13.2 Hz, 1H), 7.01 (d, J = 8.2 Hz, 2H), 6.81 (d, J = 8.0 Hz, 2H), 5.41 (s, 1H), 4.68 (s, 1H), 3.76 (s, 3H), 2.76 (m, 3H), 2.12 (m, 2H), 1.87 (m, 2H). Prepared as described in Example 5 using 3-(4-methoxyphenyl)-pentanedial and 6-(trifluoromethyl)pyridine-3-sulfonyl chloride.	D

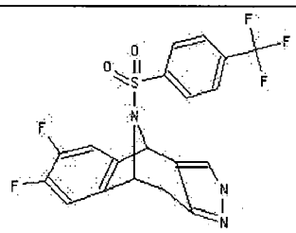
47	5,5-dimethyl-9-{[4-(trifluoromethyl)phenyl]sulfonyl}-5,6,7,8-tetrahydro-1H-4,7-epiminopyrazolo[4,3-b]azepine; and 6,6-dimethyl-9-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,8-tetrahydro-1H-4,7-epiminopyrazolo[3,4-c]azepine; MS 387.1. ^{1}H-NMR ($CDCl_3$) δ7.92 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.28 (s, 1H), 4.87(m, 1H), 3.09 (dd, J = 16.5, 4.8 Hz, 1H), 2.51 (d, J = 16.2 Hz, 1H), 2.40 (m, 1H), 1.55 (d, J = 12.0 Hz, 1H), 1.28 (s, 3H), 1.02 (s, 3H). Prepared as described in Example 25.	B
48	(±)-6-phenyl-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 449.1. ^{1}H NMR ($CDCl_3$) δ 8.96 (d, J = 1.7 Hz, 1H), 8.16 (dd, J = 8.1, 1.7 Hz, 1H), 7.64, (d, J = 8.1 Hz, 1H), 7.23 (m, 4H), 7.08 (d, J = 6.9 Hz, 2H), 5.43 (s, 1H), 4.69 (s, 1H), 2.78 (m, 3H), 2.68 (d, J = 17.3 Hz, 1H), 2.21 (ddd, J = 12.8, 11.2, 3.8 Hz, 2H), 1.89 (m, 2H). Prepared as described in Example 5 using 3-phenylglutar-aldehyde and 6-(trifluoromethyl)pyridine-3-sulfonyl chloride.	D
49	(±)-6-phenyl-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 448.1. ^{1}H NMR ($CDCl_3$) δ 7.86 (d, J = 8.2 Hz, 2H), 7.62 (d, J = 8.3, 2H), 7.22, (m, 4H), 7.04 (m, 2H), 5.41 (s, 1H), 4.67 (s, 1H), 2.85 (dd, J = 17.1, 7.7 Hz, 1H), 2.76 (m, 1H), 2.65 (d, J = 17.1 Hz, 1H), 2.13 (m, 2H), 1.86 (m, 2H). Prepared as described in Example 5 using 3-phenylglutaraldehyde and 4-(trifluoromethyl)benzene-1-sulfonyl chloride.	D
50	(±)-10-[(5-chlorothiophen-2-yl)sulfonyl]-6-phenyl-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 420.0. ^{1}H NMR ($CDCl_3$) δ 7.34 (s, 1H), 7.24 (m, 4H), 7.22, (m, 4H), 7.06 (m, 2H), 6.76 (d, J = 4.0, 1H), 5.38 (s, 1H), 4.67 (t, J = 5.5 Hz, 1H), 3.11 (dd, J = 17.0, 7.7 Hz 1H), 2.77 (m, 1H), 2.72 (d, J = 17.0 Hz , 2H), 2.15 (m, 2H), 1.86 (m, 2H). Prepared as described Example 5 using 3-phenylglutaraldehyde and 5-chlorothiophene-2-sulfonyl chloride.	D

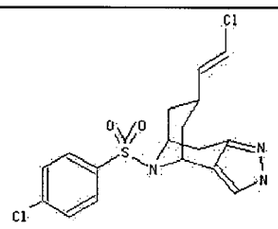
51	6-(1-methyl-1H-pyrazol-3-yl)-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole and 6-(1-methyl-1H-pyrazol-5-yl)-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 452.1. ^{1}H NMR ($CDCl_3$) δ 7.83 (m, 2H), 7.58 (m, 2H), 7.35 (d, J = 1.8 Hz, 1H), 7.30 (s, 1H), 7.21 (s, 1H), 5.96 (d, J = 1.9 Hz, 1H), 5.94 (d, J = 2.1 Hz, 1H), 5.40 (s, 1H), 5.36 (s, 1H), 4.62 (m, 1H), 3.76 (s, 3H), 3.54 (s, 3H), 2.88 (m, 6H), 2.59 (dd, J = 17.1, 12.6 Hz, 2H), 2.02 (m, 8H).	C
52	(±)-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 452.1. ^{1}H NMR ($CDCl_3$) δ 7.71(d, J = 9 Hz, 2H), 7.46-7.44 (m, 3H), 7.06-6.99 (m, 1H), 6.98 – 6.93 (m, 3H), 5.83 (s, 1H), 5.38 (d, J = 5.1 Hz, 1H), 4.57 (bs, 1H), 3.53 (dd, J = 5.1, 16.2 Hz, 1H), 2.85 (d, J = 16.5 Hz, 1H). Prepared as described in Example 8.	D
53	(±)-exo-6-(4-fluorophenyl)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 467.1. ^{1}H NMR ($CDCl_3$) δ 8.94 (s, 1H), 8.16 (dd, J = 8.1, 1.5 Hz, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.30 (s, 1H), 7.00 (m, 4H), 5.42 (s, 1H), 4.67 (s, 1H), 2.75 (m, 3H), 2.11 (m, 2H), 1.87 (m, 2H). Prepared as described in Example 5 using 3-(4-fluorophenyl)pentanedial and 6-(trifluoromethyl)pyridine-3-sulfonyl chloride.	D
54	(±)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-6-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 524.1. ^{1}H NMR ($CDCl_3$) δ 8.96 (s, 1H), 8.15 (d, 1H, J = 8.2 Hz), 7.66 (s, 1H), 7.64 (d, 1H, J = 8.2 Hz), 7.32 (s, 1H), 5.46 (s, 1H), 4.72 (br s, 1H), 3.31(br s, 1H), 2.76 (m, 2H), 2.26 (m, 4H).	D

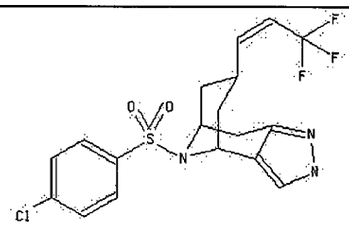
55	 (±)-6-(5-methyl-1,3-oxazol-2-yl)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 454.1. ^{1}H NMR ($CDCl_3$) δ 8.9 (d, J = 1.6 Hz, 1H), 8.13 (dd, J = 8.2, 1.9 Hz, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.22 (s, 1H), 6.52 (s, 1H), 5.39 (s, 1H), 4.64 (s, 1H), 2.95 (m, 1H), 2.78 (dd, J = 17.3, 7.6 Hz, 1H), 2.62 (d, J = 17.3 Hz, 1H), 2.14 (m, 8H). Prepared as described in Example using 3-(5-methyl-oxazol-2-yl)pentanedial and 6-(trifluoromethyl)pyridine-3-sulfonyl chloride.	D
56	(±)-endo-6-(4-fluorophenyl)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 467.1 ^{1}H NMR ($CDCl_3$) δ 9.0 (d, J = 1.9 Hz, 1H), 8.24 (dd, J = 8.2, 2.0 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.39 (s, 1H), 6.96 (m, 4H), 5.32 (d, J = 9.3 Hz, 1H), 4.73 (m, 1H), 2.89 (m, 1H), 2.68 (m, 2H), 2.58 (d, J = 15.9 Hz, 1H), 2.27 (m, 1H), 1.54 (m, 2H). Prepared as described in Example 5 using 3-(4-fluorophenyl)pentanedial and 6-(trifluoromethyl)pyridine-3-sulfonyl chloride.	D
57	(±)-6-(5-methyl-1,3-thiazol-2-yl)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 470.1. ^{1}H NMR ($CDCl_3$) δ 8.99 (s, 1H), 8.18 (d, 1H, J = 8.0 Hz), 7.70 (d, 1H, J = 8.0 Hz), 7.46 (s, 1H), 7.40 (s, 1H), 5.46 (br s, 1H), 4.72 (br s, 1H), 3.38 (br s, 1H), 2.87 (m, 2H), 2.48 (s, 3H), 2.21 (m, 4H).	C

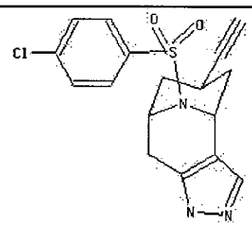
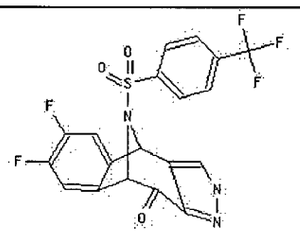
58	(±)-6-(1*H*-benzimidazol-2-yl)-10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole; MS 454.1. ^{1}H-NMR (CD_3OD) δ 7.76 – 7.71 (m, 4H), 7.61 – 7.60 (m, 2H), 7.49 (s, 1H), 7.44 – 7.40 (m, 3H), 5.61 – 5.56 (m, 1H), 4.58 – 4.54 (m, 1H), 3.48 – 3.50 (m, 1H), 2.86 (dd, J = 17.6, 7.7 Hz, 1H), 2.70 (d, J = 18.1 Hz, 1H), 2.50 – 2.41 (m, 4H). Prepared by alkylation of methyl 10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[c]pyrazole-6-carboxylate (WO 2007022502) with trimethylsilylethoxymethyl chloride followed by hydrolysis with KOH and amide formation using 1,2-benzenediamine, HBTU, and i-Pr_2EtN in DMF. The amide was then treated with TFA in EtOH at 120 °C in a microwave reactor to afford the benzamidazole, which was dealkylated using 4N HCl/dioxane.	C
59	(±)-5-(4-fluorophenyl)-9-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,7,8-tetrahydro-4,7-epiminocyclohepta[*c*]pyrazole; MS 450.0. ^{1}H NMR ($CDCl_3$) δ 7.86 (d, 2H, J=8.2 Hz), 7.70 (d, 2H, J = 8.3 Hz), 7.41 (s, 1H), 7.05-7.10 (m, 2H), 6.92-6.98 (m, 2H), 5.76 (s, 1H), 5.64 (d, 1H, J = 2.6 Hz), 5.04-5.06 (m, 1H), 3.34 (dd, 1H, J = 16.4, 5.6 Hz), 2.73 (d, 1H, J = 16.3 Hz).	C
60	6-(4-fluorophenyl)-9-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,7,8-tetrahydro-4,7-epiminocyclohepta[*c*]pyrazole; MS 449.9. ^{1}H NMR ($CDCl_3$) δ 7.87 (d, 2H, J = 8.1 Hz), 7.60 (d, 2H, J = 8.3 Hz), 7.42 (s, 1H), 7.08-7.13 (m, 2H), 6.95-7.01(m, 2H), 6.24 (d, 1H, J = 2.4 Hz), 5.50 (d, 1H, J = 2.4 Hz), 5.34 (d, 1H, J = 5.5 Hz), 3.39 (dd, 1H, J = 16.6, 5.7 Hz), 2.89 (d, 1H, J = 16.7 Hz).	C
61	5-(4-fluorophenyl)-9-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,5,6,7,8-hexahydro-4,7-epiminocyclohepta[*c*]pyrazole; MS 452.1. ^{1}H NMR ($CDCl_3$) δ 7.95 (d, 2H, J = 8.2 Hz), 7.71 (d, 2H, J = 8.3 Hz), 6.80-6.95 (m, 3H), 6.77-6.82 (m, 2H), 5.12 (d, 1H, J = 5.5 Hz), 4.76-4.81 (m, 1H), 3.80-3.87 (m, 1H), 3.15 (dd, 1H, J = 16.5 Hz, J = 4.4 Hz), 2.73-2.82 (m, 2H), 1.77 (dd, 1H, J = 12.3 Hz, J=8.5 Hz).	D

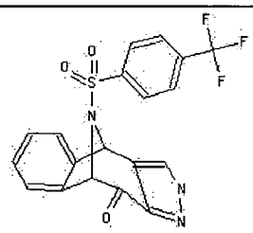
185

62	 (±)-6,7-difluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazole; MS 442.1. ^{1}H NMR ($CDCl_3$) δ 7.78 (d, 2H, J = 8.3 Hz), 7.61 (d, 2H, J = 8.3 Hz), 7.50 (s, 1H), 6.94-7.01 (dd, 1H, J = 8.9, 6.9 Hz), 6.77-6.83 (dd, 1H, J = 8.8, 6.9 Hz), 5.84 (s, 1H), 5.39 (d, 1H, J = 5.3 Hz), 3.52 (dd, 1H, J = 16.6, 5.6 Hz), 2.86 (d, 1H, J = 16.6 Hz). Prepared as described in Example 8 using 2-bromo-4,5-difluorobenzaldehyde.	D
63	6-(4-fluorophenyl)-9-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,5,6,7,8-hexahydro-4,7-epiminocyclohepta[*c*]pyrazole; MS 452.0. ^{1}H NMR ($CDCl_3$) δ 7.94 (d, 2H, J = 8.2 Hz), 7.71 (d, 2H, J = 8.3 Hz), 7.59 (s, 1H), 6.92-6.99 (m, 2H), 6.76-6.82 (m, 2H), 5.27 (d, 1H, J = 6.5 Hz), 4.68-4073 (m, 1H), 3.95-4.03(m, 1H), 2.75-2.89 (m, 2H), 2.13-2.26 (m, 2H).	B

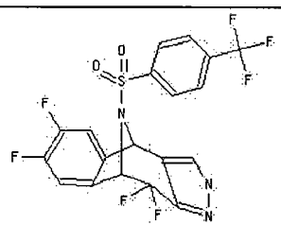
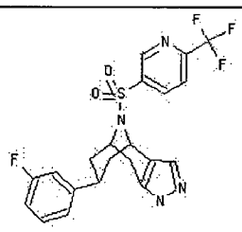
64	 6-[(E)-2-chloroethenyl]-10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 398.0. ^{1}H NMR ($CDCl_3$)δ 11.30 (broad s, 1H), 7.66 (d, J=8.4 Hz, 2H), 7.50 (broad s, 1H), 7.38 (d, J=8.4 Hz, 2H), 5.91 (d, J=13.2 Hz, 1H), 5.70 (dd, J=13.2 and 7.2 Hz, 1H), 5.34 (broad s, 1H), 4.57 (broad s, 1H), 2.95 (broad s, 1H), 2.63 (broad m, 1H), 2.22 (broad m, 1H), 1.78 (broad m, 4H). Prepared by protection of ethyl 10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta-[c]pyrazole-6-carboxylate (WO2007/022502) with SEM-Cl followed by reduction of the ester with LiBH4, oxidation with Dess-Martin periodinane, and treatment with (chloromethylene)triphenyl-phosphorane followed by treatment with 4N HCl in dioxane and chromatographic separation of isomers.	D
65	10-[(4-chlorophenyl)sulfonyl]-6-[(1E)-3,3,3-trifluoroprop-1-en-1-yl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 432.0 ^{1}H NMR ($CDCl_3$)δ 8.40 (broad s, 1H), 7.65 (d, J=8.4 Hz, 2H), 7.50 (broad s, 1H), 7.37 (d, J=8.4 Hz, 2H), 6.19 (m, 1H), 5.54 (m, 1H), 5.39 (broad s, 1H), 4.60 (broad s, 1H), 2.95 (broad s, 1H), 2.63 (broad s, 1H), 2.31 (broad s, 1H), 1.83 (broad m, 4H). Prepared by protection of ethyl 10-[(4-chlorophenyl)-sulfonyl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]-pyrazole-6-carboxylate (WO2007/022502) with SEM-Cl followed by reduction of the ester with LiBH4, oxidation with Dess-Martin periodinane, and treatment with diphenyl(2,2,2-trifluoroethyl)phosphine oxide and TBAF in THF, followed by treatment with 4N HCl in dioxane and chromatographic separation of isomers.	D

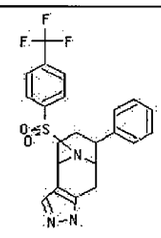
66	 10-[(4-chlorophenyl)sulfonyl]-6-[(1Z)-3,3,3-trifluoroprop-1-en-1-yl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 432.0 ^{1}H NMR ($CDCl_3$) δ 7.62 (d, J=8.1 Hz, 2H), 7.32 (d, J=8.1 Hz, 3H), 5.75 (m, 1H), 5.59 (m, 1H), 5.34 (broad s, 1H), 4.59 (broad s, 1H), 4.34 (broad s, 1H), 2.80 (broad m, 2H), 2.58 (broad s, 1H), 1.78 (broad m, 4H). Prepared by protection of ethyl 10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]-pyrazole-6-carboxylate (WO2007/022502) with SEM-Cl followed by reduction of the ester with LiBH4, oxidation with Dess-Martin periodinane, and treatment with diphenyl(2,2,2-trifluoroethyl)-phosphine oxide and TBAF in THF, followed by treatment with 4N HCl in dioxane and chromatographic separation of isomers.	D
67	6-[(Z)-2-chloroethenyl]-10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 398.0. ^{1}H NMR ($CDCl_3$)δ 10.13 (broad s, 1H), 7.65 (d, J=8.1 Hz, 2H), 7.38 (broad s, 1H), 7.32 (d, J=8.1 Hz, 2H), 5.99 (d, J=7.2 Hz, 1H), 5.52 (t, J=7.2 Hz, 1H), 5.35 (broad s, 1H), 4.59 (broad s, 1H), 2.92 (broad s, 1H), 2.70 (broad m, 2H), 1.80 (broad m, 4H). Prepared by protection of ethyl 10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]-pyrazole-6-carboxylate (WO2007/022502) with SEM-Cl followed by reduction of the ester with LiBH4, oxidation with Dess-Martin periodinane, and treatment with (chloromethylene)triphenylphosphorane followed by treatment with 4N HCl in dioxane and chromatographic separation of isomers.	D

68	 10-[(4-chlorophenyl)sulfonyl]-6-ethynyl-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 362.1. ^{1}H NMR ($CDCl_3$) δ 7.66 (d, J = 8.0 Hz, 2H), 7.41 (bs, 1H), 7.38 (d, J = 8.0 Hz, 2H), 5.33 (s, 1H), 4.54 (s, 1H), 2.94-2.92 (m, 1H), 2.63-2.58 (m, 1H), 2.42-2.40 (m, 1H), 2.11-1.91 (m, 5H). Prepared by protection of ethyl 10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole-6-carboxylate (WO2007/022502) with SEM-Cl followed by reduction of the ester with LiBH4, and oxidation with Dess-Martin periodinane to give 10-[(4-chlorophenyl)sulfonyl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole-6-carbaldehyde. The aldehyde was then treated with dimethyl (1-diazo-2-oxopropyl)phosphonate and K2CO3 in CH3CN to give 10-[(4-chlorophenyl)sulfonyl]-6-ethynyl-1-{[2-(trimethylsilyl)ethoxy]-methyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole which was deprotected with 4N HCl in dioxane.	D
69	 (±)-6,7-difluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazol-10(1*H*)-one; MS 456.1. ^{1}H NMR (CD_3OD) δ 7.89 (d, 2H, J = 8.2 Hz), 7.71 (s, 1H), 7.67 (d, 2H, J = 8.6 Hz), 7.22-7.28(m, 1H), 7.09-7.15 (m, 1H), 6.30 (s, 1H), 5.53 (s, 1H). Prepared by oxidation of 6,7-difluoro-11-{[4-(trifluoromethyl)phenyl]-sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole using the methods described in Example 15.	D

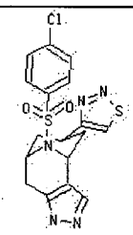
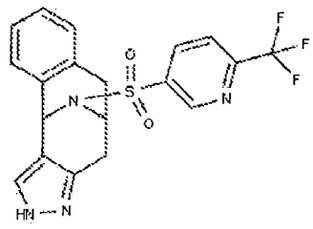
70	(±)-6-(3-fluorophenyl)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole; MS 467.1 ^{1}H NMR ($CDCl_3$) δ 8.94 (d, *J* = 1.9 Hz, 1H), 8.16 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.31 (s, 1H), 7.20 (m, 1H), 6.81 (m, 3H), 5.43 (s, 1H), 4.69 (s, 1H), 2.74 (m, 2H), 2.67 (d, *J* = 17.3 Hz, 1H), 2.14 (m, 2H), 1.88 (m, 2H). Prepared as described in Example 5 using 3-(3-fluorophenyl)pentanedial and 6-(trifluoromethyl)pyridine-3-sulfonyl chloride.	D
71	 (±)-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazol-10(1*H*)-one; MS 420.0 ^{1}H NMR ($CDCl_3$) δ 7.74 (d, 2H, J = 8.2 Hz), 7.65 (s, 1H), 7.48 (d, 2H, J = 8.3 Hz), 7.25-7.30 (m, 1H), 7.04-7.14 (m, 3H), 6.15 (s, 1H), 5.42 (s, 1H). Prepared as described in Example 15.	D
72	(-)-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazole; MS 406.1. ^{1}H NMR ($CDCl_3$) δ 7.72 (d, 2H, J = 8.3 Hz), 7.46 (d, 2H, J = 8.3 Hz), 7.37 (s, 1H), 7.04-7.08 (m, 1H), 6.84-6.98 (m, 3H), 5.83 (s, 1H), 5.39 (d, 1H, J = 5.4 Hz), 3.50 (dd, 1H, J = 16.2, 5.5 Hz), 2.85 (d, 1H, J = 16.2 Hz). Prepared as described in Example 8 followed by chiral chromatographic separation of enantiomers.	A
73	(+)-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazole; MS 406.1. ^{1}H NMR ($CDCl_3$) δ 7.72 (d, 2H, J = 8.3 Hz), 7.46 (d, 2H, J = 8.3 Hz), 7.37 (s, 1H), 7.04-7.08 (m, 1H), 6.84-6.98 (m, 3H), 5.83 (s, 1H), 5.39 (d, 1H, J = 5.4 Hz), 3.50 (dd, 1H, J = 16.2, 5.5 Hz), 2.85 (d, 1H, J = 16.2 Hz). Prepared as described in Example 8 followed by chiral chromatographic separation of enantiomers.	D

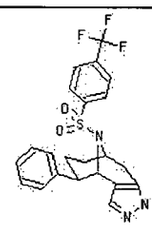
74	(±)-10,10-difluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazole; MS 442.1 ^{1}H NMR ($CDCl_3$) δ 7.79 (d, 2H, J = 8.2 Hz), 7.52 (d, 2H, J = 8.3 Hz), 7.45 (s, 1H), 7.25-7.29 (m, 1H), 6.94-7.06 (m, 3H), 6.00 (s, 1H), 5.47 (d, 1H, J = 10.6 Hz). Prepared as described in Example 15.	D
75	(±)-7-phenyl-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole; MS 448.1. ^{1}H-NMR ($CDCl_3$) δ 7.81 (d, 2H, *J* = 8.0 Hz), 7.56 (d, 2H, *J* = 8.0 Hz), 7.34 (m, 1H), 7.32 (d, 2H, *J* = 7.2 Hz), 7.26 (s, 1H), 7.18 (d, 2H, *J* = 7.2 Hz), 5.36 (m, 1H), 4.53 (m, 1H), 3.30 (m, 1H), 2.43-2.15 (m, 2H), 1.76 (m, 2H), 1.38-1.16 (m, 2H). Prepared as described in Example 5 using 3-phenyltetrahydro-2H-pyran-2,6-diol and 4-trifluoromethylbenzenesulfonyl chloride.	D
76	(±)-10-[(4-chlorophenyl)sulfonyl]-6-(3-methylisoxazol-5-yl)-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole; MS 419.0. ^{1}H NMR ($CDCl_3$) δ7.68 (d, *J* = 8.2 Hz, 2H), 7.56 (s, 1H), 7.41 (d, *J* = 8.2 Hz, 2H), 5.79 (s, 1H), 5.43 (s, 1H), 4.67-4.64 (m, 1H), 3.09 (dd, *J* = 18.3, 7.26 Hz, 1H),2.93-2.91 (m, 1H), 2.76 (d *J* = 18, 1H), 2.26 (s, 3H), 2.20-2.03 (m, 4H). Prepared by alkylation of 10-[(4-chlorophenyl)sulfonyl]-6-ethynyl-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole with trimethylsilylethoxymethyl chloride followed by treatment with acetaldehyde oxime, NCS, and Et_3N in CH_2Cl_2 and deprotection with 4N HCl/dioxane.	D

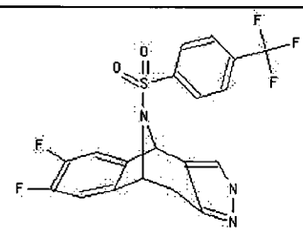
77	 (±)-6,7,10,10-tetrafluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazole; MS 478.0 ^{1}H NMR ($CDCl_3$) δ 7.85 (d, 2H, J = 8.0 Hz), 7.64 (d, 2H, J = 8.2 Hz), 7.43 (s, 1H), 7.13-7.20 (m, 1H), 6.85-6.93 (m, 1H), 5.95 (s, 1H), 5.44 (d, 1H, J = 10.2 Hz). Prepared by fluorination of 6,7-difluoro-11-{[4-(trifluoromethyl)-phenyl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one using the methods described in Example 15.	D
78	 (+)-6-(3-fluorophenyl)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole; MS 467.1 ^{1}H NMR ($CDCl_3$) δ 8.94 (d, *J* = 1.9 Hz, 1H), 8.16 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.31 (s, 1H), 7.20 (m, 1H), 6.81 (m, 3H), 5.43 (s, 1H), 4.69 (s, 1H), 2.74 (m, 2H), 2.67 (d, *J* = 17.3 Hz, 1H), 2.14 (m, 2H), 1.88 (m, 2H). Prepared as described in Example 5 using 3-(3-fluorophenyl)-pentanedial and 6-(trifluoromethyl)pyridine-3-sulfonyl chloride followed by chiral chromatographic separation of stereoisomers.	D
79	(-)-6-(3-fluorophenyl)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole; MS 467.1 ^{1}H NMR ($CDCl_3$) δ 8.94 (d, *J* = 1.9 Hz, 1H), 8.16 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.31 (s, 1H), 7.20 (m, 1H), 6.81 (m, 3H), 5.43 (s, 1H), 4.69 (s, 1H), 2.74 (m, 2H), 2.67 (d, *J* = 17.3 Hz, 1H), 2.14 (m, 2H), 1.88 (m, 2H). Prepared as described above for the stereoisomer.	A

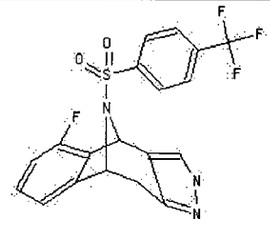
80	(±)-6-(1,3-dimethyl-1*H*-1,2,4-triazol-5-yl)-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole; MS 467.1. ^{1}H NMR ($CDCl_3$) δ 7.86 (d, *J* = 8.3 Hz, 2H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.33 (s, 1H), 5.40 (s, 1H), 4.63 (t, *J* = 5.3 Hz, 1H), 3.52 (s, 3H), 2.92 (m, 2H), 2.65 (d, *J* = 15.9 Hz, 1H), 2.32 (m, 5H), 1.86 (m, 2H).	B
81	(±)-9-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,7,8-tetrahydro-4,7-epiminocyclohepta[*c*]pyrazole; MS 322.1. ^{1}H NMR ($CDCl_3$) δ 7.75 (d, J = 8.6 Hz, 2H), 7.52 (d, J = 8.6 Hz, 2H), 7.41 (s, 1H), 6.10 (m, 1H), 5.58 (dd, J = 5.9, 2.3 Hz, 1H), 5.41 (d, J = 2.3 Hz, 1H), 4.66 (s, 1H), 3.09 (dd, J = 16.5, 5.8 Hz, 1H), 2.58 (d, J = 16.5 Hz, 1H).	C
82	(±)-6-(1H-1,2,4-triazol-3-yl)-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 439.1 ^{1}H NMR ($CDCl_3$) δ 8.16 (s, 1H), 7.86 (d, 2H, J = 8.2 Hz, 2H), 7.64 (d, J = 8.3 Hz, 2H), 7.36 (s, 1H), 5.42 (m, 1H), 4.64 (m, 1H), 3.04-3.13 (m, 1H), 2.89-2.97 (m, 1H), 2.66-2.72 (m, 1H), 2.02-2.38 (m, 4H).	B
83	 (-)-7-phenyl-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 448.1. ^{1}H-NMR ($CDCl_3$) δ 7.82 (d, J = 8.2 Hz, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.37 (m, 1H), 7.33 (d, J = 7.3 Hz, 2H), 7.29 (s, 1H), 7.20 (d, J = 7.3 Hz, 2H), 5.37 (m, 1H), 4.54 (dd, J = 4.6, 7.6 Hz, 1H), 3.31 (m, 1H), 2.44-2.14 (m, 3H), 1.86-1.70 (m, 3H). Prepared as described in Example 5 using 3-phenyltetrahydro-2H-pyran-2,6-diol and 4-trifluoromethylbenzenesulfonyl chloride, followed by chiral chromatographic separation of stereoisomers.	A

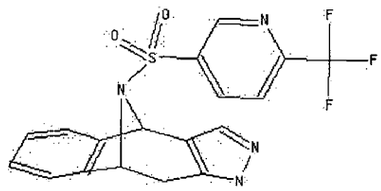
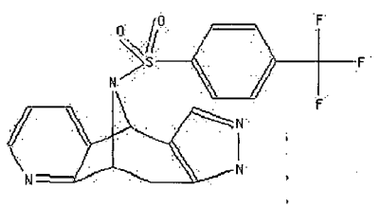
84	(+)-7-phenyl-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 448.0 ^{1}H-NMR ($CDCl_3$) δ 7.82 (d, J = 8.2 Hz, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.37 (m, 1H), 7.33 (d, J = 7.3 Hz, 2H), 7.29 (s, 1H), 7.20 (d, J = 7.3 Hz, 2H), 5.37 (m, 1H), 4.54 (dd, J = 4.6, 7.6 Hz, 1H), 3.31 (m, 1H), 2.44-2.14 (m, 3H), 1.86-1.70 (m, 3H). Prepared as described above for the stereoisomer.	D
85	(±)-6-(5-methyl-1H-1,2,4-triazol-3-yl)-10-{[4-(trifluoromethyl)-phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 453.1. ^{1}H NMR ($CDCl_3$) δ 7.93 (d, J = 8.2 Hz, 2H), 7.69 (d, J = 8.3 Hz, 2H), 7.41 (s, 1H), 5.49 (s, 1H), 4.72 (m, 1H), 3.09 (m, 1H), 2.83 (dd, J = 17.4, 7.6 Hz, 1H), 2.63 (d, J = 17.4 Hz, 1H), 2.51 (s, 3H), 2.16 (m, 4H).	A
86	10-[(4-chlorophenyl)sulfonyl]-6-(prop-1-yn-1-yl)-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 376.0. ^{1}H NMR ($CDCl_3$) δ 7.68 (d, J = 8.4 Hz, 2H), 7.47 (s, 1H), 7.37 (d, J = 8.4 Hz, 2H), 5.29 (bs, 1H), 4.53-4.51 (m, 1H), 2.96 (dd, J = 17.6, 6.7 Hz, 1H), 2.61 (d, J = 17.6, 1H), 2.35 (bs, 1H), 2.03-1.74 (m, 4H), 1.73 (d, J = 2.1 Hz, 3H). Prepared by alkylation of 10-[(4-chlorophenyl)sulfonyl]-6-ethynyl-1-{[2-(trimethylsilyl)ethoxy]-methyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole with methyl-iodide and LHMDS in THF followed by deprotection with 4N HCl in dioxane.	D

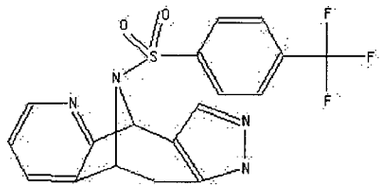
87	 (±)-6-(1,2,3-thiadiazol-4-yl)-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 422.0 ^{1}H-NMR ($CDCl_3$) δ 8.15 (s, 1H), 7.70 (d, J = 8.8 Hz, 2H), 7.54 (s, 1H), 7.40 (d, J = 8.8 Hz, 2H), 5.50 – 5.44 (m, 1H), 4.80 – 4.65 (m, 1H), 3.50 – 3.38 (m, 1H), 3.08 (dd, J = 17.6 Hz, 7.7 Hz, 1H), 2.78 (d, J = 17.6 Hz, 1H), 2.40 – 2.17 (m, 4H). Prepared by alkylation of methyl 10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole-6-carboxylate (WO 2007022502) with trimethylsilylethoxymethyl chloride followed by treatment with methoxymethylamine hydrochloride and HATU in THF and Et_3N to afford the amide which was converted to the ketone with methylmagnesium bromide. The ketone was sequentially treated with tosylhydrazine/HOAc, thionyl chloride, and finally 4N HCl/dioxane.	D
88	 (±)-12-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,10,11-tetrahydro-1H-4,10-epiminobenzo[5,6]cycloocta[1,2-c]pyrazole; MS 421.0. 1H NMR (CD_3OD) δ 8.82 (s, 1H), 8.11 (d, J = 8.3 Hz, 1H), 7.58 (d, J = 8.7 Hz, 1H), 7.47 (br, 1H), 7.26 (d, J = 6.4 Hz, 1H), 7.06 (t, J = 7.3 Hz, 1H), 6.91 (t, J = 7.5 Hz, 1H), 6.60 (d, J = 6.7 Hz, 1H), 6.07 (br, 1H), 5.04 - 4.98 (br, 1H), 3.20 – 3.10 (m, 2H), 2.77 (d, J = 19 Hz, 1H), 2.46 (d, J = 18 Hz, 1H). Prepared as described in Example 11 using 6-(trifluoromethyl)pyridine-3-sulfonyl chloride.	D

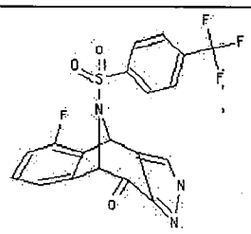
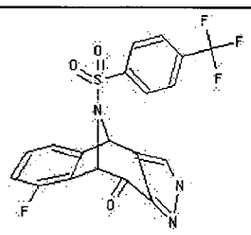
89	 5-phenyl-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 448.1. ^{1}H-NMR ($CDCl_3$) (Mixture of isomers) δ 7.68 (d, J = 8.2 Hz, 1H), 7.59-7.39 (m, 12H), 7.37-7.24 (m, 6H), 5.60 (s, 1H), 5.35 (m, 1H), 4.77 (d, J = 7.6 Hz, 1H), 5.37 (m, 1H), 4.48 (t, J = 6.2 Hz, 1H), 3.10-2.89 (m, 4H), 2.72 (d, J = 17.2 Hz, 1H), 2.60 (d, J = 17.2 Hz, 1H), 2.27 (m, 2H), 2.02-1.80 (m, 4H), 1.59 (m, 2H).	D
90	6-(pyridin-3-yl)-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 449.0. ^{1}H-NMR ($CDCl_3$) δ 8.44 (m,1H), 8.35 (s,1H), 7.92 (d, J = 6.0 Hz, 2H, major diast.), 7.86 (d, J = 9.0 Hz, 2H, minor diast.), 7.70 (d, J = 6.0 Hz, 2H, major diast.), 7.63 (d, J = 9 Hz, 2H, minor diast.), 7.41 - 7.30 (m, 1H), 2.71 - 7.16 (m, 2H), 5.46 (s, 1H minor diast.), 5.37 (d, J = 9 Hz, 1H, major diast.), 4.78 – 4.71(m, 1H), 2.96 – 2.82 (m, 1H), 2.78 – 2.71 (m, 2H), 2.69 – 2.46 (m, 1H), 2.37 – 2.27(m, 1H), 2.07 – 2.05 (m, 1H), 1.67 – 1.60 (m, 1H), 1.08 – 0.87 (m, 1H).	C
91	(±)-12-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,10,11-tetrahydro-4,10-epimino[1,3]benzodioxolo[5',6':4,5]cyclohepta[1,2-c]pyrazole; MS 449.9 ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.54 (s, 1H), 6.54 (s, 1H), 6.39 (s, 1H), 5.86 (s, 1H), 5.82 (s, 1H), 5.73 (s, 1H), 5.31 (d, J = 5.2 Hz, 1H), 3.54 (dd, J = 16.9, 5.5 Hz, 1H), 2.88 (d, J = 16.7 Hz, 1H). Prepared as described in Example 8 using 6-bromo-3,4-(methylenedioxy)-benzaldehyde.	D

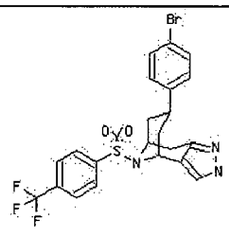
92	(±)-10-[(4-chlorophenyl)sulfonyl]-6-(5-methyl-1,3,4-thiadiazol-2-yl)-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 436.1 ^{1}H-NMR ($CDCl_3$) δ 7.66 (d, J = 7.7 Hz, 2H), 7.39 (d, J = 8.2 Hz, 2H), 7.26 (s, 1H), 5.60 – 5.40 (m, 1H), 4.70 – 4.60 (m, 1H), 3.97 – 3.86 (m, 1H), 3.40 – 3.25 (m, 2H), 2.75 (s, 3H), 2.36 – 2.13 (m, 4H). Prepared by alkylation of methyl 10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole-6-carboxylate (WO 2007022502) with trimethylsilylethoxymethyl chloride followed by hydrolysis with LiOH•H_2O and acylhydrazide formation using acetylhydrazine and HATU. The acylhydrazide was then treated with Lawesson's reagent and $NaHCO_3$ in toluene followed by dealkylation with 4N HCl/dioxane.	B
93	(±)-10-[(4-chlorophenyl)sulfonyl]-6-(1H-1,2,3-triazol-4-yl)-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 405.0. ^{1}H NMR ($CDCl_3$) δ 7.68 (d, J = 7.7 Hz, 2H), 7.46 (m, 2H), 7.37 (d, J = 7.7 Hz, 2H), 5.42-5.44 (m, 1H), 4.65-4.67 (m, 1H), 2.99 (dd, J = 17.7, 8.2, 1H), 2.81 (d, J = 17.7 Hz, 1H), 2.01-2.21 (m, 5H). Prepared by alkylation of 10-[(4-chlorophenyl)sulfonyl]-6-ethynyl-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole with trimethylsilylethoxymethyl chloride followed by treatment with sodium azide and $CuSO_4$ in DMF/H_2O followed by deprotection with 4N HCl/dioxane.	D
94	 (-)-6,7-difluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 442.1. ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 8.1 Hz, 2H), 7.38 (s, 1H), 6.92-6.97 (m, 1H), 6.73-6.78 (m, 1H), 5.82 (s, 1H), 5.37 (d, J = 5.6 Hz, 1H), 3.47 (dd, J = 16.3, 5.7 Hz, 1H), 2.82 (d, J = 16.4 Hz, 1H). Prepared as described in Example 8 using 2-bromo-4,5-difluorobenzaldehyde followed by chiral chromatographic separation of enantiomers.	A

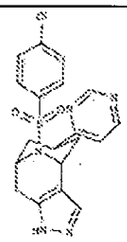
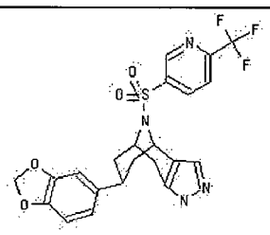
95	(+)-6,7-difluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 442.1 ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 8.1 Hz, 2H), 7.38 (s, 1H), 6.92-6.97 (m, 1H), 6.73-6.78 (m, 1H), 5.82 (s, 1H), 5.37 (d, J = 5.6 Hz, 1H), 3.47 (dd, J = 16.3, 5.7 Hz, 1H), 2.82 (d, J = 16.4 Hz, 1H). Prepared as described above for the (-)-enantiomer.	D
96	 (±)-5-fluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 424.0 ^{1}H NMR ($CDCl_3$) δ 7.76 (d, J = 7.7 Hz, 2H), 7.50 (d, J = 7.3 Hz, 2H), 7.43 (s, 1H), 6.90-6.97 (m, 1H), 6.84 (d, J = 7.2 Hz, 1H), 6.60 (t, J = 8.6 Hz, 1H), 6.03 (s, 1H), 5.41 (d, 1H, J = 5.6 Hz), 3.56 (dd, J = 16.3, 5.7 Hz, 1H), 2.87 (d, J = 16.2 Hz, 1H). Prepared as described in Example 8 using 6-fluoro-2-iodobenzaldehyde followed by chromatographic separation of regioisomers.	D
97	(±)-8-fluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 424.0. ^{1}H NMR ($CDCl_3$) δ 7.75 (d, J = 7.9 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H), 7.38 (s, 1H), 6.87-6.97 (m, 1H), 6.55-6.70 (m, 2H), 5.85 (s, 1H), 5.57 (d, 1H, J = 4.5 Hz), 3.53 (dd, J = 16.3, 5.4 Hz, 1H), 2.92 (d, J = 16.5 Hz, 1H). Prepared as described in Example 8 using 6-fluoro-2-iodobenzaldehyde followed by chromatographic separation of regioisomers.	D

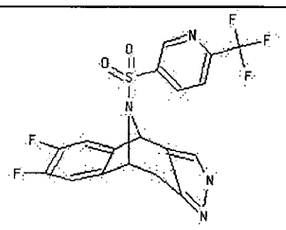
98	 (±)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 407.0. ^{1}H NMR ($CDCl_3$) δ 8.86 (d, J = 1.8 Hz, 1H), 8.00 (dd, J = 1.8, 7.8 Hz, 1H),7.48 (d, J = 8.4 Hz, 1H), 7.35 (s, 1H), 7.09-7.07 (m, 2H), 6.97-6.89 (m, 3H), 5.86 (s, 1H), 5.38 (d, 1H, J = 5.1 Hz), 3.45 (dd, J = 16.8, 5.7 Hz, 1H), 2.83 (d, J = 16.8 Hz, 1H). Prepared as described in Example 9.	D
99	(-)-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminopyrazolo[4',3':4,5]cyclohepta[1,2-b]pyridine; MS 407.0 ^{1}H-NMR ($CDCl_3$) δ 8.03 (d, 1H, J = 5.0 Hz), 7.75 (d, J = 8.2 Hz, 1H), 7.50 (d, J = 8.2 Hz, 1H), 7.47 (s, 1H), 7.33 (d, J = 7.6 Hz, 1H), 6.83 (dd, J = 5.0, 7.6 Hz, 1H), 5.84 (s, 1H), 5.39 (d, J = 5.6 Hz, 1H), 3.55 (dd, J = 5.6, 16.4 Hz, 2H). Prepared as described in Example 8 using 2-bromo-3-pyridinecarbox-aldehyde followed by chromatographic separation of regio and stereoisomers.	A
100	 (+)-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminopyrazolo[4',3':4,5]cyclohepta[1,2-b]pyridine; MS 407.0. ^{1}H-NMR ($CDCl_3$) δ 8.03 (d, J = 5.0 Hz, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.50 (d, J = 8.2 Hz, 1H), 7.47 (s, 1H), 7.33 (d, J = 7.6 Hz, 1H), 6.83 (dd, J = 5.0, 7.6 Hz, 1H), 5.84 (s, 1H), 5.39 (d, J = 5.6 Hz, 1H), 3.55 (dd, J = 5.6, 16.4 Hz, 2H). Prepared as described in Example 8 using 2-bromo-3-pyridinecarboxaldehyde followed by chromatographic separation of regio and stereoisomers.	D

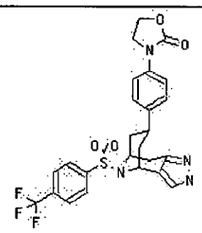
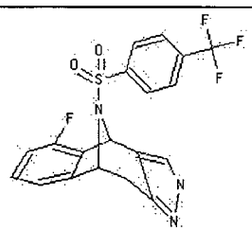
101	 (+)-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-b]pyridine; MS 407.0. ^{1}H-NMR ($CDCl_3$) δ 8.15 (d, J = 5.0 Hz, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.52 (d, J = 8.2 Hz, 1H), 7.40 (s, 1H), 7.13 (d, J = 7.6 Hz, 1H), 6.81 (dd, J = 5.0, 7.6 Hz, 1H), 5.88 (s, 1H), 5.40 (d, J = 5.6 Hz, 1H), 3.53 (dd, J = 5.6, 16.4 Hz, 2H). Prepared as described in Example 8 using 2-bromo-3-pyridinecarboxaldehyde followed by chromatographic separation of regio and stereoisomers.	D
102	(-)-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-b]pyridine; MS 407.0. ^{1}H-NMR ($CDCl_3$) δ 8.15 (d, J = 5.0 Hz, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.52 (d, J = 8.2 Hz, 1H), 7.40 (s, 1H), 7.13 (d, J = 7.6 Hz, 1H), 6.81 (dd, J = 5.0, 7.6 Hz, 1H), 5.88 (s, 1H), 5.40 (d, J = 5.6 Hz, 1H), 3.53 (dd, J = 5.6, 16.4 Hz, 2H). Prepared as described in Example 8 using 2-bromo-3-pyridinecarboxaldehyde followed by chromatographic separation of regio and stereoisomers.	B

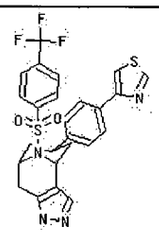
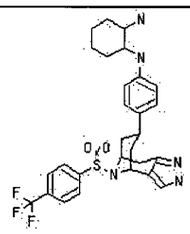
103	 (±)-5-fluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one; MS 438.1 ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 8.1 Hz, 2H), 7.72 (s, 1H), 7.52 (d, J = 8.3 Hz, 2H), 7.00-7.10 (m, 2H), 6.74 (t, J = 8.1 Hz, 1H), 6.35 (s, 1H), 5.47 (s, 1H). Prepared by oxidation of 5-fluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole using the methods described in Example 15.	D
104	 (±)-8-fluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one; MS 438.0 ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 8.2 Hz, 2H), 7.72 (s, 1H), 7.52 (d, J = 8.3 Hz, 2H), 7.03-7.10 (m, 1H), 6.93 (d, J = 7.3 Hz, 1H), 6.73 (t, J = 8.3 Hz, 1H), 6.17 (s, 1H), 5.63 (s, 1H). Prepared by oxidation of 8-fluoro-11-{[4-(trifluoromethyl)phenyl]-sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo-[4,5]cyclohepta[1,2-c]pyrazole using the methods described in Example 15.	D

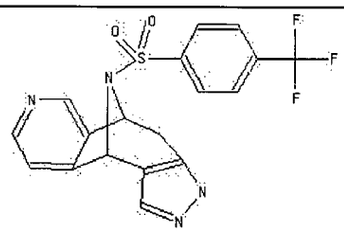
105	(±)-6,7-difluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 443.1 ^{1}H NMR ($CDCl_3$) δ 8.94 (s, 1H), 8.13 (dd, J = 8.3, 2.1 Hz, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.41 (s, 1H), 7.02 (dd, J = 8.8, 6.9 Hz, 1H), 6.84 (dd, J = 8.7, 6.8 Hz, 1H), 5.87 (s, 1H), 5.41 (d, J = 5.4 Hz, 1H), 3.41 (dd, J = 16.5, 5.6 Hz, 1H), 2.83 (d, J = 16.5 Hz, 1H). Prepared as described in Example 9 using 5-(2-bromo-4,5-difluorophenyl)-4-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)cyclohex-2-enone, which was prepared as described in Example 8 using 2-bromo-4,5-difluorobenzaldehyde and sulfonamide **23**.	D
106	 (±)-6-(4-bromophenyl)-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 528.0 ^{1}H NMR ($CDCl_3$) δ 7.88 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.37 (s, 1H), 6.96 (d, J = 8.4 Hz, 2H), 5.44 (s, 1H), 4.69 (s, 1H), 2.96 (dd, J = 17.4 and 7.5 Hz, 1H), 2.69 (m, 2H), 2.13 (m, 2H), 1.86 (m, 2H). Prepared as described in Example 23 using 1-bromo-4-(hepta-1,6-dien-4-yl)benzene.	D

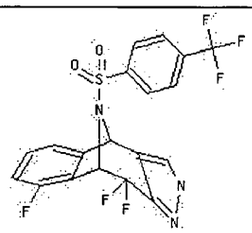
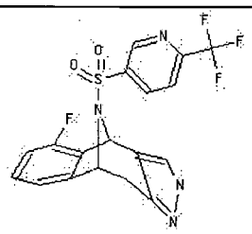
107	 (±)-10-[(4-chlorophenyl)sulfonyl]-6-(pyridin-4-yl)-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 416.1. ^{1}H-NMR ($CDCl_3$) δ 9.11 (s, 1H), 8.66 (d, J = 5.5 Hz, 1H), 7.68 (d, J = 8.8 Hz, 2H), 7.49 (s, 1H), 7.39 (d, J = 8.24 Hz, 2H), 7.15 (d, J = 5.5 Hz, 1H), 5.52 – 5.43 (m, 1H), 4.75 – 4.64 (m, 1H), 3.04 (dd, J = 17.6, 7.7 Hz, 1H), 2.95 – 2.82 (m, 1H), 2.72 (d, J = 18.2 Hz, 1H), 2.33 – 2.19 (m, 2H), 2.03 – 1.95 (m, 2H). Prepared by alkylation of methyl 10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole-6-carboxylate (WO 2007022502) with trimethylsilylethoxymethyl chloride followed by treatment with methoxymethylamine hydrochloride and HATU in THF and Et_3N to afford the amide, which was converted to the ketone with methylmagnesium bromide. The ketone was then treated with ethyl formate and NaOEt in THF, formamidine hydrochloride and NaOEt in EtOH, and 4N HCl/dioxane.	D
108	 (±)-6-(1,3-benzodioxol-5-yl)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 493.1 ^{1}H NMR ($CDCl_3$) δ 8.94 (d, J = 1.9 Hz, 1H), 8.15 (dd, J = 8.2, 1.9 Hz, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.30 (s, 1H), 6.70 (d, J = 7.9 Hz, 1H), 6.58 (d, J = 1.6 Hz, 1H), 6.52 (dd, J = 8.0, 1.6 Hz, 1H), 5.90 (s, 2H), 5.41 (s, 1H), 4.67 (s, 1H), 2.71 (m, 3H), 2.10 (m, 2H), 1.86 (m, 2H). Prepared as described in Example 5 using dialdehyde **100**.	D

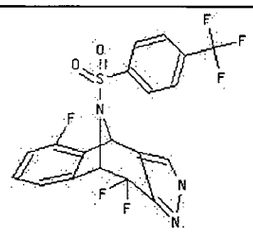
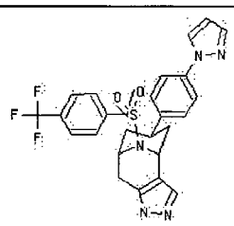
109	(±)-12-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,10,11-tetrahydro-4,10-epimino[1,3]benzodioxolo[5',6':4,5]cyclohepta[1,2-c]pyrazol-7-one; MS 464.0. ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 8.2 Hz, 2H), 7.54 (d, 2H, J = 8.2 Hz), 7.35 (s, 1H), 7.06 (s, 1H), 6.87 (s, 1H), 5.88 (s, 1H), 5.42 (d, J = 5.4 Hz, 1H), 3.38 (dd, J = 16.2, 5.6 Hz, 1H), 2.78 (d, J = 16.4 Hz, 1H).	>100
110	 (-)-6,7-difluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 443.0 ^{1}H NMR ($CDCl_3$) δ 8.94 (s, 1H), 8.13 (dd, J = 8.3, 2.1 Hz, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.41 (s, 1H), 7.02 (dd, J = 8.8, 6.9 Hz, 1H), 6.84 (dd, J = 8.7, 6.8 Hz, 1H), 5.87 (s, 1H), 5.41 (d, J = 5.4 Hz, 1H), 3.41 (dd, J = 16.5, 5.6 Hz, 1H), 2.83 (d, J = 16.5 Hz, 1H). Prepared as described in Example 9 using 5-(2-bromo-4,5-difluorophenyl)-4-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-cyclohex-2-enone, followed by chiral chromatographic separation of stereoisomers.	A
111	(+)-6,7-difluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 443.0 ^{1}H NMR ($CDCl_3$) δ 8.94 (s, 1H), 8.13 (dd, J = 8.3, 2.1 Hz, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.41 (s, 1H), 7.02 (dd, J = 8.8, 6.9 Hz, 1H), 6.84 (dd, J = 8.7, 6.8 Hz, 1H), 5.87 (s, 1H), 5.41 (d, J = 5.4 Hz, 1H), 3.41 (dd, J = 16.5, 5.6 Hz, 1H), 2.83 (d, J = 16.5 Hz, 1H). Prepared as described above for the enantiomer.	D

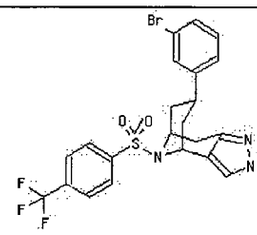
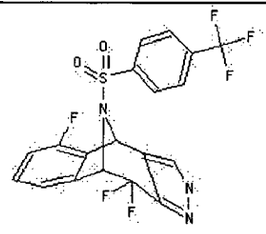
112	 (±)-3-[4-(10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazol-6-yl)phenyl]-1,3-oxazolidin-2-one; MS 533.0. ^{1}H NMR ($CDCl_3$) δ 7.88 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.7 Hz, 2H), 7.42 (s, 1H), 7.02 (d, J = 8.7 Hz, 2H), 5.45 (s, 1H), 4.69 (s, 1H), 4.50 (m, 2H), 4.05 (m, 2H), 2.96 (dd, J = 17.7 and 7.2 Hz, 1H), 2.69 (m, 2H), 2.00 (broad m, 4H). Prepared as described in Example 23 using 1-bromo-4-(hepta-1,6-dien-4-yl)benzene and oxazolidin-2-one.	D
113	(±)-6-[4-(1H-imidazol-1-yl)phenyl]-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 514.0. ^{1}H NMR ($CDCl_3$) δ 8.71 (s, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.48 (s, 1H), 7.39 (broad m, 6H), 5.48 (s, 1H), 4.73 (s, 1H), 2.90 (dd, J = 17.1 and 7.8 Hz, 1H), 2.70 (m, 2H), 2.24 (m, 2H), 1.98 (m, 2H). Prepared as described in Example 23 using 1-bromo-4-(hepta-1,6-dien-4-yl)benzene and imidazole.	D
114	 (-)-5-fluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 424.1. ^{1}H NMR ($CDCl_3$) δ 7.76 (d, J = 7.7 Hz, 2H), 7.50 (d, J = 7.3 Hz, 2H), 7.43 (s, 1H), 6.90-6.97 (m, 1H), 6.84 (d, J = 7.2 Hz, 1H), 6.60 (t, J = 8.6 Hz, 1H), 6.03 (s, 1H), 5.41 (d, 1H, J = 5.6 Hz), 3.56 (dd, J = 16.3, 5.7 Hz, 1H), 2.87 (d, J = 16.2 Hz, 1H). Prepared as described in Example 8 using 6-fluoro-2-iodobenzaldehyde followed by chromatographic separation of regio- and stereoisomers.	B

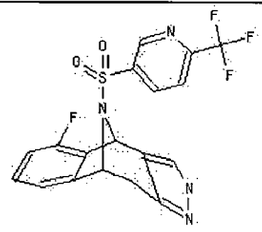
115	(+)-5-fluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 424.1. ^{1}H NMR ($CDCl_3$) δ 7.76 (d, J = 7.7 Hz, 2H), 7.50 (d, J = 7.3 Hz, 2H), 7.43 (s, 1H), 6.90-6.97 (m, 1H), 6.84 (d, J = 7.2 Hz, 1H), 6.60 (t, J = 8.6 Hz, 1H), 6.03 (s, 1H), 5.41 (d, 1H, J = 5.6 Hz), 3.56 (dd, J = 16.3, 5.7 Hz, 1H), 2.87 (d, J = 16.2 Hz, 1H). Prepared as described above for the enantiomer.	D
116	 (±)-6-[4-(1,3-thiazol-4-yl)phenyl]-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 531.1 ^{1}H NMR ($CDCl_3$) δ 8.99 (d, J = 2.2 Hz, 1H), 7.91 (d, J = 8.24 Hz, 2H), 7.80 (d, J = 8.24 Hz, 2H), 7.65 (d, J = 8.8 Hz, 2H), 7.55- 7.50 (m, 2H), 7.13 (d, J = 8.24 Hz, 2H), 5.47 (m, 1H), 4.80 – 4.70 (m, 1H), 3.07 (dd, J = 17.6, 7.7 Hz, 1H), 2.82 – 2.64 (m, 2H), 2.25 – 2.08 (m, 2H), 2.0 – 1.91 (m, 2H).	D
117	 N-[4-(10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazol-6-yl)phenyl]cyclohexane-1,2-diamine; MS 560.0. ^{1}H NMR (DMSO-d_6) δ 7.95 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 8.4 Hz, 4H), 7.33 (s, 1H), 6.74 (d, J = 8.4 Hz, 2H), 6.51 (d, J = 8.4 Hz, 2H), 5.28 (s, 1H), 4.53 (s, 1H), 1.70 (broad m, 8H), 1.21 (m, 4H). Prepared as described in Example 23 using 1-bromo-4-(hepta-1,6-dien-4-yl)benzene and cyclohexane-1,2-diamine.	A

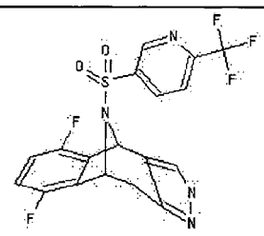
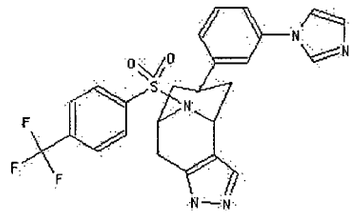
118	 (+)-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminopyrazolo[4',3':4,5]cyclohepta[1,2-c]pyridine; MS 407.0. ^{1}H NMR ($CDCl_3$) δ 8.40 (s, 1H), 8.20 (d, J = 5.0 Hz, 1H), 7.76 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 8.2 Hz, 2H), 7.36 (s, 1H), 6.85 (d, J = 5.0 Hz, 1H), 5.87 (s, 1H), 5.52 (d, J = 5.6 Hz, 1H), 3.51 (dd, J = 5.6, 16.2 Hz, 1H), 2.83 (d, J = 16.2 Hz, 1H). Prepared as described in Example 8 using 3-bromo-4-pyridine-carboxaldehyde followed by chromatographic separation of regio- and stereoisomers.	D
119	(+)-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-c]pyridine; MS 407.0. ^{1}H NMR ($CDCl_3$) δ 8.26 (d, J = 5.0 Hz, 1H), 8.23 (s, 1H), 7.76 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 8.2 Hz, 2H), 7.37 (s, 1H), 7.06 (d, J = 5.0 Hz, 1H), 6.00 (s, 1H), 5.38 (d, J = 5.6 Hz, 1H), 3.49 (dd, J = 5.6, 16.2 Hz, 1H), 2.81 (d, J = 16.2 Hz, 1H). Prepared as described in Example 8 using 3-bromo-4-pyridinecarbox-aldehyde followed by chromatographic separation of regio- and stereoisomers.	D
120	(-)-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-c]pyridine; MS 407.0 ^{1}H NMR ($CDCl_3$) δ 8.26 (d, J = 5.0 Hz, 1H), 8.23 (s, 1H), 7.76 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 8.2 Hz, 2H), 7.37 (s, 1H), 7.06 (d, J = 5.0 Hz, 1H), 6.00 (s, 1H), 5.38 (d, J = 5.6 Hz, 1H), 3.49 (dd, J = 5.6, 16.2 Hz, 1H), 2.81 (d, J = 16.2 Hz, 1H). Prepared as described above for the enantiomer.	A

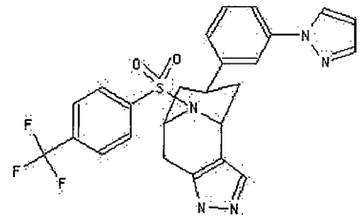
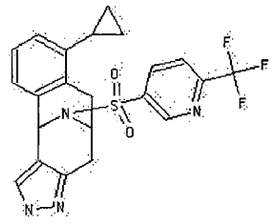
121	 (±)-8,10,10-trifluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 460.1 ^{1}H NMR ($CDCl_3$) δ 7.81 (d, J = 6.8 Hz, 2H), 7.56 (d, J = 7.7 Hz, 2H), 7.49 (s, 1H), 6.99-7.06 (m, 1H), 6.68-6.79 (m, 2H), 5.99 (s, 1H), 5.66 (d, J = 10.2 Hz, 1H). Prepared as described in Example 15 using (±)-8-fluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]-cyclohepta[1,2-c]pyrazol-10(1H)-one.	D
122	 (±)-5-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 425.0 ^{1}H NMR ($CDCl_3$) δ 8.90 (s, 1H), 8.10 (d, J = 8.3 Hz, 1H), 7.55 (d, J = 8.2 Hz, 1H), 7.44 (s, 1H), 6.96-7.03(m, 1H), 6.91 (d, J = 7.3 Hz, 1H), 6.66 (t, 1H, J = 8.4 Hz), 6.08 (s, 1H), 5.44 (d, J = 5.3 Hz, 1H), 3.50 (dd, J = 16.4, 5.7 Hz, 1H), 2.88 (d, J = 16.4 Hz, 1H). Prepared as described in Example 9 using 5-(2-bromo-6-fluorophenyl)-4-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)cyclohex-2-enone which was prepared as described in Example 8 using 6-fluoro-2-iodobenzaldehyde and sulfonamide **23**.	D

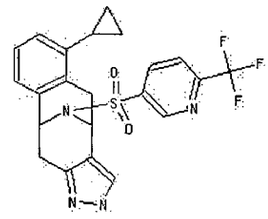
123	 (±)-5,10,10-trifluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 460.0 ^{1}H NMR ($CDCl_3$) δ 7.82 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 8.2 Hz, 2H), 7.49 (s, 1H), 6.98-7.10 (m, 2H), 6.68 (t, J = 8.0 Hz, 1H), 6.18 (s, 1H), 5.49 (d, J = 10.6 Hz, 1H). Prepared by fluorination of 5-fluoro-11-{[4-(trifluoromethyl)-phenyl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]-cyclohepta[1,2-c]pyrazol-10(1H)-one using the methods described in Example 15.	D
124	 (±)-6-[4-(1*H*-pyrazol-1-yl)phenyl]-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 514.1 ^{1}H NMR ($CDCl_3$) δ 7.91-7.89 (m, 3H), 7.74-7.67 (m, 3H), 7.60 (d, J = 8.3 Hz, 2H), 7.46 (s, 1H), 7.15 (d, J = 8.6 Hz, 2H), 6.47 (dd, J = 2.0, 1.9 Hz, 1H), 5.46 (s, 1H), 4.72 (bs, 1H), 2.99 (dd, J = 17.8, 7.7 Hz, 1H), 2.77-2.69 (m, 2H), 2.22 (dd, J = 12.8, 4.5 Hz, 1H), 2.14 (dd, J = 12.8, 3.9 Hz, 1H), 1.96-1.87 (m, 2H). Prepared as described in Example 23 using 1-bromo-4-(hepta-1,6-dien-4-yl)benzene.	D

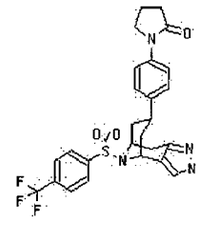
125	 (±)-6-(3-bromophenyl)-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 526.0. ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H), 7.50 (s, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.21 (s, 1H), 1.16 (t, J = 7.8 Hz, 1H), 7.00 (d, J = 7.8 Hz, 1H), 5.46 (s, 1H), 4.71 (s, 1H), 2.96 (dd, J = 17.4 and 7.8 Hz, 1H), 2.70 (m, 2H), 2.17 (m, 2H), 1.90 (m, 2H). Prepared as described in Example 23.	D
126	(±)-6-(1*H*-tetrazol-5-yl)-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 440.1. ^{1}H NMR (MeOD) δ 7.93 (d, J = 8.2 Hz, 2H), 7.70 (d, J = 8.3 Hz, 2H), 7.48 (s, 1H), 5.50 (s, 1H), 4.74 (m, 1H), 3.23 (m, 1H), 2.86 (dd, J = 17.5, 7.6 Hz, 1H), 2.68 (d, J = 17.5 Hz, 1H), 2.18 (m, 1H).	A
127	 (-)-5,10,10-trifluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 460.1 ^{1}H NMR ($CDCl_3$) δ 7.82 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 8.2 Hz, 2H), 7.49 (s, 1H), 6.98-7.10 (m, 2H), 6.68 (t, J = 8.0 Hz, 1H), 6.18 (s, 1H), 5.49 (d, J = 10.6 Hz, 1H). Prepared by fluorination of 5-fluoro-11-{[4-(trifluoromethyl)-phenyl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one using the methods described in Example 15 followed by chiral chromatographic separation of stereoisomers.	D

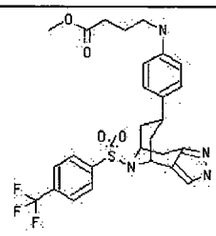
128	(+)-5,10,10-trifluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 460.1 ^{1}H NMR ($CDCl_3$) δ 7.82 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 8.2 Hz, 2H), 7.49 (s, 1H), 6.98-7.10 (m, 2H), 6.68 (t, J = 8.0 Hz, 1H), 6.18 (s, 1H), 5.49 (d, J = 10.6 Hz, 1H). Prepared as described above for the enantiomer.	D
129	 (-)-5-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 425.1 ^{1}H NMR ($CDCl_3$) δ 8.90 (s, 1H), 8.10 (dd, J = 8.2, 1.7 Hz, 1H), 7.55 (dd, J = 8.2, 0.6 Hz, 1H), 7.46 (s, 1H), 6.96-7.03(m, 1H), 6.91 (d, 1H, J = 7.3 Hz), 6.66 (t, 1H, J = 8.43 Hz), 6.08 (s, 1H), 5.44 (d, 1H, J = 5.6 Hz), 3.50 (dd, J = 16.4, 5.7 Hz, 1H), 2.88 (d, J = 16.4 Hz, 1H). Prepared as described in Example 9 using 5-(2-bromo-6-fluorophenyl)-4-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)cyclohex-2-enone which was prepared as described in Example 8 using 6-fluoro-2-iodobenzaldehyde and sulfonamide **23** followed by chiral chromatographic separation of stereoisomers.	>10
130	(+)-5-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 425.1 ^{1}H NMR ($CDCl_3$) δ 8.90 (s, 1H), 8.10 (dd, J = 8.2, 1.7 Hz, 1H), 7.55 (dd, J = 8.2, 0.6 Hz, 1H), 7.46 (s, 1H), 6.96-7.03(m, 1H), 6.91 (d, 1H, J = 7.3 Hz), 6.66 (t, 1H, J = 8.43 Hz), 6.08 (s, 1H), 5.44 (d, 1H, J = 5.6 Hz), 3.50 (dd, J = 16.4, 5.7 Hz, 1H), 2.88 (d, J = 16.4 Hz, 1H). Prepared as described above for the enantiomer.	D

131	 (±)-5,8-difluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 443.0 ^{1}H NMR ($CDCl_3$) δ 8.93 (d, J = 1.7 Hz, 1H), 8.16 (dd, J = 8.3, 2.2 Hz, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.48 (s, 1H), 6.67 (t, J = 5.4 Hz, 2H), 6.08 (s, 1H), 5.61 (d, J = 5.6 Hz, 1H), 3.51 (dd, J = 16.6, 5.7 Hz, 1H), 2.95 (d, J = 16.6 Hz, 1H). Prepared as described in Example 9 using 5-(2-bromo-3,6-difluorophenyl)-4-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)cyclohex-2-enone which was prepared as described in Example 8 using 2-bromo-3,6-difluorobenzaldehyde and sulfonamide **23**.	D
132	 (±)-6-[3-(1H-imidazol-1-yl)phenyl]-10-{[4-(trifluoromethyl)phenyl]-sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 514.1. ^{1}H NMR ($CDCl_3$) δ 7.84 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 8.3 Hz, 2H), 7.37 (m, 2H), 7.22 (m, 3H), 7.10 (m, 2H), 5.43 (s, 1H), 4.68 (m, 1H), 2.85 (2H), 2.65 (d, J = 17.1 Hz, 1H), 2.19 (m, 2H), 1.88 (m, 2H). Prepared as described in Example 23 using imidazole.	D

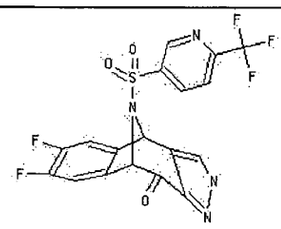
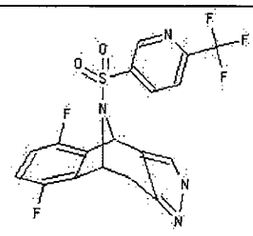
133	 (±)-6-[3-(1H-pyrazol-1-yl)phenyl]-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 514.1 ^{1}H NMR ($CDCl_3$) δ 7.87 (m, 3H), 7.64 (m, 10H), 7.45 (m, 2H), 7.32 (m, 3H), 7.99 (m, 1H), 6.44 (m, 1H), 5.42 (s, 1H), 4.64 (m, 1H), 3.77 (m, 1H), 3.60 (m, 2H), 2.85 (m, 2H), 2.65 (d, J = 17.0 Hz, 1H), 2.16 (m, 2H), 1.88 (m, 2H). Prepared as described in Example 23.	D
134	 (±)-7-cyclopropyl-12-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,11-tetrahydro-3H-5,11-epiminobenzo[4,5]cycloocta[1,2-c]pyrazole; MS 461.0 ^{1}H NMR ($CDCl_3$) δ 8.88 (d, *J* = 1.9 Hz, 1H), 7.87 (dd, *J* = 1.9, 8.2 Hz, 1H), 7.50 (s, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.06 (t, *J* = 4.4 Hz, 1H), 6.76-6.71 (m, 1H), 6.06 (s, 1H), 5.05-5.00 (m, 1H), 3.42 (dd, *J* = 5.6, 16.5 Hz, 1H), 3.30 (dd, *J* = 9.9, 18.5 Hz, 1H), 2.95 (d, *J* = 16.5 Hz, 1H), 2.38 (d, *J* = 18.6 Hz, 1H); 1.32-1.23 (m, 1H); 0.84-0.72 (m, 2H), 0.46-0.37 (m, 1H), 0.30-0.24 (m, 1H). Prepared as described in Example 13.	D

135	 (±)-6-cyclopropyl-12-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,10,11-tetrahydro-1H-4,10-epiminobenzo[5,6]cycloocta[1,2-c]pyrazole; MS 461.0 ^{1}H NMR ($CDCl_3$) δ 9.07 (d, *J* = 2.0 Hz, 1H), 8.20 (dd, *J* = 1.9, 8.2 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.54 (s, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 5.64 (d, *J* = 5.7 Hz, 1H), 5.53 (d, *J* = 5.1 Hz, 1H), 3.35 (dd, *J* = 6.3, 16.5 Hz, 1H), 3.16 (dd, *J* = 5.8, 17 Hz, 1H), 3.00 (d, *J* = 11.1 Hz, 1H), 2.94 (d, *J* = 11.4 Hz, 1H); 1.58-1.49 (m, 1H); 0.91-0.77 (m, 2H); 0.51-0.35 (m, 2H). Prepared as described in Example 13.	D
136	(±)-10-[(4-chlorophenyl)sulfonyl]-6-(1-methyl-1H-1,2,3-triazol-5-yl)-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 419.1 ^{1}H NMR ($CDCl_3$) δ 7.68 (d, J = 8.2 Hz, 2H), 7.44 (s, 1H), 7.37 (d, J = 8.2 Hz, 2H), 7.30 (s, 1H), 5.42-5.43 (m, 1H), 4.63-4.65 (m, 1H), 4.11 (s, 3H), 2.91-2.96 (m, 2H), 2.69 (d, J = 17.6 Hz, 1H), 1.96-2.16 (m, 4H).	D
137	10-[(4-chlorophenyl)sulfonyl]-6-(1-methyl-1H-1,2,3-triazol-4-yl)-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole (enantiomer A); MS 419.1 ^{1}H NMR ($CDCl_3$) δ 7.68 (d, J = 8.0 Hz, 2H), 7.51 (s, 1H), 7.46 (s, 1H), 7.38 (d, J = 8.0 Hz, 2H), 5.45-5.47 (m, 1H), 4.66-4.69 (m, 1H), 3.96 (s, 3H), 2.98-3.07 (m, 2H), 2.67 (d, J = 17.6 Hz, 1H), 1.92-2.16 (m, 4H). Prepared from the racemic mixture by chiral separation.	A

138	10-[(4-chlorophenyl)sulfonyl]-6-(1-methyl-1H-1,2,3-triazol-4-yl)-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole (enantiomer B); MS 419.1 ^{1}H NMR ($CDCl_3$) δ 7.67 (d, J = 8.3 Hz, 2H), 7.45 (s, 1H), 7.37 (s, 1H), 7.36 (d, J = 8.3 Hz, 2H), 5.45-5.47 (m, 1H), 4.65-4.68 (m, 1H), 3.85 (s, 3H), 2.87-2.97 (m, 2H), 2.62 (d, J = 17.1 Hz, 1H), 1.88-2.18 (m, 4H). Prepared from the racemic mixture by chiral separation	B
139	(-)-10-[(4-chlorophenyl)sulfonyl]-6-(2-methyl-2H-1,2,3-triazol-4-yl)-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 419.1 ^{1}H NMR ($CDCl_3$) δ 7.64 (d, J = 8.9 Hz, 2H), 7.28-7.33 (m, 3H), 7.22 (s, 1H) 5.40-5.43 (m, 1H), 4.61-4.63 (m, 1H), 4.07 (s, 3H), 3.05-3.08 (m, 1H), 2.85 (dd, J = 17.2, 7.8 Hz, 1H), 2.62 (d, J = 17.2 Hz, 1H), 2.00-2.18 (m, 4H).	>300
140	(+)-10-[(4-chlorophenyl)sulfonyl]-6-(2-methyl-2H-1,2,3-triazol-4-yl)-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 419.1 ^{1}H NMR ($CDCl_3$) δ 7.70 (d, J = 8.2 Hz, 2H), 7.55 (s, 1H), 7.41 (d, J = 8.2 Hz, 2H), 7.30 (s, 1H) 5.41-5.43 (m, 1H), 4.63-4.65 (m, 1H), 4.08 (s, 3H), 3.01-3.08 (m, 2H), 2.80 (d, J = 17.8 Hz, 1H), 2.03-2.15 (m, 4H).	C
141	 (±)-1-[4-(10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazol-6-yl)phenyl]pyrrolidin-2-one; MS 531.0 ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.46 (s, 1H), 7.06 (d, J = 8.4 Hz, 2H), 5.44 (s, 1H), 4.69 (s, 1H), 3.85 (t, J = 7.2 Hz, 2H), 3.00 (dd, J = 17.4 and 7.5 Hz, 1H), 2.68 (m, 4H), 2.18 (m, 4H), 1.87 (m, 2H). Prepared as described in Example 23 using 1-bromo-4-(hepta-1,6-dien-4-yl)benzene and pyrrolidin-2-one.	D

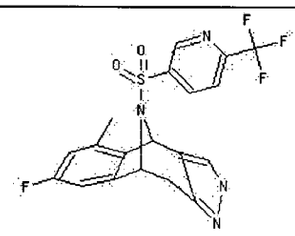
142	 (±)-methyl 4-{[4-(10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazol-6-yl)phenyl]amino}butanoate; MS 563.0. ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.43 (s, 1H), 6.98 (d, J = 7.8 Hz, 2H), 6.87 (d, J = 7.8 Hz, 2H), 5.43 (s, 1H), 4.67 (s, 1H), 3.69 (s, 3H), 3.26 (m, 2H), 2.96 (dd, J = 16.5 and 7.2 Hz, 1H), 2.66 (m, 2H), 2.45 (m, 2H), 2.04 (m, 4H), 1.94 (m, 2H). Prepared as described in Example 23 using 1-bromo-4-(hepta-1,6-dien-4-yl)benzene and methyl 4-aminobutanoate.	D
143	(±)-4-[4-(10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazol-6-yl)phenyl]morpholin-3-one; MS 547.0 ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.40 (s, 1H), 7.23 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 5.45 (s, 1H), 4.69 (s, 1H), 4.35 (s, 2H), 4.04 (m, 2H), 3.74 (m, 2H), 2.96 (m, 1H), 2.73 (m, 2H), 2.13 (m, 2H), 1.86 (m, 2H). Prepared as described in Example 23 using 1-bromo-4-(hepta-1,6-dien-4-yl)benzene and morpholin-3-one.	B
144	(±)-methyl (2-{[4-(10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazol-6-yl)phenyl]amino}-ethoxy)acetate; MS 579.0. ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 8.1 Hz, 2H), 7.68 (d, J = 8.1 Hz, 2H), 7.47 (s, 1H), 7.00 (s, 4H), 5.44 (s, 1H), 4.68 (s, 1H), 4.19 (s, 2H), 3.87 (t, J = 4.8 Hz, 2H), 3.80 (s, 3H), 3.45 (t, J = 4.5 Hz, 2H), 3.00 (dd, J = 17.7 and 7.8 Hz, 1H), 2.65 (m, 2H), 2.12 (m, 2H), 1.86 (m, 2H). Prepared as described in Example 23 using 1-bromo-4-(hepta-1,6-dien-4-yl)benzene and methyl 2-(2-aminoethoxy)acetate.	A

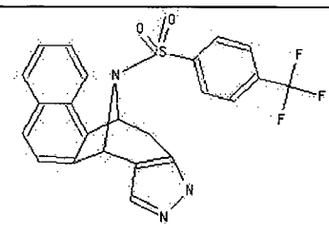
145	(±)-(2-{[4-(10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazol-6-yl)phenyl]amino}ethoxy)acetic acid; MS 565.0. ^{1}H NMR (DMSO-d_6) δ 8.68 (s, 1H), 7.93 (d, J = 8.1 Hz, 2H), 7.68 (d, J = 8.1 Hz, 2H), 7.34 (s, 1H), 6.80 (d, J = 8.1 Hz, 2H), 6.60 (d, J = 8.1 Hz, 2H), 5.39 (s, 1H), 4.68 (s, 1H), 2.70 (m, 2H), 1.77 (m, 4H). Prepared as described in Example 23 using 1-bromo-4-(hepta-1,6-dien-4-yl)benzene and 2-(2-aminoethoxy)acetic acid.	D
146	(±)-methyl N-[4-(10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazol-6-yl)phenyl]-b-alaninate; MS 549.0. ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.33 (s, 1H), 6.95 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 5.44 (s, 1H), 4.69 (s, 1H), 3.72 (s, 3H), 3.52 (t, J = 6.3 Hz, 2H), 3.00 (dd, J = 17.7 and 7.8 Hz, 1H), 2.70 (m, 4H), 2.12 (m, 2H), 1.86 (m, 2H). Prepared as described in Example 23 using 1-bromo-4-(hepta-1,6-dien-4-yl)benzene and methyl 3-aminopropanoate.	D
147	(±)-6-[4-(1H-1,2,4-triazol-1-yl)phenyl]-10-{[4-(trifluoromethyl)phenyl]-sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole; MS 515.0. ^{1}H NMR ($CDCl_3$) δ 8.63 (s, 1H), 8.16 (s, 1H), 7.89 (d, J = 8.1 Hz, 2H), 7.70 (d, J = 8.1 Hz, 2H), 7.61 (d, J = 8.7 Hz, 2H), 7.51 (s, 1H), 7.23 (d, J = 8.7 Hz, 2H), 5.49 (s, 1H), 4.74 (s, 1H), 3.00 (dd, J = 17.4 and 7.5 Hz, 1H), 2.80 (m, 2H), 2.19 (m, 2H), 1.94 (m, 2H). Prepared as described in Example 23 using 1-bromo-4-(hepta-1,6-dien-4-yl)benzene and 4H-1,2,4-triazole.	C

148	 (±)-6,7-difluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one; MS 457.0 ^{1}H NMR ($CDCl_3$) δ 8.93 (d, J = 1.5 Hz, 1H), 8.15 (dd, J = 8.2, 1.7 Hz, 1H), 7.71 (s, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.21-7.28 (m, 1H), 7.09 (dd, J = 8.4, 6.9 Hz, 1H), 6.21 (s, 1H), 5.43 (s, 1H). Prepared by oxidation of 6,7-difluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epimino-benzo-[4,5]cyclohepta[1,2-c]pyrazole using the methods described in Example 15.	D
149	 (-)-5,8-difluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 443.1 ^{1}H NMR ($CDCl_3$) δ 8.93 (d, J = 1.7 Hz, 1H), 8.16 (dd, J = 8.3, 2.2 Hz, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.48 (s, 1H), 6.67 (t, J = 5.4 Hz, 2H), 6.08 (s, 1H), 5.61 (d, J = 5.6 Hz, 1H), 3.51 (dd, J = 16.6, 5.7 Hz, 1H), 2.95 (d, J = 16.6 Hz, 1H). Prepared as described in Example 9 using 5-(2-bromo-3,6-difluorophenyl)-4-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)cyclohex-2-enone, followed by chiral chromatographic separation of stereoisomers.	C
150	(+)-5,8-difluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 443.1 ^{1}H NMR ($CDCl_3$) δ 8.93 (d, J = 1.7 Hz, 1H), 8.16 (dd, J = 8.3, 2.2 Hz, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.48 (s, 1H), 6.67 (t, J = 5.4 Hz, 2H), 6.08 (s, 1H), 5.61 (d, J = 5.6 Hz, 1H), 3.51 (dd, J = 16.6, 5.7 Hz, 1H), 2.95 (d, J = 16.6 Hz, 1H). Prepared as described above for the enantiomer.	D

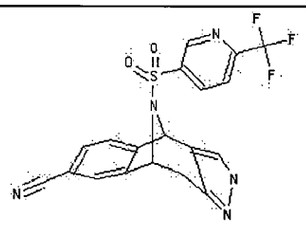
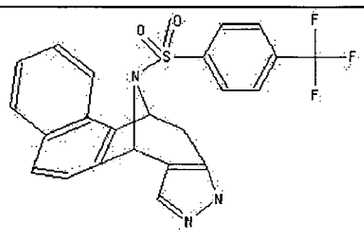
151	(±)-7-fluoro-5-methyl-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 439.1. ^{1}H NMR ($CDCl_3$) δ 8.90 (s, 1H), 8.07 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.40 (s, 1H), 6.91 (d, J = 6.5 Hz, 1H), 6.62 (d, J = 8.5 Hz, 1H), 5.83 (s, 1H), 5.33 (d, J = 5.4 Hz, 1H), 3.44 (dd, J = 16.4, 5.6 Hz, 1H), 2.83 (d, J = 16.4 Hz, 1H). Prepared as described in Example 9 using 5-(2-bromo-4-fluoro-6-methylphenyl)-4-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)cyclohex-2-enone, which was prepared as described in Example 8 using 2-bromo-4-fluoro-6-methylbenzaldehyde and sulfonamide **23**.	D
152	(±)-N-[4-(10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazol-6-yl)phenyl]acetamide; MS 505.0 ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 8.7 Hz, 2H), 7.70 (d, J = 8.7 Hz, 2H), 7.46 (s, 1H), 7.40 (d, J = 9.0 Hz, 2H), 7.18 (s, 1H), 7.01 (d, J = 9.0 Hz, 2H), 5.44 (s, 1H), 4.69 (s, 1H), 3.00 (dd, J = 17.1, 7.2 Hz, 1H), 2.66 (m, 2H), 2.18 (s, 3H), 2.20 (m, 2H), 1.87 (m, 2H). Prepared as described in Example 23 using 1-bromo-4-(hepta-1,6-dien-4-yl)benzene and acetamide.	D
153	(±)-1-[4-(10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazol-6-yl)phenyl]azetidin-2-one; MS 517.0 ^{1}H NMR (CD_3OD) δ 7.94 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H), 7.38 (s, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 5.45 (s, 1H), 4.70 (s, 1H), 3.66 (t, J = 4.5 Hz, 2H), 3.10 (t, J = 4.5 Hz, 2H), 2.85 (m, 3H), 2.10 (m, 2H), 1.87 (m, 2H). Prepared as described in Example 23 using 1-bromo-4-(hepta-1,6-dien-4-yl)benzene and azetidin-2-one.	D
154	(±)-1-[4-(10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazol-6-yl)phenyl]ethanone; MS 490.0. ^{1}H NMR ($CDCl_3$) δ 7.87 (m, 4H), 7.64 (d, J = 8.7 Hz, 2H), 7.38 (s, 1H), 7.17 (d, J = 8.7 Hz, 2H), 5.46 (s, 1H), 4.71 (s, 1H), 2.87 (m, 2H), 2.66 (m, 1H), 2.60 (s, 3H), 2.20 (m, 2H), 1.90 (m, 2H). Prepared as described in Example 27.	C

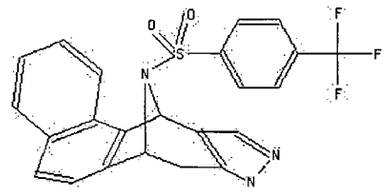
155	(±)-6-(trifluoromethyl)-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 474.0 ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.1 Hz, 2H), 7.50-7.47 (m, 3H), 7.34 (s, 1H), 7.24 (d, J = 7.2 Hz, 1H), 7.01 (d, J = 7.2 Hz, 1H), 5.90 (s, 1H), 5.45 (d, J = 6.0 Hz, 1H), 3.58 (dd, J = 6.0, 16.5 Hz, 1H), 2.90 (d, J = 16.5 Hz, 1H). Prepared as described in Example 8 using 2-bromo-5-(trifluoromethyl)benzaldehyde, followed by chromatographic separation of regioisomers.	D
156	(±)-7-(trifluoromethyl)-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 474.1 ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.1 Hz, 2H), 7.50-7.47 (m, 3H), 7.28-7.26 (m, 1H), 7.20 (d, J = 7.8 Hz, 1H), 7.15 (s, 1H), 5.91 (s, 1H), 5.45 (d, J = 5.7 Hz, 1H), 3.58 (dd, J = 5.4, 16.5 Hz, 1H), 2.89 (d, J = 16.5 Hz, 1H). Prepared as described in Example 8 using 2-Bromo-5-(trifluoromethyl)benzaldehyde followed by chromatographic separation of regioisomers.	D
157	(±)-6,7,10,10-tetrafluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 479.0. ^{1}H NMR ($CDCl_3$): δ 9.01 (s, 1H), 8.22 (d, J = 8.3 Hz, 1H), 7.72 (d, J = 8.3 Hz, 1H), 7.52 (s, 1H), 7.30-7.20 (m, 1H), 7.02-6.96 (m, 1H), 6.05 (s, 1H), 5.52 (d, J = 10.1 Hz, 1H). Prepared by fluorination of 6,7-difluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo-[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one using the methods described in Example 15.	D

158	 (-)-7-fluoro-5-methyl-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 439.1. ^{1}H NMR ($CDCl_3$): δ 8.90 (s, 1H), 8.07 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 8.23 Hz, 1H), 7.40 (s, 1H), 6.91 (d, J = 6.5 Hz, 1H), 6.62 (d, J = 8.5 Hz, 1H), 5.83 (s, 1H), 5.33 (d, J = 5.4 Hz, 1H), 3.44 (dd, J = 16.4, 5.6 Hz, 1H), 2.83 (d, J = 16.4 Hz, 1H). Prepared as described in Example 9 using 5-(2-bromo-4-fluoro-6-methylphenyl)-4-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)cyclo-hex-2-enone, followed by chiral chromatographic separation of stereoisomers.	>10
159	(+)-7-fluoro-5-methyl-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 439.1. ^{1}H NMR ($CDCl_3$): δ 8.90 (s, 1H), 8.07 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 8.23 Hz, 1H), 7.40 (s, 1H), 6.91 (d, J = 6.5 Hz, 1H), 6.62 (d, J = 8.5 Hz, 1H), 5.83 (s, 1H), 5.33 (d, J = 5.4 Hz, 1H), 3.44 (dd, J = 16.4, 5.6 Hz, 1H), 2.83 (d, J = 16.4 Hz, 1H). Prepared as described above for the enantiomer.	D

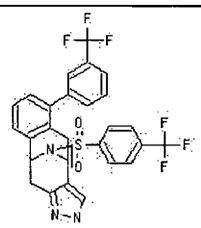
160	 13-{[4-(trifluoromethyl)phenyl]sulfonyl}-7,10,11,12-tetrahydro-7,12-epiminonaphtho[2',1':4,5]cyclohepta[1,2-c]pyrazole; MS 456.1. ^{1}H-NMR ($CDCl_3$) (Diastereomers) δ 7.71-7.60 (m, 2H), 7.67 (m, 2H), 7.62 (d, *J* = 8.2 Hz, 4H), 7.51 (t, *J* = 7.2 Hz, 2H), 7.45-7.37 (m, 2H), 7.46 (d, *J* = 8.6 Hz, 1H), 7.43 (s, 1H), 7.41 (m, 1H), 7.39 (s, 1H), 7.17 (d, *J* = 8.6 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 4H), 7.02 (d, *J* = 8.6 Hz, 1H), 6.27 (s, 1H), 5.93 (s, 1H), 5.85 (d, *J* = 5.5 Hz, 1H), 5.52 (d, *J* = 5.5 Hz, 1H), 3.60 (dd, *J* = 5.5, 16.0 Hz, 1H), 3.58 (dd, *J* = 5.5, 16.0 Hz, 1H), 2.98 (d, *J* = 16.0 Hz, 1H) 2.90 (d, *J* = 16.0 Hz, 1H). Prepared as described in Example 8 using 1-bromo-2-naphthalene-carboxaldehyde.	D
161	(-)-5-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one; MS 439.0. ^{1}H NMR ($CDCl_3$): δ 8.96 (d, *J* = 1.8 Hz, 1H), 8.21 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.77 (s, 1H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.13-7.02 (m, 2H), 6.74 (t, *J* = 8.2 Hz, 1H), 6.51 (s, 1H), 5.57 (s, 1H). Prepared by oxidation of 5-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole using the methods described in Example 15.	D
162	(±)-7-(4-fluorophenyl)-12-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,11-tetrahydro-3H-5,11-epiminobenzo[4,5]cycloocta[1,2-c]pyrazole; MS 514.1. ^{1}H NMR ($CDCl_3$) δ 7.61 (d, *J* = 7.9 Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 2H), 7.41 (s, 1H), 7.25 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.17 (t, *J* = 7.4 Hz,1H), 7.02 (t, *J* = 8.7 Hz, 2H), 6.89 (dd, *J* = 1.4, 7.5 Hz, 1H), 6.83-6.79 (m, 2H), 6.12 (s, 1H), 4.77-4.72 (m, 1H), 3.26 (dd, *J* = 5.6, 15.9 Hz, 1H), 2.87-2.81 (m, 1H), 2.75 (d, *J* = 16.9 Hz, 1H), 2.28 (d, *J* = 18.6 Hz, 1H). Prepared as described in Example 12.	D

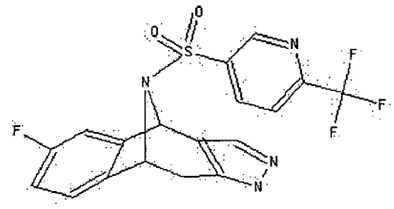
163	(±)-12-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,10,11-tetrahydro-1H-4,10-epiminobenzo[5,6]cycloocta[1,2-c]pyrazole; MS 419.9. ^{1}H NMR ($CDCl_3$) δ 7.90 (d, J = 8.1 Hz, 2H), 7.64 (d, J = 8.2 Hz, 2H), 7.40 (s, 1H), 7.19-7.09 (m, 3H), 6.93 (d, J = 7.7 Hz, 1H), 5.53 (d, J = 5.3 Hz, 1H), 5.49 (d, J = 5.2 Hz, 1H), 3.32 (dd, J = 6.1, 16.5 Hz, 1H), 3.16 (dd, J = 5.7, 15.9 Hz, 1H), 2.85 (d, J = 16.3 Hz, 1H), 2.73 (d, J = 16.4 Hz, 1H). Prepared as described in Example 11.	D
164	(±)-12-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,11-tetrahydro-3H-5,11-epiminobenzo[4,5]cycloocta[1,2-c]pyrazole; MS 419.9. ^{1}H NMR ($CDCl_3$) δ 7.62 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.33 (s, 1H), 7.15 (d, *J* = 7.4 Hz, 1H), 7.06 (d, *J* = 7.4 Hz, 1H), 6.95 (dt, *J* = 1.5, 7.5 Hz, 1H), 6.59 (d, *J* = 7.6 Hz, 1H), 6.01 (s, 1H), 4.88-4.84 (m, 1H), 3.24 (dd, *J* = 6.1, 16.1 Hz, 1H), 3.08 (d, *J* = 9.6, 17.9 Hz, 1H), 2.75 (dd, *J* = 1.1, 17.3 Hz, 1H); 2.46 (d, *J* = 17.9 Hz, 1H). Prepared as described in Example 11.	D
165	(±)-6-(4-fluorophenyl)-12-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,10,11-tetrahydro-1H-4,10-epiminobenzo[5,6]cycloocta[1,2-c]pyrazole; MS 514.1 ^{1}H NMR ($CDCl_3$) δ 7.90 (d, *J* = 8.2 Hz, 2H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.30 (s, 1H), 7.25-7.18 (m, 2H), 7.08-6.93 (m, 5H), 5.59 (d, *J* = 5.3 Hz, 1H), 5.44 (d, *J* = 5.5 Hz, 1H), 3.20 (dd, *J* = 5.7, 16.0 Hz, 1H), 3.04 (dd, *J* = 5.4, 16.3 Hz, 1H), 2.92 (d, *J* = 16.8 Hz, 1H), 2.42 (d, *J* = 15.7 Hz, 1H). Prepared as described in Example 12.	D
166	5,10,10-trifluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 461.0. ^{1}H NMR ($CDCl_3$): δ 8.96 (s, 1H), 8.18 (d, *J* = 8.3 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.57 (s, 1H), 7.18-7.07 (m, 2H), 6.82-6.76 (m, 1H), 6.23 (s, 1H), 5.54 (d, *J* = 10.4 Hz, 1H). Prepared by fluorination of 5-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo-[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one using the methods described in Example 15.	D

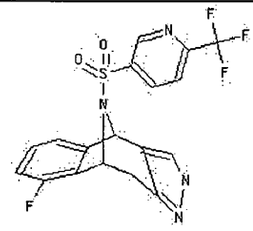
167	 (±)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole-7-carbonitrile; MS 432.0 ^{1}H NMR ($CDCl_3$): δ 8.92 (d, J = 2.0 Hz, 1H), 8.13 (dd, J = 8.2, 2.1 Hz, 1H), 7.61 (d, J = 8.2 Hz, 1H), 7.49 (s, 1H), 7.41 (s, 1H), 7.38 (dd, J = 7.8, 1.4 Hz, 1H), 7.14 (d, J = 7.8 Hz, 1H), 6.00 (s, 1H), 5.49 (d, J = 5.3 Hz, 1H), 3.42 (dd, J = 16.6, 5.7 Hz, 1H), 2.83 (d, J = 16.6 Hz, 1H). Prepared as described in Example 9 using 3-bromo-4-(5-oxo-2-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)cyclohex-3-enyl)benzonitrile, which was prepared as described in Example 8 using 2-bromo-4-cyanobenzaldehdye and sulfonamide **23**.	D
168	 (+)-13-{[4-(trifluoromethyl)phenyl]sulfonyl}-7,10,11,12-tetrahydro-7,12-epiminonaphtho[2',1':4,5]cyclohepta[1,2-c]pyrazole; MS 456.1. ^{1}H-NMR ($CDCl_3$) δ 7.67 (m, 2H), 7.62 (d, J = 8.2 Hz, 2H), 7.51 (t,J = 7.2 Hz, 1H), 7.45-7.37 (m, 2H), 7.39 (s, 1H), 7.15 (d, J = 8.2 Hz, 2H), 7.02 (d, J = 8.6 Hz, 1H), 5.93 (s, 1H), 5.85 (d, J = 5.5 Hz, 1H), 3.60 (dd, J = 5.5, 16.0 Hz, 1H), 2.98 (d, J = 16.0 Hz, 1H). Prepared as described in Example 8 using 1-bromo-2-naphthalenecarboxaldehyde, followed by chromatographic separation of regio- and stereoisomers.	D

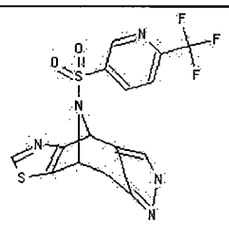
169	(-)-13-{[4-(trifluoromethyl)phenyl]sulfonyl}-7,10,11,12-tetrahydro-7,12-epiminonaphtho[2',1':4,5]cyclohepta[1,2-c]pyrazole; MS 456.1. ^{1}H-NMR ($CDCl_3$) δ 7.67 (m, 2H), 7.62 (d, J = 8.2 Hz, 2H), 7.51 (t,J = 7.2 Hz, 1H), 7.45-7.37 (m, 2H), 7.39 (s, 1H), 7.15 (d, J = 8.2 Hz, 2H), 7.02 (d, J = 8.6 Hz, 1H), 5.93 (s, 1H), 5.85 (d, J = 5.5 Hz, 1H), 3.60 (dd, J = 5.5, 16.0 Hz, 1H), 2.98 (d, J = 16.0 Hz, 1H). Prepared as described above for the enantiomer.	C
170	 (+)-13-{[4-(trifluoromethyl)phenyl]sulfonyl}-7,8,9,12-tetrahydro-7,12-epiminonaphtho[1',2':4,5]cyclohepta[1,2-c]pyrazole; MS 456.1. ^{1}H-NMR ($CDCl_3$) δ 7.71-7.60 (m, 2H), 7.62 (d, J = 8.2 Hz, 2H), 7.51 (t, J = 7.2 Hz, 1H), 7.46 (d, J = 8.6 Hz, 1H), 7.43 (s, 1H), 7.41 (m, 1H), 7.17 (d, J = 8.6 Hz, 1H), 7.15 (d, J = 8.2 Hz, 2H), 6.27 (s, 1H), 5.52 (d, J = 5.5 Hz, 1H), 3.58 (dd, J = 5.5, 16.0 Hz, 1H), 2.90 (d, J = 16.0 Hz, 1H). Prepared as described in Example 8 using 1-bromo-2-naphthalenecarboxaldehyde, followed by chromatographic separation of regio- and stereoisomers.	D
171	(-)-13-{[4-(trifluoromethyl)phenyl]sulfonyl}-7,8,9,12-tetrahydro-7,12-epiminonaphtho[1',2':4,5]cyclohepta[1,2-c]pyrazole; MS 456.1. ^{1}H-NMR ($CDCl_3$) δ 7.71-7.60 (m, 2H), 7.62 (d, J = 8.2 Hz, 2H), 7.51 (t, J = 7.2 Hz, 1H), 7.46 (d, J = 8.6 Hz, 1H), 7.43 (s, 1H), 7.41 (m, 1H), 7.17 (d, J = 8.6 Hz, 1H), 7.15 (d, J = 8.2 Hz, 2H), 6.27 (s, 1H), 5.52 (d, J = 5.5 Hz, 1H), 3.58 (dd, J = 5.5, 16.0 Hz, 1H), 2.90 (d, J = 16.0 Hz, 1H). Prepared as described above for the enantiomer.	C

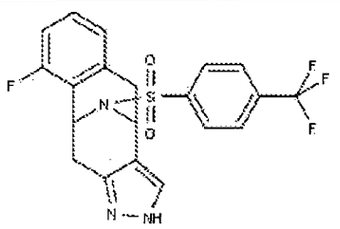
172	(-)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole-7-carbonitrile; MS 432.0 ^{1}H NMR ($CDCl_3$): δ 8.92 (d, J = 2.0 Hz, 1H), 8.13 (dd, J = 8.2, 2.1 Hz, 1H), 7.61 (d, J = 8.2 Hz, 1H), 7.49 (s, 1H), 7.41 (s, 1H), 7.38 (dd, J = 7.8, 1.4 Hz, 1H), 7.14 (d, J = 7.8 Hz, 1H), 6.00 (s, 1H), 5.49 (d, J = 5.3 Hz, 1H), 3.42 (dd, J = 16.6, 5.7 Hz, 1H), 2.83 (d, J = 16.6 Hz, 1H). Prepared as described in Example 9 using 3-bromo-4-(5-oxo-2-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)cyclohex-3-enyl)benzonitrile, followed by chiral chromatographic separation of stereoisomers.	A
173	(-)-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one; MS 420.1. ^{1}H NMR ($CDCl_3$): δ 7.77 (d, J = 8.3 Hz, 2H), 7.62 (s, 1H), 7.53 (d, J = 8.3 Hz, 2H), 7.25-7.28 (m, 1H), 7.11-7.02 (m, 3H), 6.18 (s, 1H), 5.44 (s, 1H). Prepared as described in Example 15 followed by chiral chromatographic separation of stereoisomers.	D
174	(+)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole-7-carbonitrile; MS 432.0. ^{1}H NMR ($CDCl_3$): δ 8.92 (d, J = 2.0 Hz, 1H), 8.13 (dd, J = 8.2, 2.1 Hz, 1H), 7.61 (d, J = 8.2 Hz, 1H), 7.49 (s, 1H), 7.41 (s, 1H), 7.38 (dd, J = 7.8, 1.4 Hz, 1H), 7.14 (d, J = 7.8 Hz, 1H), 6.00 (s, 1H), 5.49 (d, J = 5.3 Hz, 1H), 3.42 (dd, J = 16.6, 5.7 Hz, 1H), 2.83 (d, J = 16.6 Hz, 1H). Prepared as described in Example 9 using 3-bromo-4-(5-oxo-2-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)cyclohex-3-enyl)benzonitrile which was prepared as described in Example 8 using 2-bromo-4-cyanobenzaldehdye and sulfonamide **23** followed by chiral chromatographic separation of stereoisomers.	D
175	(+)-endo-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10-ol; MS 422.1. ^{1}H NMR ($CDCl_3$): δ 7.82 (d, J = 8.3 Hz, 2H), 7.53 (d, J = 8.3 Hz, 2H), 7.48 (s, 1H), 7.10-7.07 (m, 1H), 6.93-6.86 (m, 3H), 5.91 (s, 1H), 5.30-5.23 (m, 2H). Prepared as described in Example 15.	D

176	(±)-6-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 425.1. ^{1}H-NMR ($CDCl_3$) δ 8.96 (s, 1H), 8.08 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 8.6 Hz, 1H) 7.36 (s, 1H), 7.08 (m, 1H), 6.67 (m, 2H), 6.86 (s, 1H), 5.38 (d, J = 5.5 Hz, 1H), 3.40 (dd, J = 5.5, 16.0 Hz, 1H), 2.77 (d, J = 16.0 Hz, 1H). Prepared as described in Example 9 using 5-(2-bromo-5-fluorophenyl)-4-(6-(trifluoro-methyl)pyridin-3-ylsulfonyl)cyclohex-2-enone which was prepared as described in Example 8 using 2-bromo-5-fluorobenzaldehyde and sulfonamide **23**.	D
177	 (±)-6-[3-(trifluoromethyl)phenyl]-12-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,10,11-tetrahydro-1H-4,10-epiminobenzo[5,6]cycloocta[1,2-c]pyrazole; MS 564.1. ^{1}H NMR ($CDCl_3$) δ 7.91 (d, J = 8.2 Hz, 2H), 7.65 (d, J = 8.2 Hz, 2H), 7.63-7.57 (m, 1H), 7.49 (d, J = 7.7 Hz, 1H), 7.30 (s, 1H), 7.26-7.20 (m, 3H), 7.03 (dd, J = 1.6, 7.1 Hz, 1H), 5.60 (d, J = 5.3 Hz, 1H), 5.47 (d, J = 5.5 Hz, 1H), 3.25 (dd, J = 5.6, 16.0 Hz, 1H), 3.08 (dd, J = 5.8, 16.5 Hz, 1H), 2.93 (d, J = 15.4 Hz, 1H), 2.38 (d, J = 17.8 Hz, 1H). Prepared as described in Example 12 using 3-trifluoromethylphenylboronic acid	D
178	(±)-7-[3-(trifluoromethyl)phenyl]-12-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,11-tetrahydro-3H-5,11-epiminobenzo[4,5]cycloocta[1,2-c]pyrazole; MS 564.1. ^{1}H NMR ($CDCl_3$) δ 7.62 (d, J = 8.3 Hz, 2H), 7.57 (d, J = 7.9 Hz, 1H), 7.46 (d, J = 8.7 Hz, 2H), 7.44-7.41 (m, 1H), 7.40 (s, 1H), 7.17 (t, J = 7.5 Hz, 2H), 7.09 (s, 1H), 7.02 (d, J = 7.1 Hz, 1H), 6.87 (dd, J = 1.4, 7.6 Hz, 1H), 6.12 (s, 1H), 4.77-4.74 (m, 1H), 3.24 (dd, J = 5.6, 16.0 Hz, 1H), 2.83 (dd, J = 9.5, 18 Hz, 1H), 2.73 (d, J = 16.4 Hz, 1H), 2.23 (d, J = 17.8 Hz, 1H). Prepared as described in Example 12 using 3-trifluoromethylphenylboronic acid	D

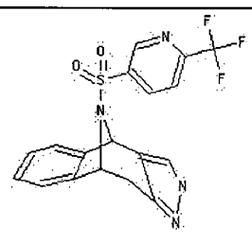
179	 (-)-6-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 425.1 ^{1}H-NMR ($CDCl_3$) δ 8.96 (s, 1H), 8.08 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 8.6 Hz, 1H) 7.36 (s, 1H), 7.08 (m, 1H), 6.67 (m, 2H), 6.86 (s, 1H), 5.38 (d, *J* = 5.5 Hz, 1H), 3.40 (dd, *J* = 5.5, 16.0 Hz, 1H), 2.77 (d, *J* = 16.0 Hz, 1H). Prepared as described in Example 9 using 5-(2-bromo-5-fluorophenyl)-4-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)cyclohex-2-enone, followed by chiral chromatographic separation of stereoisomers.	B
180	(+)-6-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 425.1 ^{1}H-NMR ($CDCl_3$) δ 8.96 (s, 1H), 8.08 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 8.6 Hz, 1H) 7.36 (s, 1H), 7.08 (m, 1H), 6.67 (m, 2H), 6.86 (s, 1H), 5.38 (d, *J* = 5.5 Hz, 1H), 3.40 (dd, *J* = 5.5, 16.0 Hz, 1H), 2.77 (d, *J* = 16.0 Hz, 1H). Prepared as described above for the enantiomer.	D
181	(±)-9-fluoro-12-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,10,11-tetrahydro-1H-4,10-epiminobenzo[5,6]cycloocta[1,2-c]pyrazole; MS 438.0 ^{1}H NMR ($CDCl_3$) δ 7.92 (d, *J* = 8.2 Hz, 2H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.41 (s, 1H), 7.11 (dt, *J* = 5.9, 8.0 Hz, 1H), 6.89 (t, *J* = 9.2 Hz, 1H), 6.75 (d, *J* = 7.7 Hz, 1H), 5.70 (d, *J* = 5.7 Hz, 1H), 5.56 (d, *J* = 5.6 Hz, 1H), 3.32 (dd, *J* = 5.8, 16.6 Hz, 1H), 3.07 (dd, *J* = 5.6, 16.3 Hz, 1H), 2.89 (d, *J* = 16.3 Hz, 1H), 2.76 (d, *J* = 16.2 Hz, 1H). Prepared as described in Example 11 using 8-fluoroisoquinoline.	D

182	(±)-10-fluoro-12-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,11-tetrahydro-3H-5,11-epiminobenzo[4,5]cycloocta[1,2-c]pyrazole; MS 438.0 ^{1}H NMR ($CDCl_3$) δ 7.73 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 8.3 Hz, 2H), 7.39 (s, 1H), 6.93 (dt, J = 5.9, 8.0 Hz, 1H), 6.77 (t, J = 8.5 Hz, 1H), 6.50 (d, J = 7.6 Hz, 1H), 6.37 (s, 1H), 4.95-4.90 (m, 1H), 3.28-3.17 (m, 2H), 2.71 (d, J = 16.3 Hz, 1H), 2.76 (d, J = 17.9 Hz, 1H). Prepared as described in Example 11 using 8-fluoroisoquinoline.	D
183	 (±)-8-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 424.9 ^{1}H NMR ($CDCl_3$): δ 8.90 (s, 1H), 8.10 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 8.2 Hz, 1H), 7.42 (s, 1H), 7.02-6.94 (m, 1H), 6.75-6.64 (m, 2H), 5.90 (s, 1H), 5.60 (d, J = 5.4 Hz, 1H), 3.49 (dd, J = 16.5, 5.6 Hz, 1H), 2.94 (d, J = 16.5 Hz, 1H). Prepared as described in Example 9 using 5-(2-bromo-3-fluorophenyl)-4-(6-(trifluoromethyl)-pyridin-3-ylsulfonyl)cyclohex-2-enone, which was prepared as described in Example 8 using 2-bromo-3-fluorobenzaldehyde and sulfonamide **23**.	D
184	(-)-8-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 425.1 ^{1}H NMR ($CDCl_3$): δ 8.90 (s, 1H), 8.10 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 8.2 Hz, 1H), 7.42 (s, 1H), 7.02-6.94 (m, 1H), 6.75-6.64 (m, 2H), 5.90 (s, 1H), 5.60 (d, J = 5.4 Hz, 1H), 3.49 (dd, J = 16.5, 5.6 Hz, 1H), 2.94 (d, J = 16.5 Hz, 1H). Prepared as described above for the racemic mixture, followed by chiral chromatographic separation of stereoisomers.	B

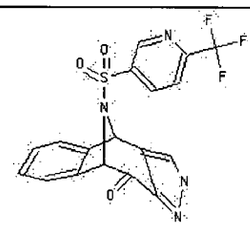
185	(+)-8-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 425.1 ^{1}H NMR ($CDCl_3$): δ 8.90 (s, 1H), 8.10 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 8.2 Hz, 1H), 7.42 (s, 1H), 7.02-6.94 (m, 1H), 6.75-6.64 (m, 2H), 5.90 (s, 1H), 5.60 (d, J = 5.4 Hz, 1H), 3.49 (dd, J = 16.5, 5.6 Hz, 1H), 2.94 (d, J = 16.5 Hz, 1H). Prepared as described above for the racemic mixture, followed by chiral chromatographic separation of stereoisomers.	D
186	(+)-exo-10-fluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 424.0 ^{1}H NMR ($CDCl_3$): δ 7.80 (d, J = 8.3 Hz, 2H), 7.49 (d, J = 8.3 Hz, 2H), 7.40 (s, 1H), 7.19-7.16 (m, 1H), 7.03-6.94 (m, 3H), 6.01 (s, 1H), 5.61-5.44 (m, 2H). Prepared as described in Example 15.	D
187	 (±)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,8,9-tetrahydro-4,8-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-d][1,3]thiazole; MS 414.0 ^{1}H NMR ($CDCl_3$): δ 8.97 (d, J = 2.2 Hz, 1H), 8.45 (s, 1H), 8.16 (dd, J = 8.2, 2.2 Hz, 1H), 7.67 (d, J = 8.2 Hz, 1H), 7.57 (s, 1H), 5.97 (s, 1H), 5.60 (d, J = 5.2 Hz, 1H), 3.53 (dd, J = 16.6, 5.5 Hz, 1H), 2.90 (d, J = 16.6 Hz, 1H). Prepared as described in Example 9 using 2-(5-bromothiazol-4-yl)-1-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-2,3-dihydropyridin-4(1H)-one which was prepared as described in Example 8 using 5-bromothiazole-4-carbaldehyde and sulfonamide **23**.	C

188	(-)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,8,9-tetrahydro-4,8-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-d][1,3]thiazole; MS 414.0 ^{1}H NMR ($CDCl_3$ with a drop of CD_3OD): δ 8.93 (s, 1H), 8.41 (s, 1H), 8.14 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.44 (s, 1H), 5.92 (s, 1H), 5.56 (d, *J* = 5.3 Hz, 1H), 3.41 (dd, *J* = 16.4, 5.5 Hz, 1H), 2.81 (d, *J* = 16.4 Hz, 1H). Prepared as described above for the racemic mixture, followed by chiral chromatographic separation of stereoisomers.	A
189	(+)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,8,9-tetrahydro-4,8-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-d][1,3]thiazole; MS 414.0 ^{1}H NMR ($CDCl_3$ with a drop of CD_3OD): δ 8.93 (s, 1H), 8.41 (s, 1H), 8.14 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.44 (s, 1H), 5.92 (s, 1H), 5.56 (d, *J* = 5.3 Hz, 1H), 3.41 (dd, *J* = 16.4, 5.5 Hz, 1H), 2.81 (d, *J* = 16.4 Hz, 1H). Prepared as described above for the racemic mixture, followed by chiral chromatographic separation of stereoisomers.	C
190	 (-)-9-fluoro-12-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,10,11-tetrahydro-1H-4,10-epiminobenzo[5,6]cycloocta[1,2-c]pyrazole; MS 438.1 ^{1}H NMR ($CDCl_3$) δ 7.92 (d, *J* = 8.2 Hz, 2H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.41 (s, 1H), 7.11 (dt, *J* = 5.9, 8.0 Hz, 1H), 6.89 (t, *J* = 9.2 Hz, 1H), 6.75 (d, *J* = 7.7 Hz, 1H), 5.70 (d, *J* = 5.7 Hz, 1H), 5.56 (d, *J* = 5.6 Hz, 1H), 3.32 (dd, *J* = 5.8, 16.6 Hz, 1H), 3.07 (dd, *J* = 5.6, 16.3 Hz, 1H), 2.89 (d, *J* = 16.3 Hz, 1H), 2.76 (d, *J* = 16.2 Hz, 1H). Prepared as described in Example 11 using 8-fluoroisoquinoline followed by chiral chromatographic separation of stereoisomers (ChiralPak AD 20 x 250 nm column).	D

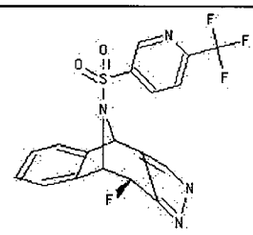
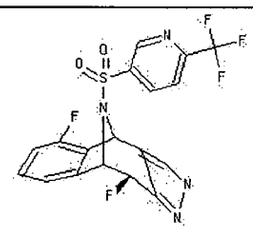
191	(+)-9-fluoro-12-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,10,11-tetrahydro-1H-4,10-epiminobenzo[5,6]cycloocta[1,2-c]pyrazole; MS 438.1 ^{1}H NMR ($CDCl_3$) δ 7.92 (d, *J* = 8.2 Hz, 2H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.41 (s, 1H), 7.11 (dt, *J* = 5.9, 8.0 Hz, 1H), 6.89 (t, *J* = 9.2 Hz, 1H), 6.75 (d, *J* = 7.7 Hz, 1H), 5.70 (d, *J* = 5.7 Hz, 1H), 5.56 (d, *J* = 5.6 Hz, 1H), 3.32 (dd, *J* = 5.8, 16.6 Hz, 1H), 3.07 (dd, *J* = 5.6, 16.3 Hz, 1H), 2.89 (d, *J* = 16.3 Hz, 1H), 2.76 (d, *J* = 16.2 Hz, 1H). Prepared as described above for the enantiomer.	D
192	(-)-8-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one; MS 439.0 ^{1}H NMR ($CDCl_3$ with a drop of CD_3OD): δ 8.84 (s, 1H), 8.13 (d, *J* = 8.3 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.56 (s, 1H), 7.15-7.08 (m, 1H), 6.97 (d, *J* = 7.5 Hz, 1H), 6.81-6.74 (m, 1H), 6.18 (s, 1H), 5.62 (s, 1H). Prepared by oxidation of 8-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole using the methods described in Example 15, followed by chiral chromatographic separation of stereoisomers.	D
193	(+)-8-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one; MS 439.0 ^{1}H NMR ($CDCl_3$): δ 8.93 (s, 1H), 8.17 (d, *J* = 7.7 Hz, 1H), 7.72 (s, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.15-7.05 (m, 1H), 7.00-6.94 (m, 1H), 6.80-6.72 (m, 1H), 6.27 (s, 1H), 5.69 (s, 1H). Prepared as described above for the enantiomer.	B

194	(±)-methyl 11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole-6-carboxylate; MS 465.1. ^{1}H-NMR ($CDCl_3$) δ 8.88 (s, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H) 7.58 (s, 1H), 7.50 (d, J = 8.4 Hz ,1H), 7.40 (s, 1H), 7.23 (d, J = 7.8 Hz, 1H), 5.90 (s, 1H), 5.47 (d, J = 5.5 Hz, 1H), 3.86 (s, 3H), 3.48 (dd, J = 5.5, 16.4 Hz, 1H), 2.86 (d, J = 16.4 Hz, 1H). Prepared as described in Example 9 using methyl 4-bromo-3-(5-oxo-2-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)cyclohex-3-enyl)benzoate which was prepared as described in Example 8 using methyl 4-bromo-3-formylbenzoate and sulfonamide **23**.	A
195	(±)-exo-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10-ol; MS 422.1. ^{1}H NMR ($CDCl_3$): δ 7.74 (d, J = 8.2 Hz, 2H), 7.46 (d, J = 8.1 Hz, 2H), 7.38 (s, 1H), 7.10-7.05 (m, 1H), 6.95-6.85 (m, 3H), 5.88 (s, 1H), 5.26 (s, 1H), 4.81 (s, 1H). Prepared as described in Example 20 using compound 16.	C
196	 (-)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 407.1. ^{1}H NMR ($CDCl_3$ with a drop of CD_3OD): δ 8.88 (s, 1H), 8.03 (d, J = 7.7 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.39 (s, 1H), 7.14-7.07 (m, 1H), 7.03-6.90 (m, 3H), 5.87 (s, 1H), 5.40 (d, J = 3.9 Hz, 1H), 3.48 (dd, J = 16.2, 4.7 Hz, 1H), 2.87 (d, J = 16.3 Hz, 1H). Prepared as described in Example 9 followed by chiral chromatographic separation of stereoisomers.	>30

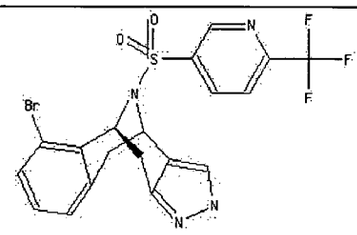
197	(+)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 407.1. ^{1}H NMR ($CDCl_3$ with a drop of CD_3OD): δ 8.88 (s, 1H), 8.03 (d, *J* = 7.7 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.39 (s, 1H), 7.14-7.07 (m, 1H), 7.03-6.90 (m, 3H), 5.87 (s, 1H), 5.40 (d, *J* = 3.9 Hz, 1H), 3.48 (dd, *J* = 16.2, 4.7 Hz, 1H), 2.87 (d, *J* = 16.3 Hz, 1H). Prepared as described in Example 9 followed by chiral chromatographic separation of stereoisomers.	D
198	(±)-exo-10-fluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 424.0 ^{1}H NMR ($CDCl_3$ with a drop of CD_3OD): δ 7.76 (d, *J* = 7.6 Hz, 2H), 7.46 (d, *J* = 7.6 Hz, 2H), 7.36 (s, 1H), 7.18-7.13 (m, 1H), 6.98-6.88 (m, 3H), 5.96 (s, 1H), 5.60-5.39 (m, 2H). Prepared as described in Example 15.	D
199	endo-5-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10-ol; MS 441.0 ^{1}H NMR (CD_3OD): δ 8.96 (s, 1H), 8.31 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.58 (s, 1H), 7.01-6.93 (m, 2H), 6.69-6.60 (m, 1H), 6.17 (s, 1H), 5.40-5.30 (m, 2H). Prepared by reduction of 5-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one using the methods described in Example 15.	D

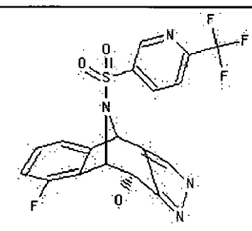
200	 (-)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one ; MS 421.0 ^{1}H NMR ($CDCl_3$): δ 8.95 (s, 1H), 8.14 (d, J = 8.3 Hz, 1H), 7.69 (s, 1H), 7.58 (d, J = 8.3 Hz, 1H), 7.32-7.27 (m, 1H), 7.15-7.02 (m, 3H), 6.31 (s, 1H), 5.52 (s, 1H). Prepared by oxidation of 11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole using the methods described in Example 15 followed by chiral chromatographic separation of stereoisomers.	D
201	(+)-6-(3-methyl-1,2,4-oxadiazol-5-yl)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 489.1. ^{1}H-NMR ($CDCl_3$) δ 8.90 (s, 1H), 8.10 (d, J = 8.6 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H) 7.70 (s, 1H), 7.53 (d, J = 8.2 Hz ,1H), 7.40 (s, 1H), 7.33 (d, J = 7.8 Hz, 1H), 5.97 (s, 1H), 5.50 (d, J = 5.5 Hz, 1H), 3.46 (dd, J = 5.5, 16.4 Hz, 1H), 2.86 (d, J = 16.4 Hz, 1H), 2.44 (s, 3H). Prepared by treatment of (±)-methyl 11-{[6-(trifluoromethyl)-pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole-6-carboxylate with N-hydroxyacetamidine as described for compound 51 in Example 16 followed by chiral chromatographic separation of stereoisomers.	A
202	(-)-6-(3-methyl-1,2,4-oxadiazol-5-yl)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 489.1. ^{1}H-NMR ($CDCl_3$) δ 8.90 (s, 1H), 8.10 (d, J = 8.6 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H) 7.70 (s, 1H), 7.53 (d, J = 8.2 Hz ,1H), 7.40 (s, 1H), 7.33 (d, J = 7.8 Hz, 1H), 5.97 (s, 1H), 5.50 (d, J = 5.5 Hz, 1H), 3.46 (dd, J = 5.5, 16.4 Hz, 1H), 2.86 (d, J = 16.4 Hz, 1H), 2.44 (s, 3H). Prepared as described above for the (+)-enantiomer.	A

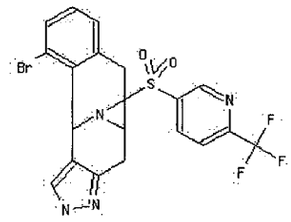
203	(-)-methyl 11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole-6-carboxylate; MS 465.1 ^{1}H-NMR ($CDCl_3$) δ 8.88 (s, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H) 7.58 (s, 1H), 7.50 (d, *J* = 8.4 Hz ,1H), 7.40 (s, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 5.90 (s, 1H), 5.47 (d, *J* = 5.5 Hz, 1H), 3.86 (s, 3H), 3.48 (dd, *J* = 5.5, 16.4 Hz, 1H), 2.86 (d, *J* = 16.4 Hz, 1H). Prepared as described in Example 9 using methyl 4-bromo-3-(5-oxo-2-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)cyclohex-3-enyl)benzoate, followed by chiral chromatographic separation of stereoisomers.	A
204	(±)-7-methyl-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,7,8,9-tetrahydro-1H-4,8-epiminocyclohepta[1,2-c:5,4-c']dipyrazole; MS 411.0 ^{1}H-NMR ($CDCl_3$) δ 8.89 (s, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.53 (s, 1H), 7.50 (d, *J* = 8.4 Hz ,1H), 7.34 (s, 1H), 5.96 (s, 1H), 5.52 (d, *J* = 5.5 Hz, 1H), 3.63 (s, 3H), 3.41 (dd, *J* = 5.5, 16.4 Hz, 1H), 2.90 (d, *J* = 16.4 Hz, 1H).	D
205	(+)-methyl 11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole-6-carboxylate; MS 465.1. ^{1}H-NMR ($CDCl_3$) δ 8.88 (s, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H) 7.58 (s, 1H), 7.50 (d, *J* = 8.4 Hz ,1H), 7.40 (s, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 5.90 (s, 1H), 5.47 (d, *J* = 5.5 Hz, 1H), 3.86 (s, 3H), 3.48 (dd, *J* = 5.5, 16.4 Hz, 1H), 2.86 (d, *J* = 16.4 Hz, 1H). Prepared as described in Example 9 using methyl 4-bromo-3-(5-oxo-2-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)cyclohex-3-enyl)benzoate, followed by chiral chromatographic separation of stereoisomers.	C

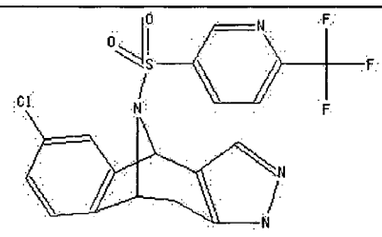
206	 exo-10-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 425.1 ^{1}H NMR (CD_3OD): δ 8.94 (d, J = 1.9 Hz, 1H), 8.26 (dd, J = 8.2, 1.9 Hz, 1H), 7.65 (d, J = 8.2 Hz, 1H), 7.60 (s, 1H), 7.30-7.27 (m, 1H), 7.02-6.91 (m, 3H), 6.13 (s, 1H), 5.70 (dd, J = 10.6, 1.6 Hz, 1H), 5.25 ((dd, J = 52.0, 1.9 Hz, 1H). Prepared by fluorination of 11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10-ol using the methods described in Example 15.	D
207	 (+)-exo-5,10-difluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 443.1. ^{1}H NMR (CD_3OD): δ 8.98 (s, 1H), 8.33 (d, J = 8.2 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.66 (s, 1H), 7.15 (d, J = 7.4 Hz, 1H), 7.08-7.00 (m, 1H), 6.73-6.66 (m, 1H), 6.34 (s, 1H), 5.78 (d, J = 10.4 Hz, 1H), 5.55 ((dd, J = 51.7, 1.9 Hz, 1H). Prepared by fluorination of 5-fluoro-11-{[6-(trifluoromethyl)-pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]-cyclohepta[1,2-c]pyrazol-10-ol using the methods described in Example 15.	D

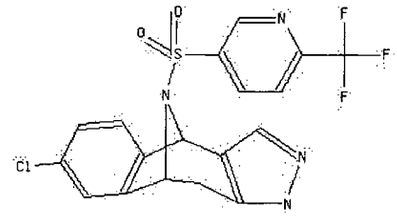
208	endo-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10-ol; MS 423.1. ^{1}H NMR ($CDCl_3$ with a drop of CD_3OD): δ 8.84 (s, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.33 (s, 1H), 7.17-7.10 (m, 1H), 6.95-6.85 (m, 3H), 5.78 (s, 1H), 5.35-5.23 (m, 2H). Prepared by reduction of 11-{[6-(trifluoro-methyl)pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]-cyclo-hepta[1,2-c]pyrazol-10(1H)-one using the methods described in Example 15.	D
209	(±)-11-[(4-chlorophenyl)sulfonyl]-5-fluoro-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 390.4. ^{1}H NMR ($CDCl_3$) δ 7.54 (m, 3H), 7.22 (m, 2H), 7.01 (m, 1H), 6.86 (m, 1H), 6.66 (t, J = 8.4 Hz, 1H), 6.01 (s, 1H), 5.42 (d, J = 5.4 Hz, 1H), 3.58 (dd, J = 16.7, 5.4 Hz, 1H), 2.85 (d, J = 16.6 Hz, 1H). Prepared as described in Example 9 using 2-(2-bromo-6-fluorophenyl)-1-(4-chlorophenylsulfonyl)-2,3-dihydropyridin-4(1H)-one which was prepared as described in Example 8 using 2-bromo-6-fluorobenzaldehyde and 4-chlorobenzenesulfonamide.	D
210	(±)-5-fluoro-11-[(4-fluorophenyl)sulfonyl]-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 374.0. ^{1}H NMR ($CDCl_3$) δ 7.62 (m, 3H), 6.96 (m, 4H), 6.67 (t, J = 8.4 Hz, 1H), 6.02 (s, 1H), 5.44 (d, J = 5.2 Hz, 1H), 3.57 (dd, J = 16.9, 5.6 Hz, 1H), 2.94 (d, J = 16.7 Hz, 1H). Prepared as described in Example 9 using 2-(2-bromo-6-fluorophenyl)-1-(4-fluorophenylsulfonyl)-2,3-dihydropyridin-4(1H)-one which was prepared as described in Example 8 using 2-bromo-6-fluorobenzaldehyde and 4-fluorobenzenesulfonamide.	D
211	(±)-5-fluoro-11-{[5-(trifluoromethyl)pyridin-2-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 425.1 ^{1}H NMR ($CDCl_3$) δ 8.56 (s, 1H), 7.90 (s, 2H), 7.35 (s, 1H), 6.91 (m, 2H), 6.59 (at, J = 8.0 Hz, 1H), 6.13 (s, 1H), 5.57 (d, J = 5.5 Hz, 1H), 3.57 (dd, J = 16.2, 5.7 Hz, 1H), 2.85 (d, J = 16.1 Hz, 1H). Prepared as described in Example 9 using 2-(2-bromo-6-fluorophenyl)-1-(4-fluorophenylsulfonyl)-2,3-dihydropyridin-4(1H)-one which was prepared as described in Example 8 using 2-bromo-6-fluorobenzaldehyde and 5-(trifluoromethyl)-2-pyridinesulfonamide.	D

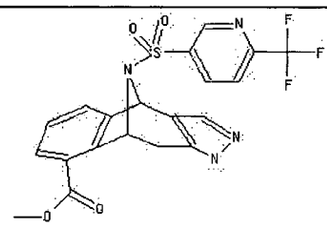
212	 (+)-9-bromo-12-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,10,11-tetrahydro-1H-4,10-epiminobenzo[5,6]cycloocta[1,2-c]pyrazole; MS 499.0 ^{1}H-NMR ($CDCl_3$) δ 9.08 (d, J = 2.1 Hz, 1H), 8.24 (dd, J = 6.5, 2.1 Hz, 1H), 7.68 (d, J = 8.1 Hz, 1H), 7.45-7.42 (m, 2H), 7.02 (t, J = 7.8 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 5.69 (d, J = 4.8 Hz, 1H), 5.50 (d, J = 5.4 Hz, 1H), 3.36 (dd, J = 16, 5.7 Hz, 1 H), 3.16-3.11 (m, 2H), 2.79 (d, J = 16 Hz, 1H). Prepared as described in Example 13 using compound 45 followed by chiral chromatographic separation of stereoisomers.	D
213	(-)-9-bromo-12-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,10,11-tetrahydro-1H-4,10-epiminobenzo[5,6]cycloocta[1,2-c]pyrazole; MS 499.0 ^{1}H NMR ($CDCl_3$) δ 9.08 (d, J = 2.1 Hz, 1H), 8.24 (dd, J = 6.5, 2.1 Hz, 1H), 7.68 (d, J = 8.1 Hz, 1H), 7.45-7.42 (m, 2H), 7.02 (t, J = 7.8 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 5.69 (d, J = 4.8 Hz, 1H), 5.50 (d, J = 5.4 Hz, 1H), 3.36 (dd, J = 16, 5.7 Hz, 1 H), 3.16-3.11 (m, 2H), 2.79 (d, J = 16 Hz, 1H). Prepared as described in Example 13 using compound 45 followed by chiral chromatographic separation of stereoisomers.	C
214	exo-8,10-difluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 443.1 ^{1}H NMR ($CDCl_3$ with a drop of CD_3OD): δ 8.96 (d, J = 1.9 Hz, 1H), 8.18 (dd, J = 8.2, 1.9 Hz, 1H), 7.60 (d, J = 8.2 Hz, 1H), 7.42 (s, 1H), 7.06-6.99 (m, 1H), 6.83 (d, J = 7.4 Hz, 1H), 6.71 (t, J = 8.4 Hz, 1H), 6.09 (s, 1H), 5.77 (dd, J = 10.0, 1.3 Hz, 1H), 5.55 (dd, J = 51.2, 1.7Hz, 1H). Prepared by fluorination of 8-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10-ol using the methods described in Example 15.	D

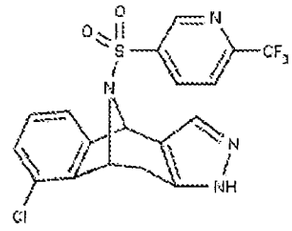
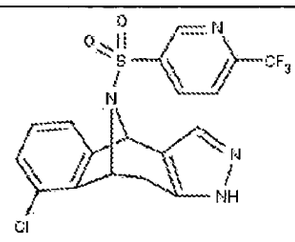
215	(+)-8,10,10-trifluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 461.1 ^{1}H NMR (CD_3OD): δ 9.02 (s, 1H), 8.37 (d, J = 6.4 Hz, 1H), 7.76-7.70 (m, 2H), 7.10-7.00 (m, 1H), 6.95-6.87 (m, 1H), 6.80-6.68 (m, 1H), 6.28 (s, 1H), 5.90 (d, J = 8.0 Hz, 1H). Prepared by fluorination of 8-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]-cyclohepta[1,2-c]pyrazol-10(1H)-one using the methods of Example 15.	D
216	 endo-8-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10-ol; MS 441.1 ^{1}H NMR (CD_3OD): δ 8.94 (s, 1H), 8.30-8.25 (m, 1H), 7.71 (d, J = 8.2 Hz, 1H), 7.55 (s, 1H), 7.00-6.90 (m, 1H), 6.83-6.79 (m, 1H), 6.67-6.60 (m, 1H), 6.05 (s, 1H), 5.56-5.52 (m, 1H), 5.38-5.30 (m, 1H). Prepared by reduction of 8-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]-cyclohepta[1,2-c]pyrazol-10(1H)-one using the methods described in Example 15.	C

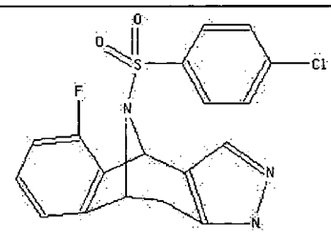
217	 (-)-10-bromo-12-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,11-tetrahydro-3H-5,11-epiminobenzo[4,5]cycloocta[1,2-c]pyrazole; MS 499.0 ^{1}H NMR ($CDCl_3$) δ 8.89 (d J = 1.5 Hz, 1H), 7.98 (dd, J = 6.0, 2.1 Hz, 1H,) 7.64 (s, 1H), 7.46 (d, J = 8.1 Hz, 1H), 7.30 (d, J = 9.3 Hz, 1H), 6.83 (t, J = 8.4 Hz, 1H), 6.60 (d, J = 6.0 Hz, 1H), 6.49 (s, 1H), 4.98, (t, J = 7.2 Hz, 1H), 3.31 (dd, J = 16, 6.3 Hz, 1H), 3.18 (dd, J = 16, 9.9 Hz, 1 H) 2.67 (d, J = 15 Hz, 1H), 2.51 (d, J = 18 Hz, 1H). Prepared as described in Example 11 using compound **45**, followed by chiral chromatographic separation of stereoisomers.	D
218	(+)-10-bromo-12-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,11-tetrahydro-3H-5,11-epiminobenzo[4,5]cycloocta[1,2-c]pyrazole; MS 499.0 ^{1}H NMR ($CDCl_3$) δ 8.89 (d J = 1.5 Hz, 1H), 7.98 (dd, J = 6.0, 2.1 Hz, 1H,) 7.64 (s, 1H), 7.46 (d, J = 8.1 Hz, 1H), 7.30 (d, J = 9.3 Hz, 1H), 6.83 (t, J = 8.4 Hz, 1H), 6.60 (d, J = 6.0 Hz, 1H), 6.49 (s, 1H), 4.98, (t, J = 7.2 Hz, 1H), 3.31 (dd, J = 16, 6.3 Hz, 1H), 3.18 (dd, J = 16, 9.9 Hz, 1 H) 2.67 (d, J = 15 Hz, 1H), 2.51 (d, J = 18 Hz, 1H). Prepared as described above for the enantiomer.	D
219	(±)-6-chloro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 441.1 ^{1}H NMR ($CDCl_3$) δ 8.90 (s, 1H), 8.06 (dd, J = 8.2, 2.0 Hz, 1H), 7.55 (d, J = 8.2 Hz, 1H), 7.35 (s, 1H), 6.97 (m, 3H), 5.83 (s, 1H), 5.39 (d, J = 5.3 Hz, 1H), 3.39 (dd, J = 16.4, 5.6 Hz, 1H), 2.79 (d, J = 16.3 Hz, 1H). Prepared as described in Example 9 using 5-(2-bromo-5-chlorophenyl)-4-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)cyclohex-2-enone which was prepared as described in Example 8 using 2-bromo-5-chlorobenzaldehyde and sulfonamide **23**.	D

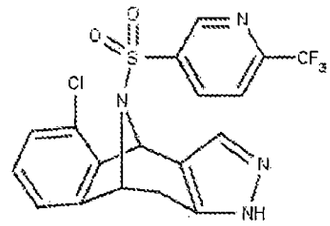
220	(±)-methyl 11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole-8-carboxylate; MS 465.1. ^{1}H NMR ($CDCl_3$) δ 8.84 (s, 1H), 8.02 (d, J = 8.2 Hz, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.46 (d, J = 8.2 Hz, 1H) 7.40 (s, 1H), 7.10 (m, 2H), 6.02 (d, J = 5.4 Hz, 1H), 7.02 (d, J = 8.6 Hz, 1H), 5.91 (s, 1H), 3.95 (s, 3H), 3.49 (dd, J = 5.4, 16.8 Hz, 1H), 3.01 (d, J = 16.8 Hz, 1H). Prepared as described in Example 9 using methyl 2-bromo-3-(5-oxo-2-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)cyclohex-3-enyl)benzoate (prepared as described in Example 8 from methyl 2-bromo-3-formylbenzoate and sulfonamide **23**).	D
221	 (-)-6-chloro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 441.1 ^{1}H NMR ($CDCl_3$) δ 8.90 (s, 1H), 8.06 (dd, J = 8.2, 2.0 Hz, 1H), 7.55 (d, J = 8.2 Hz, 1H), 7.35 (s, 1H), 6.97 (m, 3H), 5.83 (s, 1H), 5.39 (d, J = 5.3 Hz, 1H), 3.39 (dd, J = 16.4, 5.6 Hz, 1H), 2.79 (d, J = 16.3 Hz, 1H). Prepared as described in Example 9 using 5-(2-bromo-5-chlorophenyl)-4-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-cyclohex-2-enone, followed by chromatographic separation of stereoisomers.	C
222	(+)-6-chloro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 441.1 ^{1}H NMR ($CDCl_3$) δ 8.90 (s, 1H), 8.06 (dd, J = 8.2, 2.0 Hz, 1H), 7.55 (d, J = 8.2 Hz, 1H), 7.35 (s, 1H), 6.97 (m, 3H), 5.83 (s, 1H), 5.39 (d, J = 5.3 Hz, 1H), 3.39 (dd, J = 16.4, 5.6 Hz, 1H), 2.79 (d, J = 16.3 Hz, 1H). Prepared as described above for the enantiomer.	D

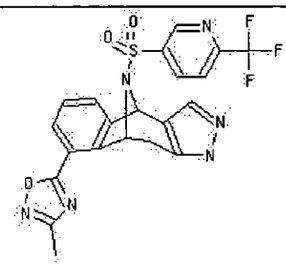
223	 (-)-7-chloro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 441.1 ^{1}H NMR ($CDCl_3$) δ 8.89 (s, 1H), 8.08 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.24 (s, 1H), 6.95 (m, 3H), 5.88 (s, 1H), 5.38 (d, *J* = 5.3 Hz, 1H), 3.41 (dd, *J* = 16.4, 5.6 Hz, 1H), 2.82 (d, *J* = 16.3 Hz, 1H). Prepared as described in Example 8 using 2-bromo-5-chlorobenzaldehyde and sulfonamide **23** followed by chromatographic separation of region- and stereoisomers.	B
224	(+)-7-chloro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 441.1 ^{1}H NMR ($CDCl_3$) δ 8.89 (s, 1H), 8.08 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.24 (s, 1H), 6.95 (m, 3H), 5.88 (s, 1H), 5.38 (d, *J* = 5.3 Hz, 1H), 3.41 (dd, *J* = 16.4, 5.6 Hz, 1H), 2.82 (d, *J* = 16.3 Hz, 1H). Prepared as described in Example 8 using 2-bromo-5-chlorobenzaldehyde and sulfonamide **23** followed by chromatographic separation of region- and stereoisomers.	D
225	(±)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-6-ol; MS 423.1. ^{1}H NMR (CD_3OD) δ 8.90 (s, 1H), 8.22 (dd, J = 8.2, 2.0 Hz, 1H), 7.66 (d, J = 8.2 Hz, 1H), 7.54 (s, 1H), 6.91 (d, J = 8.0 Hz , 3H), 6.32 (m, 2H), 5.88 (s, 1H), 5.43 (d, J = 5.0 Hz, 1H), 4.95 (s, 1H), 3.34 (dd, J = 16.4, 5.4 Hz, 1H), 2.80 (d, J = 16.3 Hz, 1H). Prepared as described in Example 9 using 5-(2-bromo-5-hydroxyphenyl)-4-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)cyclohex-2-enone which was prepared as described in Example 8 using 2-bromo-5-hydroxybenzaldehyde and sulfonamide **23**.	D

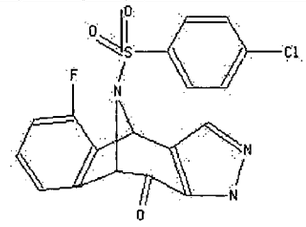
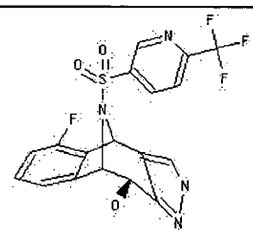
226	 (+)-methyl 11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole-8-carboxylate; MS 465.1. ^{1}H NMR ($CDCl_3$) δ 8.84 (s, 1H), 8.02 (d, J = 8.2 Hz, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.46 (d, J = 8.2 Hz, 1H) 7.40 (s, 1H), 7.10 (m, 2H), 6.02 (d, J = 5.4 Hz, 1H), 7.02 (d, J = 8.6 Hz, 1H), 5.91 (s, 1H), 3.95 (s, 3H), 3.49 (dd, J = 5.4, 16.8 Hz, 1H), 3.01 (d, J = 16.8 Hz, 1H). Prepared as described in Example 9 using methyl 2-bromo-3-(5-oxo-2-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)cyclohex-3-enyl)benzoate, followed by chiral chromatographic separation of enantiomers.	D
227	(-)-methyl 11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole-8-carboxylate; MS 465.1 ^{1}H NMR ($CDCl_3$) δ 8.84 (s, 1H), 8.02 (d, J = 8.2 Hz, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.46 (d, J = 8.2 Hz, 1H) 7.40 (s, 1H), 7.10 (m, 2H), 6.02 (d, J = 5.4 Hz, 1H), 7.02 (d, J = 8.6 Hz, 1H), 5.91 (s, 1H), 3.95 (s, 3H), 3.49 (dd, J = 5.4, 16.8 Hz, 1H), 3.01 (d, J = 16.8 Hz, 1H). Prepared as described in Example 9 using methyl 2-bromo-3-(5-oxo-2-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)cyclohex-3-enyl)benzoate, followed by chiral chromatographic separation of enantiomers.	C

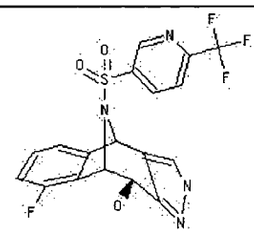
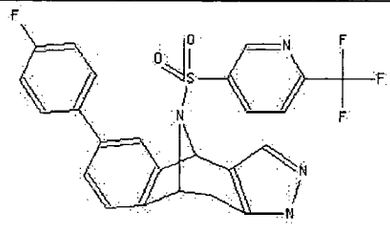
228	 (+)-8-chloro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 441.0 ^{1}H NMR (CD_3OD) δ 8.86 (s, 1H), 8.08, (d, J = 8.2 Hz, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.38 (s, 1H), 6.89 (m, 2H), 6.81 (m, 1H), 5.89 (s, 1H), 5.49 (d J = 5.5 Hz, 1H), 3.47 (dd J = 16.5, 5.6 Hz, 1H), 2.98 (d J = 16.4 Hz, 1H). Prepared as described in Example 9 using 6-(2-bromo-3-chlorophenyl)-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-1H-pyrazolo[4,3-c]pyridine, followed by chromatographic separation of regio- and stereoisomers.	D
229	 (-)-8-chloro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 441.0 ^{1}H NMR (CD_3OD) δ 8.87 (d, J = 2.0 Hz, 1H), 8.08, (dd, J = 8.2, 1.7 Hz, 1H), 7.54 (dd, J = 8.2, 0.5 Hz, 1H), 7.46 (s, 1H), 6.89 (m, 2H), 6.91 (m, 3H), 5.96 (s, 1H), 5.45 (d J = 5.4 Hz, 1H), 3.52 (dd J = 16.4, 5.6 Hz, 1H), 2.87 (d J = 15.9 Hz, 1H). Prepared as described in Example 9 using 6-(2-bromo-3-chlorophenyl)-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-1H-pyrazolo[4,3-c]pyridine, followed by chromatographic separation of regio- and stereoisomers.	C

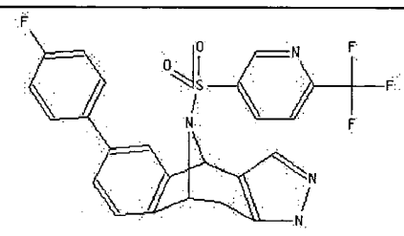
230	 (-)-11-[(4-chlorophenyl)sulfonyl]-5-fluoro-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 390.1. ^{1}H NMR (CD_3OD) δ 7.54 (m, 3H), 7.20, (m, 2H), 7.01 (m, 1H), 6.88 (d, J = 7.32 Hz, 1H), 6.66 (t, J = 8.5 Hz, 1H), 6.01 (s, 1H), 5.42 (d J = 5.4 Hz, 1H), 3.58 (dd J = 16.4, 5.6 Hz, 1H), 2.91 (d J = 15.9 Hz, 1H). Prepared as described in Example 9 using 6-(2-bromo-6-fluorophenyl)-5-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-4,5-dihydro-1H-pyrazolo[4,3-c]pyridine, followed by chromatographic separation of regio- and stereoisomers.	A
231	(+)-11-[(4-chlorophenyl)sulfonyl]-5-fluoro-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 390.1. ^{1}H NMR (CD_3OD) δ 7.54 (m, 3H), 7.20, (m, 2H), 7.01 (m, 1H), 6.88 (d, J = 7.32 Hz, 1H), 6.66 (t, J = 8.5 Hz, 1H), 6.01 (s, 1H), 5.42 (d J = 5.4 Hz, 1H), 3.58 (dd J = 16.4, 5.6 Hz, 1H), 2.91 (d J = 15.9 Hz, 1H). Prepared as described above for the (-)-stereoisomer.	D

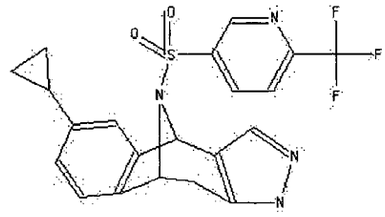
232	 (-)-5-chloro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 441.0 ^{1}H NMR (CD_3OD) δ 8.86 (s, 1H), 8.08, (d, J = 8.2 Hz, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.38 (s, 1H), 6.89 (m, 2H), 6.81 (m, 1H), 5.89 (s, 1H), 5.49 (d J = 5.5 Hz, 1H), 3.47 (dd J = 16.5, 5.6 Hz, 1H), 2.98 (d J = 16.4 Hz, 1H). Prepared as described in Example 9 using 6-(2-bromo-6-chlorophenyl)-5-(6-(trifluoro-methyl)pyridin-3-ylsulfonyl)-4,5-dihydro-1H-pyrazolo[4,3-c]pyridine, followed by chromatographic separation of regio- and stereoisomers.	B
233	(+)-5-chloro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 441.0 ^{1}H NMR (CD_3OD) δ 8.86 (s, 1H), 8.08, (d, J = 8.2 Hz, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.38 (s, 1H), 6.89 (m, 2H), 6.81 (m, 1H), 5.89 (s, 1H), 5.49 (d J = 5.5 Hz, 1H), 3.47 (dd J = 16.5, 5.6 Hz, 1H), 2.98 (d J = 16.4 Hz, 1H). Prepared as described above for the (-)-stereoisomer.	D

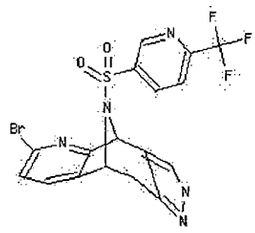
234	 (+)-8-(3-methyl-1,2,4-oxadiazol-5-yl)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 489.1. ^{1}H NMR (CD_3OD) δ 8.85 (d, J = 1.9 Hz, 1H), 8.01, (dd, J = 8.1, 1.9 Hz, 1H), 7.71 (m, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.41 (s, 1H), 7.15 (m, 2H), 6.16 (d, J = 5.7 Hz, 1H), 5.95 (s, 1H), 3.51 (dd J = 16.8, 5.9 Hz, 1H), 3.06 (d, J = 16.6 Hz, 1H), 2.53 (s, 3H). Prepared by condensation of a mixture of methyl 11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]-cyclohepta[1,2-c]pyrazole-8-carboxylate and methyl 11-{[6-(trifluoromethyl)-pyridin-3-yl]sulfonyl}-2-{[2-(trimethylsilyl)ethoxy]methyl}-2,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole-8-carboxylate, which was prepared by alkylation of methyl 11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole-8-carboxylate as described in Example 19, with *N*-hydroxyacetamidine as described in Example 16 followed by dealkylation with 4N HCl/dioxane and chromatographic separation of stereoisomers.	D
235	(-)-8-(3-methyl-1,2,4-oxadiazol-5-yl)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 489.1. ^{1}H NMR (CD_3OD) δ 8.85 (d, J = 1.9 Hz, 1H), 8.01, (dd, J = 8.1, 1.9 Hz, 1H), 7.71 (m, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.41 (s, 1H), 7.15 (m, 2H), 6.16 (d, J = 5.7 Hz, 1H), 5.95 (s, 1H), 3.51 (dd J = 16.8, 5.9 Hz, 1H), 3.06 (d, J = 16.6 Hz, 1H), 2.53 (s, 3H). Prepared as described above for the (+)-stereoisomer.	C

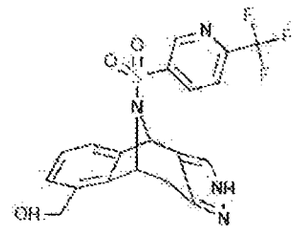
236	 (±)-11-[(4-chlorophenyl)sulfonyl]-5-fluoro-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one; MS 404.0 ^{1}H NMR (CD_3OD) δ 7.64 (s, 1H), 7.57, (m, 2H), 7.24 (m, 2H), 7.05 (m, 2H), 6.74 (m, 1H), 6.34 (s, 1H), 5.43 (s, 1H). Prepared by oxidation of (±)-11-[(4-chlorophenyl)sulfonyl]-5-fluoro-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]-cyclohepta[1,2-c]pyrazole using the methods described in Example 15.	D
237	 (-)-(10S)-5-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10-ol; MS 441.1 ^{1}H NMR ($CDCl_3$ with a drop of CD_3OD) δ 8.89 (s, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.40 (s, 1H), 6.95-6.90 (m, 2H), 6.64-6.58 (m, 1H), 6.07 (s, 1H), 5.28 (s, 1H), 4.71 (s, 1H). Prepared as described in Example 20.	A
238	(+)-(10S)-5-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10-ol; MS 441.0 ^{1}H NMR ($CDCl_3$ with a drop of CD_3OD) δ 8.89 (s, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.40 (s, 1H), 6.95-6.90 (m, 2H), 6.64-6.58 (m, 1H), 6.07 (s, 1H), 5.28 (s, 1H), 4.71 (s, 1H). Prepared as described in Example 20.	D

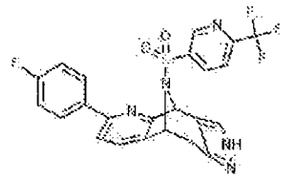
239	 (-)-(10S)-8-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10-ol; MS 441.1 ^{1}H NMR ($CDCl_3$ with a drop of CD_3OD) δ 8.90 (s, 1H), 8.13 (d, J = 8.3 Hz, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.37 (s, 1H), 6.98-6.90 (m, 1H), 6.74 (d, J = 7.4 Hz, 1H), 6.63 (t, J = 8.4 Hz,1H), 5.91 (s, 1H), 5.44 (s, 1H), 4.79 (s, 1H). Prepared as described in Example 20.	A
240	(+)-(10S)-8-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10-ol; MS 441.1 ^{1}H NMR ($CDCl_3$ with a drop of CD_3OD) δ 8.90 (s, 1H), 8.13 (d, J = 8.3 Hz, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.37 (s, 1H), 6.98-6.90 (m, 1H), 6.74 (d, J = 7.4 Hz, 1H), 6.63 (t, J = 8.4 Hz,1H), 5.91 (s, 1H), 5.44 (s, 1H), 4.79 (s, 1H). Prepared as described in Example 20.	C
241	 (±)-6-(4-fluorophenyl)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 501.1. ^{1}H NMR (CD_3OD) δ 8.94 (d, J = 1.8 Hz, 1H), 8.07 (dd, J = 8.1, 1.8 Hz, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.26 (m, 2H), 7.08 (m, 5H), 5.97 (s, 1H), 5.45 (d, J = 5.3 Hz, 1H), 3.47 (dd, J = 16.3, 5.6 Hz, 1H), 2.86 (d, J = 16.1 Hz, 1H). Prepared as described in Example 19.	D

242	(-)-11-[(4-chlorophenyl)sulfonyl]-5-fluoro-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one; MS 404.0 ^{1}H NMR (CD_3OD) δ 7.68 (s, 1H), 7.56, (m, 2H), 7.22 (m, 2H), 7.05 (m, 2H), 6.75 (m, 1H), 6.33 (s, 1H), 5.43 (s, 1H). Prepared by oxidation of (±)-11-[(4-chlorophenyl)sulfonyl]-5-fluoro-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]-cyclohepta[1,2-c]pyrazole using the methods described in Example 15 followed by chiral chromatographic separation of stereoisomers.	D
243	(+)-11-[(4-chlorophenyl)sulfonyl]-5-fluoro-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one; MS 404.0 ^{1}H NMR (CD_3OD) δ 7.68 (s, 1H), 7.56, (m, 2H), 7.22 (m, 2H), 7.05 (m, 2H), 6.75 (m, 1H), 6.33 (s, 1H), 5.43 (s, 1H). Prepared as described above for the (-)-stereoisomer.	C
244	 (-)-6-(4-fluorophenyl)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 501.0. ^{1}H NMR (CD_3OD) δ 8.91 (d, J = 2.0 Hz, 1H), 8.04 (dd, J = 8.1, 1.8 Hz, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.28 (m, 2H), 7.09 (m, 5H), 5.89 (s, 1H), 5.45 (d, J = 5.3 Hz, 1H), 3.48 (dd, J = 16.3, 5.6 Hz, 1H), 2.86 (d, J = 16.1 Hz, 1H). Prepared as described in Example 19 followed by chiral chromatographic separation of stereoisomers.	A
245	(+)-6-(4-fluorophenyl)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 501.0. ^{1}H NMR (CD_3OD) δ 8.91 (d, J = 2.0 Hz, 1H), 8.04 (dd, J = 8.1, 1.8 Hz, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.28 (m, 2H), 7.09 (m, 5H), 5.89 (s, 1H), 5.45 (d, J = 5.3 Hz, 1H), 3.48 (dd, J = 16.3, 5.6 Hz, 1H), 2.86 (d, J = 16.1 Hz, 1H). Prepared as described in Example 19 followed by chiral chromatographic separation of stereoisomers.	C

246	 (-)-6-cyclopropyl-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 447.0 ^{1}H NMR (CD_3OD) δ 8.86 (d, J = 2.0 Hz, 1H), 7.99 (dd, J = 7.8, 1.7 Hz, 1H), 7.44 (d, J = 8.2 Hz, 1H), 7.36 (s, 1H), 6.92 (d, J = 7.7 Hz, 1H), 6.61 (m, 2H), 5.76 (s, 1H), 5.34 (d, J = 5.3 Hz, 1H), 3.44 (dd, J = 16.3, 5.6 Hz, 1H), 2.80 (d, J = 16.1 Hz, 1H), 1.67 (m, 1H), 0.87 (m, 2H), 0.47 (m, 2H). Prepared as described in Example 19 using cyclopropylboronic acid followed by chromatographic separation of stereoisomers.	A
247	(+)-6-cyclopropyl-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 447.0 ^{1}H NMR (CD_3OD) δ 8.86 (d, J = 2.0 Hz, 1H), 7.99 (dd, J = 7.8, 1.7 Hz, 1H), 7.44 (d, J = 8.2 Hz, 1H), 7.36 (s, 1H), 6.92 (d, J = 7.7 Hz, 1H), 6.61 (m, 2H), 5.76 (s, 1H), 5.34 (d, J = 5.3 Hz, 1H), 3.44 (dd, J = 16.3, 5.6 Hz, 1H), 2.80 (d, J = 16.1 Hz, 1H), 1.67 (m, 1H), 0.87 (m, 2H), 0.47 (m, 2H). Prepared as described in Example 19 using cyclopropylboronic acid followed by chromatographic separation of stereoisomers.	D

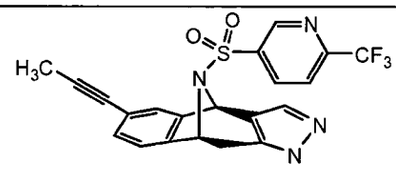
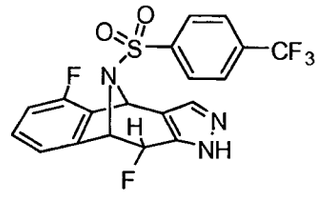
248	 (+)-6-bromo-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-b]pyridine; MS 488.0. ^{1}H NMR ($CDCl_3$) δ 8.93 (s, 1H), 8.15 (d, J = 8.2 Hz, 1H), 7.65 (d, J = 8.2 Hz, 1H), 7.54 (s, 1H), 7.35 (d, J = 7.9 Hz, 1H), 7.15 (d, J = 7.9 Hz, 1H), 5.84 (s, 1H), 5.46 (d, J = 5.0 Hz, 1H), 3.49 (dd, J = 16.6, 5.4 Hz, 1H), 2.84 (d, J = 16.6 Hz, 1H). Prepared as described in Example 9 using 2-(3,6-dibromopyridin-2-yl)-1-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-2,3-dihydropyridin-4(1H)-one which was prepared as described in Example 8 using sulfonamide **23** and 3,6-dibromopicolinaldehyde, which was prepared as described in Example 22, followed by chiral chromatographic separation of stereoisomers.	D
249	(-)-6-bromo-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-b]pyridine; MS 488.0. ^{1}H NMR ($CDCl_3$) δ 8.93 (s, 1H), 8.15 (d, J = 8.2 Hz, 1H), 7.65 (d, J = 8.2 Hz, 1H), 7.54 (s, 1H), 7.35 (d, J = 7.9 Hz, 1H), 7.15 (d, J = 7.9 Hz, 1H), 5.84 (s, 1H), 5.46 (d, J = 5.0 Hz, 1H), 3.49 (dd, J = 16.6, 5.4 Hz, 1H), 2.84 (d, J = 16.6 Hz, 1H). Prepared as described above for the (+)-stereoisomer.	A

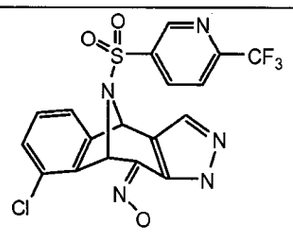
250	(+)-6-bromo-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 484.9 ^{1}H NMR ($CDCl_3$) δ 8.89 (d, J = 2.1 Hz, 1H), 8.05 (dd, J = 2.4, 8.4 Hz, 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.38 (s, 1H), 7.14 (dd, J = 1.8, 8.1 Hz, 1H), 7.08 (s, 1H), 7.00 (d, J = 7.8 Hz, 1H), 5.83 (s, 1H), 5.37 (d, J = 5.4 Hz, 1H), 3.42 (dd, J = 5.4, 16.5 Hz, 1H), 2.80 (d, J = 16.5 Hz, 1H). Prepared as described in Example 9 using 2-(2,5-dibromophenyl)-1-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-2,3-dihydropyridin-4(1H)-one which was prepared as described in Example 8 using 2,5-dibromobenzaldehyde and sulfonamide **23** followed by chromatographic separation of stereoisomers.	D
251	(-)-6-bromo-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 484.9 ^{1}H NMR ($CDCl_3$) δ 8.89 (d, J = 1.5 Hz, 1H), 8.05 (dd, J = 1.8, 8.1 Hz, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.38 (s, 1H), 7.14 (dd, J = 1.2, 7.8 Hz, 1H), 7.08 (s, 1H), 7.00 (d, J = 8.1 Hz, 1H), 5.83 (s, 1H), 5.37 (d, J = 4.8 Hz, 1H), 3.42 (dd, J = 5.4, 16.5 Hz, 1H), 2.80 (d, J = 16.5 Hz, 1H). Prepared as described above for the (+)-stereoisomer.	C
252	 (±)-(11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-8-yl)methanol; MS 437.1 ^{1}H NMR (CD_3OD with a drop of DMSO-d_6) δ 8.92 (s, 1H), 8.22 (d, J = 8.2 Hz, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.53 (s, 1H), 6.92-6.88 (m, 3H), 6.00 (s, 1H), 5.73 (d, J = 5.4 Hz, 1H), 4.56 (s, 2H), 3.40 (dd, J = 16.5, 5.4 Hz, 1H), 3.03 (d, J = 16.5 Hz, 1H). Prepared by $LiAlH_4$ reduction of (±)-methyl 11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole-8-carboxylate.	D

253	methyl (±)-11-{[6-(trifluoromethyl)-1,2-dihydropyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole-8-carboxylate; MS 467.1. ^{1}H NMR ($CDCl_3$) δ 7.83 (d, J = 7.8 Hz, 1H), 7.41-7.35 (m, 2H), 7.25 (d, J = 7.6 Hz, 1H), 6.95 (d, J = 5.5 Hz, 1H), 5.91 (d, J = 5.8 Hz, 1H), 5.83 (s, 1H), 5.78 (d, J = 4.8 Hz, 1H), 4.99 (s, 1H), 3.96 (s, 3H), 3.54 (dd, J = 16.6, 5.9 Hz, 1H), 3.06 (d, J = 16.6 Hz, 1H), 2.89 (s, 2H).	D
254	 (+)-6-(4-fluorophenyl)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-b]pyridine; MS 502.1. ^{1}H NMR ($CDCl_3$) δ 8.95 (d, J = 2.1 Hz, 1H), 8.13 (dd, J = 8.2, 1.8 Hz, 1H), 7.77-7.72 (m, 2H), 7.56 (s, 1H), 7.50 (t, J = 8.1 Hz, 2H), 7.25 (d, J = 7.9 Hz, 1H), 7.13 (t, J = 8.7 Hz, 2H), 5.91 (s, 1H), 5.50 (d, J = 5.4 Hz, 1H), 3.54 (dd, J = 16.4, 5.6 Hz, 1H), 2.90 (d, J = 16.4 Hz, 1H). Prepared by Pd-mediated coupling of (+)-6-bromo-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminopyrazolo-[3',4':5,6]cyclohepta-[1,2-b]pyridine with 4-fluorophenylboronic acid as described in Example 13.	C

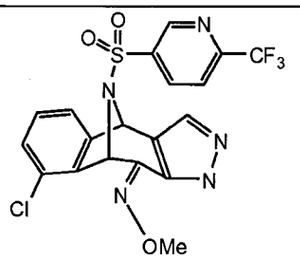
255	(+)-6-cyclopropyl-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-b]pyridine; MS 448.1. ^{1}H NMR ($CDCl_3$) δ 8.88 (s, 1H), 8.08 (d, J = 7.6 Hz, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.51 (s, 1H), 7.24 (d, J = 7.8 Hz, 1H), 6.67 (d, J = 7.8 Hz, 1H), 5.73 (s, 1H), 5.40 (d, J = 5.2 Hz, 1H), 3.51 (dd, J = 16.4, 5.5 Hz, 1H), 2.83 (d, J = 16.4 Hz, 1H), 1.86-1.82 (m, 1H), 0.97-0.73 (m, 4H). Prepared by Pd-mediated coupling of (+)-6-bromo-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminopyrazolo[3',4':5,6]cyclohepta-[1,2-b]pyridine with cyclopropyllboronic acid as described in Example 13, followed by chiral chromatographic separation of stereoisomers.	C
256	(-)-6-cyclopropyl-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-b]pyridine; MS 448.1. ^{1}H NMR ($CDCl_3$) δ 8.88 (s, 1H), 8.08 (d, J = 7.6 Hz, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.51 (s, 1H), 7.24 (d, J = 7.8 Hz, 1H), 6.67 (d, J = 7.8 Hz, 1H), 5.73 (s, 1H), 5.40 (d, J = 5.2 Hz, 1H), 3.51 (dd, J = 16.4, 5.5 Hz, 1H), 2.83 (d, J = 16.4 Hz, 1H), 1.86-1.82 (m, 1H), 0.97-0.73 (m, 4H). Prepared as described above for the (+)-stereoisomer.	A
257	(±)-8-(fluoromethyl)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 439.1 ^{1}H NMR ($CDCl_3$) δ 8.89 (s, 1H), 8.04 (d, J = 8.2 Hz, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.42 (s, 1H), 7.00-6.85 (m, 3H), 5.89 (s, 1H), 5.63 (d, J = 5.5 Hz, 1H), 5.40 (d, J = 2.5 Hz, 1H), 5.25 (d, J = 2.5 Hz, 1H), 3.51 (dd, J = 16.5, 5.7 Hz, 1H), 2.95 (d, J = 16.5 Hz, 1H). Prepared by fluorination of (±)-(11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-8-yl)methanol using DAST as described in Example 15.	D

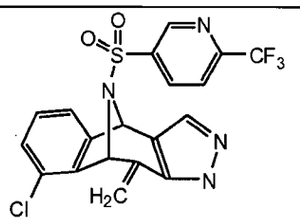
258	(±)-7-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-b]pyridine; MS 426.1. ^{1}H NMR (CD_3OD) δ 8.97 (s, 1H), 8.31 (d, J = 8.3 Hz, 1H), 7.94 (s, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.61 (s, 1H), 7.49 (d, J = 8.1 Hz, 1H), 5.92 (s, 1H), 5.65 (d, J = 5.4 Hz, 1H), 3.40 (dd, J = 16.5, 5.3 Hz, 1H), 2.83 (d, J = 16.3 Hz, 1H). Prepared as described in Example 9 using 2-(3-bromo-5-fluoropyridin-2-yl)-1-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-2,3-dihydropyridin-4(1H)-one which was prepared as described in Example 8 using 3-bromo-5-fluoropicolinaldehyde and sulfonamide **23**.	D
259	(-)-7-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-2,4,9,10-tetrahydro-4,9-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-b]pyridine; MS 426.1. ^{1}H NMR (CD_3OD) δ 8.97 (s, 1H), 8.31 (d, J = 8.3 Hz, 1H), 7.94 (s, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.61 (s, 1H), 7.49 (d, J = 8.1 Hz, 1H), 5.92 (s, 1H), 5.65 (d, J = 5.4 Hz, 1H), 3.40 (dd, J = 16.5, 5.3 Hz, 1H), 2.83 (d, J = 16.3 Hz, 1H). Prepared as described in Example 9 using 2-(3-bromo-5-fluoropyridin-2-yl)-1-(6-(trifluoromethyl)pyridin-3-ylsulfonyl)-2,3-dihydropyridin-4(1H)-one, which was prepared as described in Example 8 using 3-bromo-5-fluoropicolinaldehyde and sulfonamide **23,** followed by chiral chromatographic separation of stereoisomers.	A
260	(+)-7-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-2,4,9,10-tetrahydro-4,9-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-b]pyridine; MS 426.0. ^{1}H NMR (CD_3OD) δ 8.97 (s, 1H), 8.31 (d, J = 8.3 Hz, 1H), 7.94 (s, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.61 (s, 1H), 7.49 (d, J = 8.1 Hz, 1H), 5.92 (s, 1H), 5.65 (d, J = 5.4 Hz, 1H), 3.40 (dd, J = 16.5, 5.3 Hz, 1H), 2.83 (d, J = 16.3 Hz, 1H). Prepared as described above for the (-)-stereoisomer.	D

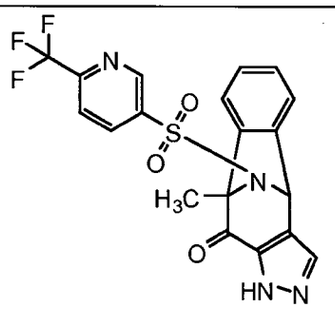
261	 (4R,9S)-6-(prop-1-yn-1-yl)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 445.0. ^{1}H NMR ($CDCl_3$) δ 8.90 (d, J = 1.8 Hz, 1H), 8.00 (dd, J = 1.8, 8.1 Hz, 1H), 7.52 (d, J = 8.1 Hz, 1H), 7.44 (s, 1H), 7.02 (bs, 2H), 6.93 (s, 1H), 5.82 (s, 1H), 5.38 (d, J = 4.8 Hz, 1H), 3.48 (dd, J = 16.5, 5.1 Hz, 1H), 2.85 (d, J = 16.5 Hz, 1H), 1.98 (s, 3H). Prepared by alkylation of 6-bromo-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole with SEM-Cl followed by Stille coupling with tributylpropynylstannane in toluene in the presence of $Pd(PPh_3)_4$.	C
262	 (-)-exo-5,10-difluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 442.1 ^{1}H NMR ($CDCl_3$) δ 7.83 (d, J = 8.2 Hz, H), 7.53 (d, J = 8.2, 2H), 7.45 (s, 1H), 6.93 (m, 2H), 6.60 (m, 1H), 6.18 (s, 1H), 5.59 (m, 1H), 5.43 (d, J = 1.9 Hz, 1H). Prepared as described in Example 15 using (±)-5-fluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]-cyclohepta[1,2-c]pyrazol-10(1H)-one followed by chiral chromatographic separation of stereoisomers.	A
263	(+)-5,10-difluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 442.1 ^{1}H NMR ($CDCl_3$) δ 7.82 (d, J = 8.2 Hz, 1H), 7.54 (d, J = 8.2, 2H), 7.46 (s, 1H), 6.97 (m, 2H), 6.64 (m, 1H), 6.14 (s, 1H), 5.58 (m, 1H), 5.42 (d, J = 1.9 Hz, 1H). Prepared as described above for the (-)-stereoisomer.	D

264	(±)-8-chloro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one; MS 455.1 ^{1}H NMR ($CDCl_3$) δ 8.86 (s, 1H), 8.20 (d, J = 8.2 Hz, 1H), 7.68 (d, J = 8.2, 1H), 7.62 (s, 1H), 7.04 (m, 3H), 6.29 (s, 1H), 5.58 (s, 1H). Prepared by oxidation of 8-chloro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole using the methods described in Example 15.	D
265	 (±)-8-chloro-N-hydroxy-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-imine; MS 470.0. ^{1}H NMR ($CDCl_3$) δ 14.8 (s, 1H), 9.34 (s, 1H), 9.15 (s, 1H), 8.37 (dd, J = 8.2, 1.6 Hz, 1H), 7.71 (d, J = 8.2 Hz, 1H), 7.64 (s, 1H), 6.92 (m, 4H), 6.63 (s, 1H). Prepared by treatment of (±)-8-chloro-11-{[6-(trifluoromethyl)-pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one with hydroxylamine hydrochloride and $NaHCO_3$ in CH_3CN/H2O (3:1).	D
266	(±)-8-(4-fluorophenyl)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 501.1. ^{1}H NMR ($CDCl_3$) δ 8.79 (d, J = 2.0 Hz, 1H), 8.00 (dd, J = 8.2, 1.8 Hz, 1H), 7.51 (d, J = 8.1 Hz, 1H), 7.41 (s, 1H), 7.19 (m, 4H), 6.95 (m, 3H), 5.92 (s, 1H), 5.39 (d, J = 5.5 Hz, 1H), 3.38 (dd, J = 16.4, 5.7 Hz, 1H), 2.85 (d, J = 16.4 Hz, 1H). Prepared as described in Example 19 using 8-chloro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole.	D

267	(4S,9S,10R)-5,10-difluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 443.1. ^{1}H NMR ($CDCl_3$) δ 10.36 (s, 1H), 8.92 (d, J = 2.1 Hz, 1H), 8.11 (dd, J = 8.2, 2.2 Hz, 1H), 7.57 (d, J = 8.3 Hz, 1H), 7.49 (s, 1H), 6.97-7.04 (m, 2H), 6.65-6.71 (m, 1H), 6.14 (dd, J = 52.8, 6.3 Hz, 1H), 6.07 (s, 1H), 5.53 (d, J = 6.2 Hz, 1H). Prepared as the minor component of fluorination of 5-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10-ol using the methods described in Example 15, followed by chiral chromatographic separation of stereoisomers.	D
268	(4R,9R,10R)-5,10-difluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 443.1. ^{1}H NMR ($CDCl_3$) δ 10.27 (s, 1H), 8.97 (d, J = 1.9 Hz, 1H), 8.20 (dd, J = 8.3, 1.8 Hz, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.51 (s, 1H), 7.05-7.11 (m, 2H), 6.74-6.81 (m, 1H), 6.23 (s, 1H), 5.65 (d, J = 10.4 Hz, 1H), 5.52 (dd, J = 52.1, 1.8 Hz, 1H). Prepared by fluorination of 5-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10-ol using the methods described in Example 15 followed by chiral chromatographic separation of stereoisomers.	A

269	 (±)-8-chloro-N-methoxy-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-imine; MS 484.2. ^{1}H NMR ($CDCl_3$) δ 8.89 (d, J = 2.1 Hz, 0.3H), 8.83 (d, J = 2.1 Hz, 1H), 8.04 (dd, J = 8.2, 1.8 Hz, 1H), 7.94 (dd, J = 8.2, 1.8 Hz, 0.3H), 7.56 (s, 1H), 7.52 (m, 1H), 7.49 (s, 1H), 7.05 (s, 1), 7.02 (s, 3H), 6.65 (s, 1H), 6.03 (m, 1.3H), 4.12 (s, 3H), 4.08 (s, 1H). Prepared by treatment of (±)-8-chloro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one with methoxylamine hydrochloride and $NaHCO_3$ in EtOH/THF (1:1).	D
270	(±)-8-cyclopropyl-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 447.0 ^{1}H NMR ($CDCl_3$) δ 8.87 (d, J = 1.9 Hz, 1H), 7.99 (dd, J = 8.2, 2.0 Hz, 1H), 7.44 (d, J = 8.2 Hz, 1H), 7.38 (s, 1H), 6.84 (t, J = 7.5 Hz, 1H), 6.72 (d, J = 7.3 Hz, 1H), 6.41 (d, J = 7.7 Hz, 1H), 5.85 (s, 1H), 5.56 (d, J = 5.5 Hz, 1H), 3.51 (dd, J = 16.2, 5.6 Hz, 1H), 2.99 (d, J = 15.7 Hz, 1H), 1.66 (m, 1H), 0.98 (m, 2H), 0.60 (m, 2H). Prepared as described in Example 19 using cyclopropylboronic acid and 8-chloro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]-cyclohepta[1,2-c]pyrazole.	D
271	exo-10-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-2,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 425.0 ^{1}H NMR (CD_3OD) δ 8.94 (s, 1H), 8.25 (d, J = 8.2 Hz, 1H), 7.62 (m, 2H), 7.27 (d, J = 6.9 Hz, 1H), 6.94 (m, 3H), 6.15 (s, 1H), 5.71 (d, J = 10.6 Hz, 1H), 5.55 (d, J = 52.1 Hz, 1H). Prepared as described in Example 15 using (-)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]-cyclohepta[1,2-c]pyrazole.	A

272	 (±)-8-chloro-10-methylidene-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 453.1. ^{1}H NMR ($CDCl_3$) δ 8.78 (d, J = 2.1 Hz, 1H), 8.11 (dd, J = 8.4, 1.8 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.38, (s, 1H), 7.05 (m, 3H), 6.06 (s, 1H), 5.74 (s, 1H), 5.60 (s, 1H), 5.49 (s, 1H). Prepared by alkylation of (±)-8-chloro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo-[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one with trimethylsilylethoxymethyl chloride as described in Example 19 followed by alkene formation using Tebbe reagent and dealkylation using 4N HCl/dioxane.	D
273	(±)-5-(4-fluorophenyl)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 501.2. ^{1}H NMR ($CDCl_3$) δ 8.65 (s, 1H), 7.93 (d, J = 6.5 Hz, 1H), 7.55 (s, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.10 (m, 6H), 6.87 (d, J = 7.4 Hz, 1H), 5.74 (s, 1H), 5.44 (d, J = 5.1 Hz, 1H), 3.60 (dd, J = 16.7, 4.7 Hz, 1H), 3.04 (d, J = 16.9 Hz, 1H). Prepared as described in Example 19 using 5-chloro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole.	>100
274	(±)-5-cyclopropyl-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole; MS 447.2 ^{1}H NMR ($CDCl_3$) δ 8.90 (d, J = 1.7 Hz, 1H), 8.02 (dd, J = 8.1, 1.7 Hz, 1H), 7.46 (d, J = 8.2 Hz, 1H), 6.89 (m, 2H), 6.43 (m, 1H), 6.07(s, 1H), 5.45 (d, J = 5.1 Hz, 1H), 3.60 (dd, J = 16.2, 5.6 Hz, 1H), 2.92 (d, J = 15.7 Hz, 1H), 1.67 (m, 1H), 0.98 (m, 2H), 0.51 (m, 2H). Prepared as described in Example 19 using 5-chloro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole and cyclopropylboronic acid.	D

275	 (-)-9-methyl-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one; MS 435.1. ^{1}H NMR ($CDCl_3$) δ 8.92 (d, 1H, J = 2.4 Hz), 8.16 (dd, J = 2.4, 8.4 Hz, 1H), 7.70 (d, 1H, J = 8.4 Hz), 7.67 (s, 1H), 7.30-7.21 (m, 4H), 6.30 (s, 1H), 1.96 (s, 3H). Prepared as described in Example 21 using 6-(trifluoromethyl)pyridine-3-sulfonyl chloride followed by chiral chromatographic separation of the stereoisomers.	D
276	(+)-9-methyl-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one; MS 435.1 ^{1}H NMR ($CDCl_3$) δ 8.94 (d, 1H, J = 2.1 Hz), 8.16 (dd, J = 2.4, 8.4 Hz, 1H), 7.70 (d, 1H, J = 8.4 Hz), 7.66 (s, 1H), 7.32-7.18 (m, 4H), 6.30 (s, 1H), 1.96 (s, 3H). Prepared as described above for the (-)-stereoisomer.	>30
277	(-)-9-methyl-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one; MS 434.0 ^{1}H NMR ($CDCl_3$) δ 7.83 (d, 2H, J = 8.4 Hz), 7.67 (s, 1H), 7.63 (d, 2H, J = 8.4 Hz), 7.29-7.17 (m, 4H), 6.28 (s, 1H), 1.92 (s, 3H). Prepared as described in Example 21 followed by chiral chromatographic separation of stereoisomers.	D
278	(+)-9-methyl-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one; MS 434.0 ^{1}H NMR ($CDCl_3$) δ 7.83 (d, 2H, J = 8.4 Hz), 7.67 (s, 1H), 7.63 (d, 2H, J = 8.4 Hz), 7.29-7.17 (m, 4H), 6.28 (s, 1H), 1.92 (s, 3H). Prepared as described above for the (-)-stereoisomer.	>30

In the above table, "A" respresents IC_{50} values of >1 μM; "B" represents IC_{50} values of 500 nM to 999 nM; "C" respresent IC_{50} values of 100 nM to 499 nM; and "D" respresent IC_{50} values of <100 nM. IC_{50} values were generated using the assay described in Example A.

Example A

Gamma-Secretase APP 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_oC 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_o C. MBPC125 substrate was then added to initiate the reaction that would run for two hours at 37_o 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_o C. Detection of the cleavage product was performed using a standard sandwich ELISA assay

and quantified using a six point standard curve. Compounds of the invention have IC50 values of less than 10 μM.

Example B

Gamma-Notch in vitro assay

This assay employs the same enzyme preparation that was used in the gamma-APP *in vitro* enzyme assay (described in Example C, below), but at a two-fold higher concentration, and the same reaction buffers and materials for diluting the enzyme. The fusion protein APP substrate was replaced by an analogous Notch fusion protein substrate expressed in bacteria and purified by affinity chromatography prior to incubation with enzyme. The Gamma Notch assay was designed to measure the specific proteolytic cleavage of a Notch substrate (Notch ΔE) at the position corresponding to Val 1744 of full-length Notch, also known as the epsilon cleavage site, on the Notch substrate. The specific product was measured by a sandwich ELISA utilizing a neo-epitope specific capture antibody 9F3 specific for the N- terminus of the cleaved NICD product and a biotinylated reporter antibody anti-HA-biotin (Roche) directed against the HA-tag at the C-terminus of the substrate.

Bacterial Expression and Affinity Purification of Notch Fusion Protein Substrate

A recombinant Notch fusion protein containing sequential HA and His-6 epitope tags at the C-terminus, was expressed in *E. coli*, and affinity purified from lysates using a Nickel-sepharose column and imidazole elution using standard procedures. This purified Notch fusion protein was employed as a substrate for in vitro cleavage by the gamma secretase enzyme (prepared from IMR32 cells). The Notch fusion protein was constructed so as to be analogous to the APP C99 fragment. Thus, the Notch fusion protein was comprised of 99 amino-acids flanking the trans-membrane domain of mouse Notch1, beginning with the17 residues amino-terminal to the trans-membrane domain, also encompassing the 17 residue trans-membrane domain, and extending 66 residues into the cytoplasmic domain. The amino-terminus of the fusion protein begins at residue #1711 of mouse Notch, and extends C-terminally to residue #1809, followed by an in-frame epitope tag fusion of the HA tag, and six histidine residues. The epitope tags were incorporated to facilitate ELISA detection of the NICD cleavage product using an anti-HA antibody, and for easier purification of the fusion protein substrate from *E.coli* lysates using Nickel column affinity chromatography, respectively.

Following overnight expression of the fusion protein in *E.coli*, the substrate was purified on a nickel-sepharose column from lysates. Purity of the 16 kDa Notch fusion protein substrate eluted from the nickel-affinity column was confirmed by SDS-PAGE. Fractions containing the desired protein were then pooled, adjusted to 0.5-0.6 mg/ml final concentration in 3M Guanidine-HCl, 0.1% Triton X-100 with 20mM DTT, and stored at –80$_o$C in aliquots until use in the enzyme reaction. This protein was not stable over long periods, and would aggregate even in the above storage buffer at –80$_o$C. Therefore, a new preparation was necessary to prepare every three months to keep an active inventory to support in-house screening activities.

Bacterial Expression and purification of recombinant Notch intracellular domain (NICD) standard for ELISA

The NICD standard was produced as a fusion protein from a construct containing an initiating methionine and an enterokinase cleavage site before the gamma-secretase product NICD (Met-EK-NICD), with a carboxy-terminal calmodulin binding peptide fusion tag, and an HA epitope tag. The fusion protein was produced in *E.coli,* affinity purified using a calmodulin affinity resin, and assayed for protein concentration. The protein was then cleaved with enterokinase in order to produce the free N-terminus of the NICD product. The enterokinase cleaved protein was separated by SDS-PAGE on a 12% Tris-glycine gel. Enterokinase cleavage products were detected by Western blotting using an antibody against the HA-tag. Densitometry was used to measure the efficiency of the EK cleavage. The estimated concentration of EK cleaved NICD standard was calculated (% of NICD/total HA-reactive protein). The standard was stored at –40$_o$C. On the day of each assay, an aliquot of the NICD standard was serially diluted 1:1 in Casein Diluent (Media Facility) to generate a standard curve with 0-200 ng/ml NICD.

In vitro reaction of Notch substrate with enzyme

Purified substrate (above) was desalted immediately prior to use on a NAP-25 column, and its concentration was determined using the Biorad DC protein assay. Substrate was diluted 1:20 in the final reaction with a 1:20 dilution of gamma-secretase enzyme (0.4mg/ml final in Type V phospholipid solubilized in BigCHAP, 50mM MES pH6.0, 4mM DTT, 0.02% TX-100) and incubated in the presence of protease inhibitors (1mM 1,10-phenanthroline, 5μg/ml E64, and 5μg/ml leupeptin), plus or minus a range of gamma-secretase inhibitor

concentrations. All reactions were incubated at 37$_o$C in 96-well plates for 3hrs and then quenched with 0.1% SDS for 10min at room temperature.

Quenched reactions were then diluted 1:1 Casein Diluent with 500mM NaCl, 0.02% TritonX-100 and transferred to a 9F3-coated ELISA capture plate overnight at 4°C. NICD standards (section 4.2 above, serially diluted 2X over a concentration range from a starting concentration of 50 ng/ml) were used for establishing a standard curve. The NICD reaction product and concentration standards captured on the plate were quantified using an ELISA detection scheme. A biotinylated-HA antibody (1 μg/ml final conc., Roche Cat#. 1666851), followed by alkaline phosphatase conjugated streptavidin (diluted 1000X from stock, Roche Cat# 1089161) were incubated in the ELISA capture plate with washing steps (Tris buffered saline, 0.1% Tween20) in between each incubation step. The alkaline phosphatase reaction was developed by incubation with 100 μl/well Fluorescent Substrate A for 15min at RT, and the extent of fluorescence, which was proportional to the amount of cleaved Notch, was quantified using a Cytofluor plate reader set @ 360nm Excitation, 460nm Emission.

Example C

Notch SignalingAssay

The Notch signaling assay is a luciferase reporter gene based readout from cellular lysates generated from the SNC dual cell assay. Following transfer of conditioned media (to measure for Aβ from SNC cells incubated overnight with inhibitors), the cells were rinsed in PBS, lysed, and assayed for Luciferase reporter gene activity using a protocol and reagents provided by the manufacturer (Promega). The samples were kept in the dark until read in a luminometer (Safire plate reader, Tecan).

Cell culture and inhibitor treatment

CHO cells stably transfected with the SweAPP and Notch E constructs were plated on 96-well tissue culture plates at 15,000 cells per well in 130 μl media/well the day before the compound treatment. Cells were cultured in DMEM containing 2 mM glutamine, 10% FBS, 0.5 mg/ml G418, 1 mg/ml hygromycin, and 2.8 mg/ml puromycin. Compounds were diluted first 4-fold and then 10-fold for six successive dilutions in DMSO as 250X final concentration stocks. The compounds were then added to cells using media which had been pre-warmed to 37 °C, at a final DMSO concentration of 0.4%. After 18h, 100 μl of conditioned media was removed from each well and saved for the ELISA assay. The wells were washed with 200 μl/well of cold PBS with $MgCl_2$ and $CaCl_2$. The wash buffer was aspirated and the cells were lysed in 40 μl lysis reagent (20 mM Tris, pH 7.5, 0.2% TX100,

100 mM NaCl, 2 mM EDTA, 2X complete protease inhibitors) per well for 30 minutes to complete the lysis. 100 µl of luciferase reagent was then added to all wells (Promega catalog number#E1501) and luminescence measured using a Safire II plate reader (Tecan). This assay was performed in a fully automated manner using the Stacatto platform (Caliper Life Sciences).

Aβ 40 and Aβ42 specific ELISA

The conditioned media (CM) from CHO cells stably transfected with the SweAPP and NotchΔE constructs was directly taken from the well undiluted for the Aβ(X-40) and Aβ (X-42) ELISA assays after overnight incubation with the test compound. The capture antibody for the Aβ(X-40) ELISA was 266 and the reporter antibody was biotinylated-2G3 (directed towards Aβ40). The capture antibody for the Aβ(X-42) ELISA assay was also 266 where the reporter antibody was biotinylated-21F12 (directed towards Aβ42). Aβ(1-40) and Aβ(1-42) synthetic peptide standard curves were used to calculate the CM Aβ concentrations. The IC_{50} determinations of the compounds were calculated using the GraphPad Prism program choosing the sigmoidal dose response variable slope equation.

Example D

SNC dual cell assay for simultaneous assay of A-beta reduction and Notch signaling following gamma secretase inhibition in cells

Production of Stably Transfected CHO Cells Overexpressing APP(SWE), Notch-Δe, and a Notch Intracellular Domain Responsive Luciferase Reporter Gene and Development of SNC Dual Cell Assay.

In order to facilitate testing the potency of gamma-secretase inhibitors on two substrates (APP and Notch) simultaneously, a dual-assay using a CHO cell line stably expressing APPSwe, a Notch substrate lacking the ecto-domain, and a Notch responsive Luciferase reporter gene was developed. CHOSwe cells stably over-express the Swedish FAD isoform of APP, and secrete large amounts of Aβ peptide into the conditioned media from endogenous β- and γ-secretase enzyme activity. A Notch intracellular domain (NICD) responsive reporter gene, and the constitutive gamma-secretase Notch substrate, NotchΔE, were stably introduced into CHOSwe cells in a two step process. CHOSwe cells were first stably transfected to express a NICD responsive luciferase reporter gene construct (pGL2-CBF-Luc). Numerous stable clones (SCH clones), were identified which displayed gamma-inhibitor-sensitive Notch signaling upon transient expression with Notch-ΔE. The best three clones SCH-32, SCH-33 and SCH-54 were selected as the host cells for subsequent stable

expression of Notch-ΔE as the final step of dual-assay line generation. Stable cell lines expressing rat NotchΔE were then identified in the second step by including a gamma-secretase inhibitor in the selection process (to suppress Notch/NICD toxicity) following transfection of the rat Notch-ΔE construct.

The SCH-32, SCH-33 and SCH-54 clones were transfected with the Notch-ΔE expression vector (pIRES-ZEDN), respectively. This vector drives expression of a truncated rat Notch construct corresponding to the c-terminal product following ecto-domain shedding of full length rat Notch protein. The c-terminal product is a constitutive substrate for gamma-secretase cleavage, resulting in release of the cytoplasmic Notch intracellular domain (NICD) product, which translocates to the nucleus and relieves CBF repressed genes. Subsequently, pIRES-ZEDN transfected cells were re-plated at low density in the presence of test compound, and selected with three antibiotics (G418 (0.5 mg/ml)/Hygro (1 mg/ml)/Puro (2.5 mg/ml)). The antibiotic-resistant colonies (named SNC clones for the dual-assay components: APP***S***we/***N***otchΔE/***C***BF) were isolated and expanded for characterization of Aβ secretion, and NICD responsive reporter gene activity (i.e. luciferase signal in the presence versus absence of test compound). Based on optimal Aβ secretion, and best signal/background of reporter gene activity, we selected the clone designated as SNC-204B8 as the dual-assay stable line for our subsequent profiling more gamma-secretase inhibitors. A typical dual-assay experiment was performed as follows:

Day 1, the SNC cells were plated in 96-well assay plates in inhibitor-free media.

Day 2, the cells were fed with fresh media (inhibitor free) and treated with test compounds over a concentration range 0 nM to 40,000 nM (in 10X incremental dilutions) one hour after the media change. The cells were treated with compounds overnight at 37$_o$C.

Day 3, Notch signaling and part I of Aβ-ELISA was performed: for the Aβ-production assay, conditioned media were collected and added to plates coated with antibody 266 for Aβ capture overnight. For the Notch signaling assay, the cells were lysed and luciferase activity from the lysate was measured using the Promega kit (see below).

Day 4, Aβ-ELISA part II was conducted using 3D6-biotin/AP- streptavidin antibodies.

Example E

Alternative Notch Signaling Assays

Assay systems described in the following references can also be used to measure modulation (*e.g.*, inhibition) of Notch signaling by compounds of the invention. An

exemplary reporter gene assay for Notch signaling was described in 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 and by Lu, F. M. and S. E. Lux, *Mol. Cell Biol.* 1996, 16(3): 952-9; "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. Another reporter gene based Notch signaling assay uses a constitutively active rat Notch1 construct (ZEDN1) 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 as described in 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). Each of the above references is incorporated herein by reference in their entirety.

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.

Notch Selectivity Data

Evidence indicates that the gamma secretase complex, comprised of the presenilin subunits, mediates the intra-membrane cleavage of amyloid precursor protein (APP) as well as the Notch family of proteins. Unexpectedly, the inventors have discovered that certain compounds of the invention potently inhibit gamma secretase-mediated cleavage of APP (inhibition of beta-amyloid synthesis, *e.g.*, as described in Example A) but exhibit reduced

proteolytic cleavage of a Notch substrate (*e.g.*, NotchΔE, as described in Example B) or inhibition of Notch signaling (*e.g.*, as described in Examples C and D). *E.g.*, compounds disclosed herein exhibit greater selectivity for the inhibition of APP cleavage (*i.e.*, gamma secretase-mediated beta-amyloid production) versus inhibition of Notch cleavage or inhibition of Notch signaling when compared to known gamma-secretase inhibitors. In the following, compounds, which can inhibit enzymatic cleavage of Notch (*e.g.*, by inhibiting the corresponding gamma secretase activity) (*e.g.*, as described in Example B) or Notch signaling (*e.g.*, as described in Example C), are referred to as having "*in vitro* Notch activity" or "Notch activity". Assays, which can be used to determine Notch activities are known to those of skill in the art. Exemplary assays are described herein in Examples B, C, D and E.

Certain compounds disclosed herein are characterized by desirable, low Notch activity. In one example, the compounds of the invention are characterized by an *in vitro* Notch activity (*e.g.*, as measured using the assay described in Example B) equivalent to an IC_{50} value larger than about 20 nM, about 30, about 40 or about 50 nM. In another example, the compounds of the invention are characterized by an *in vitro* Notch activity equivalent to an IC_{50} value larger than about 100 nM, larger than about 200 nM, larger than about 300 nM, larger than about 400 nM, larger than about 500 nM, larger than about 600 nM, larger than about 700 nM, larger than about 800 nM, larger than about 900 nM or larger than about 1 μM. In yet another example, the compounds of the invention are characterized by an *in vitro* Notch activity equivalent to an IC_{50} value larger than about 2 μM, larger than about 3 μM, larger than about 4 μM, larger than about 5 μM, larger than about 6 μM, larger than about 7 μM, larger than about 8 μM, larger than about 9 μM or larger than about 10 μM.

In yet another example, the compounds of the invention are characterized by a ratio of Notch activity (i.e., Notch IC_{50}) to APP activity (*i.e.*, Aβ IC_{50}) (*e.g.*, as measured by a *in vitro* assays as described in Examples A and B, respectively; or a dual assay as described in Example D) (*e.g.*, selectivity ratio Notch IC_{50}/Aβ ED_{50}) of larger than about 500, larger than about 400 or larger than about 300. In a further example, the Notch/APP selectivity ratio is larger than about 200, larger than about 150 or larger than about 100. In a further example, the Notch/APP selectivity ratio is larger than about 90, larger than about 80, larger than about 70, larger than about 60, larger than about 50, larger than about 40, larger than about 30, larger than about 20 or larger than about 10. In yet a further example, the Notch/APP selectivity ratio is larger than about 9, larger than about 8, larger than about 7, larger than about 6, larger than about 5, larger than about 4, larger than about 3, larger than about 2 or

larger than about 1. In a particular embodiment, the compounds of the invention are characterized by a selectivity ratio (i.e., Notch IC_{50}/Aβ ED_{50}) of larger than about 50. Exemplary compounds and their Notch/APP selectivity ratios are summarized in Table 2, below.

Table 2
Compound selectivity for cleavage of the Aβ peptide over Notch

Compound Name	Selectivity Ratio (Notch IC_{50} /Aβ ED_{50})
(±)-10-[(4-chlorophenyl)sulfonyl]-6-(3-methylisoxazol-5-yl)-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole	(++++)
(-)-5-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one	(++++)
(-)-8-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one	(++++)
(±)-10-[(4-chlorophenyl)sulfonyl]-6-(3-methyl-1,2,4-oxadiazol-5-yl)-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole	(++++)
(±)-10-[(5-chlorothiophen-2-yl)sulfonyl]-6-phenyl-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole	(++++)
(±)-exo-6-(4-fluorophenyl)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole	(+++)
(+)-endo-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10-ol	(+++)
(±)-10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole-6-carbonitrile	(+++)
(±)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-6-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole	(+++)
(+)-6-(3-fluorophenyl)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole	(+++)

(+)-5,10-difluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole	(++)
(±)-6-(1,2,3-thiadiazol-4-yl)-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole	(++)
(±)-endo-6-(4-fluorophenyl)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole	(++)
5-phenyl-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole	(++)
(±)-7-[3-(trifluoromethyl)phenyl]-12-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,11-tetrahydro-3H-5,11-epiminobenzo[4,5]cycloocta[1,2-c]pyrazole	(++)
(±)-7-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-b]pyridine	(+)
(±)-6-[3-(1H-pyrazol-1-yl)phenyl]-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole	(+)
(±)-6-(3-bromophenyl)-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole	(+)
(±)-6-(1,3-benzodioxol-5-yl)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole	(+)
(-)-6-bromo-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole	(+)

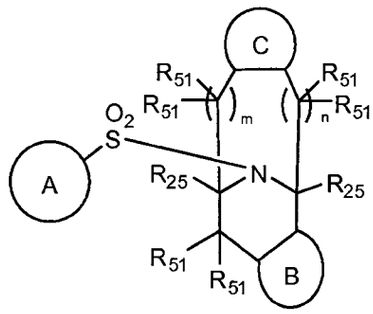
In the above table, (++++) means a ratio of Notch IC_{50}/Aβ EC_{50} (determined as described in Example D) of >200; (+++) means a ratio from about 150 to about 199; (++) means a ratio from about 100 to about 149; and (+) means a ratio from about 50 to about 99.

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 aspects 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. Compounds of the formula:



or a pharmaceutically acceptable salt or solvate thereof, wherein,

m and n are independently 0 or 1, provided that m + n is 0 or 1;

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, haloalkyl, haloalkoxy, hydroxyl, hydroxyalkyl, CN, aryloxy, -$S(O)_{0-2}$-(C_1-C_6 alkyl), -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, NO_2, CN, C_2-C_6 alkanoyl, C_0-C_3alkylCO_2R_{11}, heteroaryl, heterocycloalkyl, aryl, arylalkyl, -OCH_2O-, -OCH_2CH_2O- or -$SO_2NR_{11}R_{11}$;

the B-ring is pyrazolyl, dihydropyrazolyl, pyrazolonyl or pyrazolidinonyl, each of which is optionally substituted with C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxy, hydroxyalkyl, halo, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$ or CN;

wherein the C-ring is aryl substituted with R_{30}, R_{35}, R_{40}, and R_{45} or heteroaryl, optionally substituted with halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, CN, hydroxyl, C_1-C_6 alkoxy, -C_1-C_3 alkyl-OH, -C_1-C_3 alkyl-alkoxy, phenyloxy, -$S(O_2)R_{10}$, -$SO_2NR_{11}R_{11}$, -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl, thienyl, phenyl or phenyl C_1-C_4 alkyl, wherein the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky or halogen;

R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, -$SO_2NR_{11}R_{11}$, arylalkyl, cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, CN, NO_2, hydroxyl, C_1-C_6 alkoxy, -C_1-C_6 alkyl-OH, -C_1-C_6 alkyl-C_1-C_6 alkoxy, aryloxy, -$S(O_2)R_{10}$, -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$,

$-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, heteroarylalkyl, heteroaryl, wherein each heteroaryl group is optionally substituted with a C_1-C_6 alkyl group, heterocycloalkylalkyl, heterocycloalkyl, wherein each heterocycloalkyl group is optionally substituted with one or two groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy or halogen, aryl, aryloxy or arylalkyl, where the aryl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, C_1-C_4 haloalky or halogen; and

wherein two adjacent substituents on the C-ring together with the carbons to which they are attached optionally form a heterocycloalkyl or a heteroaryl ring, each of which is optionally substituted with one or more groups that are independently alkyl, alkoxy, halogen or C_2-C_4 alkanoyl wherein the alkanoyl group is optionally further substituted with up to 3 halogen atoms; or two adjacent carbons of the C-ring optionally form a benzo ring which is optionally substituted with 1 to 4 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2;

each R_{25} is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-C(O)OR_{11}$, -(C_1-C_6 alkyl)-$C(O)OR_{11}$, C_1-C_6 alkoxy C_1-C_6 alkyl, $-C(O)OR_{11}$, $-CONR_{11}R_{11}$, CN, C_1-C_6 alkyl-CN or hydroxy C_1-C_6 alkyl;

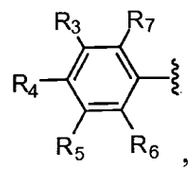
each R_{51} is independently absent, H, C_1-C_4 alkyl, halogen, CN, amino, mono alkylamino or dialkylamino, OH or C_1-C_4 haloalkyl; further when there are two R_{51} groups on a carbon atom, the two R_{51} groups and the carbon to which they are attached may form a 3 to 6 membered cycloalkyl ring; or when there are two R_{51} groups on a carbon, the two R_{51} groups may form an oxo group;

R_{10} and R_{11} at each occurrence are independently C_1-C_6 alkyl, heteroaryl that is selected from pyrazolyl, thiadiazolyl, triazolyl, isoxazolyl, isothiazolyl, imidazolyl, thiazolyl, oxadiazolyl, and pyridyl or aryl that is selected from phenyl and naphthyl, where the heteroaryl and aryl groups are optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2; and additionally R_{11} may be H; or if two R_{11} groups are on a nitrogen, then the two R_{11} groups together with the nitrogen to which they are attached, may form a 3-8 membered ring optionally including an additional heteroatom such as NH, NR_{12}, NR_{13}, O or S;

R_{12} is H, C_1-C_6 alkyl, aryl or $-SO_2$-aryl, where each aryl is optionally substituted with 1 to 5 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2; and

R_{13} is H, aryl or C_1-C_6 alkyl optionally substituted with aryl, hydroxyl or halogen, where each aryl is optionally substituted with 1 to 5 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2.

2. Compounds or salts according to claim 1, wherein the A-ring is phenyl, and has the following formula:



wherein,

R_3, R_4, R_5, R_6, R_7 are independently of each other H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, CN, hydroxyl, C_1-C_6 alkoxy, -C_1-C_3 alkyl-OH, -C_1-C_3 alkyl-alkoxy, phenyloxy, -$S(O_2)R_{10}$, -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl, thienyl, phenyl or phenyl C_1-C_4 alkyl, where the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky or halogen; or

R_4 and R_5 or R_5 and R_6 and the carbons to which they are attached form a heterocycloalkyl or a heteroaryl ring which is optionally substituted with 1, 2, 3 or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen or C_1-C_4 alkanoyl wherein the alkanoyl group is optionally substituted with up to 3 halogen atoms; or

R_4 and R_5 or R_5 and R_6 and the carbons to which they are attached form a benzo ring which is optionally substituted with 1 to 5 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2; or

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, haloalkyl, haloalkoxy, hydroxyl, hydroxyalkyl, CN, phenyloxy, -$S(O)_{0\text{-}2}$-(C_1-C_6 alkyl), -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, C_0-C_3alkylCO_2R_{10}, pyridyl, thienyl, furanyl, pyrrolyl, pyrrolidinyl, piperidinyl, piperazinyl, phenyl, phenyl C_1-C_4 alkyl or -$SO_2NR_{11}R_{11}$, where the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky or halogen; or

the A-ring is heteroaryl that is pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, thienyl, furanyl, pyrrolyl, pyrazolyl or imidazolyl, each of which is optionally substituted at one or more substitutable positions with halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, haloalkyl, haloalkoxy, hydroxyl, hydroxyalkyl, CN, phenyloxy, -$S(O)_{0-2}$-(C_1-C_6 alkyl), -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, C_0-C_3alkylCO_2R_{10}, pyridyl, thienyl, furanyl, pyrrolyl, pyrrolidinyl, piperidinyl, piperazinyl, phenyl, phenyl C_1-C_4 alkyl or -$SO_2NR_{11}R_{11}$, where the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky or halogen;

the A-ring is heterocycloalkyl that is pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl or thiomorpholinyl-S,S-dioxide, where each of the above rings 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, haloalkyl, haloalkoxy, hydroxyl, hydroxyalkyl, CN, phenyloxy, -$S(O)_{0-2}$-(C_1-C_6 alkyl), -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, C_0-C_3alkylCO_2R_{10}, pyridyl, thienyl, furanyl, pyrrolyl, pyrrolidinyl, piperidinyl, piperazinyl, phenyl, phenyl C_1-C_4 alkyl or -$SO_2NR_{11}R_{11}$, where the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky or halogen.

3. Compounds or salts according to claim 2, wherein the A-ring is phenyl or pyridyl, each of which is optionally substituted with halogen or C_1-C_4 haloalkyl.

4. Compounds or salts according to claim 2, wherein

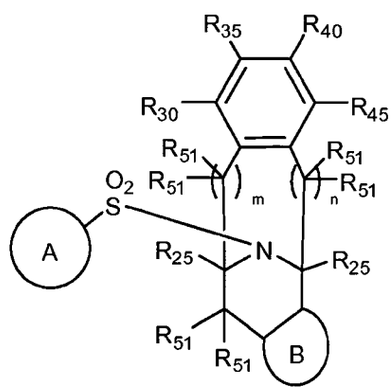
the C-ring is phenyl substituted with R_{30}, R_{35}, R_{40}, and R_{45}; or heteroaryl, wherein the heteroaryl, group is optionally substituted with H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, CN, hydroxyl, C_1-C_6 alkoxy, -C_1-C_3 alkyl-OH, -C_1-C_3 alkyl-alkoxy, phenyloxy, -$S(O_2)R_{10}$, -$SO_2NR_{11}R_{11}$, -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl, thienyl, phenyl or phenyl C_1-C_4 alkyl, wherein the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky or halogen;

R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, -$SO_2NR_{11}R_{11}$, arylalkyl, cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, CN, NO_2, hydroxyl, C_1-C_6 alkoxy, -C_1-C_6 alkyl-OH, -C_1-C_6

alkyl-C_1-C_6 alkoxy, aryloxy, -$S(O_2)R_{10}$, -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, heteroarylalkyl, heteroaryl, wherein each heteroaryl group is optionally substituted with a C_1-C_6 alkyl group, heterocycloalkylalkyl, heterocycloalkyl, wherein each heterocycloalkyl group is optionally substituted with one or two groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy or halogen, aryl, aryloxy or arylalkyl, where the aryl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, C_1-C_4 haloalky or halogen; and

wherein when the C-ring is aryl or heteroaryl, two adjacent carbons of the C-ring optionally form a heterocycloalkyl or a heteroaryl ring, each of which is optionally substituted with one or more groups that are independently alkyl, alkoxy, halogen or C_2-C_4 alkanoyl wherein the alkanoyl group is optionally further substituted with up to 3 halogen atoms; or two adjacent carbons of the C-ring optionally form a benzo ring which is optionally substituted with 1 to 4 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2.

5. Compounds or salts according to claim 4, of the formula:



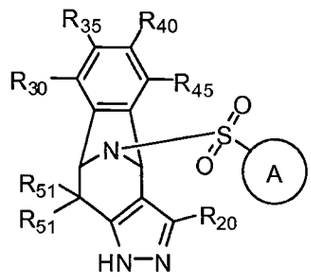
or pharmaceutically acceptable solvates, salts or mixtures thereof, wherein

each R_{25} is independently H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, hydroxy C_1-C_4 alkyl, C_1-C_4 alkoxyalkyl, -$C(O)OR_{11}$ or -$C(O)NR_{11}R_{11}$; and

each R_{51} is independently absent, H, C_1-C_4 alkyl, F, Cl, Br, CN, amino, mono alkylamino or dialkylamino, OH or CF_3; further, when there are two R_{51} groups on a carbon atom, the two R_{51} groups and the carbon to which they are attached may form a 3- to 6-membered cycloalkyl or heterocycloalkyl ring; or when there are two R_{51} groups on a carbon, the two R_{51} groups may form an oxo group.

6. Compounds or salts according to claim 5, wherein the B-ring is pyrazolyl, which is optionally substituted with $-NR_{11}$-C_2-C_6 alkanoyl, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxy C_1-C_4 alkyl, halo, CF_3, OCF_3 or CN.

7. Compounds or salts according to claim 6, of the formula:

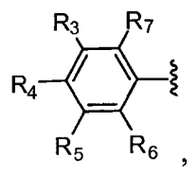


or pharmaceutically acceptable solvates, salts or mixtures thereof, wherein

R_{20} is H, C_1-C_4 alkyl, C_1-C_4 alkoxy, $-NR_{11}C(O)CH_3$, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, halo, CF_3 or CN; where R_{11} is H or C_1-C_6 alkyl; and

R_{30}, R_{35}, R_{40}, and R_{45} are independently H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, CN, hydroxyl, C_1-C_6 alkoxy, -C_1-C_3 alkyl-OH, -C_1-C_3 alkyl-alkoxy, phenyloxy, $-S(O_2)R_{10}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl, thienyl, phenyl or phenyl C_1-C_4 alkyl, where the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy or halogen.

8. Compounds or salts according to claim 7, wherein the A-ring is:



,

wherein,

R_3, R_4, R_5, R_6, R_7 are independently of each other H, halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, CN, hydroxyl, C_1-C_4 alkoxy, -C_1-C_3 alkyl-OH, -C_1-C_3 alkyl-C_1-C_4 alkoxy, phenyloxy, $-S(O_2)R_{10}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$ or C_2-C_4 alkanoyl; or

the A-ring is pyridyl, which is optionally substituted at one or more substitutable positions with groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, CF_3, OCF_3,

hydroxyl, CN, phenyloxy, $-SO_2-(C_1-C_6$ alkyl), $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, pyridyl, phenyl or $-SO_2NR_{11}R_{11}$, where

each R_{10} and R_{11} is independently C_1-C_6 alkyl or phenyl; and additionally R_{11} may be H.

9. Compounds or salts according to claim 8, wherein

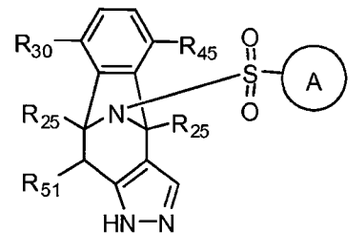
the A-ring is phenyl, R_4 is halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, CF_3, OCF_3 or CN; and R_3, R_5 R_6, and R_7 are hydrogen.

10. Compounds or salts according to claim 8, wherein the A-ring is pyridyl, optionally substituted with one halogen or CF_3.

11. Compounds or salts according to claim 8, wherein at least one R_{51} group is halogen.

12. Compounds or salts according to claim 8, wherein the two R_{51} groups are both H, both halogen or form an oxo group.

13. Compounds or salts according to claim 8, of the formula:



including stereoisomers, tautomers and mixtures of steroisomers and/or tautomers, and/or pharmaceutical salts thereof, wherein

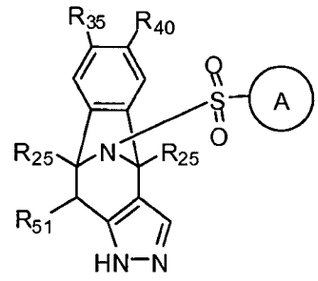
each R_{25} is independently H or CH_3;

R_{30} ane R_{45} are independently H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, CN, hydroxyl, C_1-C_6 alkoxy, $-C_1-C_3$ alkyl-OH, $-C_1-C_3$ alkyl-alkoxy, phenyloxy, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, $-C(O)OR_{11}$, $-S(O_2)R_{10}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl, thienyl, phenyl or phenyl C_1-C_4 alkyl, where the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky or halogen; and

R_{51} is H, C_1-C_4 alkyl, F, Cl, Br, CN, amino, mono alkylamino or dialkylamino, OH or CF_3.

14. Compounds or salts according to claim 13, wherein at least one of R_{30} and R_{45} is F; and R_{51} is H, F or OH.

15. Compounds or salts according to claim 8, of the formula:



including stereoisomers, tautomers and mixtures of steroisomers and/or tautomers, and/or pharmaceutical salts thereof, wherein

each R_{25} is independently H or CH_3;

R_{35} ane R_{40} are independently H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, CN, hydroxyl, C_1-C_6 alkoxy, -C_1-C_3 alkyl-OH, -C_1-C_3 alkyl-alkoxy, phenyloxy, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_6 haloalkenyl, C_2-C_6 haloalkynyl, -C(O)OR_{11}, -S(O_2)R_{10}, -$SO_2NR_{11}R_{11}$, -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alkanoyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl, thienyl, phenyl or phenyl C_1-C_4 alkyl, wherein the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky or halogen; and

R_{51} is H, C_1-C_4 alkyl, F, Cl, Br, CN, amino, mono alkylamino or dialkylamino, OH or CF_3.

16. Compounds or salts according to claim 15, wherein at least one of R_{35} and R_{40} is F; and R_{51} is H, F or OH.

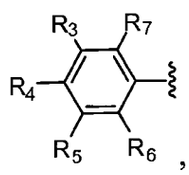
17. Compounds or salts according to claim 2, wherein the

C-ring is a heteroaryl or heterocycloalkyl ring that is optionally substituted with one or more groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, -C(O)OR_{11},

CN, hydroxyl, C_1-C_6 alkoxy, -C_1-C_3 alkyl-OH, -C_1-C_3 alkyl-alkoxy, phenyloxy, -$S(O_2)R_{10}$, -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl, thienyl, phenyl or phenyl C_1-C_4 alkyl, wherein the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky or halogen.; each R_{10} and R_{11} is independently C_1-C_6 alkyl or phenyl; and additionally R_{11} may be H; and

the B-ring is pyrazoly, which is optionally substituted with C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxy C_1-C_4 alkyl, halo, CF_3, OCF_3 or CN.

18. Compounds or salts according to claim 17, wherein the A-ring is phenyl, and has the following formula:



wherein,

R_3, R_4, R_5, R_6, R_7 are independently of each other H, halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, CN, hydroxyl, C_1-C_4 alkoxy, -C_1-C_3 alkyl-OH, -C_1-C_3 alkyl-C_1-C_4 alkoxy, phenyloxy, -$S(O_2)R_{10}$, -$SO_2NR_{11}R_{11}$, -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$ or C_2-C_4 alkanoyl; or

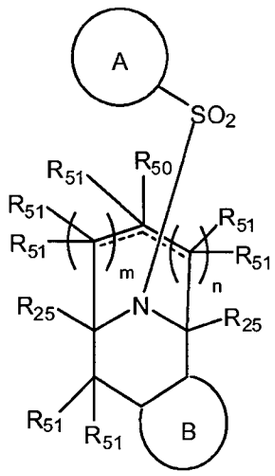
the A-ring is pyridyl, which is optionally substituted at one or more substitutable positions with groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, CF_3, OCF_3, hydroxyl, CN, phenyloxy, -SO_2-(C_1-C_6 alkyl), -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, pyridyl, phenyl or -$SO_2NR_{11}R_{11}$, where

each R_{10} and R_{11} is independently C_1-C_6 alkyl or phenyl; and additionally R_{11} may be H; and

each R_{25} is independently H or CH_3;

19. Compounds or salts according to claim 17, wherein the A-ring is phenyl or pyridyl, each of which is optionally substituted with halogen or C_1-C_4 haloalkyl.

20. Compounds having the formulas:



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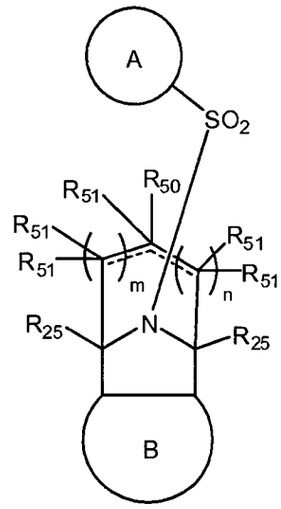
Formula 1



,

Formula 2

or a pharmaceutically acceptable salt or solvate thereof, wherein,

m and n are independently selected from 0, 1 and 2, with the proviso that (m + n) is 1 or 2;

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, haloalkyl, haloalkoxy, hydroxyl, hydroxyalkyl, CN, aryloxy, -$S(O)_{0-2}$-(C_1-C_6 alkyl), -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, NO_2, CN, C_2-C_6 alkanoyl, C_0-C_3alkylCO_2R_{11}, heteroaryl, heterocycloalkyl, aryl, arylalkyl, -OCH_2O-, -OCH_2CH_2O- or -$SO_2NR_{11}R_{11}$;

the B-ring is pyrazolyl, dihydropyrazolyl, pyrazolonyl or pyrazolidinonyl, each of which is optionally substituted with –NR_{11}-C_2-C_6 alkanoyl, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxy, hydroxyalkyl, halo, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$ or CN;

R_{50} is C_2-C_6 alkenyl, C_2-C_6 alkynyl, halo C_2-C_6 alkenyl, halo C_2-C_6 alkynyl, C_2-C_6 alkanoyl, $OS(O)_2R_{10}$, -$S(O)_2R_{10}$, -$NR_{11}R_{11}$, $C(O)OR_{11}$, -$SO_2NR_{11}R_{11}$, heteroaryl, heterocycloalkyl, C_3 –C_6 cycloalkyl, aryl; wherein the aforementioned heteroaryl, heterocycloalkyl, cycloalkyl and aryl groups are optionally substituted with 1 or more groups that are independently halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxy, hydroxyC_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 haloalkyl, halo C_2-C_6 alkenyl, halo C_2-C_6 alkynyl, -$C(O)OR_{11}$, -(C_1-C_4 alkyl)-$C(O)OR_{11}$, -$CONR_{11}R_{11}$, -$OC(O)NR_{11}R_{11}$, -$NR_{11}C(O)OR_{10}$, -$NR_{11}S(O)_2R_{10}$, -$OS(O)_2R_{10}$, -$S(O)_2R_{10}$, -$NR_{11}C(O)R_{10}$, CN, =N-NHR_{12},

$-NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, heteroaryl, heterocycloalkyl, C_3 –C_6 cycloalkyl, aryl; wherein the aforementioned heteroaryl, heterocycloalkyl, cycloalkyl and aryl substituents are optionally substituted with 1 or more groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkoxy or C_1-C_6 haloalkyl;

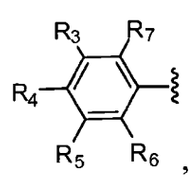
each R_{25} is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-C(O)OR_{11}$, -(C_1-C_6 alkyl)-$C(O)OR_{11}$, C_1-C_6 alkoxy C_1-C_6 alkyl, $-C(O)OR_{11}$, $-CONR_{11}R_{11}$, CN, C_1-C_6 alkyl-CN or hydroxy C_1-C_6 alkyl;

each R_{51} is independently absent, H, C_1-C_4 alkyl, halogen, CN, amino, mono alkylamino, dialkylamino, OH or C_1-C_4 haloalkyl; further when there are two R_{51} groups on a carbon atom, the two R_{51} groups and the carbon to which they are attached may form a 3 to 6 membered cycloalkyl ring or heterocycloalkyl ring; or when there are two R_{51} groups on a carbon, the two R_{51} groups may form an oxo group;

R_{10} and R_{11} at each occurrence are independently C_1-C_6 alkyl, heteroaryl that is selected from pyrazolyl, thiadiazolyl, triazolyl, isoxazolyl, isothiazolyl, imidazolyl, thiazolyl, oxadiazolyl, and pyridyl or aryl that is selected from phenyl and naphthyl, where the heteroaryl and aryl groups are optionally substituted with 1 to 3 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2; and additionally R_{11} may be H; or if two R_{11} groups are on a nitrogen, then the two R_{11} groups together with the nitrogen to which they are attached, may form a 3-8 membered ring optionally including an additional heteroatom such as NH, NR_{12}, NR_{13}, O or S;

R_{12} is H, C_1-C_6 alkyl, aryl or $-SO_2$-aryl, where each aryl is optionally substituted with 1 to 5 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2.

21. Compounds or salts according to claim 20, wherein the A-ring is phenyl, and has the following formula:



wherein,

R_3, R_4, R_5, R_6, R_7 are independently of each other H, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, CN, hydroxyl, C_1-C_6 alkoxy, -C_1-C_3 alkyl-OH, -C_1-C_3 alkyl-alkoxy, phenyloxy, $-S(O_2)R_{10}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$,

$-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, oxazolyl, pyrazolyl, thiazolyl, pyridyl, pyrimidinyl, imidazolyl, indolyl, furanyl, thienyl, phenyl or phenyl C_1-C_4 alkyl, where the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky or halogen; or

R_4 and R_5 or R_5 and R_6 and the carbons to which they are attached form a heterocycloalkyl or a heteroaryl ring which is optionally substituted with 1, 2, 3 or 4 groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen or C_1-C_4 alkanoyl wherein the alkanoyl group is optionally substituted with up to 3 halogen atoms; or

R_4 and R_5 or R_5 and R_6 and the carbons to which they are attached form a benzo ring which is optionally substituted with 1 to 5 groups that are independently halogen, hydroxyl, alkyl, alkoxy, haloalkyl, haloalkoxy, CN or NO_2; or

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, haloalkyl, haloalkoxy, hydroxyl, hydroxyalkyl, CN, phenyloxy, $-S(O)_{0-2}-(C_1-C_6$ alkyl), $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, C_0-C_3alkylCO_2R_{10}, pyridyl, thienyl, furanyl, pyrrolyl, pyrrolidinyl, piperidinyl, piperazinyl, phenyl, phenyl C_1-C_4 alkyl or $-SO_2NR_{11}R_{11}$, where the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky or halogen; or

the A-ring is heteroaryl that is pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, thienyl, furanyl, pyrrolyl, pyrazolyl or imidazolyl, each of which is optionally substituted at one or more substitutable positions with halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, haloalkyl, haloalkoxy, hydroxyl, hydroxyalkyl, CN, phenyloxy, $-S(O)_{0-2}-(C_1-C_6$ alkyl), $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, C_0-C_3alkylCO_2R_{10}, pyridyl, thienyl, furanyl, pyrrolyl, pyrrolidinyl, piperidinyl, piperazinyl, phenyl, phenyl C_1-C_4 alkyl or $-SO_2NR_{11}R_{11}$, where the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky or halogen; or

the A-ring is heterocycloalkyl that is pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl or thiomorpholinyl-S,S-dioxide, where each of the above rings 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, haloalkyl, haloalkoxy, hydroxyl, hydroxyalkyl, CN, phenyloxy, $-S(O)_{0-2}-(C_1-C_6$ alkyl), $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, C_0-C_3alkylCO_2R_{10}, pyridyl, thienyl, furanyl, pyrrolyl,

pyrrolidinyl, piperidinyl, piperazinyl, phenyl, phenyl C_1-C_4 alkyl or -$SO_2NR_{11}R_{11}$, where the phenyl portions of the above are optionally substituted with one or more groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_4 haloalky or halogen.

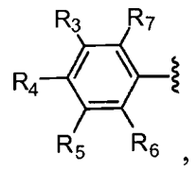
22. Compounds or salts according to claim 20, wherein the A-ring is phenyl or pyridyl, each of which is optionally substituted with halogen or C_1-C_4 haloalkyl.

23. Compounds or salts according to claim 20, wherein

R_{50} is C_2-C_6 alkenyl, C_2-C_6 alkynyl, halo C_2-C_6 alkenyl, halo C_2-C_6 alkynyl, C_2-C_6 alkanoyl, $OS(O)_2R_{10}$, -$S(O)_2R_{10}$, -$NR_{11}R_{11}$, $C(O)OR_{11}$ -$SO_2NR_{11}R_{11}$, heteroaryl that is selected from pyrazolyl, thiadiazolyl, triazolyl, isoxazolyl, isothiazolyl, imidazolyl, thiazolyl, oxadiazolyl, oxazolyl, tetrazolyl, and pyridyl, heterocycloalkyl that is selected from tetrahydrofuranyl, pyrrolidinyl, piperidinyl, morpholinyl, and imidazolidinyl, C_3 –C_6 cycloalkyl, aryl that is selected from phenyl, benzo[d][1,3]dioxolyl, and naphthyl; wherein the aforementioned heteroaryl, heterocycloalkyl, cycloalkyl and aryl groups are optionally substituted with 1 or more groups that are independently halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxy, hydroxyC_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 haloalkyl, halo C_2-C_6 alkenyl, halo C_2-C_6 alkynyl, -$C(O)OR_{11}$, -(C_1-C_4 alkyl)-$C(O)OR_{11}$, -$CONR_{11}R_{11}$, -$OC(O)NR_{11}R_{11}$, -$NR_{11}C(O)OR_{10}$, -$NR_{11}S(O)_2R_{10}$, -$OS(O)_2R_{10}$, -$S(O)_2R_{10}$, -$NR_{11}C(O)R_{10}$, CN, =N-NHR_{12}, -$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, heteroaryl that is selected from pyrazolyl, thiadiazolyl, triazolyl isoxazolyl, isothiazolyl, imidazolyl, thiazolyl, oxadiazolyl, oxazolyl, tetrazolyl, and pyridyl, heterocycloalkyl that is selected from tetrahydrofuranyl, pyrrolidinyl, piperidinyl, morpholinyl, and imidazolidinyl, C_3 –C_6 cycloalkyl, aryl that is selected from phenyl, benzo[d][1,3]dioxolyl, and naphthyl; wherein the aforementioned heteroaryl, heterocycloalkyl, cycloalkyl and aryl substituents are optionally substituted with 1 or more groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, C_1-C_6 hydroxyalkyl, C_1-C_6 haloalkoxy or C_1-C_6 haloalkyl.

24. Compounds or salts according to claim 23, wherein the B-ring is pyrazolyl, which is optionally substituted with –NR_{11}-C_2-C_6 alkanoyl, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_3-C_6 cycloalkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 alkoxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxy C_1-C_4 alkyl, halo, CF_3, OCF_3 or CN.

25. Compounds or salts according to claim 24, wherein the A-ring is:



wherein,

R_3, R_4, R_5, R_6, R_7 are independently of each other H, halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, CN, hydroxyl, C_1-C_4 alkoxy, -C_1-C_3 alkyl-OH, -C_1-C_3 alkyl-C_1-C_4 alkoxy, phenyloxy, -$S(O_2)R_{10}$, -$SO_2NR_{11}R_{11}$, -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$ or C_2-C_4 alkanoyl; or

the A-ring is pyridyl, which is optionally substituted at one or more substitutable positions with groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, CF_3, OCF_3, hydroxyl, CN, phenyloxy, -SO_2-(C_1-C_6 alkyl), -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alkanoyl, pyridyl, phenyl or -$SO_2NR_{11}R_{11}$, where

each R_{10} and R_{11} is independently C_1-C_6 alkyl or phenyl; and additionally R_{11} may be H.

26. Compounds or salts according to claim 25, wherein

the A-ring is phenyl, R_4 is halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, or CN; and R_3, R_5 R_6, and R_7 are hydrogen.

27. Compounds or salts according to claim 25, wherein the A-ring is pyridyl, optionally substituted with one halogen or CF_3.

28. Compounds or salts according to claim 25, wherein at least one R_{51} group is halogen.

29. Compounds or salts according to claim 25, wherein the two geminal R_{51} groups that are alpha to the B-ring are both H, both halogen or form an oxo group.

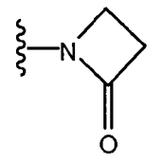
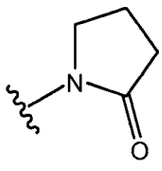
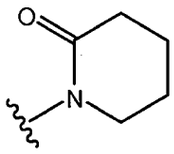
30. Compounds or salts according to claim 25, wherein

R_{50} is $NR_{11}R_{11}$ or -$SO_2NR_{11}R_{11}$ or -$S(O)_2R_{10}$ or

oxadiazolyl optionally substituted with C_1-C_4 alkyl; or

C_3-C_6 cycloalkyl optionally substituted with C_1-C_4 alkyl or C_1-C_4 alkoxy; or

phenyl optionally substituted with one or more groups that are independently C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, -OCH_2O-, -OCH_2CH_2O-, oxazolidinone, imidazolyl, thiazolyl,

-NR_{11}-cyclohexyl, where the cyclohexyl is optionally substituted with $NR_{11}R_{11}$, C_1-C_4 alkyl or C_1-C_4 alkoxy; pyrazolyl, tetrazolyl, pyrrolidinonyl, -$NR_{11}R_{11}$, morpholinyl,  ,  ,  or C_2-C_6 alkanoyl; or

pyrazolyl optionally substituted with C_1-C_4 alkyl; or

thiazolyl optionally substituted with C_1-C_4 alkyl, C_1-C_4 haloalkyl; or

oxazolyl optionally substituted with C_1-C_4 alkyl; or

benzimidazolyl optionally substituted with C_1-C_4 alkyl, C_1-C_4 alkoxy or halogen; or

C_2-C_6 alkenyl optionally substituted with a halogen or C_1-C_4 haloalkyl; or

triazolyl optionally substituted with one or two groups that are independently C_1-C_4 alkyl; or

C_2-C_6 alkynyl optionally substituted with a halogen or C_1-C_4 alkoxy; or

thiadiazolyl optionally substituted with C_1-C_4 alkyl, C_1-C_4 haloalkyl; or

pyridyl optionally substituted with one or more groups that are independently C_1-C_4 alkyl, halogen or C_1-C_4 alkoxy;

wherein R_{11} is H, C_1-C_6 alkyl or C_2-C_6 alkanoyl, where the alkyl portions of R_{11} are optionally substituted with one or two groups that are independently -CO_2-(C_1-C_6 alkyl), C_1-C_6 alkyl-O-(C_1-C_6 alkyl), C_1-C_6 alkyl-O-(C_1-C_4 alkyl)-CO_2-(C_1-C_6 alkyl), C_1-C_6 alkyl-O-(C_1-C_4 alkyl)-CO_2H.

31. A pharmaceutical composition comprising a compound of claim 1 and at least one pharmaceutically acceptable carrier.

32. A method of treating a neurodegenerative disease comprising administering a therapeutically effective amount of a compound or salt of claim 1 to a mammalian subject in need of such treatment.

33. The method of claim 32, wherein said neurodegenerative disease is selected from Alzheimer's Disease, diffuse Lewy body type of Alzheimer's disease, Parkinson's disease, Down syndrome, dementia, mild cognitive impairment (MCI), amyotrophic lateral sclerosis

(ALS), traumatic brain injuries, cerebral ischemic brain damage, ischemic or hemorrhaging stroke, hereditary cerebral hemorrhage with amyloidosis of the dutch-type and cerebral amyloid angiopathy.

34. The method of claim 33, wherein said neurodegenerative disease is Alzheimer's disease or diffuse Lewy body type of Alzheimer's disease and the mammalian subject is a human.

35. A method of treating a disease selected from multiple sclerosis, cancer, age-related macular degeneration, diabetic retinopathy and retinal neurodegeneration related to glaucoma or ocular trauma, comprising administering a therapeutically effective amount of a compound or salt of claim 20 to a mammalian subject in need of such treatment

36. A method of treating Alzheimer's Disease, diffuse Lewy body type of Alzheimer's disease, Parkinson's disease, Down syndrome, dementia, mild cognitive impairment (MCI), amyotrophic lateral sclerosis (ALS), traumatic brain injuries, cerebral ischemic brain damage, ischemic or hemorrhaging stroke, hereditary cerebral hemorrhage with amyloidosis of the dutch-type, cerebral amyloid angiopathy, multiple sclerosis, cancer, age-related macular degeneration, diabetic retinopathy or retinal neurodegeneration related to glaucoma or ocular trauma, comprising administering a therapeutically effective amount of a pharmaceutical composition of claim 31 to a human in need of such treatment.

37. A pharmaceutical composition comprising a compound of claim 20 and at least one pharmaceutically acceptable carrier.

38. A method of treating a neurodegenerative disease comprising administering a therapeutically effective amount of a compound or salt of claim 20 to a mammalian subject in need of such treatment

39. The method of claim 38, wherein said neurodegenerative disease is selected from Alzheimer's Disease, diffuse Lewy body type of Alzheimer's disease, Parkinson's disease, Down syndrome, dementia, mild cognitive impairment (MCI), amyotrophic lateral sclerosis (ALS), traumatic brain injuries, cerebral ischemic brain damage, ischemic or hemorrhaging

stroke, hereditary cerebral hemorrhage with amyloidosis of the dutch-type and cerebral amyloid angiopathy.

40. The method of claim 39, wherein said neurodegenerative disease is Alzheimer's disease or diffuse Lewy body type of Alzheimer's disease and the mammalian subject is a human.

41. A method of treating a disease selected from multiple sclerosis, cancer, age-related macular degeneration, diabetic retinopathy and retinal neurodegeneration related to glaucoma or ocular trauma, comprising administering a therapeutically effective amount of a compound or salt of claim 20 to a mammalian subject in need of such treatment

42. A method of treating Alzheimer's Disease, diffuse Lewy body type of Alzheimer's disease, Parkinson's disease, Down syndrome, dementia, mild cognitive impairment (MCI), amyotrophic lateral sclerosis (ALS), traumatic brain injuries, cerebral ischemic brain damage, ischemic or hemorrhaging stroke, hereditary cerebral hemorrhage with amyloidosis of the dutch-type, cerebral amyloid angiopathy, multiple sclerosis, age-related macular degeneration, diabetic retinopathy, retinal neurodegeneration related to glaucoma or ocular trauma, or cancer, comprising administering a therapeutically effective amount of a pharmaceutical composition of claim 37 to a human in need of such treatment.

43. A compound that is
(±)-10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole-6-carbonitrile;
(±)-10-[(4-chlorophenyl)sulfonyl]-6-(3-methyl-1,2,4-oxadiazol-5-yl)-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;
(-)-10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole-6-carbonitrile;
(+)-10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole-6-carbonitrile;
(±)-10-[(4-chlorophenyl)sulfonyl]-6-(1-methoxycyclopropyl)-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;
5-cyclopropyl-9-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,7,8-tetrahydro-4,7-

epiminocyclohepta[c]pyrazole;
5-cyclopropyl-9-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,5,6,7,8-hexahydro-4,7-epiminocyclohepta[c]pyrazole;
(±)-6-(4-methoxyphenyl)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;
5,5-dimethyl-9-{[4-(trifluoromethyl)phenyl]sulfonyl}-5,6,7,8-tetrahydro-1H-4,7-epiminopyrazolo[4,3-b]azepine;
6,6-dimethyl-9-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,8-tetrahydro-1H-4,7-epiminopyrazolo[3,4-c]azepine;
(±)-6-phenyl-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;
(±)-6-phenyl-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;
(±)-10-[(5-chlorothiophen-2-yl)sulfonyl]-6-phenyl-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;
6-(1-methyl-1H-pyrazol-3-yl)-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;
6-(1-methyl-1H-pyrazol-5-yl)-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;
(±)-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;
(±)-exo-6-(4-fluorophenyl)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;
(±)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-6-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;
(±)-6-(5-methyl-1,3-oxazol-2-yl)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;
(±)-endo-6-(4-fluorophenyl)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;
(±)-6-(5-methyl-1,3-thiazol-2-yl)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;
(±)-6-(1*H*-benzimidazol-2-yl)-10-[(4-chlorophenyl)sulfonyl]-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole;

(±)-5-(4-fluorophenyl)-9-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,7,8-tetrahydro-4,7-epiminocyclohepta[*c*]pyrazole;

6-(4-fluorophenyl)-9-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,7,8-tetrahydro-4,7-epiminocyclohepta[*c*]pyrazole;

5-(4-fluorophenyl)-9-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,5,6,7,8-hexahydro-4,7-epiminocyclohepta[*c*]pyrazole;

(±)-6,7-difluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazole;

6-(4-fluorophenyl)-9-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,5,6,7,8-hexahydro-4,7-epiminocyclohepta[*c*]pyrazole;

(±)-6,7-difluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazol-10(1*H*)-one;

(±)-6-(3-fluorophenyl)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole;

(±)-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazol-10(1*H*)-one;

(-)-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazole;

(+)-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazole;

(±)-10,10-difluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazole;

(±)-7-phenyl-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole;

(±)-10-[(4-chlorophenyl)sulfonyl]-6-(3-methylisoxazol-5-yl)-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole;

(±)-6,7,10,10-tetrafluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-*c*]pyrazole;

(+)-6-(3-fluorophenyl)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole;

(-)-6-(3-fluorophenyl)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole;

(±)-6-(1,3-dimethyl-1*H*-1,2,4-triazol-5-yl)-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-

4,5,6,7,8,9-hexahydro-1*H*-4,8-epiminocycloocta[*c*]pyrazole;
(±)-9-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,7,8-tetrahydro-4,7-epiminocyclohepta[*c*]pyrazole;
(±)-6-(1H-1,2,4-triazol-3-yl)-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;
(-)-7-phenyl-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;
(+)-7-phenyl-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;
(±)-6-(5-methyl-1H-1,2,4-triazol-3-yl)-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;
(±)-6-(1,2,3-thiadiazol-4-yl)-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;
(±)-12-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,10,11-tetrahydro-1H-4,10-epiminobenzo[5,6]cycloocta[1,2-c]pyrazole;
5-phenyl-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;
6-(pyridin-3-yl)-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;
(±)-12-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,10,11-tetrahydro-4,10-epimino[1,3]benzodioxolo[5',6':4,5]cyclohepta[1,2-c]pyrazole;
(±)-10-[(4-chlorophenyl)sulfonyl]-6-(5-methyl-1,3,4-thiadiazol-2-yl)-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;
(±)-10-[(4-chlorophenyl)sulfonyl]-6-(1H-1,2,3-triazol-4-yl)-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;
(-)-6,7-difluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;
(+)-6,7-difluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;
(±)-5-fluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;
(±)-8-fluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(±)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(-)-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminopyrazolo[4',3':4,5]cyclohepta[1,2-b]pyridine;

(+)-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminopyrazolo[4',3':4,5]cyclohepta[1,2-b]pyridine;

(+)-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-b]pyridine;

(-)-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-b]pyridine;

(±)-5-fluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one;

(±)-8-fluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one;

(±)-6,7-difluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(±)-6-(4-bromophenyl)-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;

(±)-10-[(4-chlorophenyl)sulfonyl]-6-(pyridin-4-yl)-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;

(±)-6-(1,3-benzodioxol-5-yl)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;

(±)-12-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,10,11-tetrahydro-4,10-epimino[1,3]benzodioxolo[5',6':4,5]cyclohepta[1,2-c]pyrazol-7-one;

(-)-6,7-difluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(+)-6,7-difluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(±)-3-[4-(10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazol-6-yl)phenyl]-1,3-oxazolidin-2-one;

(±)-6-[4-(1H-imidazol-1-yl)phenyl]-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;

(-)-5-fluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-

epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(+)-5-fluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(±)-6-[4-(1,3-thiazol-4-yl)phenyl]-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;

N-[4-(10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazol-6-yl)phenyl]cyclohexane-1,2-diamine;

(+)-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminopyrazolo[4',3':4,5]cyclohepta[1,2-c]pyridine;

(+)-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-c]pyridine;

(-)-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-c]pyridine;

(±)-8,10,10-trifluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(±)-5-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(±)-5,10,10-trifluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(±)-6-[4-(1*H*-pyrazol-1-yl)phenyl]-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;

(±)-6-(3-bromophenyl)-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;

(±)-6-(1*H*-tetrazol-5-yl)-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;

(-)-5,10,10-trifluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(+)-5,10,10-trifluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(-)-5-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(+)-5-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(±)-5,8-difluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(±)-6-[3-(1H-imidazol-1-yl)phenyl]-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;

(±)-6-[3-(1H-pyrazol-1-yl)phenyl]-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;

(±)-7-cyclopropyl-12-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,11-tetrahydro-3H-5,11-epiminobenzo[4,5]cycloocta[1,2-c]pyrazole;

(±)-6-cyclopropyl-12-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,10,11-tetrahydro-1H-4,10-epiminobenzo[5,6]cycloocta[1,2-c]pyrazole;

(±)-10-[(4-chlorophenyl)sulfonyl]-6-(1-methyl-1H-1,2,3-triazol-5-yl)-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;

10-[(4-chlorophenyl)sulfonyl]-6-(1-methyl-1H-1,2,3-triazol-4-yl)-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;

10-[(4-chlorophenyl)sulfonyl]-6-(1-methyl-1H-1,2,3-triazol-4-yl)-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;

(-)-10-[(4-chlorophenyl)sulfonyl]-6-(2-methyl-2H-1,2,3-triazol-4-yl)-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;

(+)-10-[(4-chlorophenyl)sulfonyl]-6-(2-methyl-2H-1,2,3-triazol-4-yl)-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;

(±)-1-[4-(10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazol-6-yl)phenyl]pyrrolidin-2-one;

(±)-methyl 4-{[4-(10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazol-6-yl)phenyl]amino}butanoate;

(±)-4-[4-(10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazol-6-yl)phenyl]morpholin-3-one;

(±)-methyl (2-{[4-(10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazol-6-yl)phenyl]amino}ethoxy)acetate;

(±)-(2-{[4-(10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazol-6-yl)phenyl]amino}ethoxy)acetic acid;

(±)-methyl N-[4-(10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazol-6-yl)phenyl]-b-alaninate;

(±)-6-[4-(1H-1,2,4-triazol-1-yl)phenyl]-10-{[4-(trifluoromethyl)phenyl]sulfonyl}-

4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazole;
(±)-6,7-difluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one;
(-)-5,8-difluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;
(+)-5,8-difluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;
(±)-7-fluoro-5-methyl-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;
(±)-N-[4-(10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazol-6-yl)phenyl]acetamide;
(±)-1-[4-(10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazol-6-yl)phenyl]azetidin-2-one;
(±)-1-[4-(10-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,7,8,9-hexahydro-1H-4,8-epiminocycloocta[c]pyrazol-6-yl)phenyl]ethanone;
(±)-6-(trifluoromethyl)-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;
(±)-7-(trifluoromethyl)-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;
(±)-6,7,10,10-tetrafluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;
(-)-7-fluoro-5-methyl-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;
(+)-7-fluoro-5-methyl-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;
13-{[4-(trifluoromethyl)phenyl]sulfonyl}-7,10,11,12-tetrahydro-7,12-epiminonaphtho[2',1':4,5]cyclohepta[1,2-c]pyrazole;
(-)-5-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one;
(±)-7-(4-fluorophenyl)-12-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,11-tetrahydro-3H-5,11-epiminobenzo[4,5]cycloocta[1,2-c]pyrazole;
(±)-12-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,10,11-tetrahydro-1H-4,10-epiminobenzo[5,6]cycloocta[1,2-c]pyrazole;

(±)-12-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,11-tetrahydro-3H-5,11-epiminobenzo[4,5]cycloocta[1,2-c]pyrazole;

(±)-6-(4-fluorophenyl)-12-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,10,11-tetrahydro-1H-4,10-epiminobenzo[5,6]cycloocta[1,2-c]pyrazole;

5,10,10-trifluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(±)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole-7-carbonitrile;

(+)-13-{[4-(trifluoromethyl)phenyl]sulfonyl}-7,10,11,12-tetrahydro-7,12-epiminonaphtho[2',1':4,5]cyclohepta[1,2-c]pyrazole;

(-)-13-{[4-(trifluoromethyl)phenyl]sulfonyl}-7,10,11,12-tetrahydro-7,12-epiminonaphtho[2',1':4,5]cyclohepta[1,2-c]pyrazole;

(+)-13-{[4-(trifluoromethyl)phenyl]sulfonyl}-7,8,9,12-tetrahydro-7,12-epiminonaphtho[1',2':4,5]cyclohepta[1,2-c]pyrazole;

(-)-13-{[4-(trifluoromethyl)phenyl]sulfonyl}-7,8,9,12-tetrahydro-7,12-epiminonaphtho[1',2':4,5]cyclohepta[1,2-c]pyrazole;

(-)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole-7-carbonitrile;

(-)-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one;

(+)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole-7-carbonitrile;

(+)-endo-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10-ol;

(±)-6-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(±)-6-[3-(trifluoromethyl)phenyl]-12-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,10,11-tetrahydro-1H-4,10-epiminobenzo[5,6]cycloocta[1,2-c]pyrazole;

(±)-7-[3-(trifluoromethyl)phenyl]-12-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,11-tetrahydro-3H-5,11-epiminobenzo[4,5]cycloocta[1,2-c]pyrazole;

(-)-6-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(+)-6-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-

epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(±)-9-fluoro-12-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,10,11-tetrahydro-1H-4,10-epiminobenzo[5,6]cycloocta[1,2-c]pyrazole;

(±)-10-fluoro-12-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,6,11-tetrahydro-3H-5,11-epiminobenzo[4,5]cycloocta[1,2-c]pyrazole;

(±)-8-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(-)-8-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(+)-8-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(+)-exo-10-fluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(±)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,8,9-tetrahydro-4,8-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-d][1,3]thiazole;

(-)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,8,9-tetrahydro-4,8-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-d][1,3]thiazole;

(+)-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,8,9-tetrahydro-4,8-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-d][1,3]thiazole;

(-)-9-fluoro-12-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,10,11-tetrahydro-1H-4,10-epiminobenzo[5,6]cycloocta[1,2-c]pyrazole;

(+)-9-fluoro-12-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,5,10,11-tetrahydro-1H-4,10-epiminobenzo[5,6]cycloocta[1,2-c]pyrazole;

(-)-8-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one;

(+)-8-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one;

(±)-methyl 11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole-6-carboxylate;

(±)-exo-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10-ol;

(-)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(+)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(±)-exo-10-fluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

endo-5-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10-ol;

(-)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one;

(+)-6-(3-methyl-1,2,4-oxadiazol-5-yl)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(-)-6-(3-methyl-1,2,4-oxadiazol-5-yl)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(-)-methyl 11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole-6-carboxylate;

(±)-7-methyl-10-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,7,8,9-tetrahydro-1H-4,8-epiminocyclohepta[1,2-c:5,4-c']dipyrazole;

(+)-methyl 11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole-6-carboxylate;

exo-10-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(+)-exo-5,10-difluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

endo-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10-ol;

(±)-11-[(4-chlorophenyl)sulfonyl]-5-fluoro-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(±)-5-fluoro-11-[(4-fluorophenyl)sulfonyl]-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(±)-5-fluoro-11-{[5-(trifluoromethyl)pyridin-2-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(+)-9-bromo-12-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,10,11-tetrahydro-1H-4,10-epiminobenzo[5,6]cycloocta[1,2-c]pyrazole;

(-)-9-bromo-12-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,10,11-tetrahydro-1H-

4,10-epiminobenzo[5,6]cycloocta[1,2-c]pyrazole;
exo-8,10-difluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;
(+)-8,10,10-trifluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;
endo-8-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10-ol;
(-)-10-bromo-12-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,11-tetrahydro-3H-5,11-epiminobenzo[4,5]cycloocta[1,2-c]pyrazole;
(+)-10-bromo-12-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,5,6,11-tetrahydro-3H-5,11-epiminobenzo[4,5]cycloocta[1,2-c]pyrazole;
(±)-6-chloro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;
(±)-methyl 11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole-8-carboxylate;
(-)-6-chloro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;
(+)-6-chloro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;
(-)-7-chloro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;
(+)-7-chloro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;
(±)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-6-ol;
(+)-methyl 11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole-8-carboxylate;
(-)-methyl 11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole-8-carboxylate;
(+)-8-chloro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;
(-)-8-chloro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(-)-11-[(4-chlorophenyl)sulfonyl]-5-fluoro-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(+)-11-[(4-chlorophenyl)sulfonyl]-5-fluoro-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(-)-5-chloro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(+)-5-chloro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(+)-8-(3-methyl-1,2,4-oxadiazol-5-yl)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(-)-8-(3-methyl-1,2,4-oxadiazol-5-yl)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(±)-11-[(4-chlorophenyl)sulfonyl]-5-fluoro-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one;

(-)-(10*S*)-5-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10-ol;

(+)-(10*S*)-5-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10-ol;

(-)-(10*S*)-8-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10-ol;

(+)-(10S)-8-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10-ol;

(±)-6-(4-fluorophenyl)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(-)-11-[(4-chlorophenyl)sulfonyl]-5-fluoro-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one;

(+)-11-[(4-chlorophenyl)sulfonyl]-5-fluoro-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one;

(-)-6-(4-fluorophenyl)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(+)-6-(4-fluorophenyl)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(-)-6-cyclopropyl-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-

epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(+)-6-cyclopropyl-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(+)-6-bromo-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-b]pyridine;

(+)-6-bromo-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-b]pyridine;

(+)-6-bromo-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(-)-6-bromo-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(±)-(11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-8-yl)methanol;

methyl (±)-11-{[6-(trifluoromethyl)-1,2-dihydropyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole-8-carboxylate;

(+)-6-(4-fluorophenyl)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-b]pyridine;

(+)-6-cyclopropyl-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-b]pyridine;

(-)-6-cyclopropyl-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-b]pyridine;

(±)-8-(fluoromethyl)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(±)-7-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-b]pyridine;

(-)-7-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-2,4,9,10-tetrahydro-4,9-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-b]pyridine;

(+)-7-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-2,4,9,10-tetrahydro-4,9-epiminopyrazolo[3',4':5,6]cyclohepta[1,2-b]pyridine;;

(4R,9S)-6-(prop-1-yn-1-yl)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(-)-exo-5,10-difluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;

(+)-5,10-difluoro-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;
(±)-8-chloro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one;
(±)-8-chloro-N-hydroxy-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-imine;
(±)-8-(4-fluorophenyl)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;
(4S,9S,10R)-5,10-difluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;
(4R,9R,10R)-5,10-difluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;
(±)-8-chloro-N-methoxy-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-imine;
(±)-8-cyclopropyl-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;
exo-10-fluoro-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-2,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;
(±)-8-chloro-10-methylidene-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;
(±)-5-(4-fluorophenyl)-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;
(±)-5-cyclopropyl-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-1,4,9,10-tetrahydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazole;
(-)-9-methyl-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one;
(+)-9-methyl-11-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one;
(-)-9-methyl-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one;
(+)-9-methyl-11-{[4-(trifluoromethyl)phenyl]sulfonyl}-4,9-dihydro-4,9-epiminobenzo[4,5]cyclohepta[1,2-c]pyrazol-10(1H)-one,
or a pharmaceutically acceptable salt or solvate thereof.

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Compuestos N- Sulfonamido Pirazolil Policíclicos

ANTECEDENTES DE LA INVENCIÓN

Campo de la invención

La invención está relacionada con Compuestos N- Sulfonamido Pirazolil Policíclicos que tienen un anillo aril fusionado o colgante en el anillo policíclico, el cual inhibe la liberación y/o síntesis de péptidos ß-amiloides y gamma secretasa. Por lo tanto, los Compuestos N- Sulfonamido Pirazolil Policíclicos de la presente invención son útiles en la prevención de desórdenes cognitivos en pacientes susceptibles a desórdenes cognitivos y/o en el tratamiento de pacientes con desórdenes cognitivos con el objeto de inhibir ulterior deterioro de su condición.

Estado del Arte

La Enfermedad de Alzheimer (AD) es un desorden degenerativo del cerebro caracterizado clínicamente por la pérdida progresiva de la memoria, cognición, razonamiento, juicio y estabilidad emocional que conduce gradualmente a un profundo deterioro mental y finalmente a la muerte. La Enfermedad de Alzheimer (AD) es una causa muy común de deterioro mental progresivo (demencia) en humanos viejos y se cree que representa la cuarta más común causa médica de muerte en los Estados Unidos. La Enfermedad de Alzheimer (AD) ha sido observada en grupos raciales y étnicos en todo el mundo y representa un gran problema de salud pública actual y a futuro. La enfermedad se estima que afecta actualmente alrededor de dos a tres millones de individuos solamente en los Estados Unidos. La Enfermedad de Alzheimer (AD) es incurable actualmente. No se conoce hoy en día ningún tratamiento preventivo efectivo, o que revierta sus síntomas y el curso de la enfermedad.

Los cerebros de individuos con Enfermedad de Alzheimer (AD) presentan lesiones características llamadas placas seniles (o amiloides), angiopatía amiloide (depósitos amiloides en los vasos sanguíneos) y ovillos neurofibrilares. Grandes números de estas lesiones, particularmente placas amiloides y ovillos neurofibrilares, se encuentran generalmente en varias áreas del cerebro humano

importantes para la memoria y la función cognitiva en pacientes con Enfermedad de Alzheimer (AD). Números más pequeños de estas lesiones en una distribución anatómica más restringida son también encontrados en los cerebros de la mayoría de humanos viejos que no tienen Enfermedad de Alzheimer (AD) clínica. Placas amiloides y angiopatía amiloide también son características de los cerebros de individuos con Trisomía 21 (Síndrome de Down) y Hemorragia Cerebral Hereditaria con Amiloidosis de Tipo Holandés (HCHWA-D). En el presente, un diagnóstico definitivo de Enfermedad de Alzheimer (AD) usualmente requiere de la observación de las lesiones antes mencionadas en el tejido cerebral de pacientes que han muerto con la enfermedad, o, como cosa rara, en pequeñas muestras de biopsias de tejido cerebral tomadas durante un procedimiento neuro - quirúrgico invasivo.

El principal constituyente químico de las placas amiloides y los depósitos amiloides vasculares (angiopatía amiloide) característicos de la Enfermedad de Alzheimer (AD) y de los otros desórdenes arriba mencionados es una proteína de aproximadamente 4.2 kilodalton (kD) que tiene alrededor de 39 – 43 amino ácidos, denominada como el péptido ß-amiloide (ßAP) Aß, AßP o a veces ß/A4. El péptido ß-amiloide fue primero purificado y fue proporcionada una secuencia parcial de amino ácidos por Glenner et al., Biochem. Biophys. Res. Commun., 120:885-890 (1984). El procedimiento de aislamiento y la data de la secuencia para los primeros 28 amino ácidos se describen en la Patente de los EE.UU. No. 4,666,829. Análisis químicos de proteínas y biología molecular han mostrado que el péptido ß-amiloide es un pequeño fragmento de una proteína precursora mucho mayor llamada la proteína precursora de amiloide (APP), que es normalmente producida por las células en muchos tejidos de varios animales, incluyendo los humanos. El conocimiento de la estructura del gen codificador de APP ha demostrado que el péptido ß-amiloide emerge como un fragmento péptido que es partido de la APP por enzima (s) proteasa (s).El procesamiento secuencial de la proteína precursora por las enzimas referidas genéricamente como beta y gamma secretasas, da lugar al fragmento péptido ß-amiloide. Ambas enzimas hoy han sido clonadas molecularmente y caracterizadas a diferentes niveles.

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Varias líneas de evidencia indican que la deposición cerebral progresiva de péptido ß-amiloide juega un papel muy importante en la patogénesis de la Enfermedad de Alzheimer (AD) y puede preceder a los síntomas cognitivos por años o décadas. Ver, *e.g.*, Selkoe, Neuron, 6:487-498 (1991). La línea de evidencia más importante es el descubrimiento de que mutaciones sin sentido DNA en el amino ácido 717 de la iso-forma amino ácido-770 de APP puede encontrarse en miembros afectados, pero no en miembros no afectados, de varias familias con una forma de Enfermedad de Alzheimer (AD) genéticamente determinada (familiar) (Goate et al., Nature, 349:704-706 (1990); Chartier Harlan et al., Nature, 353:844-846 (1989); y Murrell et al., Science, 254:97-99 (1991.). Otra de dichas mutaciones, conocida como la variante sueca, está compuesta de una doble mutación cambiando lisina595-metionina596 a asparagina595-leucina596 (en referencia a la isoforma 695 encontrada en una familia sueca) fue reportada en 1992 (Mullan et al., Nature Genet., 1:345-347 (1992). Análisis de lazos genéticos han demostrado que estas mutaciones, así como también ciertas otras mutaciones en el gen APP, son la específica causa molecular de Enfermedad de Alzheimer (AD) en los miembros afectados de tales familias. Además, una mutación en el amino ácido 693 de la iso –forma amino ácido -770 de APP ha sido identificada como la causa de la enfermedad de deposición de péptido ß-amiloide, HCHWA-D y un cambio de alanina a glicina en el amino ácido 692 parece causar un fenotipo que se asemeja a la Enfermedad de Alzheimer (AD) en algunos pacientes pero a HCHWA-D en otros. El descubrimiento de estas y otras mutaciones en APP en casos de Enfermedad de Alzheimer (AD) con base genética prueba que la alteración del metabolismo de la APP y la subsiguiente deposición de su fragmento péptido ß-amiloide, puede ocasionar Enfermedad de Alzheimer (AD).

A pesar de todos los progresos que se han hecho en la comprensión de los mecanismos suporacentes de la Enfermedad de Alzheimer (AD) y otras enfermedades relacionadas con péptido ß-amiloide, existe aún la necesidad de desarrollar métodos y composiciones para el tratamiento de la (s) enfermedad (es). idealmente, los métodos de tratamiento deberían ventajosamente basarse en

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drogas, que sean capaces de inhibir la liberación de péptido ß-amiloide y/o su síntesis en *vivo*.

Un enfoque hacia la inhibición de la síntesis de péptido ß-amiloide en *vivo es* inhibiendo la gamma secretasa, que es la enzima responsable de la partición carboxi – terminal que da como resultado la producción de fragmentos de péptido ß-amiloide de 40 a 42 residuos en longitud. Los sustratos inmediatos para la gamma secretasa son □-partidos fragmentos carboxi – terminal (CTF) de APP. El sitio de partición de la gamma secretasa en fragmentos □- y □-CTF ocurre en el dominio predicho transmembrana de APP. Inhibidores de la gamma secretasa han demostrado efectos sobre la patología amiloide en modelos de ratones trangénicos (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). ("Inhibidores Funcionales Gamma secretasa reducen los niveles de péptido ß-amiloide en el cerebro" J Neurochem 76(1): 173-81.)

La gamma secretasa es reconocida como un complejo de múltiples sub – unidades compuestas de las presenilinas (PS1 o PS2), Nicastrin, Aph-1, y Pen 2 (De Strooper, B. (2003). "Aph-1, Pen-2, y Nicastrin con Presenilina genera un activo complejo gamma-Secretasa." Neuron 38(1): 9-12; Edbauer, D., E. Winkler, J. T. Regula, B. Pesold, H. Steiner y C. Haass (2003). "Reconstitución de actividad gamma-secretasa." Nat Cell Biol 5(5): 486-8; Kimberly, W. T., M. J. LaVoie, B. L. Ostaszewski, W. ie, M. S. Wolfe y D. J. Selkoe (2003). "Gamma-secretasa es un complejo proteico de membrana compuesta de presenilina, nicastrin, Aph-1, y Pen-2." Proc Natl Acad Sci U S A 100(11): 6382-7). Muchas evidencias indican que PS comprende la mitad catalítica del complejo, mientras que las otras subunidades son necesarias para la correcta maduración y localización sub-celular del complejo enzimático activo (revisado en De Strooper, B. (2003). "Aph-1, Pen-2, y Nicastrin con Presenilina genera un activo complejo gamma-Secretasa." Neuron 38(1): 9-12.) Consistente con esta hipótesis: Ratones KO PS exhiben significativas reducciones en producción ß-amiloide (De Strooper, B., P. Saftig, K. Craessaerts, H. Vanderstichele, G. Guhde, W. Annaert, K. Von Figura y F. Van Leuven (1998). "Deficiencia de presenilina-1 inhibe la partición normal de la

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proteína precursora amiloide"." Nature 391(6665): 387-90; Haass, C. y D. J. Selkoe (1998)." Enfermedad de Alzheimer: un KO técnico de péptido ß-amiloide" Nature 391(6665): 339-40; Herreman, A., L. Serneels, W. Annaert, D. Collen, L. Schoonjans y B. De Strooper (2000). Inactivación total de la activación de la gamma secretasa en células madre embrionarias deficientes en presenilina" Nat Cell Biol 2(7): 461-2); mutaciones de punto de residuos putativos de sitios de aspartato en dominios PS trans-membrana inhiben la producción ß-amiloide en las células de un modo dominante negativo (Wolfe, M. S., W. Xia, B. L. Ostaszewski, T. S. Diehl, W. T. Kimberly y D. J. Selkoe (1999)."Dos aspartatos transmembrana en la pre-senilina-1 se requieren para la endoproteolisis de la presenilina y la actividad gamma – secretasa" Nature 398(6727): 513-7; Kimberly, W. T., W. Xia, T. Rahmati, M. S. Wolfe y D. J. Selkoe (2000). "Los aspartatos Transmembrana en las presenilinas 1 y 2 son obligatorias para la actividad gamma secretasa y la generación de beta – proteínas amiloides" J Biol Chem 275(5): 3173-8); isoésteres en estado de transición basados en sustratos dirigidos a sitios activos diseñados para inhibir gamma secretasa directamente conjugada a 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). "Inhibidores análogos en estado de transición de la gamma secretasa unidos directamente a la presenilina 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). "Inhibidores foto – activados de la gamma secretasa dirigidos al sitio activo etiquetado covalentemente presenilina 1" Nature 405(6787): 689-94); finalmente, inhibidores alostéricos de la gamma secretasa también han demostrado unirse directamente a PS (Seiffert, D., J. D. Bradley, C. M. Rominger, D. H. Rominger, F. iang, J. E. Meredith, Jr., Q. Wang, A. H. Roach, L. A. Thompson, S. M. Spitz et al. (2000)."Presenilina 1 y 2 son objetivos moleculares para inhibidores de la gamma secretasa" J Biol Chem 275(44): 34086-91.)

La evidencia actual indica que además del procesamiento APP conducente a la síntesis ß-amiloide, la gamma secretasa también media en la partición intra – membrana de otro de proteínas tipo y transmembrana (revisado en Fortini, M. E.

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(2002). "Proteolisis gamma secretasa – mediada en señalización de receptor – superficie celular"." Nat Rev Mol Cell Biol 3(9): 673-84, ver también Struhl, G. y A. Adachi (2000). "Requerimientos para partición presenilina – dependiente de Notch y otras proteínas transmembrana" Mol Cell 6(3): 625-36). Notable entre los sustratos conocidos de la gamma secretasa es la Notch 1 de mamífero. La proteína Notch 1 es importante para la determinación del destino de la célula durante el desarrollo y la homeostasis tisular en el adulto. Luego de la unión de ligando via ecto-dominio de Notch, la Notch experimenta un procesamiento secuencial intra-membrana y extra- celular análogo a APP. El procesamiento intra-membrana de la Notch mediado por la gamma secretasa conduce a la liberación del dominio intracelular de la Notch (NICD). El fragmento NICD media en la señalización via tras locación al núcleo donde regula la expresión de genes mediando en la diferenciación celular en muchos tejidos durante el desarrollo, así como también en el adulto. Alteración de la señalización Notch por vía de noqueo genético resulta en un fenotipo embrionario letal en ratones (Swiatek, P. J., C. E. Lindsell, F. F. del Amo, G. Weinmaster y T. Gridley (1994). "Notch 1 es esencialmente para desarrollo de post-implantación en ratones" Genes Dev 8(6): 707-19; Conlon, R. A., A. G. Reaume y J. Rossant (1995). "Notch 1 es requerida para la segmentación coordinada de somitas" Development 121(5): 1533-45.) El fenotipo Notch KO es muy similar al fenotipo observado en ratones PS1 KO y reproducido precisamente ratones por PS1/PS2 doble KO (De Strooper et al. (1998). "Deficiencia de presenilina 1 inhibe la partición normal de la proteína precursora de amiloide" Nature 391(6665): 387-90; Donoviel, D. B., A. K. Hadjantonakis, M. ikeda, H. Zheng, P. S. Hyslop y A. Bernstein (1999). "Ratones carentes de ambos genes presenilina presentan tempranos defectos de patrones" Genes Dev 13(21): 2801-10; Herreman, A., L. Serneels, W. Annaert, D. Collen, L. Schoonjans y B. De Strooper (2000). "Total inactivación de la actividad de la gamma secretasa en células madre embrionarias deficientes en presenilina"." Nat Cell Biol 2(7): 461-2.) Esta convergencia de fenotipos observada en ratones noqueados tanto del sustrato (Notch) como de la enzima (PS) sugiere que los inhibidores de la gamma secretasa que también inhiben la función Notch deben

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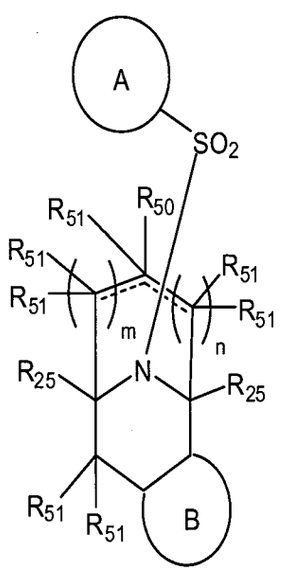
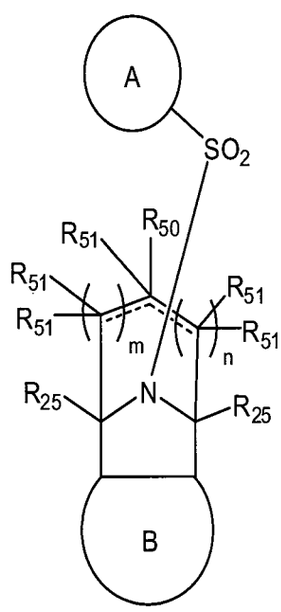
limitarse como agentes terapéuticos debido a la importancia de la función Notch en tejidos adultos (Fortini, M. E. (2002). "Proteolisis gamma secretasa mediada en señalización de receptores de superficies celulares" Nat Rev Mol Cell Biol 3(9): 673-84.) Mientras ratones APP KO se desarrollan normalmente y sin un fenotipo abierto 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). "Ratones deficientes para el gen de proteína precursora de amiloide" 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). "Ratones deficientes en proteína precursora de beta amiloides muestran gliosis reactiva y disminuida actividad locomotora" Cell 81(4): 525-31, la evidencia acumulativa, por lo tanto, sugiere que los preferidos inhibidores de gamma secretasa tendrían selectividad para inhibir el procesamiento de gamma secretasa de APP sobre el procesamiento de gamma secretasa de Notch.

SUMARIO DE LA INVENCIÓN

Son proporcionados aquí compuestos de fórmulas 1, 2, 3, y 4 que tienen las siguientes fórmulas:



Fórmula 1



Fórmula 2

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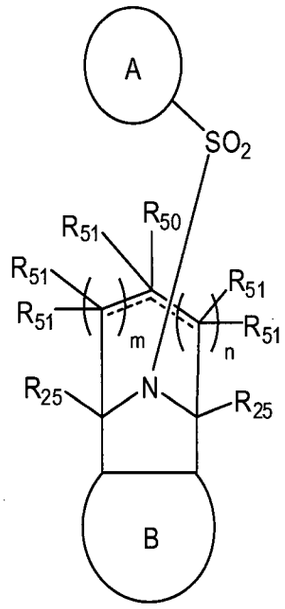

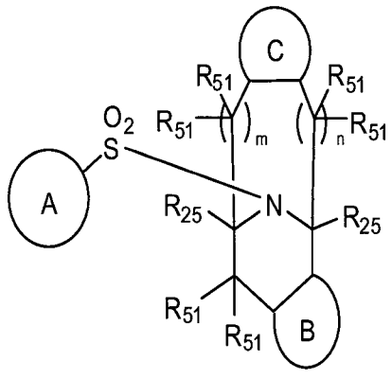

Fórmula 3 Fórmula 4

O estereo isómeros, enantiómeros, sales farmacéuticamente aceptables, o solvatos de éstos, donde en las fórmulas 1 y 2 m y n son independientemente selccionados de 0, 1 y 2 con la provisión de que (m + n) es 1 o 2; en Fórmula 3 n es 0 ó 1; en Fórmula 4, m y n son independientemente 0 o 1, siempre que m + n = 0 o 1; donde el anillo- C es aril (*e.g.*, fenil) sustituido con R_{30}, R_{35}, R_{40}, y R_{45}, hetero aril, hetero ciclo alquil o cicloalquil, donde los grupos hetero aril, hetero ciclo alquil y ciclo alquil son opcionalmente sustituidos, *e.g.*, con halógeno, C_1-C_6 alquil, C_1-C_6 haloalquil, C_1-C_6 haloalcoxi, C_2-C_8 alquenil, C_2-C_8 alquinil, C_2-C_8 haloalquenil, C_2-C_8 haloalquinil, -C(O)OR_{11}, CN, hidroxil, C_1-C_6 alquoxi, -C_1-C_6 alquil-OH, -C_1-C_6 alquil-C_1-C_6 alcoxi, ariloxi (*e.g.*, feniloxi), -S(O_2)R_{10}, -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alcanoil, oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil, tienil, fenil o fenil C_1-C_4 alquil, donde las porciones fenil de arriba son opcionalmente sustituidas *e.g.*, con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_4 halo alquil (*e.g.* CF_3), C_1-C_4 halo alcoxi (*e.g.* OCF_3), hidroxilo, CN, NO_2 o halógeno;

R_{30}, R_{35}, R_{40}, y R_{45} son independientemente H, halógeno, C_1-C_6 alquil, C_2-C_8 alquenil, C_2-C_8 alquinil, C_2-C_8 halo alquenil, C_2-C_8 halo alquinil, -C(O)OR_{11}, -$SO_2NR_{11}R_{11}$, aril alquil, ciclo alquil, C_1-C_6 halo alquil, C_1-C_6 halo alcoxi, CN, NO_2,

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hidroxil, C_1-C_6 alcoxi, -C_1-C_6 alquil-OH, -C_1-C_6 alquil-C_1-C_6 alcoxi, ariloxi, -$S(O_2)R_{10}$, -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, hetero aril alquil, hetero aril, donde cada grupo hetero aril es opcionalmente sustituido con un grupo alquilo C_1-C_6, hetero cicloalquilo C_1-C_6 alquilo, hetero ciclo alquilo (*e.g.*, pirrolidinil, imidazolidinil, piperidinil, morfolinil), donde cada grupo hetero ciclo alquil es opcionalmente sustituido, *e.g.*, con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi o halógeno, aril (*e.g.*, fenil o naftil), ariloxi (*e.g.*, feniloxi o naftiloxi) o aril alquil (*e.g.*, fenil C_1-C_6 alquil), donde las porciones aril de los anteriores son opcionalmente sustituidas *e.g.*, con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_4 halo alquil (*e.g.* CF_3), C_1-C_4 halo alcoxi (*e.g.* OCF_3), hidroxil, CN, NO_2 o halógeno; y

donde cuando el anillo-C es aril o hetero aril, dos sustitutos adyacentes del anillo-C, junto a los carbonos a los que están anexados, forman opcionalmente un hetero ciclo alquil (*e.g.*, -OCH_2O-, -OC(O)O- o –OCH_2CH_2O-) o un anillo hetero aril, cada uno opcionalmente sustiuido, *e.g.*, con uno o más grupos que son independientemente alquilo, alcoxi, halógeno o C_2-C_4 alcanoil donde el grupo alcanoil es opcionalmente sustituido con hasta 3 átomos halógeno; o dos carbonos adyacentes del anillo-C opcionalmente forman un anillo benzo opcionalmente sustituido, *e.g.*, con 1 a 4 grupos que son independientemente halógeno, hidroxilo, alquilo, alcoxi, halo alquilo, halo alcoxi, CN o NO_2;

las uniones en líneas punteadas pueden ser una unión sencilla o doble,

el anillo-A es aril, ciclo alquil, hetero aril o hetero ciclo alquil, donde cada anillo es opcionalmente sustituido *e.g.*, en una sustituible posición con halògeno, C_1-C_6 alquil, C_2-C_6 alquenil, C_2-C_6 alquinil, C_1-C_6 alcoxi, halo alquil, halo alcoxi, hidroxil, hidroxialquil, CN, ariloxi, -$S(O)_{0-2}$-(C_1-C_6 alquil), -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, NO_2, CN, C_2-C_6 alcanoil, C_0-C_3alquilCO_2R_{11}, hetero aril, hetero ciclo alquil, aril, aril alquil, -OCH_2O-, -OCH_2CH_2O- o -$SO_2NR_{11}R_{11}$;

el B-anillo es un heteroaril anillo (*e.g.*, imidazolil o pirazolil) o un heterocicloalquil anillo (*e.g.* dihidropirazolil, pirazolonil o pirazolidinonil) cada uno de los cuales es opcionalmente sustituido en una sustituible posición *e.g.*, con uno o más grupos R_{20}, que son independientemente seleccionados de $-NR_{11}$-C_2-C_6 alcanoil, C_1-C_6 alquil, C_3-C_8 cicloalquil, C_2-C_6 alquenil, C_2-C_6 alquinil, C_1-C_6 alcoxi, amino, C_1-C_6 alquil amino, C_1-C_6 dialquil amino, $-S(O)_{0-2}R_{10}$, hidroxi, hidroxialquil, halo, C_1-C_4 haloalquil, C_1-C_4 halo alcoxi, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-C(O)R_{10}$, $-C(O)O_{11}$, -C(O)alquilOC(O)R_{10}; $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, oxo, CN o C_0-C_1alquil aril (donde el grupo aril es, *e.g.*, fenil o naftil, donde fenil es preferido), donde el aril es opcionalmente sustituido *e.g.*, con 1, 2, 3, 4 o 5 grupos que son independientemente seleccionados de halògeno, C_1-C_6 alquil, $-CO_2R_{11}$, C_1-C_6 alcoxi, halo alquil, halo alcoxi, hidroxil, CN, NO_2, ariloxi, $-S(O)_{0-2}$-(C_1-C_6 alquil), -$NR_{11}R_{11}$, C_2-C_6 alcanoil, piridil, fenil, y $-SO_2NR_{11}R_{11}$;

R_{50} es oxo, =N-NHR_{12} o =N-O-R_{13} (previsto que R_{51} está ausente, y R_{50} no está unida a una unión doble carbono-carbono) o R_{50} es halògeno, C_1-C_6 alquil, C_2-C_8 alquenil, C_2-C_8 alquinil, hidroxi, hidroxi C_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_6 haloalcoxi, C_1-C_6 haloalquil, halo C_2-C_8 alquenil, C_2-C_6 alcanoil, halo C_2-C_8 alquinil, $-C(O)O_{11}$, -(C_1-C_4 alquil)-$C(O)O_{11}$, $-CONR_{11}R_{11}$, $-OC(O)NR_{11}R_{11}$, $-NR_{11}C(O)O_{10}$, -$NR_{11}S(O)_2R_{10}$, $-OS(O)_2R_{10}$, $-S(O)_2R_{10}$, $-NR_{11}C(O)R_{10}$, CN, $-NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, heteroaril, por ejemplo, pirazolil, tiadiazolil, triazolil, esoxazolil, esotiazolil, imidazolil, tiazolil, oxadiazolil, y piridil, heterocicloalquil, por ejemplo, tetra hidro furanil, pirrolidinil, piperidinil, morfolinil, e imidazolidinil, C_3 –C_6 cicloalquil, aril, por ejemplo, fenil y naftil; donde los antes nombrados hetero aril, hetero ciclo alquil, ciclo alquil y grupos aril están opcionalmente sustituidos con 1 o más grupos que son independientemente halògeno, C_1-C_6 alquil, C_2-C_6 alquenil, C_2-C_6 alquinil, hidroxi, hidroxi C_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_6 halo alcoxi, C_1-C_6 halo alquil, halo C_2-C_6 alquenil, halo C_2-C_6 alquinil, $-C(O)O_{11}$, -(C_1-C_4 alquil)-$C(O)O_{11}$, $-CONR_{11}R_{11}$, $-OC(O)NR_{11}R_{11}$, $-NR_{11}C(O)O_{10}$, $-NR_{11}S(O)_2R_{10}$, $-OS(O)_2R_{10}$, $-S(O)_2R_{10}$, $-NR_{11}C(O)R_{10}$, CN, =N-NHR_{12}, $-NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, heteroaril seleccionado de pirazolil, tiadiazolil, triazolil esoxazolil, esotiazolil, imidazolil, tiazolil, oxadiazolil, oxazolil, tetrazolil, y piridil, heterocicloalquil seleccionado de tetrahidrofuranil,

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pirrolidinil, piperidinil, morfolinil, e imidazolidinil, C_3 –C_6 cicloalquil, aril seleccionado de fenil, benzo[d][1,3]dioxolil, y naftil o =N-O-R_{13}; donde los antes nombrados sustitutos heteroaril, heterocicloalquil, cicloalquil y aril son opcionalmente sustituidos con uno o más grupos que son independientemente halógeno, C_1-C_6 alquil, C_1-C_6 alcoxi, hidroxi, C_1-C_6 hidroxialquil, C_1-C_6 haloalcoxi o C_1-C_6 haloalquil;

cada R_{51} está independientemente ausente, H, C_1-C_4 alquil, halógeno (*e.g.*, F o Cl), OH, C_1-C_4 alcoxi, CN, amino, mono alquil amino, dialquil amino, C_1-C_4 halo alcoxi (*e.g.*, OCF_3) o C_1-C_4 halo alquil (*e.g.*, CF_3); o cuando hay dos grupos R_{51} en un átomo de carbono, los dos grupos R_{51} y el carbono al cual están unidos pueden formar un anillo de 3- a 6-miembros ciclo alquil o hetero ciclo alquil; o cuando hay dos R_{51} grupos en un carbono, los dos R_{51} grupos pueden formar un grupo oxo; o cuando hay dos R_{51} grupos en un carbono, los dos R_{51} grupos pueden formar un grupo alqueno; o cuando hay dos R_{51} grupos en un carbono, los dos R_{51} grupos pueden formar una oxima o una C_1-C_4 alquilada oxima (*e.g.*, O-metil oxima);

un no-cabeza de puente carbono (y cualquier sustituto o sustitutos en él) en el sistema de anillos [3.3.1], [3.2.1] o [2.2.1] puede ser reemplazado con un grupo NR_{15};

R_{10} y R_{11} en cada ocurrencia son independientemente C_3-C_6 ciclo alquil, hetero aril, hetero ciclo alquil, aril, C_2-C_6 alcanoil o C_1-C_6 alquil opcionalmente substituido *e.g.*, con -C(O)OR_{11} o alcoxi, donde el grupo alcoxi es opcionalmente sustituido con -C(O)OR_{11}, y donde los grupos hetero aril y aril son opcionalmente sustituidos con *e.g.*, 1 a 3 grupos que son independientemente halógeno, hidroxil, alquil, alcoxi, halo alquil, halo alcoxi, CN o NO_2; o si dos R_{11} grupos están en un nitrógeno, entonces los dos R_{11} grupos junto al nitrógeno al que están unidos pueden formar un anillo de 3-8 miembros incluyendo opcionalmente un hetero átomo adicional tal como *e.g.*, NH, NR_{12}, NR_{13}, O o S, y adicionalmente R_{11} puede ser H;

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R_{12} es H, C_1-C_6 alquil, aril o $-SO_2$-aril, donde cada aril es opcionalmente sustituido *e.g.*, con 1 a 5 grupos que son independientemente halógeno, hidroxilo, alquil, alcoxi, halo alquil, halo alcoxi, CN o NO_2;

R_{13} es H, aril o C_1-C_6 alquil opcionalmente sustituido *e.g.*, con aril (tal como fenil o naftil, preferiblemente fenil), hidroxilo, C_1-C_6 alcoxi o halógeno, donde cada grupo aril es opcionalmente sustituido *e.g.*, con 1 a 5 grupos que son independientemente halógeno, hidroxilo, alquil, alcoxi, halo alquil, halo alcoxi, CN o NO_2;

R_{15} es H, fenil, piridil, pirimidinil, oxazolil, tiazolil, imidazolil, tienil, furanil, pirrolil, piperidinil, piperazinil, pirrolidinil, imidazolidinil, indolil, quinolinil, $-SO_2R_{10}$, $-C(O)R_{10}$, $-C(O)OR_{11}$ o C_1-C_6 alquil opcionalmente sustituido *e.g.*, con fenil, hidroxil o halógeno, donde los grupos cíclicos de arriba son opcionalmente sustituidos *e.g.*, con 1 a 5 grupos que son independientemente halógeno, hidroxilo, C_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_6 halo alquil (*e.g.*, CF_3 o CH_2CF_3), C_1-C_4 halo alcoxi (*e.g.*, OCF_3 o OCH_2CF_3), CN, amino, NH(C_1-C_6 alquil), N(C_1-C_6 alquil) (C_1-C_6 alquil) o NO_2; y

cada R_{25} es independientemente H, C_1-C_6 alquilo, C_1-C_6 halo alquilo, -$C(O)OR_{11}$, -(C_1-C_6 alquilo)-$C(O)OR_{11}$, C_1-C_6 alcoxi C_1-C_6 alquilo, $-CONR_{11}R_{11}$, CN o hidroxi C_1-C_6 alquilo. Un carbono cabeza de puente y su correspondiente grupo R_{25} en las Fórmulas 1, 2, 3, 4 y/o 5 es opcionalmente reemplazado con un N; y en un núcleo [3.3.1], un carbono no-cabeza de puente puede ser reemplazado con un grupo Z, donde Z es N.

Los compuestos de las Fórmulas 1, 2, 3, y 4 inhiben la liberación de péptido ß-amiloide y/o su síntesis y por lo tanto son útiles en la prevención de enfermedades neuro – degenerativas, tales como la Enfermedad de Alzheimer (AD), en paciente susceptibles a la Enfermedad de Alzheimer (AD) y/o en el tratamiento de pacientes con Enfermedad de Alzheimer (AD) a objeto de inhibir el ulterior deterioro de su condición. La invención también comprende composiciones farmacéuticas conteniendo un compuesto de la invención y métodos empleando

dichos compuestos o composiciones en el tratamiento de enfermedades cognitivas, incluyendo la Enfermedad de Alzheimer.

Los compuestos de las Fórmulas 1, 2, 3, y 4 también proporcionan métodos para el tratamiento de un paciente que tiene Enfermedad de Alzheimer (AD), métodos para prevenir la Enfermedad de Alzheimer en un paciente, métodos para ayudar a prevenir o mejorar el establecimiento de la Enfermedad de Alzheimer, para tratar pacientes con discapacidad cognitiva leve (MCI) y prevenir o demorar el inicio de la Enfermedad de Alzheimer en aquellos que podrían progresar desde MCI hasta la Enfermedad de Alzheimer, para tratar el síndrome de Down, para tratar seres humanos con Hemorragia cerebral Hereditaria con amiloidosis de tipo holandés, para tratar la angiopatía cerebral amiloide, y prevenir sus potenciales consecuencias. y.e., hemorragias lobulares sencillas y recurrentes, para tratar otras demencias degenerativas, incluyendo demencias de origen mixto, vascular y degenerativo, demencia asociada con la enfermedad de Parkinson, demencia asociada con parálisis progresiva supra-nuclear, demencia asociada con degeneración cortical basal, degeneración macular asociada con la edad o un tipo difuso corporal tipo Lewy de la Enfermedad de Alzheimer, y que esté en necesidad de dicho tratamiento que comprende la administración de cantidades terapéuticamente efectivas de un compuesto de la invención.

DESCRIPCIÓN DETALLADA DE LA iNVENCIÓN

En un aspecto, aquí se proporcionan compuestos de Fórmula 1a, y.e., compuestos de Fórmula 1 teniendo la fórmula:

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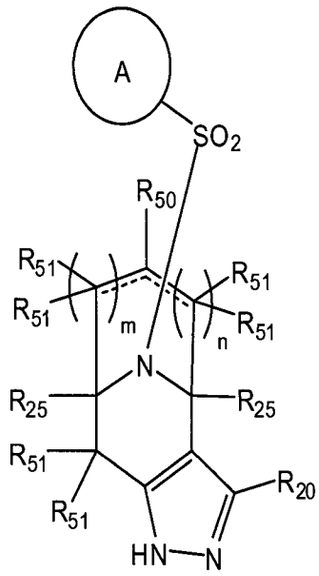
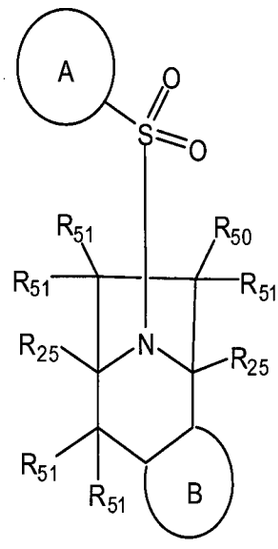


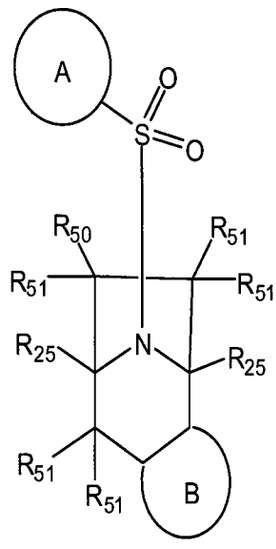
Fórmula 1a

o estéreo isómeros, enantiómeros o sales farmacéuticamente aceptables de éstos, en donde R_{25}, R_{50}, R_{51}, m, n, la línea punteada y el A-anillo es como se define arriba, y en donde R_{20} es H, C_1-C_6 alquil, C_1-C_6 alcoxi, amino, C_1-C_6 alquil amino, C_1-C_6 dialquil amino, halo, CF_3 o $-NR_{11}C(O)R_{10}$.

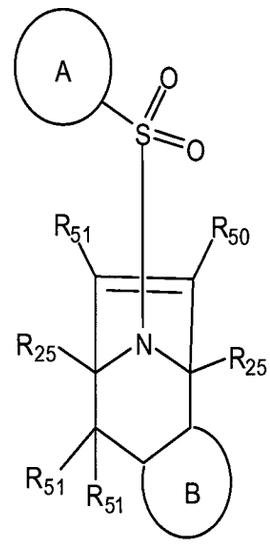
En otro aspecto, aquí se proporcionan compuestos de Fórmulas 1b, 1c, 1d, 1e, 1f o 1g, y.*e.*, compuestos de Fórmula 1 que tienen las siguientes fórmulas:



Fórmula 1b



Fórmula 1c



Fórmula 1d

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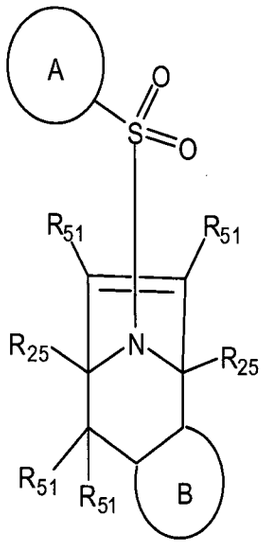
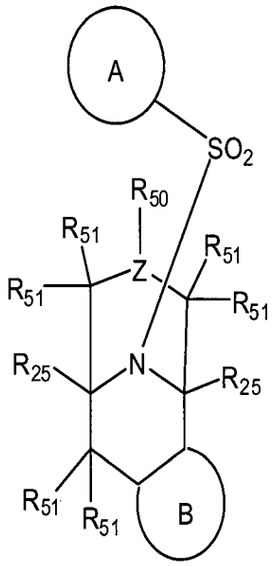
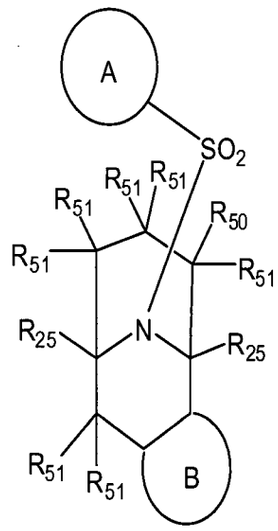


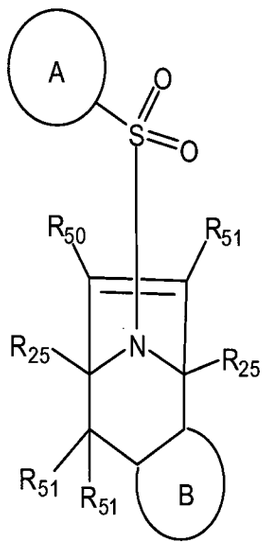
Fórmula 1e



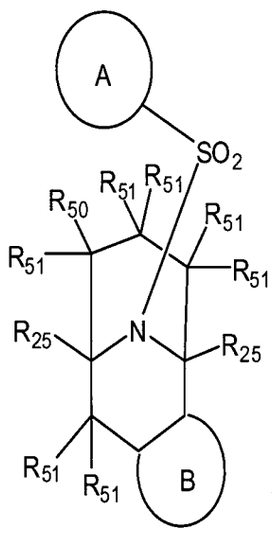
Fórmula 1f



Fórmula 1g



Fórmula 1h



Fórmula 1i

y enantiómeros y/o sales farmacéuticamente aceptables de éstos, en donde los A-anillo, B-anillo, R_{25}, R_{50} y R_{51} son como se define arriba y donde Z es N o CH.

En un primer aspecto, en los compuestos de Fórmulas 1b, 1c, 1d, 1e, 1f, 1g, 1h, y 1i, el B-anillo es pirazolil, dihidro pirazolil, pirazolonil o pirazolidinonil, cada uno de los cuales es opcionalmente sustituido con $-NR_{11}$-C_2-C_6 alcanoil, C_1-C_6 alquil, C_3-C_6 cicloalquil, C_2-C_4 alquenil, C_2-C_4 alquinil, C_1-C_4 alcoxi, amino, C_1-C_4 alquil amino, C_1-C_4 dialquil amino, hidroxi, hidroxi alquil, halo, C_1-C_4 halo alquil, C_1-C_4 halo alcoxi, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ o CN.

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En una incorporación de este aspecto, en las Fórmulas de arriba, R_{50} es oxo, =N-NHR$_{12}$ o =N-O-R$_{13}$ (excepto en las Fórmulas 2d, 2e, y 2f) o R_{50} es halógeno, C_1-C_6 alquil, C_2-C_6 alquenil, C_2-C_6 alquinil, hidroxi, hidroxi C_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_6 haloalcoxi, C_1-C_6 haloalquil, halo C_2-C_6 alquenil, halo C_2-C_6 alquinil, -C(O)OR$_{11}$, -(C_1-C_4 alquil)-C(O)OR$_{11}$, -CONR$_{11}$R$_{11}$, -OC(O)NR$_{11}$R$_{11}$, -NR$_{11}$C(O)OR$_{10}$, -NR$_{11}$S(O)$_2$R$_{10}$, -OS(O)$_2$R$_{10}$, -S(O)$_2$R$_{10}$, -NR$_{11}$C(O)R$_{10}$, CN, -NR$_{11}$R$_{11}$, -SO$_2$NR$_{11}$R$_{11}$, heteroaril que es seleccionado de pirazolil, tiadiazolil, triazolil, isoxazolil, isotiazolil, imidazolil, tiazolil, oxadiazolil, y piridil, hetero cicloalquil que es seleccionado de tetrahidro furanil, pirrolidinil, piperidinil, morfolinil, e imidazolidinil, C_3 –C_6 cicloalquil, aril que es seleccionado de fenil y naftil; en donde los antes nombrados grupos hetero aril, hetero ciclo alquil, ciclo alquil y aril son opcionalmente sustituidos con 1 o más grupos que son independientemente halógeno, C_1-C_6 alquil, C_2-C_6 alquenil, C_2-C_6 alquinil, hidroxi, hidroxiC_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_6 halo alcoxi, C_1-C_6 halo alquil, halo C_2-C_6 alquenil, halo C_2-C_6 alquinil, -C(O)OR$_{11}$, -(C_1-C_4 alquil)-C(O)OR$_{11}$, -CONR$_{11}$R$_{11}$, -OC(O)NR$_{11}$R$_{11}$, -NR$_{11}$C(O)OR$_{10}$, -NR$_{11}$S(O)$_2$R$_{10}$, -OS(O)$_2$R$_{10}$, -S(O)$_2$R$_{10}$, -NR$_{11}$C(O)R$_{10}$, CN, =N-NHR$_{12}$, -NR$_{11}$R$_{11}$, -SO$_2$NR$_{11}$R$_{11}$, heteroaril que es seleccionado de pirazolil, tiadiazolil, triazolil isoxazolil, isotiazolil, imidazolil, tiazolil, oxadiazolil, oxazolil, tetrazolil, y piridil, hetero cicloalquil que es seleccionado de tetra hidro furanil, pirrolidinil, piperidinil, morfolinil, e imidazolidinil, C_3 –C_6 ciclo alquil, aril que es seleccionado de fenil, benzo[d][1,3]dioxolil, y naftil o =N-O-R$_{13}$; en donde los antes nombrados sustitutos hetero aril, hetero ciclo alquil, ciclo alquil y aril son opcionalmente sustituidos con 1 o más grupos que son independientemente halógeno, C_1-C_6 alquil, C_1-C_6 alcoxi, hidroxi, C_1-C_6 hidroxi alquil, C_1-C_6 halo alcoxi o C_1-C_6 halo alquil;

siempre y cuando que en las Fórmulas 1d y 1h, R_{50} no es oxo, =N-O-R$_{13}$ o =N-NHR$_{12}$;

cada R_{51} está independientemente ausente, H, C_1-C_4 alquil, halógeno (*e.g.*, F, Cl o Br), CN, amino, mono alquilamino, dialquilamino, OH, C_1-C_4 haloalcoxi (*e.g.*, OCF$_3$) o C_1-C_4 haloalquil (*e.g.*, CF$_3$); o cuando hay dos grupos R_{51} en un átomo de carbono, los dos grupos R_{51} y el carbono al cual están unidos pueden formar un

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anillo de 3- a 6-miembros cicloalquil o heterocicloalquil; o cuando hay dos grupos R_{51} en un carbono, los dos grupos R_{51} pueden formar un grupo oxo; o cuando hay dos grupos R_{51} en un carbono, los dos grupos R_{51} pueden formar un grupo alqueno; o cuando hay dos grupos R_{51} en un carbono, los dos grupos R_{51} pueden formar una oxima o una oxima C_1-C_4 alquilada (*e.g.*, O-metil oxima);

R_{10} y R_{11} en cada ocurrencia son independientemente C_1-C_6 alquil, heteroaril que es seleccionado de pirazolil, tiadiazolil, triazolil, isoxazolil, isotiazolil, imidazolil, tiazolil, oxadiazolil, y piridil o aril que es seleccionado de fenil y naftil, donde los grupos heteroaril y aril son opcionalmente sustituidos con 1 a 3 grupos que son independientemente halógeno, hidroxil, alquil, alcoxi, haloxalquil, haloxalcoxi, CN o NO_2; o si dos grupos R_{11} están en un nitrógeno, entonces los dos grupos R_{11} junto con el nitrógeno al cual están unidos, pueden formar un anillo de 3-8 miembros opcionalmente incluyendo un adicional hetero átomo tal como NH, NR_{12}, NR_{13}, O o S; y adicionalmente R_{11} puede ser H;

R_{12} es H, C_1-C_6 alquil, aril o $-SO_2$-aril (*e.g.*, fenil o naftil, donde fenil es preferido), donde cada grupo aril es opcionalmente sustituido con 1 a 5 grupos que son independientemente halógeno, hidroxil, alquil, alcoxi, halo alquil, halo alcoxi, CN o NO_2;

R_{13} es H, aril o C_1-C_6 alquil opcionalmente sustituidos con aril (tal como fenil o naftil, más preferible, fenil), hidroxil o halógeno, donde cada grupo aril es opcionalmente sustituido con 1 a 5 grupos que son independientemente halógeno, hidroxil, alquil, alcoxi, haloalquil, haloalcoxi, CN o NO_2. En una ulterior incorporación de este aspecto, R_{50} es oxo, $=N-NHR_{12}$ o $=N-O-R_{13}$, (siempre y cuando que R_{51} esté ausente, y R_{50} no esté unido con una unión doble carbono-carbono) o R_{50} es C_2-C_8 alquenil, C_2-C_8 alquinil, halo C_2-C_8 alquenil, halo C_2-C_8 alquinil, C_2-C_6 alcanoil, $-C(O)OR_{11}$, $-OS(O)_2R_{10}$, $-S(O)_2R_{10}$, $-NR_{11}R_{11}$,$-SO_2NR_{11}R_{11}$, hetero aril, hetero ciclo alquil, ciclo alquil o aril, en donde los grupos hetero aril, hetero ciclo alquil, ciclo alquil y aril son opcionalmente sustituidos *e.g.*, 1 o más grupos que son independientemente halógeno, C_1-C_6 alquil, C_2-C_6 alquenil, C_2-C_6 alquinil, hidroxi, hidroxiC_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_6 haloalcoxi, C_1-C_6 haloalquil,

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halo C_2-C_6 alquenil, halo C_2-C_6 alquinil, -C(O)OR_{11}, -(C_1-C_4 alquil)-C(O)OR_{11}, -CO$NR_{11}R_{11}$, -OC(O)$NR_{11}R_{11}$, -NR_{11}C(O)OR_{10}, -NR_{11}S(O)$_2R_{10}$, -OS(O)$_2R_{10}$, -S(O)$_2R_{10}$, -NR_{11}C(O)R_{10}, CN, =N-NHR_{12}, -$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, heteroaril que es seleccionado de pirazolil, tiadiazolil, triazolil isoxazolil, isotiazolil, imidazolil, tiazolil, oxadiazolil, oxazolil, tetrazolil, y piridil, heterocicloalquil que es seleccionado de tetrahidrofuranil, pirrolidinil, piperidinil, morfolinil, e imidazolidinil, C_3 –C_6 cicloalquil, aril que es seleccionado de fenil, benzo[d][1,3]dioxolil, y naftil o =N-O-R_{13}; en donde los antes nombrados sustitutos hetero aril, hetero ciclo alquil, ciclo alquil y aril son opcionalmente sustituidos con 1 o más grupos que son independientemente halógeno, C_1-C_6 alquil, C_1-C_6 alcoxi, hidroxi, C_1-C_6 hidroxi alquil, C_1-C_6 halo alcoxi o C_1-C_6 halo alquil. En una ulterior incorporación, R_{50} es C_2-C_6 alquenil, C_2-C_6 alquinil, halo C_2-C_6 alquenil, halo C_2-C_6 alquinil, C_2-C_6 alcanoil, OS(O)$_2R_{10}$, -S(O)$_2R_{10}$, -$NR_{11}R_{11}$, C(O)OR_{11} -$SO_2NR_{11}R_{11}$, hetero aril que es seleccionado de pirazolil, tiadiazolil (*e.g.*, 1,2,4-tiadiazolil o 1,3,4-tiadiazolil), triazolil (*e.g.*, 1,2,3-triazolil o 1,2,4-triazolil), isoxazolil, isotiazolil, imidazolil, tiazolil, oxadiazolil (*e.g.*, 1,2,4-oxadiazolil o 1,3,4-oxadiazolil), oxazolil, tetrazolil, y piridil, heterocicloalquil que es seleccionado de tetra hidro furanil, pirrolidinil, piperidinil, morfolinil, e imidazolidinil, C_3 –C_6 cicloalquil, aril que es seleccionado de fenil, benzo[d][1,3]dioxolil, y naftil o =N-O-R_{13}; en donde los antes nombrados grupos hetero aril, hetero ciclo alquil, ciclo alquil y aril son opcionalmente sustituidos con 1 o más grupos que son independientemente halógeno, C_1-C_6 alquil, C_2-C_6 alquenil, C_2-C_6 alquinil, hidroxi, hidroxiC_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_6 halo alcoxi, C_1-C_6 halo alquil, halo C_2-C_6 alquenil, halo C_2-C_6 alquinil, -C(O)OR_{11}, -(C_1-C_4 alquil)-C(O)OR_{11}, -CO$NR_{11}R_{11}$, -OC(O)$NR_{11}R_{11}$, -NR_{11}C(O)OR_{10}, -NR_{11}S(O)$_2R_{10}$, -OS(O)$_2R_{10}$, -S(O)$_2R_{10}$, -NR_{11}C(O)R_{10}, CN, =N-NHR_{12}, -$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, heteroaril que es seleccionado de pirazolil, tiadiazolil, triazolil isoxazolil, isotiazolil, imidazolil, tiazolil, oxadiazolil, oxazolil, tetrazolil, y piridil, heterocicloalquil que es seleccionado de tetra hidro furanil, pirrolidinil, piperidinil, morfolinil, e imidazolidinil, C_3 –C_6 ciclo alquil, aril que es seleccionado de fenil, benzo[d][1,3]dioxolil, y naftil o =N-O-R_{13}; en donde los antes nombrados sustitutos heteroaril, heterocicloalquil, cicloalquil y aril son opcionalmente sustituidos con 1 o más grupos que son

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independientemente halógeno, C_1-C_6 alquil, C_1-C_6 alcoxi, hidroxi, C_1-C_6 hidroxi alquil, C_1-C_6 halo alcoxi o C_1-C_6 halo alquil;

En un aspecto, aquí se proporcionan compuestos de Fórmulas 1b, 1c, 1d, 1e, 1f, 1g, 1h, y 1i, en donde el B-anillo es pirazolil, dihidro pirazolil, pirazolonil o pirazolidinonil, cada uno como se define en el primer aspecto, y R_{50} es halógeno, C_1-C_6 alquil, C_2-C_6 alquenil, C_2-C_6 alquinil, hidroxi C_1-C_6 alquil, C_1-C_6 alcoxi, halo C_2-C_6 alquenil, halo C_2-C_6 alquinil, C_1-C_6 haloalcoxi o C_1-C_6 haloalquil. En una incorporación, R_{50} es halógeno, C_1-C_4 alquil, hidroxi, hidroxi C_1-C_4 alquil, C_1-C_4 alcoxi, halo C_2-C_4 alquenil, halo C_2-C_4 alquinil, C_1-C_4 haloalcoxi o C_1-C_4 haloalquil. En otra incorporación, R_{50} es C_1-C_4 alquil, C_1-C_4 halo alquil, hidroxi C_1-C_4 alquil o C_1-C_4 alcoxi. En otra incorporación más, R_{50} es C_1-C_4 alquil. En otra incorporación, R_{50} es C_1-C_4 halo alquil (*e.g.*, CF_3 o CH_2CF_3), hidroxi C_1-C_4 alquil o C_1-C_4 alcoxi (*e.g.*, metoxi o etoxi). En otra incorporación, R_{50} es C_2-C_4 alquenil, C_2-C_4 alquinil, halo C_2-C_4 alquenil, halo C_2-C_4 alquinil. En otra incorporación más, R_{50} es halógeno, hidroxi o hidroxi C_1-C_4 alquil. En otra incorporación, R_{50} es halógeno. En otra incorporación más, R_{50} es hidroxi o hidroxi C_1-C_4 alquil.

En otro aspecto, aquí se proporcionan compuestos de Fórmula 1b, 1c, 1d, 1e, 1f, 1g, 1h, y 1i, en donde el B-anillo es pirazolil, dihidro pirazolil, pirazolonil o pirazolidinonil, cada cual siendo como se define arriba y en donde R_{50} es $-C(O)OR_{11}$, $-(C_1$-C_4 alquil$)-C(O)OR_{11}$, $-CONR_{11}R_{11}$, $-OC(O)NR_{11}R_{11}$, $-NR_{11}C(O)OR_{11}$, $-NR_{11}S(O)_2R_{10}$, $-OS(O)_2R_{10}$, $-S(O)_2R_{10}$, $-NR_{11}C(O)R_{10}$, CN, $=N-NHR_{12}$, $=N-O-R_{13}$, $NR_{11}R_{11}$ o $-SO_2NR_{11}R_{11}$;

R_{10} y R_{11} en cada ocurrencia son independientemente C_1-C_6 alquil, hetero aril que es seleccionado de pirazolil, tiadiazolil, triazolil, isoxazolil, isotiazolil, imidazolil, tiazolil, oxadiazolil, y piridil o aril que es seleccionado de fenil y naftil, donde los grupos heteroaril y aril son opcionalmente sustituidos con 1 a 3 grupos que son independientemente halógeno, hidroxil, C_1-C_6 alquil, C_1-C_6 alcoxi, halo C_1-C_4 alquil, halo C_1-C_4 alcoxi, CN o NO_2; y adicionalmente R_{11} puede ser H; o si dos

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grupos R_{11} están en un nitrógeno, los dos grupos R_{11} junto con el nitrógeno al cual están unidos, pueden formar un anillo de 3-8 miembros opcionalmente incluyendo un adicional hetero átomo tal como NH, NR_{12}, NR_{13}, O o S;

R_{12} es H, C_1-C_6 alquil, aril o $-SO_2$-aril (*e.g.*, fenil o naftil, donde fenil es preferido), donde cada grupo aril es opcionalmente sustituido con 1 a 5 grupos que son independientemente halógeno, hidroxil, alquil, alcoxi, haloalquil, haloalcoxi, CN o NO_2;

R_{13} es H, aril o C_1-C_6 alquil opcionalmente sustituidos con aril (tal como fenil o naftil, más preferible, fenil), hidroxil o halógeno, donde cada grupo aril es opcionalmente sustituido con 1 a 5 grupos que son independientemente halógeno, hidroxil, alquil, alcoxi, halo alquil, halo alcoxi, CN o NO_2.

. En una incorporación de este aspecto, R_{10} es C_1-C_4 alquil y R_{11} es independientemente hidrógenoo o C_1-C_4 alquil.

En otra incorporación más de este aspecto, R_{11} es H.

En otra incorporación más de este aspecto, uno de R_{10} y R_{11} es CH_3.

En otra incorporación de este aspecto, R_{10} y R_{11} junto con el nitrógeno al cual están unidos pueden formar un anillo de 3-8 miembros, el cual opcionalmente incluye un adicional hetero átomo que es NH, NR_{12}, NR_{13}, O o S.

En otra incorporación más de este aspecto, R_{10} y R_{11} en cada ocurrencia son independientemente fenil opcionalmente sustituido con 1 a 3 grupos que son independientemente halógeno, hidroxil, C_1-C_6 alquil, C_1-C_6 alcoxi, halo C_1-C_4 alquil, halo C_1-C_4 alcoxi, CN o NO_2; y adicionalmente R_{11} puede ser H.

En otra incorporación de este aspecto, R_{10} y R_{11} en cada ocurrencia son independientemente pirazolil, isoxazolil, isotiazolil, imidazolil o tiazolil, cada cual opcionalmente sustituido con 1 a 3 grupos que son independientemente halógeno, hidroxil, C_1-C_6 alquil, C_1-C_6 alcoxi, halo C_1-C_4 alquil, halo C_1-C_4 alcoxi, CN o NO_2; y adicionalmente R_{11} puede ser H.

En otra incorporación de este aspecto, R_{10} y R_{11} en cada ocurrencia son independientemente tiadiazolil, triazolil o oxadiazolil, cada cual opcionalmente

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sustituido con 1 a 3 grupos que son independientemente halógeno, hidroxil, C_1-C_6 alquil, C_1-C_6 alcoxi, halo C_1-C_4 alquil, halo C_1-C_4 alcoxi, CN o NO_2; y adicionalmente R_{11} puede ser H.

En otra incorporación más de este aspecto, R_{13} es H, C_1-C_4 alquil o benzil, donde la porción fenil es opcionalmente sustituida con halógeno, hidroxil, C_1-C_4 alquil, C_1-C_4 alcoxi, CF_3 o OCF_3. En otra incorporación, R_{13} es C_1-C_4 alquil o benzil.

En otro aspecto, aquí se proporcionan compuestos de Fórmula 1b, 1c, 1d, 1e, 1f, 1g, 1h, y 1i, en donde el B-anillo es pirazolil, dihidro pirazolil, pirazolonil o pirazolidinonil, cada cual como se define arriba, y en donde R_{50} es $-C(O)OR_{11}$, $-CONR_{11}R_{11}$, $-OC(O)NR_{11}R_{11}$, $-NR_{11}C(O)OR_{10}$, $-NR_{11}S(O)_2R_{10}$, $-OS(O)_2R_{10}$, $-S(O)_2R_{10}$, $-NR_{11}C(O)R_{10}$, $NR_{11}R_{11}$ o $-SO_2NR_{11}R_{11}$, en donde R_{10} y R_{11} en cada ocurrencia son independientemente C_1-C_6 alquil, heteroaril que es seleccionado de pirazolil, tiadiazolil, triazolil, isoxazolil, isotiazolil, imidazolil, tiazolil, oxadiazolil, y piridil o aril que es seleccionado de fenil y naftil, donde los grupos heteroaril y aril son opcionalmente sustituidos con 1 a 3 grupos que son independientemente halógeno, hidroxilo, C_1-C_6 alquil, C_1-C_6 alcoxi, halo C_1-C_4 alquil, halo C_1-C_4 alcoxi, CN o NO_2; o si dos grupos R_{11} están en un nitrógeno, los dos grupos R_{11} junto con el nitrógeno al cual están unidos, pueden formar un anillo de 3-8 miembros opcionalmente incluyendo un adicional hetero átomo como NH, NR_{12}, NR_{13}, O o S, y adicionalmente R_{11} puede ser H;

R_{12} es H, C_1-C_6 alquil, aril o $-SO_2$-aril (*e.g.*, fenil o naftil, donde fenil es preferido), donde cada grupo aril es opcionalmente sustituidoo con 1 a 5 grupos que son independientemente halógeno, hidroxil, alquil, alcoxi, haloalquil, haloalcoxi, CN o NO_2;

R_{13} es H, aril o C_1-C_6 alquil opcionalmente sustituidos con aril (tal como fenil o naftil, más preferible, fenil), hidroxil o halógeno, donde cada aril es opcionalmente sustituido con 1 a 5 grupos que son independientemente halógeno, hidroxil, alquil, alcoxi, halo alquil, halo alcoxi, CN o NO_2.

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En una incorporación de este aspecto, R_{10} es C_1-C_4 alquil y R_{11} es independientemente hidrógenoo o C_1-C_4 alquil.

En otra incorporación más de este aspecto, R_{11} es H.

En otra incorporación más de este aspecto, uno de R_{10} y R_{11} es CH_3.

En otra incorporación de este aspecto, la dos grupos R_{11} junto con el nitrógeno al cual están unidos forman un anillo de 3-8 miembros, el cual opcionalmente incluye un adicional hetero átomo que es NH, NR_{12}, NR_{13}, O o S.

En otra incorporación de este aspecto, R_{10} y R_{11} en cada ocurrencia son independientemente fenil opcionalmente sustituido con 1 a 3 grupos que son independientemente halógeno, hidroxil, C_1-C_6 alquil, C_1-C_6 alcoxi, halo C_1-C_4 alquil, halo C_1-C_4 alcoxi, CN o NO_2; y adicionalmente R_{11} puede ser H.

En otra incorporación de este aspecto, R_{10} y R_{11} en cada ocurrencia son independientemente pirazolil, isoxazolil, isotiazolil, imidazolil o tiazolil, cada cual opcionalmente sustituido con 1 a 3 grupos que son independientemente halógeno, hidroxil, C_1-C_6 alquil, C_1-C_6 alcoxi, halo C_1-C_4 alquil, halo C_1-C_4 alcoxi, CN o NO_2; y adicionalmente R_{11} puede ser H.

En otra incorporación de este aspecto, R_{10} y R_{11} en cada ocurrencia son independientemente H, tiadiazolil, triazolil o oxadiazolil, cada cual opcionalmente sustituido con 1 a 3 grupos que son independientemente halógeno, hidroxil, C_1-C_6 alquil, C_1-C_6 alcoxi, halo C_1-C_4 alquil, halo C_1-C_4 alcoxi, CN o NO_2; y adicionalmente R_{11} puede ser H.

En otra incorporación de este aspecto, R_{13} es H, C_1-C_4 alquil o benzil, donde la porción fenil es opcionalmente sustituida con halógeno, hidroxil, C_1-C_4 alquil, C_1-C_4 alcoxi, CF_3 o OCF_3. En otra incorporación, R_{13} es C_1-C_4 alquil o benzil.

En otro aspecto, los que aquí se proporcionan son compuestos de Fórmula 1b, 1c, 1d, 1e, 1f, 1g, 1h, y 1i, en donde el B-anillo es pirazolil, dihidro pirazolil, pirazolonil o pirazolidinonil, cada cual siendo como se define arriba, y en donde R_{50} es heteroaril que es seleccionado de pirazolil, tiadiazolil, triazolil, isoxazolil,

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isotiazolil, imidazolil, tiazolil, oxadiazolil, y piridil, hetero cicloalquil que es seleccionado de tetra hidro furanil, pirrolidinil, piperidinil, morfolinil, e imidazolidinil, cada cual opcionalmente sustituido con 1 o más grupos que son independientemente halógeno, C_1-C_6 alquil, C_1-C_6 alcoxi, hidroxi, C_1-C_6 hidroxi alquil, C_1-C_6 halo alcoxi o C_1-C_6 halo alquil.

En una incorporación de este aspecto, R_{50} es pirazolil o imidazolil, cada cual opcionalmente sustituido con 1 o más grupos que son independientemente halógeno, C_1-C_4 alquil, C_1-C_4 alcoxi, hidroxi, C_1-C_4 hidroxi alquil, C_1-C_4 halo alcoxi (*e.g.*, OCF_3) o C_1-C_4 halo alquil (*e.g.*, CF_3). En una ulterior incorporación de este aspecto, R_{50} es no-sustituido.

En una incorporación de este aspecto, R_{50} es tiazolil u oxadiazolil cada cual opcionalmente sustituido con 1 o más grupos que son independientemente halógeno, C_1-C_4 alquil, C_1-C_4 alcoxi, hidroxi, C_1-C_4 hidroxi alquil, C_1-C_4 halo alcoxi (*e.g.*, OCF_3) o C_1-C_4 halo alquil (*e.g.*, CF_3). En una ulterior incorporación de este aspecto, R_{50} es no-sustituido

En un incorporación de este aspecto, R_{50} es piridil, el cual es opcionalmente sustituido con 1 o más grupos que son independientemente halógeno, C_1-C_4 alquil, C_1-C_4 alcoxi, hidroxi, C_1-C_4 hidroxi alquil, C_1-C_4 halo alcoxi (*e.g.*, OCF_3) o C_1-C_4 haloalquil (*e.g.*, CF_3). En una ulterior incorporación de este aspecto, R_{50} es no-sustituido.

En un incorporación de este aspecto, R_{50} es tiadiazolil, el cual es opcionalmente sustituido con 1 o más grupos que son independientemente halógeno, C_1-C_4 alquil, C_1-C_4 alcoxi, hidroxi, C_1-C_4 hidroxi alquil, C_1-C_4 halo alcoxi (*e.g.*, OCF_3) o C_1-C_4 halo alquil (*e.g.*, CF_3). En una ulterior incorporación de este aspecto, R_{50} es no-sustituido.

En una incorporación de este aspecto, R_{50} es triazolil, el cual es opcionalmente sustituido con 1 o más grupos que son independientemente halógeno, C_1-C_4 alquil, C_1-C_4 alcoxi, hidroxi, C_1-C_4 hidroxi alquil, C_1-C_4 halo alcoxi (*e.g.*, OCF_3) o C_1-C_4 halo alquil (*e.g.*, CF_3). En una ulterior incorporación de este aspecto, R_{50} es no-sustituido.

En una incorporación de este aspecto, R_{50} es isoxazolil, el cual es opcionalmente sustituido con 1 o más grupos que son independientemente halógeno, C_1-C_4 alquil, C_1-C_4 alcoxi, hidroxi, C_1-C_4 hidroxi alquil, C_1-C_4 halo alcoxi (*e.g.*, OCF_3) o C_1-C_4 halo alquil (*e.g.*, CF_3). En una ulterior incorporación de este aspecto, R_{50} es no-sustituido.

En una incorporación de este aspecto, R_{50} es isotiazolil, el cual es opcionalmente sustituido con 1 o más grupos que son independientemente halógeno, C_1-C_4 alquil, C_1-C_4 alcoxi, hidroxi, C_1-C_4 hidroxi alquil, C_1-C_4 halo alcoxi (*e.g.*, OCF_3) o C_1-C_4 halo alquil (*e.g.*, CF_3). En una ulterior incorporación de este aspecto, R_{50} es no-sustituido. En una incorporación de este aspecto, R_{50} es seleccionado de tetra hidrofuranil, pirrolidinil, e imidazolidinil, cada cual opcionalmente sustituido con 1 o más grupos que son independientemente halógeno, C_1-C_4 alquil, C_1-C_4 alcoxi, hidroxi, C_1-C_4 hidroxi alquil, C_1-C_4 halo alcoxi (*e.g.*, OCF_3) o C_1-C_4 halo alquil (*e.g.*, CF_3). En unaa ulterior incorporación de este aspecto, R_{50} es no-sustituido.

En una incorporación de este aspecto, R_{50} es piperidinil o morfolinil, cada cual opcionalmente sustituido con 1 o más grupos que son independientemente halógeno, C_1-C_4 alquil, C_1-C_4 alcoxi, hidroxi, C_1-C_4 hidroxi alquil, C_1-C_4 halo alcoxi (*e.g.*, OCF_3) o C_1-C_4 halo alquil (*e.g.*, CF_3). En unaa ulterior incorporación de este aspecto, R_{50} es no-sustituido.

En una ulterior incorporación de este aspecto, R_{50} es no-sustituido.

En una ulterior incorporación de este aspecto, R_{50} es sustituido con un grupo que es halógeno, C_1-C_2 alquil, C_1-C_2 alcoxi, hidroxi, C_1-C_2 hidroxi alquil, C_1-C_2 halo alcoxi (*e.g.*, OCF_3) o C_1-C_2 halo alquil (*e.g.*, CF_3).

En otro aspecto, aquí se proporcionan compuestos de Fórmula 1b, 1c, 1d, 1e, 1f, 1g, 1h, y 1i, en donde el B-anillo es pirazolil, dihidro pirazolil, pirazolonil o pirazolidinonil, cada cual siendo como se define arriba, y en donde R_{50} es C_3 –C_6 ciclo alquil, el cual es opcionalmente sustituido con 1 o más grupos que son independientemente halógeno, C_1-C_6 alquil, C_1-C_6 alcoxi, hidroxi, C_1-C_6 hidroxi alquil, C_1-C_6 halo alcoxi o C_1-C_6 halo alquil.

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En una incorporación de este aspecto, R_{50} es no-sustituido C_3 –C_6 ciclo alquil. En una ulterior incorporación, R_{50} es ciclo propil.

En otra incorporación de este aspecto, R_{50} es C_3 –C_6 ciclo alquil sustituido con uno o dos grupos que son independientemente halógeno, C_1-C_4 alquil, C_1-C_4 alcoxi, hidroxi, C_1-C_4 hidroxi alquil, C_1-C_4 halo alcoxi (*e.g.*, OCF_3) o C_1-C_4 halo alquil (*e.g.*, CF_3).

En otra incorporación más, R_{50} es ciclopropil, ciclopentil o ciclohexil, cada cual opcionalmente sustituido con halógeno, C_1-C_2 alquil, C_1-C_2 alcoxi (*e.g.*, metoxi), hidroxi, C_1-C_2 hidroxi alquil, C_1-C_2 halo alcoxi (*e.g.*, OCF_3) o C_1-C_2 halo alquil (*e.g.*, CF_3).

En otra incorporación más, R_{50} es ciclo propil, sustituido con un grupo que es halógeno, C_1-C_2 alquil, C_1-C_2 alcoxi (*e.g.*, metoxi), hidroxi o C_1-C_2 hidroxi alquil.

En otro aspecto, los que aquí se proporcionan son compuestos de Fórmula 1b, 1c, 1d, 1e, 1f, 1g, 1h, y 1i, en donde el B-anillo es pirazolil, dihidropirazolil, pirazolonil o pirazolidinonil, cada cual siendo como se define arriba, y en donde R_{50} es aril que es seleccionado de fenil, benzo[d][1,3]dioxolil, y naftil, cada cual opcionalmente sustituido con uno o más grupos que son independientemente halógeno, C_1-C_6 alquil, C_1-C_6 alcoxi, hidroxi, C_1-C_6 hidroxi alquil, C_1-C_6 halo alcoxi o C_1-C_6 halo alquil.

En una incorporación de este aspecto, R_{50} es fenil, el cual es opcionalmente sustituido con uno o más grupos que son independientemente halógeno (*e.g.*, F), C_1-C_4 alquil, C_1-C_4 alcoxi, hidroxi, C_1-C_4 hidroxi alquil, C_1-C_4 halo alcoxi (*e.g.*, OCF_3) o C_1-C_4 halo alquil (*e.g.*, CF_3).

En otra incorporación de este aspecto, R_{50} es fenil no-sustituido.

En otra incorporación más de este aspecto, R_{50} es fenil, el cual es sustituido con al menos un grupo que es halógeno (*e.g.*, F), C_1-C_2 alquil, C_1-C_2 alcoxi, hidroxi, C_1-C_2 hidroxi alquil, C_1-C_2 halo alcoxi (*e.g.*, OCF_3), C_1-C_2 halo alquil (*e.g.*, CF_3) o –CN. En una ulterior incorporación, el grupo fenil es sustituido con dos grupos independientemente seleccionados.

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En todavía otra incorporación más de este aspecto, R_{50} es fenil, que es sustituido con al menos un grupo que es halógeno (*e.g.*, F), C_1-C_2 alquilo, C_1-C_2 alcoxi, hidroxi, C_1-C_2 hidroxi alquilo, C_1-C_2 halo alcoxi (*e.g.*, OCF_3), C_1-C_2 halo alquilo (*e.g.*, CF_3) or –CN. En una incorporación ulterior, el grupo fenil es sustituido con dos grupos. En otra incorporación más, los grupos par R_{51} que son alfa al anillo-B forman un grupo oxo. En otra incorporación más, los grupos par R_{51} que son alfa al anillo-B forman un grupo C_2-C_4 alquenil. En otra incorporación más, los grupos par R_{51} que son alfa al anillo-B forman una oxima o una oxima C_1-C_4 alquilada (*e.g.*, O- metil oxima).

En todavía otra incorporación más de este aspecto, R_{50} es fenil, que es sustituido con un grupo que es halógeno (*e.g.*, F), C_1-C_2 alquilo, C_1-C_2 alcoxi, hidroxi, C_1-C_2 hidroxi alquilo, C_1-C_2 halo alcoxi (*e.g.*, OCF_3) o C_1-C_2 haloalquilo (*e.g.*, CF_3).

En una incorporación de este aspecto, R_{50} es benzo[d][1,3]dioxolil, que es opcionalmente sustituido con uno o más grupos que son independientemente halógeno, C_1-C_4 alquilo, C_1-C_4 alcoxi, hidroxi, C_1-C_4 hidroxi alquilo, C_1-C_4 halo alcoxi (*e.g.*, OCF_3) o C_1-C_4 halo alquilo (*e.g.*, CF_3). En una incorporación ulterior, el grupo metileno del grupo benzo[d][1,3]dioxolil es sustituido con uno o dos grupos C_1-C_4 alquilo (tales como, *e.g.*, uno o dos grupos metilo).

En otra incorporación de este aspecto, R_{50} es benzo[d][1,3]dioxolil, que es no - sustituido.

En todavía otra incorporación más de este aspecto, R_{50} es benzo[d][1,3]dioxolil, que es sustituido con al menos un grupo que es halógeno, C_1-C_2 alquilo, C_1-C_2 alcoxi, hidroxi, C_1-C_2 hidroxi alquilo, C_1-C_2 halo alcoxi (*e.g.*, OCF_3), C_1-C_2 halo alquilo (*e.g.*, CF_3) o –CN.

En todavía otra incorporación más de este aspecto, R_{50} es benzo[d][1,3]dioxolil, que es sustituido con un grupo que es halógeno , C_1-C_2 alquilo, C_1-C_2 alcoxi, hidroxi, C_1-C_2 hidroxi alquilo, OCF_3 o CF_3.

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En otro aspecto, aquí se proporcionan compuestos de Fórmula 1b, 1c, 1d, 1e, 1f, 1g, 1h, 1i, en donde el anillo-B es pirazolil, dihidro pirazolil, pirazolonil o pirazolidinonil, cada uno como se define arriba, en donde R_{50} es C_1-C_4 alquilo R_{51} H o C_1-C_4 alquilo. En una incorporación ulterior, R_{50} R_{51} son ambos metil.

En un aspecto de la Fórmula 1f, Z es N. En una ulterior incorporación de este aspecto, R_{50} es -C(O)OR_{11}, C_2-C_6 alcanoil, -SO_2R_{10} o -$CONR_{11}R_{11}$; en donde R_{10} es C_1-C_4 alquilo o C_3-C_6 ciclo alquilo; R_{11} es H o C_1-C_6 alquilo; R_{13} es H o C_1-C_4 alquilo opcionalmente sustituido con C_1-C_4 alcoxi . En una incorporación de este aspecto, R_{50} es -C(O) OR_{11} R_{13} es C_1-C_4 alquilo o C_1-C_4 alquilo sustituido con C_1-C_4 alcoxi. En otra incorporación de este aspecto, R_{50} es C_2-C_4 alcanoil. En una incorporación de este aspecto, R_{50} es -SO_2R_{10} R_{10} es C_1-C_3 alquilo o ciclo propil. En una ulterior incorporación de este aspecto, R_{50} es -$CONR_{11}R_{11}$ cada R_{11} es H o C_1-C_4 alquilo.

En una ulterior incorporación de este aspecto, todos los grupos R_{51} son H, el anillo-B es pirazolil, dihidro pirazolil, pirazolonil o pirazolidinonil, cada uno como se define arriba.

En un aspecto de Fórmula 1e (cuando Z es CH) y en un aspecto de Fórmula 1a,

en donde R_{50} es $NR_{11}R_{11}$, o –$SO_2NR_{11}R_{11}$, o –$S(O)_2R_{10}$, o Ute said to remove the haloalkyl, CN and alkoxyalkyl groups.

oxadiazolil, opcionalmente sustituido con C_1-C_4 alquilo , o

C_3-C_6 ciclo alquilo opcionalmente sustituido con C_1-C_4 alquilo o C_1-C_4 alcoxi, o

fenil opcionalmente sustituido con uno o más grupos que son independientemente C_1-C_4 alquilo, C_1-C_4 alcoxi, halógeno, -OCH_2O-, -OCH_2CH_2O,oxazolidinona (*e.g.*, oxazolidin-2-ona), imidazolil, tiazolil, -NR_{11}-ciclo hexil, donde el ciclo hexil es opcionalmente sustituido con $NR_{11}R_{11}$, C_1-C_4

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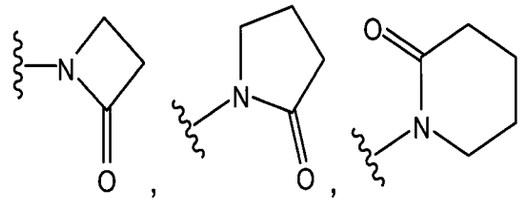
alquilo o C_1-C_4 alcoxi; pirazolil, tetrazolil, pirrolidinonil, -$NR_{11}R_{11}$, morfolinil (*e.g.*, morfolin-2-onil),  o C_2-C_6 alcanoil; o

pirazolil opcionalmente sustituido con C_1-C_4 alquilo; o

tiazolil opcionalmente sustituido con C_1-C_4 alquilo, C_1-C_4 halo alquilo (*e.g.*, CF_3 o CHF_2); o

oxazolil opcionalmente sustituido con C_1-C_4 alquilo ; o

benzimidazolil opcionalmente sustituido con C_1-C_4 alquilo, C_1-C_4 alcoxi o halógeno; o

C_2-C_6 alquenil opcionalmente sustituido con un halógeno (*e.g.*, Cl) o C_1-C_4 halo alquilo (*e.g.*, CF_3); o

triazolil opcionalmente sustituido con uno o dos grupos que son independientemente C_1-C_4 alquilo; o

C_2-C_6 alquinil opcionalmente sustituido con un halógeno (*e.g.*, Cl) o C_1-C_4 alcoxi ; o

tiadiazolil opcionalmente sustituido con C_1-C_4 alquilo, C_1-C_4 halo alquilo (*e.g.*, CF_3 o CHF_2); o

piridil opcionalmente sustituido con uno o más grupos que son independientemente C_1-C_4 alquilo, halógeno o C_1-C_4 alcoxi ; o

en donde R_{11} es H, C_1-C_6 alquilo o C_2-C_6 alcanoil, donde la porción alquilo de R_{11} es opcionalmente sustituida con uno o dos grupos que son independientemente -CO_2-(C_1-C_6 alquilo), C_1-C_6 alquilo -O-(C_1-C_6 alquilo), C_1-C_6 alquilo -O-(C_1-C_4 alquilo)-CO_2-(C_1-C_6 alquilo), C_1-C_6 alquilo -O-(C_1-C_4 alquilo)-CO_2H.

En una incorporación de este aspecto, R_{50} es C_1-C_4 halo alquilo (*e.g.*, CF_3 o CHF_2), CN, C_1-C_4 alcoxi, C_1-C_6 alquilo o $NR_{11}R_{11}$; donde cada R_{11} es independientemente H o C_1-C_4 alquilo. En una incorporación ulterior, R_{50} es

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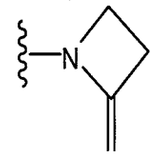
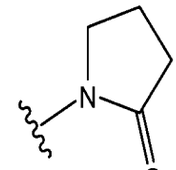
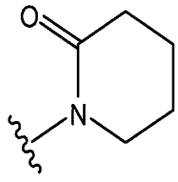
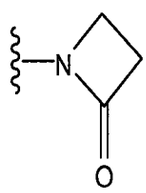
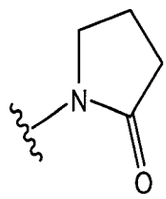
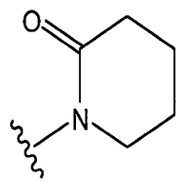
CN. En otra incorporación más, R_{50} es metoxi metil, metoxi etil, etoxi metil o etoxi etil.

En una incorporación de este aspecto, R_{50} es oxadiazolil, sustituido con un C_1-C_2 alquilo.

En una incorporación de este aspecto, R_{50} es fenil opcionalmente sustituido con uno o más grupos que son independientemente C_1-C_4 alquilo , C_1-C_4 alcoxi , halógeno , -OCH_2O-, -OCH_2CH_2O-, oxazolidinona (*e.g.*, oxazolidin-2-ona), imidazolil, tiazolil, -NR_{11}-ciclohexil, donde el ciclohexil es opcionalmente sustituido con $NR_{11}R_{11}$, C_1-C_4 alquilo o C_1-C_4 alcoxi ; pirazolil, tetrazolil, pirrolidinonil, -$NR_{11}R_{11}$, morfolinil (*e.g.*, morfolin-2-onil),  ,  ,  o C_2-C_6 alcanoil. En una incorporación ulterior, R_{50} es un no - sustituido fenil. En otra incorporación, R_{50} es fenil sustituido con uno o más grupos que son independientemente C_1-C_4 alquilo, C_1-C_4 alcoxi o halógeno (*e.g.*, F, Cl o Br). En una incorporación ulterior, R_{50} es fenil sustituido con un grupo que es C_1-C_4 alquilo, C_1-C_4 alcoxi o halógeno (*e.g.*, F, Cl o Br). En otra incorporación, R_{50} es fenil sustituido con un grupo que es seleccionado de oxazolidinonil, imidazolil, tiazolil, pirazolil, tetrazolil, morfolinil pirrolidinonil. En otra incorporación, R_{50} es fenil sustituido con -$NR_{11}R_{11}$. En una incorporación ulterior, el grupo -$NR_{11}R_{11}$ es -$NHC(O)CH_3$, -NH-(C_1-C_4 alquilo)-CO_2-(C_1-C_4 alquilo), -NH-(C_1-C_4 alquilo)-O-(C_1-C_4 alquilo)-CO_2-(C_1-C_4 alquilo) o -NH-(C_1-C_4 alquilo)-O-(C_1-C_4 alquilo)-CO_2H. En otra incorporación, R_{50} es fenil sustituido con un grupo que es  ,  o  . En otra incorporación, R_{50} es fenil

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sustituido con C_2-C_4 alcanoil. En una incorporación ulterior, el fenil es sustituido en la posición-cuatro.

En una incorporación de este aspecto , R_{50} es pirazolil opcionalmente sustituido con C_1-C_4 alquilo ; tiazolil opcionalmente sustituido con C_1-C_4 alquilo (*e.g.*, metil), C_1-C_4 haloalquilo (*e.g.*, CF_3 o CHF_2); oxazolil opcionalmente sustituido con C_1-C_4 alquilo (*e.g.*, metil); triazolil opcionalmente sustituido con uno o dos grupos que son independientemente C_1-C_4 alquilo ; o benzimidazolil opcionalmente sustituido con C_1-C_4 alquilo (*e.g.*, metil), C_1-C_4 alcoxi o halógeno.

En una incorporación de este aspecto, R_{50} es C_2-C_6 alquenil opcionalmente sustituido con un halógeno (*e.g.*, Cl) o C_1-C_4 haloalquilo (*e.g.*, CF_3).

En una incorporación de este aspecto, R_{50} es C_2-C_6 alquinil opcionalmente sustituido con una halógeno (*e.g.*, Cl) o C_1-C_4 alcoxi.

En una incorporación de este aspecto, R_{50} es piridil opcionalmente sustituido con uno o más grupos que son independientemente C_1-C_4 alquilo, halógeno o C_1-C_4 alcoxi.

En un aspecto de la Fórmula 1f, todos los grupos R_{51} son H, el anillo-B es no - sustituido pirazolil. En una incorporación de este aspecto, Z es CH, R_{50} es CHF_2, CN, -CH_2-O-(C_1-C_4 alquilo), oxadiazolil opcionalmente sustituido con metil, ciclopropil, fenil opcionalmente sustituido con un grupo que es halógeno, C_1-C_4 alquilo, oxazolidinonil, imidazolil, tiazolil, pirazolil, -$NR_{11}R_{11}$ o C_1-C_4 alcoxi, oxazolil opcionalmente sustituido con C_1-C_4 alquilo, esoxazolil opcionalmente substituido con C_1-C_4 alquilo , tiazolil opcionalmente sustituido con CF_3, C_2-C_4 alquenil opcionalmente sustituido con un halógeno o un grupo CF_3, C_2-C_4 alquinil, tiadiazolil, triazolil opcionalmente sustituido con C_1-C_4 alquilo o piridil opcionalmente sustituido con C_1-C_4 alquilo o C_1-C_4 alcoxi.

En un aspecto de las Fórmulas 1g 1i, R_{50} es fenil opcionalmente sustituido con uno o más grupos que son independientemente fenil , opcionalmente sustituido con un grupo que es halógeno , C_1-C_4 alquilo , oxazolidinonil,

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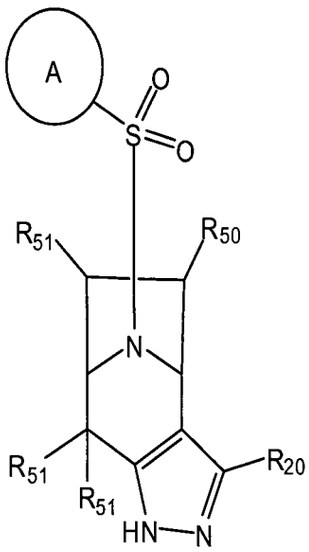
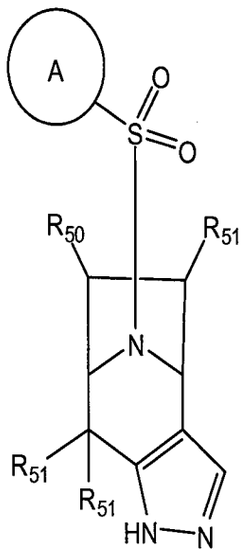
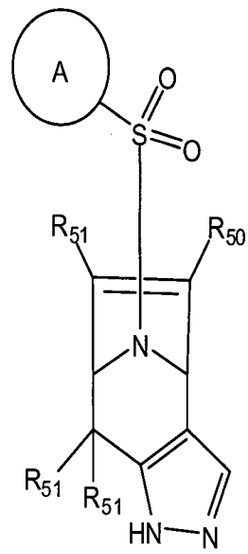
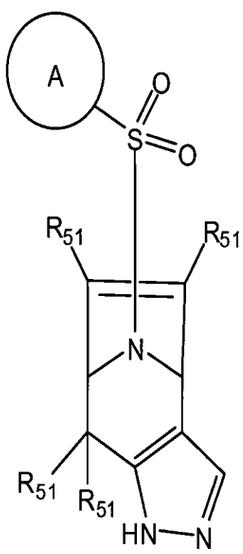
imidazolil, tiazolil, pirazolil, $-NR_{11}R_{11}$ o C_1-C_4 alcoxi. En una incorporación de este aspecto, R_{50} es fenil no - sustituido.

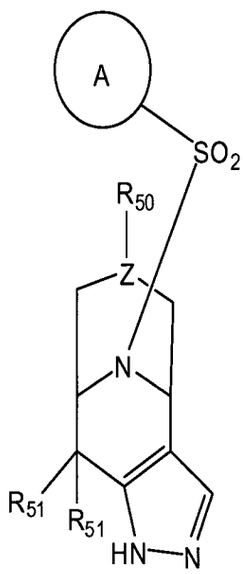
En un aspecto, los compuestos de 1b, 1c, 1d, 1e, 1f, 1g, 1h 1i son de las siguientes fórmulas, respectivamente:

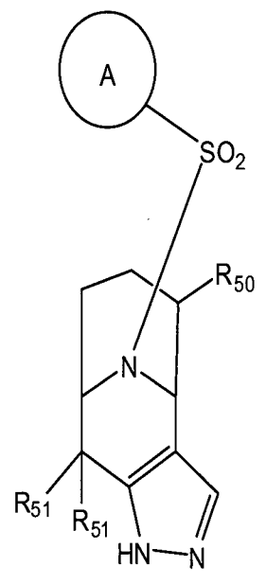












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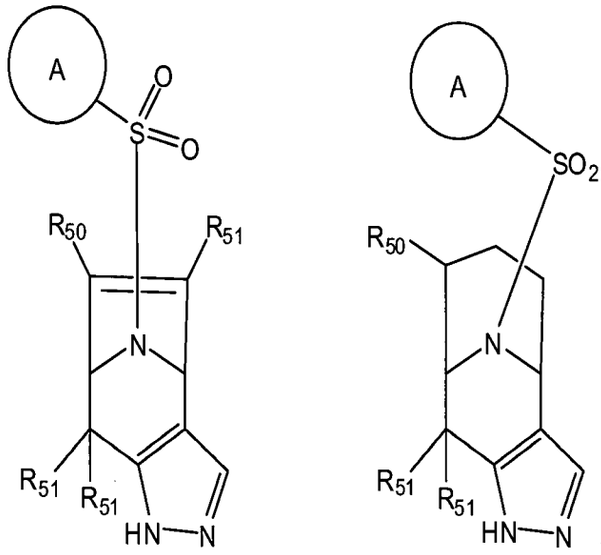

en donde R_{51} R_{50} son como fueron previamente definidos en los anteriores aspectos y/ o incorporaciones.

En otra incorporación más, R_{13} es C_1-C_4 alquilo sustituido con fenil , hidroxilo, C_1-C_6 alcoxi o halógeno , donde el fenil es opcionalmente sustituido *e.g.*, con 1 uno de 5 grupos que son independientemente halógeno , hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , C_1-C_4 haloalquilo (*e.g.*, CF_3), C_1-C_4 haloalcoxi (*e.g.*, OCF_3), CN o NO_2. En una aún más ulterior incorporación, R_{13} es C_1-C_4 alquilo sustituido con un no - sustituido fenil. En otra incorporación más, R_{13} es C_1-C_4 alquilo sustituido con fenil, que es sustituido con al menos un grupo que es independientemente halógeno , hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , CF_3, OCF_3, CN o NO_2.

En un aspecto, el compuesto de Fórmula 1 es el compuestos de Fórmula 1b.

En un aspecto, los compuestos de Fórmula 1 son los compuestos de Fórmula 1c.

En un aspecto, los compuestos de Fórmula 1 son los compuestos de Fórmula 1d.

En un aspecto, los compuestos de Fórmula 1 son los compuestos de Fórmula 1e.

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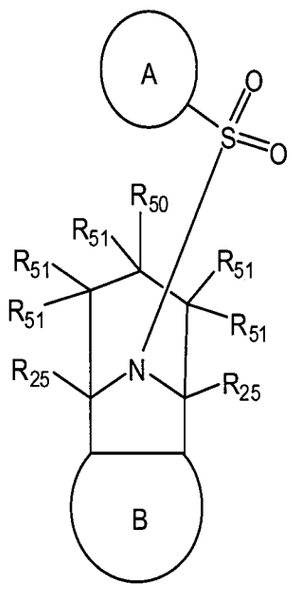
En un aspecto, los compuestos de Fórmula 1 son los compuestos de Fórmula 1f.

En un aspecto, los compuestos de Fórmula 1 son los compuestos de Fórmula 1g.

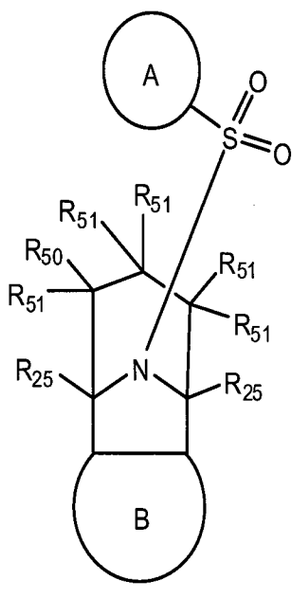
En un aspecto, los compuestos de Fórmula 1 son los compuestos de Fórmula 1h.

En un aspecto, los compuestos de Fórmula 1 son los compuestos de Fórmula 1i.

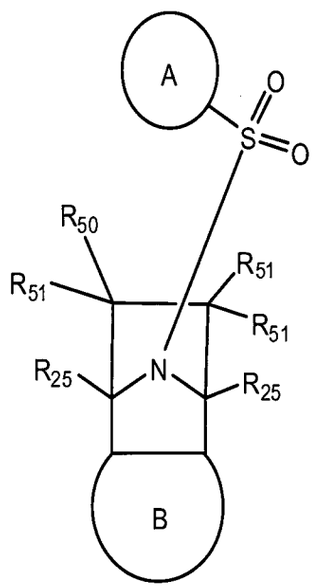
En un aspecto, aquí se proporcionan compuestos de Fórmulas 2a, 2b, 2c, 2d, 2e o 2f, *.e.*, compuestos de Fórmula 2 que tienen las siguientes fórmulas:



Fórmula 2a



Fórmula 2b



Fórmula 2c

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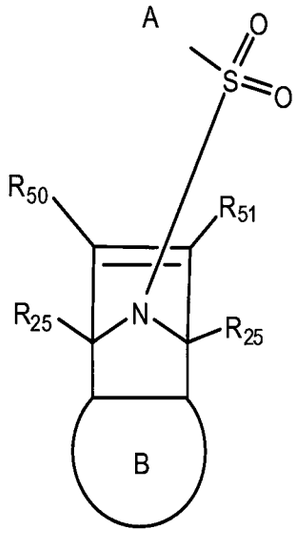
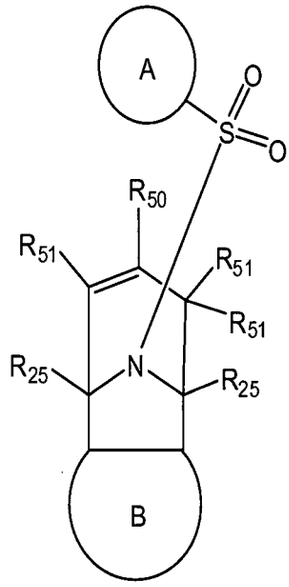
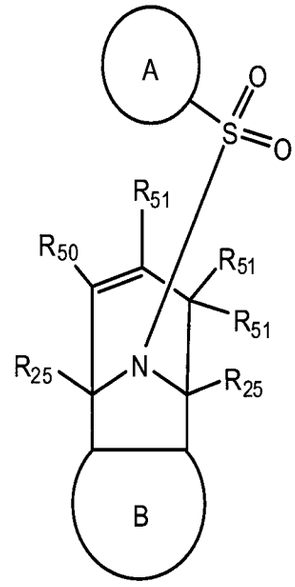


Fórmula 2d



Fórmula 2e



Fórmula 2f

incluyendo enantiómeros, farmacéuticamente aceptables sales, solvatos terede, en donde,

anillo-B es pirazolil, dihidro pirazolil, pirazolonil o pirazolidinonil, cada uno opcionalmente sustituido con $-NR_{11}$-C_2-C_6 alcanoil, C_1-C_6 alquilo , C_3-C_6 ciclo alquilo , C_2-C_4 alquenil, C_2-C_4 alquinil, C_1-C_4 alcoxi , amino, C_1-C_4 alquilo amino, C_1-C_4 dialquilo amino, hidroxi , hidroxi alquilo , halo, C_1-C_4 haloalquilo , C_1-C_4 haloalcoxi , $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ o CN;

R_{50} es oxo, $=N-NHR_{12}$ o $=N-O-R_{13}$ (excepto en las Fórmulas 2d, 2e, 2f) o R_{50} es halógeno , C_1-C_6 alquilo , C_2-C_6 alquenil, C_2-C_6 alquinil, hidroxi , hidroxi C_1-C_6 alquilo , C_1-C_6 alcoxi , C_1-C_6 haloalcoxi , C_1-C_6 haloalquilo , halo C_2-C_6 alquenil, halo C_2-C_6 alquinil, $--C(O)OR_{11}$, $-(C_1$-C_4 alquilo $)-C(O)OR_{11}$, $-CONR_{11}R_{11}$, $-OC(O)NR_{11}R_{11}$, $-NR_{11}C(O)OR_{10}$, $-NR_{11}S(O)_2R_{10}$, $-OS(O)_2R_{10}$, $-S(O)_2R_{10}$, $-NR_{11}C(O)R_{10}$, CN, $-NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, heteroaril que es seleccionado de pirazolil, tiadiazolil, triazolil, esoxazolil, esotiazolil, imidazolil, tiazolil, oxadiazolil, piridil, hetero ciclo alquilo que es seleccionado de tetra hidrodeuranil, pirrolidinil, piperidinil, morfolinil, imidazolidinil, C_3 –C_6 cicloalquilo , aril que es seleccionado de fenil naftil; en donde los antes nombrados grupos heteroaril, heterocicloalquilo , cicloalquilo aril son opcionalmente sustituidos con 1 o más grupos que son independientemente halógeno ,

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C_1-C_6 alquilo , C_2-C_6 alquenil, C_2-C_6 alquinil, hidroxi , hidroxi C_1-C_6 alquilo , C_1-C_6 alcoxi , C_1-C_6 haloalcoxi , C_1-C_6 haloalquilo , halo C_2-C_6 alquenil, halo C_2-C_6 alquinil, -C(O)OR_{11}, -(C_1-C_4 alquilo)-C(O)OR_{11}, -CO$NR_{11}R_{11}$, -OC(O)$NR_{11}R_{11}$, -NR_{11}C(O)OR_{10}, -NR_{11}S(O)$_2R_{10}$, -OS(O)$_2R_{10}$, -S(O)$_2R_{10}$, -NR_{11}C(O)R_{10}, CN, =N-NHR_{12}, -$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, heteroaril que es seleccionado de pirazolil, tiadiazolil, triazolil esoxazolil, esotiazolil, imidazolil, tiazolil, oxadiazolil, oxazolil, tetrazolil, piridil, heterocicloalquilo que es seleccionado de tetrahidrodeuranil, pirrolidinil, piperidinil, morfolinil, imidazolidinil, C_3 –C_6 cicloalquilo , aril que es seleccionado de fenil , benzo[d][1,3]dioxolil, naftil o =N-O-R_{13}; en donde los antes nombrados sustitutos heteroaril, heterocicloalquilo , cicloalquilo aril son opcionalmente sustituidos con 1 o más grupos que son independientemente halógeno , C_1-C_6 alquilo , C_1-C_6 alcoxi , hidroxi , C_1-C_6 hidroxi alquilo , C_1-C_6 haloalcoxi o C_1-C_6 haloalquilo ;

cada R_{51} está independientementeausente, H, C_1-C_4 alquilo , halógeno (*e.g.*, F, Cl o Br), CN, amino, mono alquilo amino, dialquilo amino, OH, C_1-C_4 haloalcoxi (*e.g.*, OCF_3) o C_1-C_4 haloalquilo (*e.g.*, CF_3); o cuando hay dos grupos R_{51} sobre un átomo de carbono, los dos grupos R_{51} y el carbono al que están unidos pueden formar un anillo de 3- 6-miembros cicloalquilo o heterocicloalquilo; o cuando hay dos R_{51} grupos en un carbono, los dos grupos R_{51} pueden formar un grupo oxo; o cuando hay dos grupos R_{51} en un carbono, los dos grupos R_{51} pueden formar un grupo alqueno; o cuando hay dos grupos R_{51} en un carbono, el dos grupos R_{51} pueden fomar una oxima o una alquilada C_1-C_4 oxima (*e.g.*, O- metil oxima);

un carbono no-cabeza de puente (o cualquier sustituto o sustitutos en él) en el sistema de anillos [3.3.1], [3.2.1] o [2.2.1] puede ser reemplzado con un grupo NR_{15}; siempre que en las Fórmulas 2d, 2e, 2f, R_{50} no sea oxo, =N-O-R_{13} o =N-NHR_{12};

R_{10} R_{11} en cada ocurrencia son independientemente C_1-C_6 alquilo , heteroaril que es seleccionado de pirazolil, tiadiazolil, triazolil, esoxazolil, esotiazolil, imidazolil, tiazolil, oxadiazolil, piridil o aril que es seleccionado de fenil naftil,

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donde los grupos heteroaril , aril son opcionalmente sustituidos con 1 uno a 3 grupos que son independientemente halógeno , hidroxilo, alquilo , alcoxi , haloalquilo , haloalcoxi , CN o NO_2; o si dos grupos R_{11} están en un nitrógeno, los dos grupos R_{11} junto con el nitrógeno al que están unidos, pueden formar un anillo de 3-8 miembros opcionalmenteincluyendo un adicional hetero átomo tales como NH, NR_{12}, NR_{13}, O o S, además todo R_{11} puede ser H;

R_{12} es H, C_1-C_6 alquilo , aril o $-SO_2$-aril (*e.g.*, fenil o naftil, donde fenil es preferido), donde cada grupo aril es opcionalmente sustituido con 1 uno a 5 grupos que son independientemente halógeno , hidroxilo, alquilo , alcoxi , haloalquilo , haloalcoxi , CN o NO_2;

R_{13} es H, aril o C_1-C_6 alquilo opcionalmente sustituido con aril (tales como fenil o naftil, más preferible, fenil), hidroxilo o halógeno , donde cada aril es opcionalmente sustituido con 1 uno de 5 grupos que son independientemente halógeno , hidroxilo, alquilo , alcoxi , haloalquilo , haloalcoxi , CN o NO_2. En una incorporación ulterior, R_{50} es C_2-C_6 alquenil, C_2-C_6 alquinil, halo C_2-C_6 alquenil, halo C_2-C_6 alquinil, C_2-C_6 alcanoil, $OS(O)_2R_{10}$, $-S(O)_2R_{10}$, $-NR_{11}R_{11}$,$C(O)OR_{11}C(O)OR_{11}$ $-SO_2NR_{11}R_{11}$, heteroaril que es seleccionado de pirazolil, tiadiazolil (*e.g.*, 1,2,4-tiadiazolil o 1,3,4-tiadiazolil), triazolil (*e.g.*, 1,2,3-triazolil o 1,2,4-triazolil), esoxazolil, esotiazolil, imidazolil, tiazolil, oxadiazolil (*e.g.*, 1,2,4-oxadiazolil o 1,3,4-oxadiazolil), oxazolil, tetrazolil, piridil, hetero cicloalquilo que es seleccionado de tetrahidrodeuranil, pirrolidinil, piperidinil, morfolinil, imidazolidinil, C_3 –C_6 cicloalquilo , aril que es seleccionado de fenil , benzo[d][1,3]dioxolil, naftil o $=N-O-R_{13}$; en donde los antes mencionados grupos heteroaril, heterocicloalquilo , cicloalquilo aril son opcionalmente sustituidos con 1 o más grupos que son independientemente halógeno , C_1-C_6 alquilo , C_2-C_6 alquenil, C_2-C_6 alquinil, hidroxi , hidroxi C_1-C_6 alquilo , C_1-C_6 alcoxi , C_1-C_6 haloalcoxi , C_1-C_6 haloalquilo , halo C_2-C_6 alquenil, halo C_2-C_6 alquinil, $-C(O)OR_{11}$, -(C_1-C_4 alquilo)-$C(O)OR_{11}$, $-CONR_{11}R_{11}$, $-OC(O)NR_{11}R_{11}$, $-NR_{11}C(O)OR_{10}$, $-NR_{11}S(O)_2R_{10}$, $-OS(O)_2R_{10}$, $-S(O)_2R_{10}$, $-NR_{11}C(O)R_{10}$, CN, $=N-NHR_{12}$, $-NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, heteroaril que es seleccionado de pirazolil, tiadiazolil, triazolil esoxazolil, esotiazolil, imidazolil,

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tiazolil, oxadiazolil, oxazolil, tetrazolil, piridil, hetero ciclo alquilo que es seleccionado de tetra hidro deuranil, pirrolidinil, piperidinil, morfolinil, imidazolidinil, C_3 –C_6 cicloalquilo , aril que es seleccionado de fenil , benzo[d][1,3]dioxolil, naftil o =N-O-R_{13}; en donde los antes mencionados sustitutos heteroaril, heterocicloalquilo , cicloalquilo aril son opcionalmente sustituidos con 1 o más grupos que son independientemente halógeno , C_1-C_6 alquilo , C_1-C_6 alcoxi , hidroxi , C_1-C_6 hidroxi alquilo , C_1-C_6 haloalcoxi o C_1-C_6 haloalquilo .

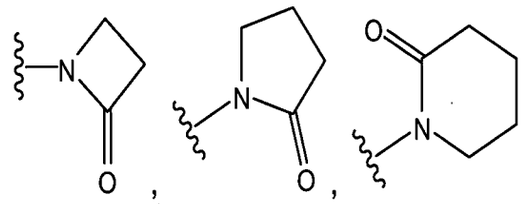
En un aspecto, aquí se proporcionan compuestos de Fórmula 2a, 2b, 2c, 2d, 2e o 2f, en donde R_{50} es halógeno , C_1-C_6 alquilo, C_2-C_6 alquenil, C_2-C_6 alquinil, hidroxi C_1-C_6 alquilo, C_1-C_6 alcoxi, C_1-C_6 haloalcoxi o C_1-C_6 haloalquilo. En una incorporación, R_{50} es halógeno , C_1-C_4 alquilo, hidroxi, hidroxi C_1-C_4 alquilo, C_1-C_4 alcoxi, C_1-C_4 halo alcoxi o C_1-C_4 halo alquilo. En otra incorporación, R_{50} es C_1-C_4 alquilo, C_1-C_4 halo alquilo, hidroxi C_1-C_4 alquilo o C_1-C_4 alcoxi. En otra incorporación, R_{50} es C_1-C_4 alquilo. En otra incorporación más, R_{50} es C_1-C_4 halo alquilo (*e.g.*, CF_3 o CH_2CF_3), hidroxi C_1-C_4 alquilo o C_1-C_4 alcoxi (*e.g.*, metoxi o etoxi). En otra incorporación, R_{50} es C_2-C_4 alquenil o C_2-C_4 alquinil. En otra incorporación, R_{50} es halógeno , hidroxi o hidroxi C_1-C_4 alquilo. En aún otra incorporación más, R_{50} es halógeno . En aún otra incorporación, R_{50} es hidroxi o hidroxi C_1-C_4 alquilo.

En un aspecto, aquí se proporcionan compuestos de Fórmula 2a, 2b, 2c, 2d, 2e o 2f, en donde R_{50} es $NR_{11}R_{11}$, o –$SO_2NR_{11}R_{11}$, o –$S(O)_2R_{10}$, o Ute said to remove the haloalkyl, CN and alkoxyalkyl groups.

oxadiazolil, opcionalmente sustituido con C_1-C_4 alquilo , o

C_3-C_6 cicloalquilo opcionalmente sustituido con C_1-C_4 alquilo o C_1-C_4 alcoxi , o

fenil opcionalmente sustituido con uno o más grupos que son independientemente C_1-C_4 alquilo , C_1-C_4 alcoxi , halógeno , -OCH_2O-, -OCH_2CH_2O-, oxazolidinona (*e.g.*, oxazolidin-2-ona), imidazolil, tiazolil, -NR_{11}-ciclohexil, donde el ciclohexil es opcionalmente sustituido con $NR_{11}R_{11}$, C_1-C_4

alquilo o C_1-C_4 alcoxi ; pirazolil, tetrazolil, pirrolidinonil, $-NR_{11}R_{11}$, morfolinil (*e.g.*, morfolin-2-onil),  o C_2-C_6 alcanoil; o

pirazolil opcionalmente sustituido con C_1-C_4 alquilo ; o

tiazolil opcionalmente sustituido con C_1-C_4 alquilo , C_1-C_4 haloalquilo (*e.g.*, CF_3 o CHF_2); o

oxazolil opcionalmente sustituido con C_1-C_4 alquilo ; o

benzimidazolil opcionalmente sustituido con C_1-C_4 alquilo , C_1-C_4 alcoxi o halógeno ; o

C_2-C_6 alquenil opcionalmente sustituido con un halógeno (*e.g.*, Cl) o C_1-C_4 halo alquilo (*e.g.*, CF_3); o

triazolil opcionalmente sustituido con uno o dos grupos que son independientemente C_1-C_4 alquilo ; o

C_2-C_6 alquinil opcionalmente sustituido con un halógeno (*e.g.*, Cl) o C_1-C_4 alcoxi ; o

tiadiazolil opcionalmente sustituido con C_1-C_4 alquilo , C_1-C_4 halo alquilo (*e.g.*, CF_3 o CHF_2); o

piridil opcionalmente sustituido con uno o más grupos que son independientemente C_1-C_4 alquilo , halógeno o C_1-C_4 alcoxi ; o

en donde R_{11} es H, C_1-C_6 alquilo o C_2-C_6 alcanoil, donde la porción alquilo de R_{11} es opcionalmente sustituida con uno o dos grupos que son independientemente $-CO_2$-(C_1-C_6 alquilo), C_1-C_6 alquilo -O-(C_1-C_6 alquilo), C_1-C_6 alquilo -O-(C_1-C_4 alquilo)-CO_2-(C_1-C_6 alquilo), C_1-C_6 alquilo -O-(C_1-C_4 alquilo)-CO_2H.

En una incorporación de este aspecto, R_{50} es C_1-C_4 haloalquilo (*e.g.*, CF_3 o CHF_2), CN, C_1-C_4 alcoxi C_1-C_6 alquilo o $NR_{11}R_{11}$; donde cada R_{11} es independientemente H o C_1-C_4 alquilo. En una incorporación ulterior, R_{50} es

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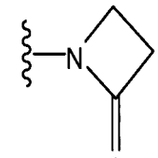
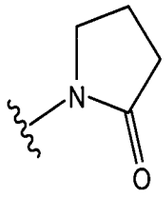
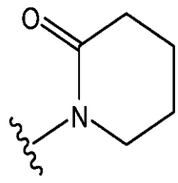
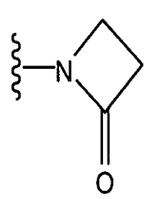
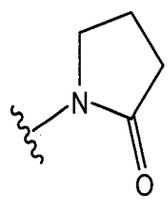
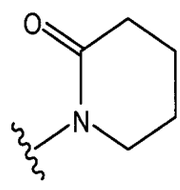
CN. En otra incorporación más, R_{50} es metoxi metil, metoxieti, etoxi metil o etoxietil.

En una incorporación de este aspecto, R_{50} es oxadiazolil, sustituido con un C_1-C_2 alquilo.

En una incorporación de este aspecto , R_{50} es fenil opcionalmente sustituido con uno o más grupos que son independientemente C_1-C_4 alquilo , C_1-C_4 alcoxi , halógeno , -OCH_2O-, -OCH_2CH_2O-, oxazolidinona (*e.g.*, oxazolidin-2-ona), imidazolil, tiazolil, -NR_{11}-ciclohexil, donde el ciclohexil es opcionalmente sustituido con $NR_{11}R_{11}$, C_1-C_4 alquilo o C_1-C_4 alcoxi ; pirazolil, tetrazolil, pirrolidinonil, -$NR_{11}R_{11}$, morfolinil (*e.g.*, morfolin-2-onil),  ,  ,  o C_2-C_6 alcanoil. En una incorporación ulterior, R_{50} es fenil no - sustituido. En otra incorporación, R_{50} es fenil sustituido con uno o más grupos que son independientemente C_1-C_4 alquilo, C_1-C_4 alcoxi o halógeno (*e.g.*, F, Cl o Br). En una incorporación ulterior, R_{50} es fenil sustituido con un grupo que es C_1-C_4 alquilo, C_1-C_4 alcoxi o halógeno (*e.g.*, F, Cl o Br). En otra incorporación, R_{50} es fenil sustituido con un grupo que es seleccionado de oxazolidinonil, imidazolil, tiazolil, pirazolil, tetrazolil, morfolinil pirrolidinonil. En otra incorporación, R_{50} es fenil sustituido con -$NR_{11}R_{11}$. En una incorporación ulterior, el grupo -$NR_{11}R_{11}$ es -$NHC(O)CH_3$, -NH-(C_1-C_4 alquilo)-CO_2-(C_1-C_4 alquilo), -NH-(C_1-C_4 alquilo)-O-(C_1-C_4 alquilo)-CO_2-(C_1-C_4 alquilo) o -NH-(C_1-C_4 alquilo)-O-(C_1-C_4 alquilo)-CO_2H. En otra incorporación, R_{50} es fenil sustituido con un grupo que es  ,  o  . En otra incorporación, R_{50} es fenil

sustituido con C_2-C_4 alcanoil. En una incorporación ulterior, el fenil es sustituido en la posición-cuatro.

En una incorporación de este aspecto, R_{50} es pirazolil opcionalmente sustituido con C_1-C_4 alquilo; tiazolil opcionalmente sustituido con C_1-C_4 alquilo (*e.g.*, metil), C_1-C_4 haloalquilo (*e.g.*, CF_3 o CHF_2); oxazolil opcionalmente sustituido con C_1-C_4 alquilo (*e.g.*, metil); triazolil opcionalmente sustituido con uno o dos grupos que son independientemente C_1-C_4 alquilo ; o benzimidazolil opcionalmente sustituido con C_1-C_4 alquilo (*e.g.*, metil), C_1-C_4 alcoxi o halógeno.

En una incorporación de este aspecto, R_{50} es C_2-C_6 alquenil opcionalmente sustituido con un halógeno (*e.g.*, Cl) o C_1-C_4 halo alquilo (*e.g.*, CF_3).

En una incorporación de este aspecto, R_{50} es C_2-C_6 alquinil opcionalmente sustituido con un halógeno (*e.g.*, Cl) o C_1-C_4 alcoxi.

En una incorporación de este aspecto, R_{50} es piridil opcionalmente sustituido con uno o más grupos que son independientemente C_1-C_4 alquilo, halógeno o C_1-C_4 alcoxi.

En otro aspecto , aquí se proporcionan compuestos de Fórmula 2a, 2b, 2c, 2d, 2e o 2f, en donde R_{50} es $-C(O)OR_{11}OR_{11}$, -(C_1-C_4 alquilo)-$C(O)OR_{11}$, $-CONR_{11}R_{11}$, $-OC(O)NR_{11}R_{11}$, $-NR_{11}C(O)OR_{10}$, $-NR_{11}S(O)_2R_{10}$, $-OS(O)_2R_{10}$, $-S(O)_2R_{10}$, $-NR_{11}C(O)R_{10}$, CN, $=N-NHR_{12}$, $-NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, o $=N-O-R_{13}$;

R_{10} R_{11} en cada ocurrencia son independientemente C_1-C_6 alquilo , heteroaril que es seleccionado de pirazolil, tiadiazolil, triazolil, esoxazolil, esotiazolil, imidazolil, tiazolil, oxadiazolil, piridil o aril que es seleccionado de fenil naftil, donde los grupos heteroaril aril son opcionalmente sustituidos con 1 uno a 3 grupos que son independientemente halógeno , hidroxilo, C_1-C_6 alquilo , C_1-C_6 alcoxi , halo C_1-C_4 alquilo , halo C_1-C_4 alcoxi , CN o NO_2; adicionalmente R_{11} puede ser H; o si dos grupos R_{11} están en un nitrógeno, los dos grupos R_{11} junto con el nitrógeno al que están unidos, pueden formar un anillo de 3-8 miembros opcionalmente incluyendo un adicional hetero átomo tal como NH, NR_{12}, NR_{13}, O o S;

R_{12} es H, C_1-C_6 alquilo , aril o $-SO_2$-aril (*e.g.*, fenil o naftil, donde fenil es preferido), donde cada aril es opcionalmente sustituido con 1 a 5 grupos que son independientemente halógeno , hidroxilo, alquilo , alcoxi , haloalquilo , haloalcoxi , CN o NO_2;

R_{13} es H, aril o C_1-C_6 alquilo opcionalmente sustituido con aril (tales como fenil o naftil, más preferible, fenil), hidroxilo o halógeno , donde cada aril es opcionalmente sustituido con 1 a 5 grupos que son independientemente halógeno , hidroxilo, alquilo , alcoxi , haloalquilo , haloalcoxi , CN o NO_2.

En una incorporación de este aspecto, R_{10} es C_1-C_4 alquilo R_{11} es independientemente hidrógeno o C_1-C_4 alquilo.

En otra incorporación más de este aspecto, R_{11} es H.

En otra incorporación de este aspecto, uno de R_{10} R_{11} es CH_3.

En otra incorporación de este aspecto, R_{11} R_{11} junto con el nitrógeno al están unidos pueden formar un anillo de 3-8 miembros, que opcionalmente incluye un adicional hetero atomo que es NH, NR_{12}, NR_{13}, O o S.

En otra incorporación de este aspecto , R_{10} R_{11} en cada ocurrencia son independientemente fenil opcionalmente sustituido con 1 a 3 grupos que son independientemente halógeno , hidroxilo, C_1-C_6 alquilo , C_1-C_6 alcoxi , halo C_1-C_4 alquilo , halo C_1-C_4 alcoxi , CN o NO_2, y adicionalmente R_{11} puede ser H.

En otra incorporación de este aspecto, R_{10} R_{11} en cada ocurrencia son independientemente pirazolil, esoxazolil, esotiazolil, imidazolil o tiazolil, cada uno opcionalmente sustituido con 1 a 3 grupos que son independientemente halógeno , hidroxilo, C_1-C_6 alquilo , C_1-C_6 alcoxi , halo C_1-C_4 alquilo , halo C_1-C_4 alcoxi , CN o NO_2, y adicionalmente R_{11} puede ser H.

En otra incorporación de este aspecto, R_{10} R_{11} en cada ocurrencia son independientemente tiadiazolil, triazolil o oxadiazolil, cada uno opcionalmente sustituido con 1 a 3 grupos que son independientemente halógeno , hidroxilo, C_1-C_6 alquilo , C_1-C_6 alcoxi , halo C_1-C_4 alquilo , halo C_1-C_4 alcoxi , CN o NO_2, y adicionalmente R_{11} puede ser H.

En aún otra incorporación más de este aspecto, R_{13} es H, C_1-C_4 alquilo o benzil, donde la porción fenil es opcionalmente sustituida con halógeno, hidroxilo, C_1-C_4 alquilo, C_1-C_4 alcoxi, CF_3 o OCF_3. En otra incorporación, R_{13} es C_1-C_4 alquilo o benzil.

En otro aspecto, aquí se proporcionan compuestos de Fórmula 2a, 2b, 2c, 2d, 2e o 2f, en donde R_{50} es $-C(O)OR_{11}$, $-CONR_{11}R_{11}$, $-OC(O)NR_{11}R_{11}$, $-NR_{11}C(O)OR_{10}$, $-NR_{11}S(O)_2R_{10}$, $-OS(O)_2R_{10}$, $-S(O)_2R_{10}$ o $-NR_{11}C(O)R_{10}$; en donde R_{10} R_{11} en cada ocurrencia son independientemente C_1-C_6 alquilo , heteroaril que es seleccionado de pirazolil, tiadiazolil, triazolil, esoxazolil, esotiazolil, imidazolil, tiazolil, oxadiazolil, piridil o aril que es seleccionado de fenil naftil, donde los grupos heteroaril aril son opcionalmente sustituidos con 1 a 3 grupos que son independientemente halógeno , hidroxilo, C_1-C_6 alquilo , C_1-C_6 alcoxi , halo C_1-C_4 alquilo , halo C_1-C_4 alcoxi , CN o NO_2; y adicionalmente R_{11} puede ser H ; o si dos R_{11} grupos están en un nitrógeno, entonces los dos grupos R_{11} junto con el nitrógeno al que están unidos pueden formar un anillo de 3-8 miembros opcionalmente incluyendo un hetero átomo adicional tal como NH, NR_{12}, NR_{13}, O o S;

R_{12} es H, C_1-C_6 alquilo , aril o $-SO_2$-aril (*e.g.*, fenil o naftil, donde fenil es preferido), donde cada grupo aril es opcionalmente sustituido con 1 a 5 grupos que son independientemente halógeno , hidroxilo, alquilo , alcoxi , haloalquilo , haloalcoxi , CN o NO_2;

R_{13} es H, aril o C_1-C_6 alquilo opcionalmente sustituido con aril (tales como fenil o naftil, más preferible, fenil), hidroxilo o halógeno , donde cada aril es opcionalmente sustituido con 1 a 5 grupos que son independientemente halógeno , hidroxilo, alquilo , alcoxi , haloalquilo , haloalcoxi , CN o NO_2.

En una incorporación de este aspecto , R_{10} es C_1-C_4 alquilo R_{11} es independientemente hidrógeno o C_1-C_4 alquilo .

En otra incorporación de este aspecto, R_{11} es H.

En otra incorporación de este aspecto, uno de R_{10} R_{11} es CH_3.

En otra incorporación de este aspecto, R_{11} R_{11} junto con el nitrógeno al que están unidos forman un anillo de 3-8 miembros, que opcionalmente incluye un adicional hetero átomo que es NH, NR_{12}, NR_{13}, O o S.

En otra incorporación de este aspecto , R_{10} R_{11} en cada ocurrencia son independientemente fenil opcionalmente sustituido con 1 a 3 grupos que son independientemente halógeno , hidroxilo, C_1-C_6 alquilo , C_1-C_6 alcoxi , halo C_1-C_4 alquilo , halo C_1-C_4 alcoxi , CN o NO_2, y adicionalmente R_{11} puede ser H;.

En otra incorporación de este aspecto , R_{10} R_{11} en cada ocurrencia son independientemente pirazolil, esoxazolil, esotiazolil, imidazolil o tiazolil, cada uno opcionalmente sustituido con 1 a 3 grupos que son independientemente halógeno , hidroxilo, C_1-C_6 alquilo , C_1-C_6 alcoxi , halo C_1-C_4 alquilo , halo C_1-C_4 alcoxi , CN o NO_2, y adicionalmente R_{11} puede ser H.

En otra incorporación de este aspecto, R_{10} R_{11} en cada ocurrencia son independientemente tiadiazolil, triazolil o oxadiazolil, cada uno opcionalmente sustituido con 1 a 3 grupos que son independientemente halógeno , hidroxilo, C_1-C_6 alquilo , C_1-C_6 alcoxi , halo C_1-C_4 alquilo , halo C_1-C_4 alcoxi , CN o NO_2, y adicionalmente R_{11} puede ser H.

En aún otra incorporación de este aspecto, R_{13} es H, C_1-C_4 alquilo o benzil, donde la porción fenil es opcionalmente sustituida con halógeno , hidroxilo, C_1-C_4 alquilo, C_1-C_4 alcoxi, CF_3 o OCF_3. En otra incorporación, R_{13} es C_1-C_4 alquilo o benzil.

En otro aspecto , aquí se proporcionan compuestos de Fórmula 2a, 2b, 2c, 2d, 2e o 2f, en donde R_{50} es heteroaril que es seleccionado de pirazolil, tiadiazolil (*e.g.*, 1,2,4-tiadiazolil o 1,3,4-tiadiazolil), triazolil (*e.g.*, 1,2,3-triazolil o 1,2,4-triazolil), esoxazolil, esotiazolil, imidazolil, tiazolil, oxadiazolil (*e.g.*, 1,2,4-oxadiazolil o 1,3,4-oxadiazolil), oxazolil, tetrazolil, piridil, hetero ciclo alquilo que es seleccionado de tetrahidrodeuranil, pirrolidinil, piperidinil, morfolinil, imidazolidinil, hetero ciclo alquilo que es seleccionado de tetrahidro deuranil, pirrolidinil, piperidinil, morfolinil, imidazolidinil, cada uno opcionalmente sustituido con 1 o

más grupos que son independientemente halógeno , C_1-C_6 alquilo , C_1-C_6 alcoxi , hidroxi , C_1-C_6 hidroxi alquilo , C_1-C_6 haloalcoxi o C_1-C_6 halo alquilo.

En una incorporación de este aspecto, R_{50} es pirazolil o imidazolil, cada uno opcionalmente sustituido con 1 o más grupos que son independientemente halógeno , C_1-C_4 alquilo, C_1-C_4 alcoxi, hidroxi, C_1-C_4 hidroxi alquilo, C_1-C_4 haloalcoxi (*e.g.*, OCF_3) o C_1-C_4 haloalquilo (*e.g.*, CF_3).

En una incorporación de este aspecto , R_{50} es tiazolil u oxadiazolil cada uno opcionalmente sustituido con 1 o más grupos que son independientemente halógeno , C_1-C_4 alquilo , C_1-C_4 alcoxi , hidroxi , C_1-C_4 hidroxi alquilo , C_1-C_4 halo alcoxi (*e.g.*, OCF_3) o C_1-C_4 halo alquilo (*e.g.*, CF_3).

En una incorporación de este aspecto, R_{50} es piridil, que es opcionalmente sustituido con 1 o más grupos que son independientemente halógeno , C_1-C_4 alquilo, C_1-C_4 alcoxi, hidroxi, C_1-C_4 hidroxi alquilo, C_1-C_4 halo alcoxi (*e.g.*, OCF_3) o C_1-C_4 halo alquilo (*e.g.*, CF_3).

En una incorporación de este aspecto, R_{50} es tiadiazolil, que es opcionalmente sustituido con 1 o más grupos que son independientemente halógeno , C_1-C_4 alquilo, C_1-C_4 alcoxi, hidroxi, C_1-C_4 hidroxi alquilo, C_1-C_4 halo alcoxi (*e.g.*, OCF_3) o C_1-C_4 halo alquilo (*e.g.*, CF_3).

En una incorporación de este aspecto, R_{50} es triazolil, que es opcionalmente sustituido con 1 o más grupos que son independientemente halógeno , C_1-C_4 alquilo, C_1-C_4 alcoxi, hidroxi, C_1-C_4 hidroxi alquilo, C_1-C_4 haloalcoxi (*e.g.*, OCF_3) o C_1-C_4 halo alquilo (*e.g.*, CF_3).

En una incorporación de este aspecto, R_{50} es esoxazolil, que es opcionalmente sustituido con 1 o más grupos que son independientemente halógeno , C_1-C_4 alquilo, C_1-C_4 alcoxi, hidroxi, C_1-C_4 hidroxi alquilo, C_1-C_4 halo alcoxi (*e.g.*, OCF_3) o C_1-C_4 halo alquilo (*e.g.*, CF_3).

En una incorporación de este aspecto, R_{50} es esotiazolil, que es opcionalmente sustituido con 1 o más grupos que son

independientemente halógeno, C_1-C_4 alquilo, C_1-C_4 alcoxi, hidroxi, C_1-C_4 hidroxi alquilo, C_1-C_4 halo alcoxi (*e.g.*, OCF_3) o C_1-C_4 halo alquilo (*e.g.*, CF_3).

En una incorporación más de este aspecto , R_{50} es seleccionado de tetrahidrodeuranil, pirrolidinil, imidazolidinil, cada uno opcionalmente sustituido con 1 o más grupos que son independientemente halógeno , C_1-C_4 alquilo , C_1-C_4 alcoxi , hidroxi , C_1-C_4 hidroxi alquilo , C_1-C_4 haloalcoxi (*e.g.*, OCF_3) o C_1-C_4 haloalquilo (*e.g.*, CF_3).

En otra incorporación de este aspecto , R_{50} es piperidinil o morfolinil, cada uno opcionalmente sustituido con 1 o más grupos que son independientemente halógeno , C_1-C_4 alquilo , C_1-C_4 alcoxi , hidroxi , C_1-C_4 hidroxi alquilo , C_1-C_4 halo alcoxi (*e.g.*, OCF_3) o C_1-C_4 halo alquilo (*e.g.*, CF_3).

En una ulterior incorporación de este aspecto, R_{50} es no - sustituido.

En una ulterior incorporación de este aspecto , R_{50} es sustituido con un grupo que es halógeno , C_1-C_2 alquilo , C_1-C_2 alcoxi , hidroxi , C_1-C_2 hidroxi alquilo , C_1-C_2 halo alcoxi (*e.g.*, OCF_3) o C_1-C_2 halo alquilo (*e.g.*, CF_3).

En otro aspecto , los que aquí se proporcionan son compuestos de Fórmula 2a, 2b, 2c, 2d, 2e o 2f, en donde R_{50} es C_3 –C_6 ciclo alquilo , que es opcionalmente sustituido con 1 o más grupos que son independientemente halógeno , C_1-C_6 alquilo , C_1-C_6 alcoxi , hidroxi , C_1-C_6 hidroxi alquilo , C_1-C_6 haloalcoxi o C_1-C_6 haloalquilo .

En una incorporación de este aspecto, R_{50} es no - sustituido C_3 –C_6 cicloalquilo.

En otra incorporación de este aspecto, R_{50} es C_3 –C_6 ciclo alquilo sustituido con uno o dos grupos que son independientemente halógeno, C_1-C_4 alquilo, C_1-C_4 alcoxi, hidroxi, C_1-C_4 hidroxi alquilo, C_1-C_4 haloalcoxi (*e.g.*, OCF_3) o C_1-C_4 halo alquilo (*e.g.*, CF_3).

En otra incorporación, R_{50} es ciclopropil, ciclopentil o ciclohexil, cada uno opcionalmente sustituido con halógeno , C_1-C_2 alquilo, C_1-C_2 alcoxi (*e.g.*,

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metoxi), hidroxi, C_1-C_2 hidroxi alquilo , C_1-C_2 haloalcoxi (*e.g.*, OCF_3) o C_1-C_2 halo alquilo (*e.g.*, CF_3).

En otra incorporación, R_{50} es ciclopropil, sustituido con un grupo que es halógeno , C_1-C_2 alquilo, C_1-C_2 alcoxi (*e.g.*, metoxi), hidroxi o C_1-C_2 hidroxi alquilo.

En otro aspecto , aquí se proporcionan compuestos de Fórmula 2a, 2b, 2c, 2d, 2e o 2f, en donde R_{50} es aril que es seleccionado de fenil , benzo[d][1,3]dioxolil, naftil, cada uno opcionalmente sustituido con uno o más grupos que son independientemente halógeno , C_1-C_6 alquilo , C_1-C_6 alcoxi , hidroxi , C_1-C_6 hidroxi alquilo , C_1-C_6 haloalcoxi o C_1-C_6 haloalquilo.

En una incorporación de este aspecto, R_{50} es fenil, que es opcionalmente sustituido con uno o más grupos que son independientemente halógeno , C_1-C_4 alquilo, C_1-C_4 alcoxi, hidroxi, C_1-C_4 hidroxi alquilo, C_1-C_4 haloalcoxi (*e.g.*, OCF_3) o C_1-C_4 haloalquilo (*e.g.*, CF_3).

En otra incorporación de este aspecto, R_{50} es fenil, que es no – sustituido.

En todavía otra incorporación más de este aspecto, R_{50} es fenil, que es sustituido con al menos un grupo que es halógeno , C_1-C_2 alquilo , C_1-C_2 alcoxi , hidroxi , C_1-C_2 hidroxi alquilo , C_1-C_2 haloalcoxi (*e.g.*, OCF_3), C_1-C_2 haloalquilo (*e.g.*, CF_3) o –CN.

En todavía otra incorporación más de este aspecto, R_{50} es fenil, que es sustituido con un grupo que es halógeno , C_1-C_2 alquilo, C_1-C_2 alcoxi, hidroxi, C_1-C_2 hidroxi alquilo, C_1-C_2 haloalcoxi (*e.g.*, OCF_3) o C_1-C_2 haloalquilo (*e.g.*, CF_3).

En una incorporación de este aspecto , R_{50} es benzo[d][1,3]dioxolil, que es opcionalmente sustituido con uno o más grupos que son independientemente halógeno , C_1-C_4 alquilo , C_1-C_4 alcoxi , hidroxi , C_1-C_4 hidroxi alquilo , C_1-C_4 haloalcoxi (*e.g.*, OCF_3) o C_1-C_4 halo alquilo (*e.g.*, CF_3). En una incorporación ulterior, el grupo metileno del grupo benzo[d][1,3]dioxolil

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es sustituido con uno o dos grupos C_1-C_4 alquilo (tales como, *e.g.*, uno o dos grupos metilo).

En otra incorporación de este aspecto, R_{50} es benzo[d][1,3]dioxolil, que es no - sustituido .

En todavía otra incorporación más de este aspecto, R_{50} es benzo[d][1,3]dioxolil, que es sustituido con al menos un grupo que es halógeno , C_1-C_2 alquilo , C_1-C_2 alcoxi , hidroxi , C_1-C_2 hidroxi alquilo , C_1-C_2 haloalcoxi (*e.g.*, OCF_3), C_1-C_2 haloalquilo (*e.g.*, CF_3) o –CN.

En todavía otra incorporación más de este aspecto, R_{50} es benzo[d][1,3]dioxolil, que es sustituido con un grupo que es halógeno , C_1-C_2 alquilo , C_1-C_2 alcoxi , hidroxi , C_1-C_2 hidroxi alquilo , OCF_3 o CF_3.

En un aspecto, los compuestos de Fórmula 2 son los compuestos de Fórmula 2a.

En un aspecto, los compuestos de Fórmula 2 son los compuestos de Fórmula 2b.

En un aspecto, los compuestos de Fórmula 2 son los compuestos de Fórmula 2c.

En un aspecto, los compuestos de Fórmula 2 son los compuestos de Fórmula 2d.

En un aspecto, los compuestos de Fórmula 2 son los compuestos de Fórmula 2e.

En un aspecto, los compuestos de Fórmula 2 son los compuestos de Fórmula 2f.

En un aspecto, aquí se proporcionan compuestos de Fórmulas 3a, 3b o 3c, y.*e.*, compuestos de Fórmula 3 teniendo las fórmulas:

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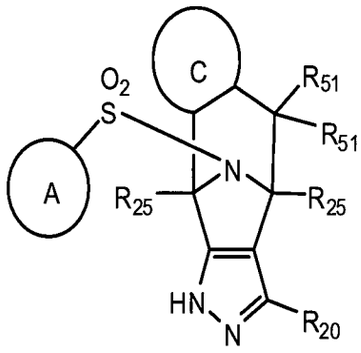
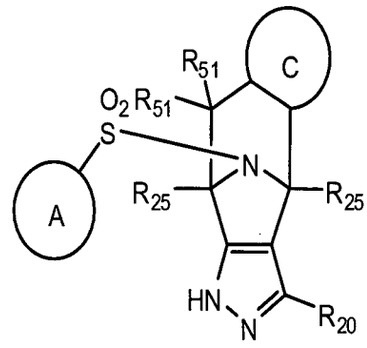
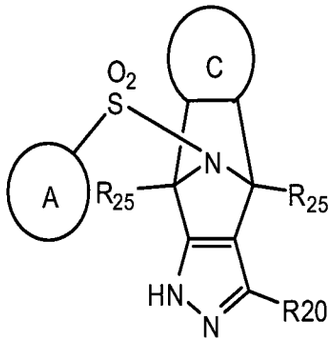


Fórmula 3a



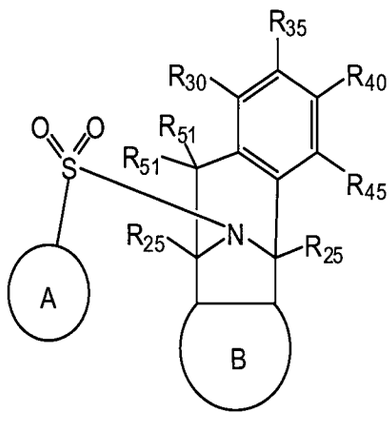
Fórmula 3b



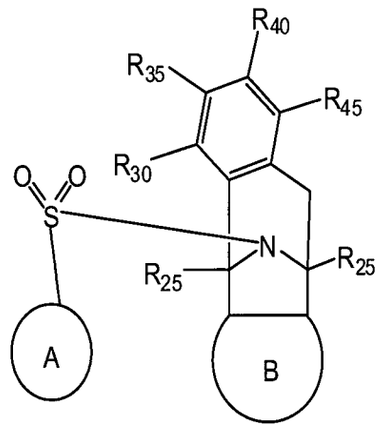
o

Fórmula 3c

En un aspecto, aquí se proporcionan compuestos de Fórmulas 3d, 3e o 3f, y.e., compuestos de Fórmula 3 que tienen las siguientes fórmulas:



,



o

Fórmula 3d

Fórmula 3e

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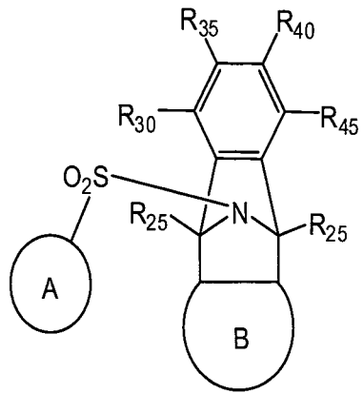

Fórmula 3f

incluyendo enantiómeros / o farmacéuticamente aceptables sales de éstos, en donde,

el anillo-A es como se define abajo;

anillo-B es pirazolil, dihidropirazolil, pirazolonil o pirazolidinonil, cada uno opcionalmente sustituido con $-NR_{11}$-C_2-C_6 alcanoil, C_1-C_6 alquilo , C_3-C_6 cicloalquilo , C_2-C_4 alquenil, C_2-C_4 alquinil, C_1-C_4 alcoxi , amino, C_1-C_4 alquilo amino, C_1-C_4 dialquilo amino, hidroxi , hidroxi alquilo , halo, C_1-C_4 haloalquilo , C_1-C_4 haloalcoxi , $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ o CN, donde

R_{10} R_{11} en cada ocurrencia son independientemente C_1-C_6 alquilo , heteroaril que es seleccionado de pirazolil, tiadiazolil, triazolil, esoxazolil, esotiazolil, imidazolil, tiazolil, oxadiazolil, piridil o aril que es seleccionado de fenil naftil, donde los grupos heteroaril aril son opcionalmente sustituidos con 1 a 3 grupos que son independientemente halógeno , hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , C_1-C_4 haloalquilo , C_1-C_4 haloalcoxi , CN o NO_2; y adicionalmente R_{11} puede ser H; o si dos R_{11} grupos están en un nitrógeno,entonces los dos grupos R_{11} junto con el nitrógeno al que están unidos, pueden formar un anillo de 3-8 miembros opcionalmente incluyendo un adicional hetero átomo tal como NH, NR_{12}, NR_{13}, O o S;

R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno , C_1-C_6 alquilo , C_2-C_6 alquenil, C_2-C_6 alquinil, C_2-C_8 halo alquenil, C_2-C_8 halo alquilonil, $-C(O)OR_{11}$, $-SO_2NR_{11}R_{11}$, aril C_1-C_6 alquilo , C_3-C_6 cicloalquilo , C_1-C_6 haloalquilo , C_1-C_6 haloalcoxi , CN, NO_2, hidroxilo, C_1-C_6 alcoxi , $-C_1$-C_6 alquilo -OH, $-C_1$-C_6 alquilo -

C_1-C_6 alcoxi , fenil oxi, -S(O_2)R_{10}, -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alcanoil, heteroaril C_1-C_6 alquilo , hetero aril, donde los grupos heteroaril son oxazolil, oxadiazolil pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil o tienil, en donde cada grupo heteroaril es opcionalmente sustituido con un grupo C_1-C_6 alquilo; hetero cicloalquilo alquilo , heterocicloalquilo , en donde los grupos heterocicloalquilo son pirrolidinil, imidazolidinil, piperidinil o morfolinil, en donde cada heterocicloalquilo es opcionalmente sustituido con uno o dos grupos que son independientemente C_1-C_6 alquilo , C_1-C_6 alcoxi o halógeno , fenil , naftil, fenil oxi, naftiloxi o fenil C_1-C_6 alquilo , donde la porción fenil de arriba es opcionalmente sustituida con uno a cinco grupos que son independientemente C_1-C_6 alquilo , C_1-C_6 alcoxi , hidroxilo, C_1-C_4 halo alquilo (*e.g.*, CF_3) o halógeno ; en donde dos adyacentes carbonos del Anillo-C opcionalmente forman un heterocicloalquilo o un anillo heteroaril, cada uno opcionalmente sustituido con 1, 2, 3 o 4 grupos que son independientemente C_1-C_4 alquilo , C_1-C_4 alcoxi , halógeno o C_2-C_4 alcanoil en donde el alcanoil es opcionalmente sustituido con hasta unos 3 átomps de halógeno; o

dos adyacentes carbonos de anillo fusionado aril forman un anillo benzo que es opcionalmente sustituido con 1 a 4 grupos que son independientemente halógeno , hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , C_1-C_4 haloalquilo , C_1-C_4 haloalcoxi , CN o NO_2; R_{51} es como se definió previamente. En una ulterior incorporación de este aspecto , R_{10} R_{11} en cada ocurrencia son independientemente C_1-C_6 alquilo , heteroaril que es seleccionado de pirazolil, tiadiazolil, triazolil, esoxazolil, esotiazolil, imidazolil, tiazolil, oxadiazolil, piridil o aril que es seleccionado de fenil naftil, donde los grupos heteroaril aril son opcionalmente sustituidos con 1 a 3 grupos que son independientemente halógeno , hidroxilo, C_1-C_6 alquilo , C_1-C_6 alcoxi , halo C_1-C_4 alquilo , halo C_1-C_4 alcoxi , CN o NO_2; y adicionalmente R_{11} puede ser H; o si dos R_{11} grupos estánen un nitrógeno, entonces los dos grupos R_{11} junto con el nitrógeno al que están unidos, pueden formar un anillo de 3-8

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miembros opcionalmente incluyendo un adicional hetero átom tal como NH, NR_{12}, NR_{13}, O o S;

R_{12} es H, C_1-C_6 alquilo , aril o $-SO_2$-aril (*e.g.*, fenil o naftil, donde fenil es preferido), donde cada grupo aril es opcionalmente sustituido con 1 a 5 grupos que son independientemente halógeno , hidroxilo, alquilo , alcoxi , haloalquilo , haloalcoxi , CN o NO_2;

R_{13} es H, aril o C_1-C_6 alquilo opcionalmente sustituido con aril (tales como fenil o naftil, más preferiblemente, fenil), hidroxilo o halógeno , donde cada aril es opcionalmente sustituido con 1 a 5 grupos que son independientemente halógeno , hidroxilo, alquilo , alcoxi , haloalquilo , haloalcoxi , CN o NO_2.

En una incorporación de este aspecto, R_{10} es C_1-C_4 alquilo R_{11} es independientemente hidrógeno o C_1-C_4 alquilo.

En otra incorporación de este aspecto, R_{11} es H.

En otra incorporación de este aspecto, uno de R_{10} R_{11} es CH_3.

En otra incorporación de este aspecto, R_{11} R_{11} junto con el nitrógeno al que están unidos pueden formar un anillo de 3-8 miembros, que opcionalmente incluye un adicional hetero átomo que es NH, NR_{12}, NR_{13}, O o S.

En otra incorporación de este aspecto , R_{10} R_{11} en cada ocurrencia son independientemente fenil opcionalmente sustituido con 1 a 3 grupos que son independientemente halógeno , hidroxilo, C_1-C_6 alquilo , C_1-C_6 alcoxi , halo C_1-C_4 alquilo , halo C_1-C_4 alcoxi , CN o NO_2; y adicionalmente R_{11} puede ser H.

En otra incorporación de este aspecto , R_{10} R_{11} en cada ocurrencia son independientemente pirazolil, esoxazolil, esotiazolil, imidazolil o tiazolil, cada uno opcionalmente sustituido con 1 a 3 grupos que son independientemente halógeno , hidroxilo, C_1-C_6 alquilo , C_1-C_6 alcoxi , halo C_1-C_4 alquilo , halo C_1-C_4 alcoxi , CN o NO_2; y adicionalmente R_{11} puede ser H.

En otra incorporación de este aspecto , R_{10} R_{11} en cada ocurrencia son independientemente tiadiazolil, triazolil o oxadiazolil, cada uno opcionalmente sustituido con 1 a 3 grupos que son independientemente halógeno , hidroxilo, C_1-C_6 alquilo , C_1-C_6 alcoxi , halo C_1-C_4 alquilo , halo C_1-C_4 alcoxi , CN o NO_2; y adicionalmente R_{11} puede ser H.

En aún otra incorporación más de este aspecto, R_{13} es H, C_1-C_4 alquilo o benzil, donde la porción fenil es opcionalmente sustituida con halógeno, hidroxilo, C_1-C_4 alquilo, C_1-C_4 alcoxi, CF_3 o OCF_3. En otra incorporación, R_{13} es C_1-C_4 alquilo o benzil.

En otro aspecto , aquí se proporcionan compuestos de Fórmulas 3a, 3b, 3c (cuando el Anillo-C es benzo sustituido con R_{30}, R_{35}, R_{40}, R_{45}) 3d, 3e / o 3f, en donde R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno , C_1-C_6 alquilo , C_2-C_6 alquenil, C_2-C_6 alquinil, C_2-C_8 halo alquenil, C_2-C_8 halo alquilonil, -C(O)OR_{11}, -$SO_2NR_{11}R_{11}$, arilalquilo , cicloalquilo , C_1-C_6 haloalquilo , C_1-C_6 haloalcoxi , CN, NO_2, hidroxilo, C_1-C_6 alcoxi , -C_1-C_3 alquilo -OH, -C_1-C_3 alquilo -C_1-C_4 alcoxi , fenil oxi, -S(O_2)R_{10}, -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alcanoil, oxazolil, oxadiazolil pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil o tienil, en donde cada grupo heteroaril es opcionalmente sustituido con un grupo C_1-C_6 alquilo, fenil o fenil C_1-C_4 alquilo , donde la porción fenil de arriba es opcionalmente sustituida con uno o más grupos que son independientemente C_1-C_6 alquilo , C_1-C_6 alcoxi , C_1-C_4 halo alquilo (*e.g.* CF_3) o halógeno .

En una incorporación de este aspecto , R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno , C_1-C_6 alquilo , hidroxilo, C_1-C_6 alcoxi , -C_1-C_3 alquilo -OH o -C_1-C_3 alquilo -alcoxi .

En una incorporación de este aspecto , R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno , C_1-C_4 alquilo , hidroxilo, C_1-C_4 alcoxi , -C_1-C_2 alquilo -OH o -C_1-C_2 alquilo - C_1-C_4 alcoxi .

En una incorporación de este aspecto, R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, C_2-C_6 alquenil, C_2-C_6 alquinil, C_2-C_6 halo alquenil o C_2-C_6

halo alquilonil. En una incorporación, laporción halo del grupo halo alquenil o halo alquilonil es F, Cl o Br.

En una incorporación de este aspecto , R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, $-C(O)OR_{11}$, $-S(O_2)R_{10}$, $-NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$ o C_2-C_6 alcanoil.

En una incorporación de este aspecto , R_{30} R_{35} o R_{35} R_{40} o R_{40} R_{45} son $-OCH_2O-$ o $-OCH_2CH_2O-$ en donde cada metileno de $-OCH_2O-$ o $-OCH_2CH_2O-$ es opcionalmente sustituido con uno o dos grupos C_1-C_4 alquilo.

En otra incorporación de este aspecto, R_{11} es H.

En otra incorporación de este aspecto, uno de R_{10} R_{11} es CH_3.

En otra incorporación de este aspecto, R_{11} R_{11} junto con el nitrógeno al que están unidos forman un anillo de 3-8 miembros, que opcionalmente incluye un adicional hetero átomo que es NH, NR_{12}, NR_{13}, O o S.

En otra incorporación de este aspecto , R_{10} R_{11} en cada ocurrencia son independientemente fenil opcionalmente sustituidos con 1 a 3 grupos que son independientemente halógeno , hidroxilo, C_1-C_6 alquilo , C_1-C_6 alcoxi , halo C_1-C_4 alquilo , halo C_1-C_4 alcoxi , CN o NO_2; y adicionalmente R_{11} puede ser H.

En otra incorporación de este aspecto , R_{10} R_{11} en cada ocurrencia son independientemente pirazolil, esoxazolil, esotiazolil, imidazolil o tiazolil, cada uno opcionalmente sustituido con 1 a 3 grupos que son independientemente halógeno , hidroxilo, C_1-C_6 alquilo , C_1-C_6 alcoxi , halo C_1-C_4 alquilo , halo C_1-C_4 alcoxi , CN o NO_2; y adicionalmente R_{11} puede ser H.

En otra incorporación de este aspecto , R_{10} R_{11} en cada ocurrencia son independientemente tiadiazolil, triazolil o oxadiazolil, cada uno opcionalmente sustituido con 1 a 3 grupos que son independientemente halógeno , hidroxilo, C_1-C_6 alquilo , C_1-C_6 alcoxi , halo C_1-C_4 alquilo , halo C_1-C_4 alcoxi , CN o NO_2 y adicionalmente R_{11} puede ser H.

En otro aspecto , aquí se proporcionan compuestos de Fórmulas 3a, 3b, 3c (cuando el Anillo-C es benzo sustituido con R_{30}, R_{35}, R_{40}, R_{45}), 3d, 3e y/ o 3f, en donde R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno , C_1-C_4 alquilo , $-C(O)OR_{11}$, $-S(O_2)R_{10}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$ - $NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ o $-O-C(O)NR_{11}R_{11}$.

En una incorporación de este aspecto , al menos dos de R_{30}, R_{35}, R_{40}, R_{45} son H, mientras otro es H, halógeno o C1-C4 alquilo , el otro es $-C(O)OR_{11}$, $-S(O_2)R_{10}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ o $-O-C(O)NR_{11}R_{11}$.

En una incorporación de este aspecto , tres de R_{30}, R_{35}, R_{40}, R_{45} son H, mientras el otro es $-C(O)OR_{11}$, $-S(O_2)R_{10}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ o $-O-C(O)NR_{11}R_{11}$.

En otra incorporación de este aspecto, tres de R_{30}, R_{35}, R_{40}, R_{45} son H, mientras el otro es $-NR_{11}R_{11}$.

En otra incorporación de este aspecto, tres de R_{30}, R_{35}, R_{40}, R_{45} son H, mientras el otrao es $-C(O)OR_{11}$.

En una incorporación de este aspecto , tres de R_{30}, R_{35}, R_{40}, R_{45} son H, mientras el otro es $-C(O)NR_{11}R_{11}$ o $-NR_{11}C(O)R_{10}$.

En otra incorporación de este aspecto, tres de R_{30}, R_{35}, R_{40}, R_{45} son H, mientras el otro es $-O-C(O)NR_{11}R_{11}$.

En otra incorporación más de este aspecto , dos de R_{30}, R_{35}, R_{40}, R_{45} son H, mientras uno es metil el otro es $-NR_{11}R_{11}$ o $-C(O)NR_{11}R_{11}$.

En otra incorporación de este aspecto , al menos dos de R_{30}, R_{35}, R_{40}, R_{45} son H, uno de R_{30}, R_{35}, R_{40}, R_{45} es H o metil el otro es $-NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$ o $-NR_{11}SO_2R_{10}$.

En una incorporación de este aspecto , tres de R_{30}, R_{35}, R_{40}, R_{45} son H, mientras el otro es $-C(O)NR_{11}R_{11}$ o $-NR_{11}C(O)R_{10}$.

En otra incorporación de este aspecto, tres de R_{30}, R_{35}, R_{40}, R_{45} son H, mientras el otro es $-O-C(O)NR_{11}R_{11}$.

En otra incorporación de este aspecto , dos de R_{30}, R_{35}, R_{40}, R_{45} son H, mientras uno es metil el otro es $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$ o $-NR_{11}C(O)R_{10}$.

En una incorporación de este aspecto, tres de R_{30}, R_{35}, R_{40}, R_{45} son H, mientras el otro es $-C(O)OR_{11}$. En una incorporación ulterior, R_{11} es H o C_1-C_4 alquilo.

En otro aspecto, aquí se proporcionan compuestos de Fórmulas 3a, 3b, 3c (cuando el Anillo-C es benzo sustituido con R_{30}, R_{35}, R_{40}, R_{45}), 3d, 3e y/ o 3f, en donde R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno , C_1-C_4 alquilo , C_1-C_4 alcoxi , fenil oxi, C_2-C_6 alcanoil, oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil, tienil, fenil o fenil C_1-C_4 alquilo , donde la porción fenil de arriba es opcionalmente sustituida con uno o más grupos que son independientemente C_1-C_6 alquilo , C_1-C_6 alcoxi , C_1-C_4 halo alquilo (*e.g.* CF_3) o halógeno.

En otra incorporación de este aspecto, al menos dos de R_{30}, R_{35}, R_{40}, R_{45} son H.

En otra incorporación de este aspecto, tres de R_{30}, R_{35}, R_{40}, R_{45} son H.

En una otra incorporación de este aspecto, R_{30}, R_{35}, R_{40}, R_{45} son H.

En otra incorporación de este aspecto, al menos uno de R_{30}, R_{35}, R_{40}, R_{45} es un halógeno (*e.g.*, F, Cl o Br). En otra incorporación, al menos dos de R_{30}, R_{35}, R_{40}, R_{45} es un halógeno (*e.g.*, F, Cl o Br), donde el halógeno puede ser el mismo o diferente.

En aún otra incorporación más de este aspecto , R_{30} R_{45} son H; R_{35} R_{40} son independientemente halógeno , C_1-C_4 alquilo , C_1-C_4 alcoxi o C_2-C_6 alcanoil.

En otra incorporación de este aspecto , R_{30} R_{45} son H; R_{35} R_{40} son independientemente halógeno , C_1-C_4 alquilo , C_1-C_4 alcoxi , C_2-C_6 alcanoil, fenil oxi, fenil o fenil C_1-C_4 alquilo , donde la porción fenil de arriba es opcionalmente sustituida con uno o más grupos que son independientemente C_1-C_6 alquilo , C_1-C_6 alcoxi , C_1-C_4 halo alquilo (*e.g.* CF_3) o halógeno .

En otra incorporación de este aspecto , R_{30} R_{45} son H; R_{35} R_{40} son independientemente halógeno , C_1-C_4 alquilo , C_1-C_4 alcoxi , C_2-C_6 alcanoil, oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil o tienil.

En aún otra incorporación más de este aspecto , R_{35} R_{40} son H; R_{30} R_{45} son independientemente halógeno , C_1-C_4 alquilo , C_1-C_4 alcoxi o C_2-C_6 alcanoil.

En todavía otra incorporación de este aspecto , R_{35} R_{40} son H; R_{30} R_{45} son independientemente halógeno , C_1-C_4 alquilo , C_1-C_4 alcoxi , C_2-C_6 alcanoil, fenil oxi, fenil o fenil C_1-C_4 alquilo , donde la porción fenil de arriba es opcionalmente sustituida con uno o más grupos que son independientemente C_1-C_6 alquilo , C_1-C_6 alcoxi , C_1-C_4 halo alquilo (*e.g.* CF_3) o halógeno.

En otra incorporación de este aspecto , R_{35} R_{40} son H; R_{30} R_{45} son independientemente halógeno , C_1-C_4 alquilo , C_1-C_4 alcoxi , C_2-C_6 alcanoil, oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil o tienil.

En otro aspecto , aquí se proporcionan compuestos de Fórmulas 3a, 3b, 3c (cuando el Anillo-C es benzo sustituido con R_{30}, R_{35}, R_{40}, R_{45}), 3d, 3e y / o 3f, en donde R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno , C_1-C_4 alquilo , C_1-C_4 alcoxi , C_2-C_6 alcanoil; siempre que dos adyacentes carbonos del anillo aril fusionado (el anillo en el que los grupos R_{30}, R_{35}, R_{40} R_{45} son unidos) opcionalmente forman un heterocicloalquilo o un anillo heteroaril, cada uno opcionalmente sustituido con 1, 2, 3 o 4 grupos que son independientemente C_1-C_4 alquilo , C_1-C_4 alcoxi , halógeno o C_1-C_4 alcanoil en

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donde el grupo alcanoil es opcionalmente sustituido con hasta 3 átomos de halógeno.

En una incorporación de este aspecto, el anillo heterociclo alquilo es piperidinil, pirrolidinil o morfolinil, el anillo heteroaril es pirazolil, imidazolil o piridinil, en donde cada grupo heterociclo alquilo o hetero aril es opcionalmente sustituido con 1, 2, 3 ó 4 grupos que son independientemente C_1-C_4 alquilo , C_1-C_4 alcoxi , halógeno o C_1-C_4 alcanoil en donde el grupo alcanoil es opcionalmente sustituido con hasta 3 átomos halógeno.

En una incorporación de este aspecto, el anillo heterocicloalquilo es piperidinil o pirrolidinil, cada uno opcionalmente sustituido con 1 o 2 grupos que son independientemente C_1-C_4 alquilo , C_1-C_4 alcoxi , halógeno o C_2-C_4 alcanoil en donde el alcanoil grupo es opcionalmente sustituido con hasta 3 átomos halógeno.

En una incorporación de este aspecto , el anillo heteroaril es pirazolil, imidazolil o piridinil, cada uno opcionalmente sustituido con 1 o 2 grupos que son independientemente C_1-C_4 alquilo , C_1-C_4 alcoxi , halógeno o C_2-C_4 alcanoil en donde el grupo alcanoil es opcionalmente sustituido con hasta 3 átomos halógeno.

En otro aspecto , aquí se proporcionan compuestos de Fórmulas 3a, 3b, 3c (cuando el Anillo-C es benzo sustituido con R_{30}, R_{35}, R_{40}, R_{45}), 3d, 3e y/ o 3f, en donde R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno , C_1-C_4 alquilo , C_1-C_4 alcoxi , C_2-C_6 alcanoil, C_2-C_8 alquenil, C_2-C_8 alquinil, C_2-C_8 halo alquenil o C_2-C_8 halo alquilonil; provisto que dos adyacentes carbonos del anillo aril fusionado forman un anillo benzo, que es opcionalmente sustituido con 1 a 4 grupos que son independientemente halógeno , hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , C_1-C_4 haloalquilo , C_1-C_4 haloalcoxi , CN o NO_2. En un ulterior aspecto, el anillo benzo es no - sustituido.

En una incorporación más de este aspecto , R_{30} R_{45} son independientemente H, halógeno , hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , R_{35}, R_{40}, los carbonos unidos forman una anillo benzo, que es opcionalmente

sustituido con 1 a 4 grupos que son independientemente halógeno , hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , C_1-C_4 haloalquilo , C_1-C_4 haloalcoxi , CN o NO_2. En una incorporación ulterior, el anillo benzo es no - sustituido.

En una incorporación de este aspecto , R_{30} R_{35} son independientemente H, halógeno , hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , R_{40}, R_{45}, los carbonos a que están unidos forman un anillo benzo, que es opcionalmente sustituido con 1 a 4 grupos que son independientemente halógeno , hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , C_1-C_4 haloalquilo , C_1-C_4 haloalcoxi , CN o NO_2. En una incorporación ulterior, el anillo benzo es no - sustituido.

En una incorporación de este aspecto , R_{40} R_{45} son independientemente H, halógeno , hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , R_{30}, R_{35}, los carbonos a los que están unidos forman un anillo benzo, que es opcionalmente sustituido con 1 a 4 grupos que son independientemente halógeno , hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , C_1-C_4 haloalquilo , C_1-C_4 haloalcoxi , CN o NO_2. En una incorporación ulterior, el anillo benzo es no - sustituido.

En un aspecto , aquí se proporcionan compuestos de Fórmulas 3a, 3b, y / o 3c, en donde el Anillo-C es heteroaril o heterocicloalquilo que es opcionalmente sustituido con uno o más grupos que son independientemente halógeno , C_1-C_6 alquilo , C_1-C_6 haloalquilo , C_1-C_6 haloalcoxi , C_2-C_8 alquenil, C_2-C_8 alquinil, C_2-C_8 halo alquenil, C_2-C_8 halo alquilonil, -C(O)OR_{11}, CN, hidroxilo, C_1-C_6 alcoxi , -C_1-C_6 alquilo -OH, -C_1-C_6 alquilo -C_1-C_6 alcoxi , ariloxi (*e.g.*, fenil oxi), -S(O_2)R_{10}, -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alcanoil, oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil, tienil, fenil o fenil C_1-C_4 alquilo , en donde la porción fenil de arriba es opcionalmente sustituida *e.g.*, con uno o más grupos que son independientemente C_1-C_6 alquilo , C_1-C_6 alcoxi , C_1-C_4 haloalquilo (*e.g.* CF_3), C_1-C_4 haloalcoxi (*e.g.* OCF_3), hidroxilo, CN, NO_2 o halógeno ; en donde cada R_{11} es independientemente C_1-C_6 alquilo , heteroaril que es seleccionado de pirazolil,

tiadiazolil, triazolil, esoxazolil, esotiazolil, imidazolil, tiazolil, oxadiazolil, piridil o aril que es seleccionado de fenil naftil, donde los grupos heteroaril aril son opcionalmente sustituidos con 1 a 3 grupos que son independientemente halógeno , hidroxilo, alquilo , alcoxi , haloalquilo , haloalcoxi , CN o NO_2; o si dos grupos R_{11} están en un nitrógeno, los dos grupos R_{11} junto con el nitrógeno al que están unidos, pueden formar un anillo de 3-8 miembros opcionalmente incluyendo un adicional hetero átom tal como NH, NR_{12}, NR_{13}, O o S; y adicionalmente R_{11} puede ser H.

En una incorporación de este aspecto , el Anillo-C es heteroaril o heterocicloalquilo que es opcionalmente sustituido con uno o más grupos que son independientemente C_1-C_4 alquilo , C_1-C_4 alcoxi , halógeno , C_1-C_4 haloalquilo (*e.g.* CF_3) o C_1-C_4 haloalcoxi (*e.g.*, OCF_3); R_{51} es como se definió previamente, n es 0 o 1. This is Ute's formula (IIf)

En una incorporación más de este aspecto , el Anillo-C es heteroaril o heterocicloalquilo que es opcionalmente sustituido con uno o más grupos que son independientemente C_1-C_4 alquilo , C_1-C_4 alcoxi , halógeno , $-S(O_2)R_{10}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$ o $-C(O)OR_{11}$.

En una incorporación de este aspecto , el Anillo-C es heteroaril o heterocicloalquilo que es opcionalmente sustituido con uno o más grupos que son independientemente C_1-C_4 alquilo , halógeno , C_2-C_8 alquenil, C_2-C_8 alquinil, C_2-C_8 halo alquenil, C_2-C_8 halo alquilonil o $-C(O)OR_{11}$.

En una incorporación de este aspecto, el Anillo-C es un anillo piridil opcionalmente sustituido con uno o más grupos que son independientemente C_1-C_4 alquilo , C_1-C_4 alcoxi , halógeno , C_1-C_4 haloalquilo (*e.g.* CF_3) o C_1-C_4 haloalcoxi (*e.g.*, OCF_3). En una incorporación ulterior, el Anillo-C es un anillo no - sustituido piridil.

En una incorporación de este aspecto , el Anillo-C es un anillo piridil sustituido con uno o dos grupos que son independientemente C_1-C_4

alquilo , halógeno , C_2-C_8 alquenil, C_2-C_8 alquinil, C_2-C_8 halo alquenil, C_2-C_8 halo alquilonil o -C(O)OR_{11}, donde R_{11} es H o C_1-C_6 alquilo .

En una incorporación de este aspecto, el Anillo-C es un anillo tiazolil opcionalmente sustituido con uno o más grupos que son independientemente C_1-C_4 alquilo , C_1-C_4 alcoxi , halógeno , C_1-C_4 haloalquilo (*e.g.* CF_3) o C_1-C_4 haloalcoxi (*e.g.*, OCF_3). En una incorporación ulterior, el Anillo-C es un anillo no - sustituido tiazolil.

En una incorporación de este aspecto , el Anillo-C es un anillo tiazolil sustituido con un grupo que es C_1-C_4 alquilo , halógeno , C_2-C_8 alquenil, C_2-C_8 alquinil, C_2-C_8 halo alquenil, C_2-C_8 halo alquilonil o -C(O)OR_{11}, donde R_{11} es H o C_1-C_6 alquilo .

En una incorporación de este aspecto, el Anillo-C es un anillo pirazolil opcionalmente sustituido con uno o más grupos que son independientemente C_1-C_4 alquilo, C_1-C_4 alcoxi , halógeno , C_1-C_4 haloalquilo (*e.g.* CF_3) o C_1-C_4 haloalcoxi (*e.g.*, OCF_3). En una incorporación ulterior, el Anillo-C es un anillo no - sustituido pirazolil.

En una incorporación de este aspecto , el Anillo-C es un anillo pirazolil sustituido con un grupo que es C_1-C_4 alquilo , halógeno , C_2-C_8 alquenil, C_2-C_8 alquinil, C_2-C_8 halo alquenil, C_2-C_8 halo alquilonil o -C(O)OR_{11}, donde R_{11} es H o C_1-C_6 alquilo .

En una incorporación de este aspecto, el Anillo-C es un anillo tienil opcionalmente sustituido con uno o más grupos que son independientemente C_1-C_4 alquilo, C_1-C_4 alcoxi, halógeno , C_1-C_4 haloalquilo (*e.g.* CF_3) o C_1-C_4 haloalcoxi (*e.g.*, OCF_3). En una incorporación ulterior, el Anillo-C es un no - sustituido anillo tienil.

En una incorporación de este aspecto , el Anillo-C es un anillo tienil sustituido con un grupo que es C_1-C_4 alquilo , halógeno , C_2-C_8 alquenil, C_2-C_8 alquinil, C_2-C_8 halo alquenil, C_2-C_8 halo alquilonil o -C(O)OR_{11}, donde R_{11} es H o C_1-C_6 alquilo .

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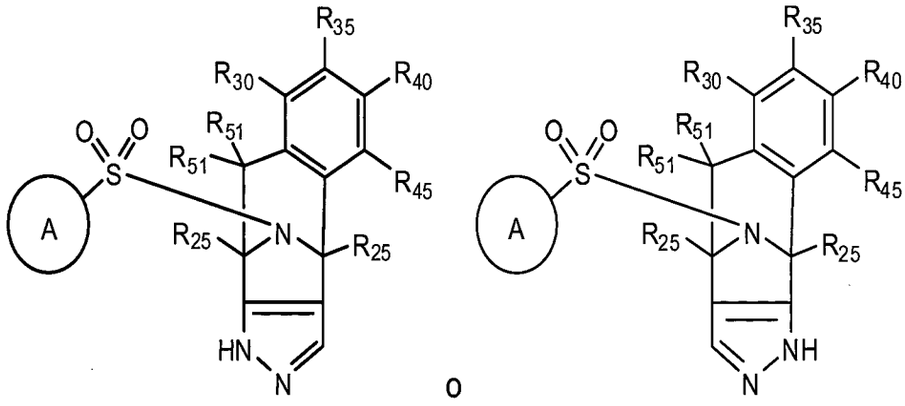
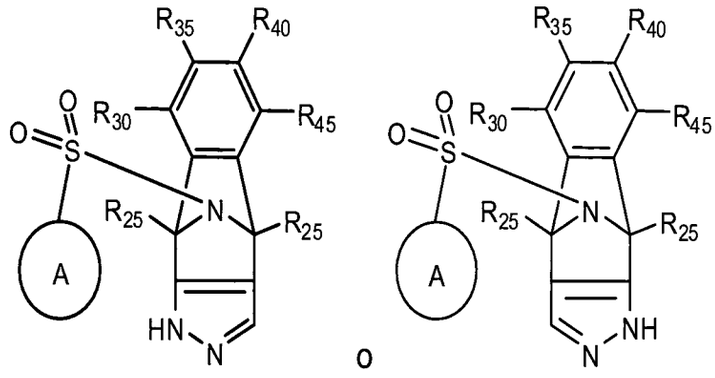
En un aspecto, los compuestos de Fórmula 3 son los compuestos de Fórmula 3a. En una incorporación ulterior, los compuestos de Fórmula 3a son de la fórmula:



donde R_{25}, R_{30}, R_{35}, R_{40}, R_{45}, R_{51} son como se describe arriba y el anillo-A es como aquí se describe.

En un aspecto, los compuestos de Fórmula 3 son los compuestos de Fórmula 3b. En una incorporación ulterior, los compuestos de Fórmula 3a son de la fórmula:



donde R_{25}, R_{30}, R_{35}, R_{40}, R_{45}, R_{51} son como se describe arriba y el anillo-A es como aquí se describe.

En un aspecto, los compuestos de Fórmula 3 son los compuestos de Fórmula 3a.

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En uno aspecto, los compuestos de Fórmula 3 son los compuestos de Fórmula 3b.

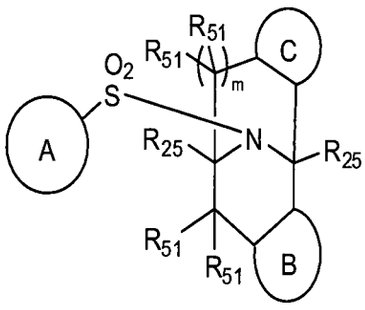
En un aspecto, el compuestos de Fórmula 3 son los compuestos de Fórmula 3c.

En un aspecto, los compuestos de Fórmula 3 son los compuestos de Fórmula 3d.

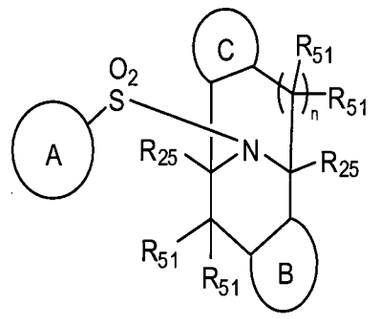
En un aspecto, los compuestos de Fórmula 3 son los compuestos de Fórmula 3e.

En un aspecto, los compuestos de Fórmula 3 son los compuestos de Fórmula 3f.

En un aspecto, aquí se proporcionan compuestos de Fórmulas 4a / o 4b, y.e., compuestos de Fórmula 4 teniendo las fórmulas:



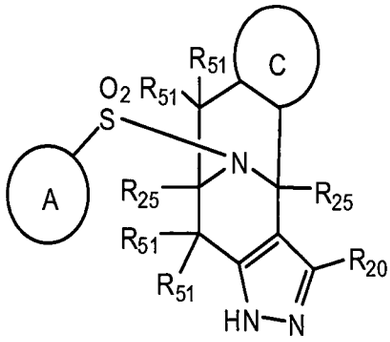
Fórmula 4a

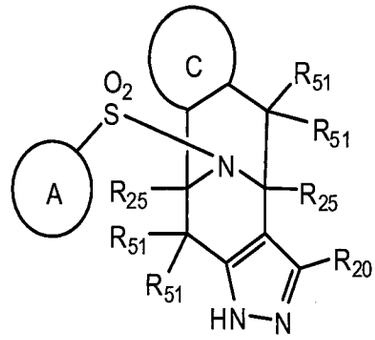


Fórmula 4b

En donde el anillo-A, anillo-B, Anillo-C, R_{25}, R_{51}, m n son como se define arriba para la Fórmula 4.

En otro aspecto , aquí se proporcionan compuestos de Fórmulas 4c y/ o 4d, y.e., compuestos de Fórmula 4 teniendo las fórmulas:

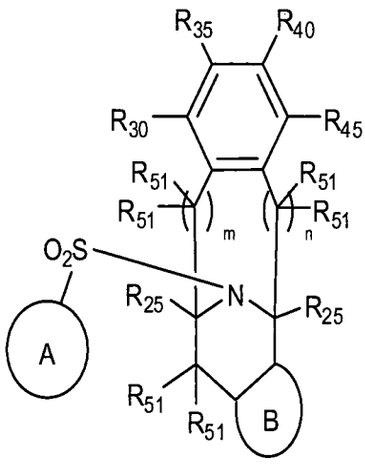




Fórmula 4c Fórmula 4d

En donde el Anillo-A, Anillo-C, R_{20}, R_{25}, R_{51} son como se define arriba.

En un aspecto, aquí se proporcionan compuestos de Fórmulas 4e, y.*e.*, compuestos de Fórmula 4 que tienen la siguiente fórmula:



En donde el Anillo-A, anillo-B, R_{20}, R_{25}, R_{30}, R_{35}, R_{40}, R_{45}, R_{51}, m n son como se define arriba.

En uno aspecto, aquí se proporcionan son compuestos de Fórmulas 4f / o 4g, .*e.*, compuestos de Fórmula 4 que tienen las siguientes fórmulas:

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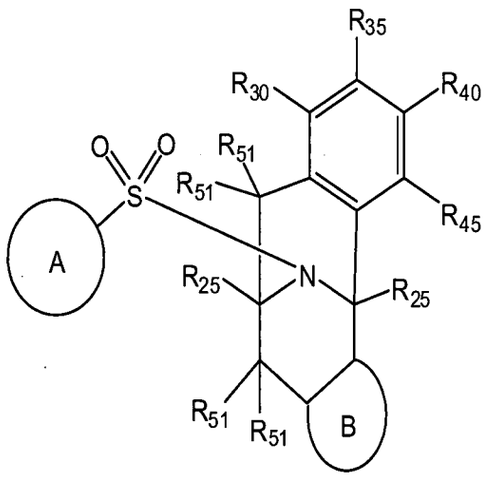
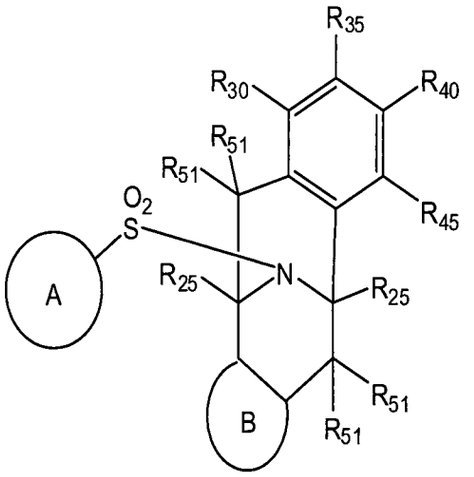


Fórmula 4f



Fórmula 4g

incluyendo enantiómeros y / o farmacéuticamente aceptables sales de éstos, en donde,

anillo-B es pirazolil, dihidropirazolil, pirazolonil o pirazolidinonil, cada uno opcionalmente sustituido con $-NR_{11}$-C_2-C_6 alcanoil, C_1-C_6 alquilo , C_3-C_6 cicloalquilo , C_2-C_4 alquenil, C_2-C_4 alquinil, C_1-C_4 alcoxi , amino, C_1-C_4 alquilo amino, C_1-C_4 dialquilo amino, hidroxi , hidroxi alquilo , halo, C_1-C_4 haloalquilo , C_1-C_4 haloalcoxi , $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ o CN;

R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno , C_1-C_6 alquilo , C_2-C_6 alquenil, C_2-C_6 alquinil, C_2-C_8 halo alquenil, C_2-C_8 halo alquilonil, $-C(O)OR_{11}$, $-SO_2NR_{11}R_{11}$, aril C_1-C_6 alquilo , C_3-C_6 cicloalquilo , C_1-C_6 haloalquilo , C_1-C_6 haloalcoxi , CN, NO_2, hidroxilo, C_1-C_6 alcoxi , -C_1-C_6 alquilo -OH, -C_1-C_6 alquilo -C_1-C_6 alcoxi , fenil oxi, $-S(O_2)R_{10}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, heteroaril C_1-C_6 alquilo , heteroaril, donde los grupos heteroaril son oxazolil, oxadiazolil pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil o tienil, en donde cada heteroaril es opcionalmente sustituido con un grupo C_1-C_6 alquilo; heterocicloalquilo alquilo , heterocicloalquilo , en donde los grupos heterocicloalquilo son pirrolidinil, imidazolidinil, piperidinil o morfolinil, en donde cada grupo heterocicloalquilo es opcionalmente sustituido con uno o dos grupos que son independientemente C_1-C_6 alquilo , C_1-C_6 alcoxi o halógeno , fenil , naftil, fenil oxi, naftiloxi o fenil C_1-C_6 alquilo , donde la porción fenil de arriba es

opcionalmente sustituida con uno a cinco grupos que son independientemente C_1-C_6 alquilo , C_1-C_6 alcoxi , hidroxilo, C_1-C_4 halo alquilo (*e.g.*, CF_3) o halógeno;

en donde dos adyacentes carbonos del anillo fusinado aril opcionalmente forman un anillo heterocicloalquilo (*e.g.*, $-OCH_2O-$ o $-OCH_2CH_2O-$) o un anillo heteroaril , cada uno opcionalmente sustituido con 1, 2, 3 o 4 grupos que son independientemente C_1-C_4 alquilo , C_1-C_4 alcoxi , halógeno o C_2-C_4 alcanoil en donde el grupo alcanoil es opcionalmente sustituido con hasta 3 átomos halógeno; o

dos adyacentes carbonos del anillo aril fusionado forman un anillo benzo que es opcionalmente sustituido con 1 a 4 grupos que son independientemente halógeno , hidroxilo, C_1-C_4alquilo , C_1-C_4 alcoxi , C_1-C_4 haloalquilo , C_1-C_4 haloalcoxi , CN o NO_2;

cada R_{51} está independientemente ausente, H, C_1-C_4 alquilo , halógeno (*e.g.*, F, Cl o Br), CN, amino, mono alquilo amino, dialquilo amino, OH, C_1-C_4 haloalcoxi (*e.g.*, OCF_3) o C_1-C_4 haloalquilo (*e.g.*, CF_3); o cuando hay dos grupos R_{51} en unátomo de carbono atom, los dos grupos R_{51} y el carbon al que están unidos pueden formar un anillo de 3- a 6-miembros cicloalquilo o heterocicloalquilo; o cuando hay dos grupos R_{51} en un carbono, los dos grupos R_{51} pueden formar un grupo oxo; o cuando hay dos grupos R_{51} en un carbon, los dos grupos R_{51} pueden formar un grupo alqueno; o cuando hay dos grupos R_{51} en un carbono, los dos grupos R_{51} pueden formar una oxima o una oxima C_1-C_4 alquilada (*e.g.*, O- metil oxima);

un no-cabeza –de- puente carbono (cualquier sustituto o sustitutos en él) en el sistema de anillos [3.3.1], [3.2.1] o [2.2.1] puede ser reeplazadocon un grupo NR_{15};

R_{10} y R_{11} en cada ocurrencia son independientemente C_1-C_6 alquilo , heteroaril que es seleccionado de pirazolil, tiadiazolil, triazolil, esoxazolil, esotiazolil, imidazolil, tiazolil, oxadiazolil, piridil o aril que es seleccionado de fenil naftil, donde los grupos heteroaril aril son opcionalmente sustituidos con 1 a 3

grupos que son independientemente halógeno , hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , C_1-C_4 haloalquilo , C_1-C_4 haloalcoxi , CN o NO_2; y adicionalmente R_{11} puede ser H; o si dos grupos R_{11} están en un nitrógeno, los dos grupos R_{11} junto con el nitrógeno al que están unidos, pueden formar un anillo de 3-8 miembros opcionalmente incluyendo un adicional hetero átomo tal como NH, NR_{12}, NR_{13}, O o S. En una incorporación de este aspecto , el anillo-B es pirazolil, que es opcionalmente sustituido con C_1-C_4 –NR_{11}-C_2-C_6 alcanoil (*e.g.*, -NR_{11}-C_2 alcanoil, donde R_{11} es H o C_1-C_4 alquilo), alquilo , C_3-C_6 cicloalquilo , C_2-C_4 alquenil, C_2-C_4 alquinil, C_1-C_4 alcoxi , amino, C_1-C_4 alquilo amino, C_1-C_4 dialquilo amino, hidroxi C_1-C_4 alquilo , halo, CF_3, OCF_3 o CN;

R_{12} es H, C_1-C_6 alquilo , aril o –SO_2-aril (*e.g.*, fenil o naftil, donde fenil es preferido), donde cada aril es opcionalmente sustituido con 1 a 5 grupos que son independientemente halógeno , hidroxilo, alquilo , alcoxi , haloalquilo , haloalcoxi , CN o NO_2;

R_{13} es H, aril o C_1-C_6 alquilo opcionalmente sustituido con aril (tales como fenil o naftil, más preferible, fenil), hidroxilo o halógeno , donde cada grupo aril es opcionalmente sustituido con 1 a 5 grupos que son independientemente halógeno , hidroxilo, alquilo , alcoxi , haloalquilo , haloalcoxi , CN o NO_2.

En otro aspecto , aquí se proporcionan compuestos de Fórmulas 4a, 4b, 4c, 4d (cuando el Anillo-C es benzo sustituido con R_{30}, R_{35}, R_{40}, R_{45}), 4e, 4f y / o 4g, en donde R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno , C_1-C_6 alquilo , C_1-C_6 haloalquilo , C_1-C_6 haloalcoxi , CN, hidroxilo, C_1-C_6 alcoxi , C_3-C_6 cicloalquilo , -C_1-C_3 alquilo -OH, -C_1-C_3 alquilo -alcoxi , fenil oxi, -C(O)OR_{11}, -S(O_2)R_{10}, -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alcanoil, oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil, tienil, fenil o fenil C_1-C_4 alquilo , donde la porción fenil de arriba es opcionalmente sustituida con uno o más grupos que son independientemente C_1-C_6 alquilo , C_1-C_6 alcoxi , C_1-C_4 halo alquilo (*e.g.* CF_3) o halógeno . En una incorporación de este aspecto, el grupo par R_{51} que

son alfa al anillo-B son ambos hidrógeno. En otra ulterior incorporación, al menos uno del par de grupos R51 que son alfa al anillo-B es halógeno . En otra ulterior incorporación, los grupos par R_{51} grupos que son alfa al anillo-B son ambos halógeno . En otra ulterior incorporación, los grupos par R_{51} que son alfa al anillo-B forman un grupo oxo. En otra incorporación más, los grupos par R_{51} que son alfa al anillo-B forman un grupo C_2-C_4 alquenil. En otra incorporación más, los grupos pares R_{51} que son alfa al anillo-B forman una oxima o una oxima alquilada C_1-C_4 alquilo (*e.g.*, O- metil oxima).

En una incorporación más de este aspecto , R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno (*e.g.*, F), C_1-C_6 alquilo , hidroxilo, C_1-C_4 haloalquilo (*e.g.*, CF_3), C_1-C_4 haloalcoxi (*e.g.*, OCF_3), C_1-C_6 alcoxi , -C_1-C_3 alquilo -OH, CN o -C_1-C_3 alquilo -alcoxi .

En una incorporación de este aspecto , R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno , C_1-C_4 alquilo , CF_3, OCF_3, hidroxilo, C_1-C_4 alcoxi , -C_1-C_2 alquilo -OH, CN o -C_1-C_2 alquilo - C_1-C_4 alcoxi .

En uno incorporación de este aspecto, R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno , metil, etil, hidroxilo, CF_3, OCF_3. En una incorporación ulterior, al menos dos de R_{30}, R_{35}, R_{40}, R_{45} son hidrógeno. En una incorporación ulterior, R_{40} es CF_3. En otra incorporación más, R_{35} es CF_3. En una incorporación ulterior, R_{40} es CN. En otra incorporación más, R_{35} es CN. En una incorporación ulterior, R_{35} o R_{40} es hidroxilo.

En una incorporación de este aspecto , R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, -C(O)OR_{11}, -S(O_2)R_{10}, -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$ o C_2-C_6 alcanoil.

En una incorporación de este aspecto , R_{30} R_{35} o R_{35} R_{40} o R_{40} R_{45} son -OCH_2O- o -OCH_2CH_2O- en donde cada metileno de -OCH_2O- o -OCH_2CH_2O- es opcionalmente sustituido con uno o dos grupos C_1-C_4 alquilo.

En otra incorporación de este aspecto, R_{11} es H.

En otra incorporación más de este aspecto, uno de R_{10} R_{11} es CH_3.

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En otra incorporación de este aspecto, R_{11} R_{11} junto con el nitrógeno al que están unidos forman un anillo de 3-8 miembros que opcionalmente incluye un adicional hetero átomo que es NH, NR_{12}, NR_{13}, O o S.

En otra incorporación de este aspecto , R_{10} R_{11} en cada ocurrencia son independientemente fenil opcionalmente sustituido con 1 a 3 grupos que son independientemente halógeno , hidroxilo, C_1-C_6 alquilo , C_1-C_6 alcoxi , halo C_1-C_4 alquilo , halo C_1-C_4 alcoxi , CN o NO_2; y adicionalmente R_{11} puede ser H.

En otra incorporación de este aspecto , R_{10} R_{11} en cada ocurrencia son independientemente pirazolil, esoxazolil, esotiazolil, imidazolil o tiazolil, cada uno opcionalmente sustituido con 1 a 3 grupos que son independientemente halógeno , hidroxilo, C_1-C_6 alquilo , C_1-C_6 alcoxi , halo C_1-C_4 alquilo , halo C_1-C_4 alcoxi , CN o NO_2; y adicionalmente R_{11} puede ser H.

En otra incorporación de este aspecto , R_{10} R_{11} en cada ocurrencia son independientemente tiadiazolil, triazolil o oxadiazolil, cada uno opcionalmente sustituido con 1 a 3 grupos que son independientemente halógeno , hidroxilo, C_1-C_6 alquilo , C_1-C_6 alcoxi , halo C_1-C_4 alquilo , halo C_1-C_4 alcoxi , CN o NO_2 y adicionalmente R_{11} puede ser H.

En otro aspecto , aquí se proporcionan compuestos de Fórmulas 4a, 4b, 4c, 4d (cuando el Anillo-C es benzo sustituido con R_{30}, R_{35}, R_{40}, R_{45}), 4e, 4f y / o 4g, en donde R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno (*e.g.*, F), C_1-C_4 alquilo , $-C(O)OR_{11}$, $-S(O_2)R_{10}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ o $-O-C(O)NR_{11}R_{11}$.

En una incorporación de este aspecto , al menos dos de R_{30}, R_{35}, R_{40}, R_{45} son H, mientras otro es H, halógeno o C1-C4 alquilo , el otro es $-C(O)OR_{11}$, $-S(O_2)R_{10}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ o $-O-C(O)NR_{11}R_{11}$. En una incorporación ulterior, el grupo de pares R_{51} que son alfa al anillo-B son ambos hidrógeno. En otra ulterior incorporación, al menos uno del par de grupos R_{51} que son alfa al anillo-B es halógeno . En otra ulterior incorporación, el par de grupos R_{51} que son alfa al anillo-B son ambos halógenos. En otra ulterior incorporación, el

par de grupos R_{51} que son alfa al anillo-B forman un grupo oxo. En otra incorporación más, el par de grupos R_{51} que son alfa al anillo-B forman un grupo C_2-C_4 alquenil. En otra incorporación más, los grupos par R_{51} que son alfa al anillo-B forman una oxima o una oxima C_1-C_4 alquilada (*e.g.*, O-metil oxima).

En una incorporación de este aspecto , tres de R_{30}, R_{35}, R_{40}, R_{45} son H, mientras el otro es $-C(O)OR_{11}$, $-S(O_2)R_{10}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ o $-O-C(O)NR_{11}R_{11}$. En una incorporación ulterior, los grupos pares R_{51} que son alfa al anillo-B son ambos hidrógeno. En otra ulterior incorporación, al menos uno del par de grupos R_{51} que son alfa al anillo-B es halógeno . En otra ulterior incorporación, los grupos pares R_{51} grupos que son alfa al anillo-B son ambos halógeno . En otra ulterior incorporación, los grupos pares R_{51} que son alfa al anillo-B forman un grupo oxo. En otra incorporación más, los grupos pares R_{51} que son alfa al anillo-B forman un grupo C_2-C_4 alquenil. En otra incorporación más, los grupos pares R_{51} que son alfa al anillo-B forman una oxima o una oxima C_1-C_4 alquilada (*e.g.*, O- metil oxima).

En otra incorporación de este aspecto, tres de R_{30}, R_{35}, R_{40}, R_{45} son H, mientras el otro es $-NR_{11}R_{11}$. En una incorporación ulterior, los grupos pares R_{51} que son alfa al anillo-B son ambos hidrógeno. En otra ulterior incorporación, al menos uno de los grupos pares R_{51} que son alfa al anillo-B es halógeno . En otra ulterior incorporación, los grupos pares R_{51} grupos que son alfa al anillo-B son ambos halógeno . En otra ulterior incorporación, los grupos pares R_{51} que son alfa al anillo-B forman un grupo oxo. En otra incorporación más, los grupos pares R_{51} que son alfa al anillo-B forman un grupo C_2-C_4 alquenil. En otra incorporación más, los grupos pares R_{51} que son alfa al anillo-B forman un oxima o una oxima C_1-C_4 alquilada (*e.g.*, O- metil oxima).

En otra incorporación de este aspecto, tres de R_{30}, R_{35}, R_{40}, R_{45} son H, mientras el otro es $-SO_2NR_{11}R_{11}$ o $-NR_{11}SO_2R_{10}$. En una incorporación ulterior,

el geminal R_{51} grupos que son alfa una el anillo-B son ambos hidrógeno. En otra ulterior incorporación, al menos uno de los grupos R_{51} pares que son alfa al anillo-B es halógeno . En otra ulterior incorporación, los grupos R_{51} pares que son alfa al anillo-B son ambos halógenos . En otra ulterior incorporación, los grupos R_{51} pares que son alfa al anillo-B forman un grupo oxo. En otra incorporación más los grupos R_{51} pares que son alfa al anillo-B forman un C_2-C_4 grupo alquenil. En otra incorporación más, los grupos R_{51} pares que son alfa al anillo-B forman un oxima o una C_1-C_4 alquilada oxima (*e.g.*, O- metil oxima).

En una incorporación de este aspecto , tres de R_{30}, R_{35}, R_{40}, R_{45} son H, mientras el otro es $-C(O)NR_{11}R_{11}$ o $-NR_{11}C(O)R_{10}$. En una incorporación ulterior, los grupos R_{51} pares que son alfa al anillo-B son ambos hidrógeno. En otra ulterior incorporación, al menos uno de los grupos R_{51} pares que son alfa al anillo-B es halógeno . En otra ulterior incorporación, los grupos R_{51} pares que son alfa al anillo-B son ambos halógenos . En otra ulterior incorporación, los grupos R_{51} pares que son alfa al anillo-B forman un grupo oxo. En otra incorporación más, los grupos R_{51} pares que son alfa al anillo-B forman un C_2-C_4 grupo alquenil. En otra incorporación más, los grupos R_{51} pares que son alfa al anillo-B forman un oxima o una oxima alquilada C_1-C_4 (*e.g.*, O- metil oxima).

En otra incorporación de este aspecto, tres de R_{30}, R_{35}, R_{40}, R_{45} son H, mientras el otro es $-O-C(O)NR_{11}R_{11}$. En una incorporación ulterior, los grupos R_{51} pares que son alfa al anillo-B son ambos hidrógeno. En otra ulterior incorporación, al menos uno de los grupos R_{51} pares que son alfa al anillo-B es halógeno . En otra ulterior incorporación, los grupos R_{51} pares que son alfa al anillo-B son ambos halógenos . En otra ulterior incorporación, los grupos R_{51} pares que son alfa al anillo-B forman un grupo oxo. En otra incorporación más, los grupos R_{51} pares que son alfa al anillo-B forman un C_2-C_4 grupo alquenil. En otra incorporación más, los grupos R_{51} pares que son alfa al anillo-B forman un oxima o una oxima C_1-C_4 alquilada (*e.g.*, O- metil oxima).

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En otra incorporación de este aspecto , dos de R_{30}, R_{35}, R_{40}, R_{45} son H, mientras uno es metil el otra es $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$ o $-NR_{11}C(O)R_{10}$. En una incorporación ulterior, los grupos R_{51} pares que son alfa al anillo-B son ambos hidrógeno. En otra ulterior incorporación, al menos uno de los grupos R_{51} pares que son alfa al anillo-B es halógeno . En otra ulterior incorporación, los grupos R_{51} pares que son alfa al anillo-B son ambos halógenos . En otra ulterior incorporación, los grupos R_{51} pares que son alfa al anillo-B forman un grupo oxo. En otra incorporación más, los grupos R_{51} pares que son alfa al anillo-B forman un C_2-C_4 grupo alquenil. En otra incorporación más, los grupos R_{51} pares que son alfa al anillo-B forman una oxima o una oxima C_1-C_4 alquilada (*e.g.*, O- metil oxima).

En una incorporación de este aspecto, tres de R_{30}, R_{35}, R_{40}, R_{45} son H, mientras el otro es $-C(O)OR_{11}$. En una incorporación ulterior, R_{11} es H o C_1-C_4 alquilo. En una incorporación ulterior, los grupos R_{51} pares que son alfa al anillo-B son ambos hidrógeno. En otra ulterior incorporación, al menos uno de los grupos R_{51} pares que son alfa al anillo-B es halógeno . En otra ulterior incorporación, los grupos R_{51} pares que son alfa al anillo-B son ambos halógenos . En otra ulterior incorporación, los grupos R_{51} pares que son alfa al anillo-B forman un grupo oxo. En otra incorporación más, los grupos R_{51} pares que son alfa al anillo-B forman un C_2-C_4 grupo alquenil. En otra incorporación más, los grupos R_{51} pares que son alfa al anillo-B forman una oxima o una oxima C_1-C_4 alquilada (*e.g.*, O- metil oxima).

En otro aspecto , aquí se proporcionan compuestos de Fórmulas 4a, 4b, 4c, 4d (cuando el Anillo-C es benzo sustituido con R_{30}, R_{35}, R_{40}, R_{45}), 4e, 4f y/ o 4g, en donde R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno , C_1-C_4 alquilo , C_1-C_4 alcoxi , C_3-C_6 cicloalquilo , fenil oxi, C_2-C_6 alcanoil, oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil, tienil, fenil o fenil C_1-C_4 alquilo donde las porciones de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquilo , C_1-C_6 alcoxi , C_1-C_4 halo alquilo (*e.g.* CF_3) o halógeno .

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En otra incorporación de este aspecto, al menos dos de R_{30}, R_{35}, R_{40}, R_{45} son H.

En otra incorporación de este aspecto, tres de R_{30}, R_{35}, R_{40}, R_{45} son H.

En otra incorporación de este aspecto, R_{30}, R_{35}, R_{40}, R_{45} son H.

En otra incorporación de este aspecto, al menos uno de R_{30}, R_{35}, R_{40}, R_{45} es halógeno (*e.g.*, F, Cl o Br). En una aún otra incorporación, al menos dos de R_{30}, R_{35}, R_{40}, R_{45} es una halógeno (*e.g.*, F, Cl o Br), donde el halógeno s puede ser el same o dsiferent.

En otra incorporación de este aspecto, R_{30}, R_{35}, R_{40}, R_{45} son H; el anillo-B es no - sustituido pirazolil.

En aún otra incorporación más de este aspecto , R_{30} R_{45} son H; R_{35} R_{40} son independientemente halógeno (*e.g.*, F, Cl o Br), C_1-C_4 alquilo , C_1-C_4 alcoxi o C_2-C_6 alcanoil.

En aún otra incorporación más de este aspecto , R_{30} R_{45} son H; R_{35} R_{40} junto al carbono al que están unidos forman un anillo heterocicloalquilo . En una incorporación ulterior, el anillo heterocicloalquilo es $-OCH_2O-$, $-OCH_2CH_2O-$ o $-OC(O)O-$. En una incorporación ulterior, los grupos R_{51} pares que son alfa al anillo-B son ambos hidrógeno. En otra ulterior incorporación, al menos uno de los grupos R_{51} pares que son alfa al anillo-B es halógeno . En otra ulterior incorporación, los grupos R_{51} pares que son alfa al anillo-B son ambos halógenos . En otra ulterior incorporación, los grupos R_{51} pares que son alfa al anillo-B forman un grupo oxo. En otra incorporación más, los grupos R_{51} pares que son alfa al anillo-B forman un C_2-C_4 grupo alquenil. En otra incorporación más, los grupos R_{51} pares que son alfa al anillo-B forman una oxima o una oxima C_1-C_4 alquiada (*e.g.*, O- metil oxima).

En aún otra incorporación de este aspecto , R_{30} R_{45} son H; R_{35} R_{40} son independientemente halógeno (*e.g.*, F, Cl o Br), C_1-C_4 alquilo , C_1-C_4 alcoxi o C_2-C_6 alcanoil. En una incorporación ulterior, los grupos R_{51} pares que son alfa al anillo-B son ambos hidrógeno. En otra ulterior incorporación, al menos

uno de los grupos R_{51} pares que son alfa al anillo-B es halógeno . En otra ulterior incorporación, los grupos R_{51} pares que son alfa al anillo-B son ambos halógenos (*e.g.*, F). En otra ulterior incorporación, los grupos R_{51} pares que son alfa al anillo-B forman un grupo oxo. En otra incorporación más, los grupos R_{51} pares que son alfa al anillo-B forman un C_2-C_4 grupo alquenil. En otra incorporación más, los grupos R_{51} pares que son alfa al anillo-B forman una oxima o una C_1-C_4 alquilada oxima (*e.g.*, O- metil oxima).

En aún otra incorporación de este aspecto , R_{30} R_{45} son H; R_{35} R_{40} son independientemente halógeno (*e.g.*, F, Cl o Br), los grupos R_{51} pares que son alfa al anillo-B son ambos halógenos.

En otra incorporación de este aspecto , R_{30} R_{45} son H; R_{35} R_{40} son independientemente halógeno (*e.g.*, F, Cl o Br), hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , C_2-C_6 alcanoil, fenil oxi, fenil o fenil C_1-C_4 alquilo , donde la porción fenil es opcionalmente sustituida con uno o más grupos que son independientemente C_1-C_6 alquilo , C_1-C_6 alcoxi , C_1-C_4 halo alquilo (*e.g.* CF_3) o halógeno .

En otra incorporación de este aspecto , R_{30} R_{45} son H; R_{35} R_{40} son independientemente halógeno (*e.g.*, F, Cl o Br), C_1-C_4 alquilo , C_1-C_4 alcoxi , C_2-C_6 alcanoil, oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil o tienil.

En aún otra incorporación más de este aspecto , R_{35} R_{40} son H; R_{30} R_{45} son independientemente halógeno (*e.g.*, F, Cl o Br), hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi o C_2-C_6 alcanoil.

En aún otra incorporación de este aspecto , R_{35} R_{40} son H; R_{30} R_{45} son independientemente halógeno (*e.g.*, F, Cl o Br), hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , ciclopropil o C_2-C_6 alcanoil; los grupos R_{51} pares que son alfa al anillo-B forman un grupo oxo, una C_2-C_4 grupo alquenil, una oxima, una C_1-C_4 alquilada oxima (*e.g.*, O- metil oxima), son ambos H o son ambos halógenos (*e.g.*, F). En una incorporación ulterior, uno de R_{30} o R_{45} es H, mientras el otro es F o Cl.

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En aún otra incorporación más de este aspecto , R_{35} R_{40} son H; R_{30} R_{45} son independientemente H, halógeno (*e.g.*, F, Cl o Br), C_1-C_4 alquilo , C_1-C_4 alcoxi , ciclopropil o C_2-C_6 alcanoil; los grupos R_{51} pares que son alfa al anillo-B son ambos halógenos, provisto que al menos uno de R_{30} R_{45} no es H. En otra incorporación, ambos grupos R_{51} que son alfa aal anillo-B son F. En una incorporación ulterior, R_{30} es halógeno mientras R_{45} es H. En otra ulterior incorporación, R_{30} es H mientras R_{45} es halógeno . En otra ulterior incorporación, R_{30} es ciclopropil, mientras R_{45} es H. En otra ulterior incorporación, R_{30} es H mientras R_{45} es ciclopropil. En una incorporación ulterior, los grupos R_{51} pares que son alfa al anillo-B son ambos hidrógeno. En otra ulterior incorporación, al menos uno de los grupos R_{51} pares que son alfa al anillo-B es halógeno . En otra ulterior incorporación, los grupos R_{51} pares que son alfa al anillo-B son ambos halógenos . En otra ulterior incorporación, los grupos R_{51} pares que son alfa al anillo-B forman un grupo oxo. En otra incorporación más, los grupos R_{51} pares que son alfa al anillo-B forman un C_2-C_4 grupo alquenil. En otra incorporación más, los grupos R_{51} pares que son alfa al anillo-B forman un oxima o una C_1-C_4 alquilada oxima (*e.g.*, O- metil oxima).

En aún otra incorporación de este aspecto , R_{35} R_{40} son H; R_{30} R_{45} son independientemente halógeno (*e.g.*, F, Cl o Br), metil o metoxi. En una incorporación ulterior, R_{30} es halógeno . En otra ulterior incorporación, R_{45} es halógeno . En una incorporación ulterior, los grupos R_{51} pares que son alfa al anillo-B son ambos hidrógeno. En otra ulterior incorporación, al menos uno de los grupos R_{51} pares que son alfa al anillo-B es halógeno . En otra ulterior incorporación, los grupos pares R_{51} que son alfa al anillo-B son ambos halógeno (*e.g.*, F). En otra ulterior incorporación, los grupos R51 pares que son alfa al anillo-B forman un grupo oxo. En otra incorporación más, los grupos R51 pares que son alfa al anillo-B forman un C_2-C_4 grupo alquenil. En otra incorporación más, los grupos R_{51} pares que son alfa al anillo-B forman un oxima o una C_1-C_4 alquilada oxima (*e.g.*, O- metil oxima).

En aún otra incorporación de este aspecto , R_{35} R_{40} son H; R_{30} R_{45} son independientemente halógeno (*e.g.*, F, Cl o Br), hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , C_2-C_6 alcanoil, fenil oxi, fenil o fenil C_1-C_4 alquilo . En una incorporación ulterior, los grupos R51 pares que son alfa al anillo-B son ambos hidrógeno. En otra ulterior incorporación, al menos uno de los grupos R_{51} pares que son alfa al anillo-B es halógeno . En otra ulterior incorporación, los grupos R51 pares que son alfa al anillo-B son ambos halógenos (*e.g.*, F). En aún otra ulterior incorporación, los grupos R51 pares que son alfa al anillo-B forman un grupo oxo. En otra incorporación más, los grupos R51 pares que son alfa al anillo-B forman un C_2-C_4 grupo alquenil. En otra incorporación más, los grupos R_{51} pares que son alfa al anillo-B forman un oxima o una C_1-C_4 alquilada oxima (*e.g.*, O- metil oxima).

En aún otra incorporación de este aspecto , R_{35} R_{40} son H; R_{30} R_{45} son independientemente halógeno (*e.g.*, F, Cl o Br), hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , C_2-C_6 alcanoil, oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil o tienil. En una incorporación ulterior, los grupos R51 pares que son alfa al anillo-B son ambos hidrógeno. En otra ulterior incorporación, al menos uno de los grupos R_{51} pares que son alfa al anillo-B es halógeno . En otra ulterior incorporación, los grupos R51 pares que son alfa al anillo-B son ambos halógenos (*e.g.*, F). En aún otra ulterior incorporación, los grupos R51 pares que son alfa al anillo-B forman un grupo oxo. En otra incorporación más, los grupos R51 pares que son alfa al anillo-B forman un C_2-C_4 grupo alquenil. En otra incorporación más, los grupos R_{51} pares que son alfa al anillo-B forman una oxima o una C_1-C_4 alquilada oxima (*e.g.*, O- metil oxima).

En aún otra incorporación de este aspecto , R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno (*e.g.*, F, Cl o Br), C_1-C_4 alquilo o C_1-C_4 alcoxi ; un grupo R_{51} es halógeno o OH, mientras el otro grupo R_{51} es H. En otra incorporación más, el anillo-B es no - sustituido. En una incorporación ulterior, al menos dos de R_{30}, R_{35}, R_{40}, R_{45} son H. En otra incorporación más, R_{30}, R_{35}, R_{40}, R_{45} son H.

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En aún otra incorporación de este aspecto , R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno (*e.g.*, F, Cl o Br), C_1-C_4 alquilo o C_1-C_4 alcoxi ; un grupo R_{51} es halógeno o OH, mientras el otro grupo R_{51} es H. En otra incorporación más, el anillo-B es no - sustituido. En una incorporación ulterior, al menos uno de R_{30}, R_{35}, R_{40}, R_{45} es halógeno (*e.g.*, F, Cl o Br), C_1-C_4 alquilo o C_1-C_4 alcoxi. En otra incorporación más, dos de R_{30}, R_{35}, R_{40}, R_{45} son H.

En otro aspecto, aquí se proporcionan compuestos de Fórmulas 4a, 4b, 4c, 4d (cuando el Anillo-C es benzo sustituido con R_{30}, R_{35}, R_{40}, R_{45}), 4e, 4f y/ o 4g, en donde R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno , C_1-C_4 alquilo , C_1-C_4 alcoxi , C_2-C_6 alcanoil, C_2-C_8 alquenil, C_2-C_8 alquinil, C_2-C_8 halo alquenil o C_2-C_8 halo alquilonil; provisto que dos adyacentes carbonos de el fusionado anillo aril (el anillo al que los grupos R_{30}, R_{35}, R_{40} R_{45} están unidos) opcionalmente forman una heterocicloalquilo o un anillo heteroaril , cada uno opcionalmente sustituido con 1, 2, 3 ó 4 grupos que son independientemente C_1-C_4 alquilo , C_1-C_4 alcoxi , halógeno o C_1-C_4 alcanoil en donde el alcanoil es opcionalmente sustituido con hasta 3 átomos halógeno. En una incorporación ulterior, el anillo heterocicloalquilo es piperidinil, pirrolidinil o morfolinil, el heteroaril es pirazolil, imidazolil o piridinil, en donde cada heterocicloalquilo o heteroaril es opcionalmente sustituido con 1, 2, 3 o 4 grupos que son independientemente C_1-C_4 alquilo , C_1-C_4 alcoxi , halógeno o C_1-C_4 alcanoil en donde el grupo alcanoil es opcionalmente sustituido con hasta 3 átomos de halógeno. En una incorporación ulterior, el heterocicloalquilo es piperidinil o pirrolidinil, cada uno opcionalmente sustituido con 1 o 2 grupos que son independientemente C_1-C_4 alquilo, C_1-C_4 alcoxi, halógeno o C_2-C_4 alcanoil en donde el grupo alcanoil es opcionalmente sustituido con hasta 3 átomos de halógeno. En una incorporación ulterior, el anillo heteroaril es pirazolil, imidazolil o piridinil, cada uno opcionalmente sustituido con 1 o 2 grupos que son independientemente C_1-C_4 alquilo, C_1-C_4 alcoxi, halógeno o C_2-C_4 alcanoil en donde el grupo alcanoil es opcionalmente sustituido con hasta 3 átomos de halógeno.

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En otro aspecto, aquí se proporcionan compuestos de Fórmulas 4a, 4b, 4c, 4d (cuando el Anillo-C es benzo sustituido con R_{30}, R_{35}, R_{40}, R_{45}), 4e, 4f y/ o 4g, en donde R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno , C_1-C_4 alquilo , C_1-C_4 alcoxi , C_2-C_6 alcanoil; provisto que dos adyacentes carbonos del anillo aril fusionado forman un anillo benzo, que es opcionalmente sustituido con 1 a 4 grupos que son independientemente halógeno , hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , C_1-C_4 haloalquilo , C_1-C_4 haloalcoxi , CN o NO_2.

En una incorporación de este aspecto , R_{30} R_{45} son independientemente H, halógeno , hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , R_{35}, R_{40}, junto al carbono al que están unidos forman una anillo benzo, que es opcionalmente sustituido con 1 a 4 grupos que son independientemente halógeno , hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , C_1-C_4 haloalquilo , C_1-C_4 haloalcoxi , CN o NO_2. En una incorporación ulterior, el anillo benzo es no - sustituido.

En una incorporación de este aspecto , R_{30} R_{35} son independientemente H, halógeno , hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , R_{40}, R_{45}, junto al carbono al que están unidos forman un anillo benzo, que es opcionalmente sustituido con 1 a 4 grupos que son independientemente halógeno , hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , C_1-C_4 haloalquilo , C_1-C_4 haloalcoxi , CN o NO_2. En una incorporación ulterior, el anillo benzo es no - sustituido.

En una incorporación de este aspecto , R_{40} R_{45} son independientemente H, halógeno , hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , R_{30}, R_{35}, junto al carbono al que están unidos forman una anillo benzo, que es opcionalmente sustituido con 1 a 4 grupos que son independientemente halógeno , hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , C_1-C_4 haloalquilo , C_1-C_4 haloalcoxi , CN o NO_2. En una incorporación ulterior, el anillo benzo es no - sustituido.

En un aspecto, los compuestos de Fórmula 4 son los compuestos de Fórmula 4a.

En un aspecto, los compuestos de Fórmula 4 son los compuestos de Fórmula 4b.

En un aspecto, los compuestos de Fórmula 4 son los compuestos de Fórmula 4c.

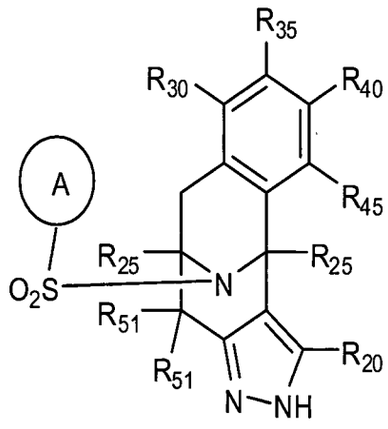
En un aspecto, los compuestos de Fórmula 4 son los compuestos de Fórmula 4d.

En un aspecto, el compuestos de Fórmula 4 son los compuestos de Fórmula 4e.

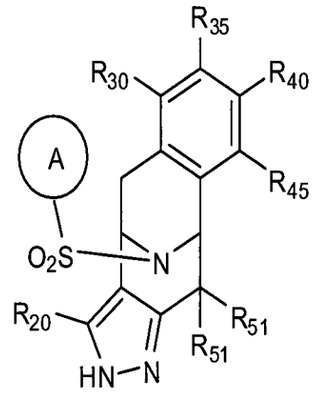
En un aspecto, los compuestos de Fórmula 4 son los compuestos de Fórmula 4f.

En un aspecto, los compuestos de Fórmula 4 son los compuestos de Fórmula 4g.

En un aspecto, los compuestos de Fórmula 4 tienen Fórmulas 4f1 4g1:



Fórmula 4f1



Fórmula 4g1

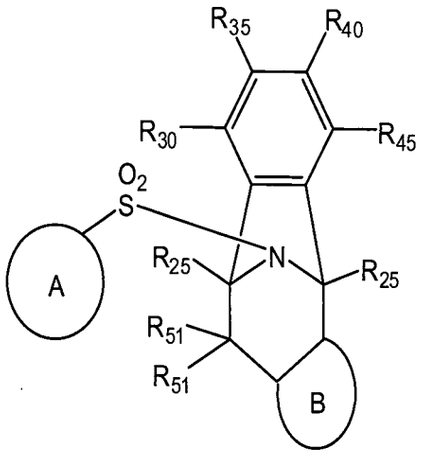
incluyendo estereoisómeros, tautómeros mezclas de estereoisómeros / o tautómeros, / o farmacéuticamente aceptables sales de éstos, en donde R_{30}, R_{35}, R_{40}, R_{45}, el anillo-A es como se definió previamente; R_{20} es H, C_1-C_6 alquilo , C_1-C_6 alcoxi , amino, C_1-C_6 alquilo amino, C_1-C_6 dialquilo amino, halo, CF_3 o –$NHC(O)CH_3$; R_{51} es H, C_1-C_4 alquilo , F, Cl, Br, CN, amino, mono alquilo amino, dialquilo amino, OH, oxo, $=CH_2$, =NOH, $=NOCH_3$, $=NOCH_2CH_3$, o CF_3. En una incorporación, R_{20} es H. En otra incorporación, R_{20} es metil. En otra incorporación, R_{51} es H. En otra incorporación, R_{51} es F. En otra

incorporación, R_{51} es OH. En otra incorporación, R_{51} es CF_3. En aún otra incorporación, R_{51} es H R_{51} es F o Cl. En otra incorporación, R_{51} es OH. En otra incorporación, R_{51} es H. En otra incorporación, R_{20} es H R_{51} es F. En otra incorporación, R_{20} es H R_{51} es OH. En otra incorporación, R_{20} es H los grupos R_{51} pares forman un grupo oxo. En otra incorporación, R_{20} es metil los grupos R_{51} pares forman un grupo oxo. En otra incorporación, R_{20} es H el geminal R_{51} grupos forman un $=CH_2$, grupo. En otra incorporación, R_{20} es metil los grupos R_{51} pares forman un $=CH_2$, grupo. En otra incorporación, R_{20} es H el geminal R_{51} grupos forman =NOH, $=NOCH_3$, o $=NOCH_2CH_3$. En otra incorporación, R_{20} es metil los grupos R_{51} pares forman un =NOH, $=NOCH_3$, o $=NOCH_2CH_3$.

En un aspecto, los compuestos de Fórmula 4 son los compuestos de Fórmula 4f1.

En otro aspecto, los compuestos de Fórmula 4 son los compuestos de Fórmula 4g1.

En un aspecto, aquí se proporcionan compuestos de Fórmula 4h, y.e., compuestos de Fórmula 4 teniendo la fórmula



incluyendo enantiómeros y / o farmacéuticamente aceptables sales de estos, en donde,

anillo-B es pirazolil, dihidropirazolil, pirazolonil o pirazolidinonil, cada uno opcionalmente sustituido con $-NR_{11}$-C_2-C_6 alcanoil, C_1-C_6 alquilo , C_3-C_6

cicloalquilo , C_2-C_4 alquenil, C_2-C_4 alquinil, C_1-C_4 alcoxi , amino, C_1-C_4 alquilo amino, C_1-C_4 dialquilo amino, hidroxi , hidroxi alquilo , halo, C_1-C_4 haloalquilo , C_1-C_4 haloalcoxi , $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ o CN;

R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno , C_1-C_6 alquilo , C_2-C_8 alquenil, C_2-C_8 alquinil, C_2-C_8 halo alquenil, C_2-C_8 halo alquilonil, $-C(O)OR_{11}$, $-SO_2NR_{11}R_{11}$, aril C_1-C_6 alquilo , C_3-C_6 cicloalquilo , C_1-C_6 haloalquilo , C_1-C_6 haloalcoxi , CN, NO_2, hidroxilo, C_1-C_6 alcoxi , $-C_1$-C_6 alquilo -OH, $-C_1$-C_6 alquilo -C_1-C_6 alcoxi , fenil oxi, $-S(O_2)R_{10}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, heteroaril C_1-C_6 alquilo , heteroaril, donde los grupos heteroaril son oxazolil, oxadiazolil pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil o tienil, en donde cada heteroaril es opcionalmente sustituido con una C_1-C_6 alquilo ; heterocicloalquilo alquilo , heterocicloalquilo , en donde el heterocicloalquilo grupos son pirrolidinil, imidazolidinil, piperidinil o morfolinil, en donde cada heterocicloalquilo es opcionalmente sustituido con uno o dos grupos que son independientemente C_1-C_6 alquilo , C_1-C_6 alcoxi o halógeno , fenil , naftil, fenil oxi, naftiloxi o fenil C_1-C_6 alquilo , donde las porciones fenil de arriba son opcionalmente sustituidas con uno a cinco grupos que son independientemente C_1-C_6 alquilo , C_1-C_6 alcoxi , hidroxilo, C_1-C_4 halo alquilo (*e.g.*, CF_3) o halógeno;

en donde dos adyacentes carbonos y del fusionado anillo aril opcionalmente forman un anillo heterocicloalquilo (*e.g.*, $-OCH_2O-$ o $-OCH_2CH_2O-$) o un anillo heteroaril, cada uno opcionalmente sustituido con 1, 2, 3 o 4 grupos que son independientemente C_1-C_4 alquilo , C_1-C_4 alcoxi , halógeno o C_2-C_4 alcanoil en donde el grupo alcanoil es opcionalmente sustituido con hasta 3 átomos de halógeno; o

dos adyacentes carbonos y del fusionado anillo aril forman un anillo benzo que es opcionalmente sustituido con 1 una 4 grupos que son independientemente halógeno , hidroxilo, alquilo , alcoxi , haloalquilo , haloalcoxi , CN o NO_2;

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cada R_{51} está independientementeausente, H, C_1-C_4 alquilo , halógeno (*e.g.*, F, Cl o Br), CN, amino, mono alquilo amino, dialquilo amino, OH, C_1-C_4 haloalcoxi (*e.g.*, OCF_3), C_1-C_4 haloalquilo (*e.g.*, CF_3) o –CN; o cuando hay dos grupos R_{51} en un átomo de carbono, los dos grupos R_{51} y el carbono al que están unidos pueden formar un anillo de 3- a 6-miembros cicloalquilo o heterocicloalquilo; o cuando hay dos grupos R_{51} en un carbono, los dos grupos R_{51} pueden formar un grupo oxo; o cuando tere son dos R_{51} grupos on una carbon, el dos R_{51} grupos pueden forman un alkene grupo; o cuando hay dos grupos R_{51} en un carbono, los dos grupos R_{51} pueden formar una oxima o una C_1-C_4 alquilada oxima (*e.g.*, O- metil oxima);

Un carbono no-cabeza-de-puente (y cualquier sustituto o sustitutos en él) en el sistema de anillos [3.3.1], [3.2.1] o [2.2.1] puede ser reemplazado con un grupo NR_{15}. En una incorporación ulterior, R_{10} R_{11} en cada ocurrencia son independientemente C_1-C_6 alquilo , heteroaril que es seleccionado de pirazolil, tiadiazolil, triazolil, esoxazolil, esotiazolil, imidazolil, tiazolil, oxadiazolil, piridil o aril que es seleccionado de fenil naftil, donde el heteroaril aril grupos son opcionalmente sustituido con 1 una 3 grupos que son independientemente halógeno , hidroxilo, alquilo , alcoxi , haloalquilo , haloalcoxi , CN o NO_2; y adicionalmente R_{11} puede ser H;

o si dos grupos R_{11} están en un nitrógeno, entonces los dos grupos R_{11} junto con el nitrógeno al que están unidos, pueden formar un anillo de 3-8 miembros opcionalmente incluyendo un adicional hetero átomo tal como NH, NR_{12}, NR_{13}, O o S;

R_{12} es H, C_1-C_6 alquilo , aril o –SO_2-aril (*e.g.*, fenil o naftil, donde fenil es preferido), donde cada aril es opcionalmente sustituido con 1 a 5 grupos que son independientemente halógeno , hidroxilo, alquilo , alcoxi , haloalquilo , haloalcoxi , CN o NO_2;

R_{13} es H, aril o C_1-C_6 alquilo opcionalmente sustituido con aril (tales como fenil o naftil, más preferible, fenil), hidroxilo o halógeno , donde cada aril es opcionalmente sustituido con 1 a 5 grupos que son independientemente

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halógeno , hidroxilo, alquilo , alcoxi , haloalquilo , haloalcoxi , CN o NO_2. En una ulterior incorporación el anillo-B es pirazolil, que es opcionalmente sustituido con $-NR_{11}$-C_2-C_6 alcanoil, C_1-C_4 alquilo , C_3-C_6 cicloalquilo , C_2-C_4 alquenil, C_2-C_4 alquinil, C_1-C_4 alcoxi , amino, C_1-C_4 alquilo amino, C_1-C_4 dialquilo amino, hidroxi C_1-C_4 alquilo , halo, CF_3, OCF_3 o CN.

En otro aspecto , aquí se proporcionan compuestos de Fórmula 4h, en donde R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno , C_1-C_6 alquilo , C_1-C_6 haloalquilo , C_1-C_6 haloalcoxi , C_2-C_8 alquenil, C_2-C_8 alquinil, C_2-C_8 halo alquenil, C_2-C_8 halo alquilonil, CN, hidroxilo, C_1-C_6 alcoxi , -C_1-C_3 alquilo -OH, -C_1-C_3 alquilo -alcoxi , fenil oxi, -$C(O)OR_{11}$, -$S(O_2)R_{10}$, -$NR_{11}R_{11}$, --$C(O)NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil, tienil, fenil o fenil C_1-C_4 alquilo , donde las porciones fenil de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquilo , C_1-C_6 alcoxi o halógeno . En una incorporación de este aspecto, los grupos R51 pares que son alfa al anillo-B son ambos hidrógeno. En otra ulterior incorporación, al menos uno de los grupos R_{51} pares que son alfa al anillo-B es halógeno . En otra ulterior incorporación, los grupos R51 pares que son alfa al anillo-B son ambos halógenos . En aún otra ulterior incorporación, los grupos R51 pares que son alfa al anillo-B forman un grupo oxo. En otra incorporación más, los grupos R51 pares que son alfa al anillo-B forman un C_2-C_4 grupo alquenil. En otra incorporación más, los grupos R_{51} pares que son alfa al anillo-B forman una oxima o una C_1-C_4 alquilada oxima (*e.g.*, O- metil oxima).

En una incorporación de este aspecto , R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno (*e.g.*, F), C_1-C_6 alquilo , hidroxilo, C_1-C_4 haloalquilo (*e.g.*, CF_3), C_1-C_4 haloalcoxi (*e.g.*, OCF_3), C_2-C_6 alquenil, C_2-C_6 alquinil, C_2-C_6 halo alquenil, C_2-C_6 halo alquilonil, C_1-C_6 alcoxi , -C_1-C_3 alquilo -OH, CN o -C_1-C_3 alquilo -alcoxi .

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En una incorporación de este aspecto , R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno , C_1-C_4 alquilo , CF_3, OCF_3, hidroxilo, C_1-C_4 alcoxi , -C_1-C_2 alquilo -OH, CN o -C_1-C_2 alquilo - C_1-C_4 alcoxi .

En una incorporación de este aspecto, R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno , C_1-C_4 alquilo, C_2-C_6 alquenil, C_2-C_6 alquinil, C_2-C_6 halo alquenil, C_2-C_6 halo alquilonil o -C(O)OR_{11}. En una incorporación ulterior, la porción halo de los grupos halo alquenil halo alquilonil es F, Cl o Br.

En una incorporación de este aspecto , dos de R_{30}, R_{35}, R_{40}, R_{45} son H, mientras al menos uno de el otro grupo es halógeno , C_1-C_4 alquilo , C_2-C_6 alquenil, C_2-C_6 alquinil, C_2-C_6 halo alquenil, C_2-C_6 halo alquilonil o -C(O)OR_{11}. En una incorporación ulterior, la porción halo de los grupos halo alquenil halo alquilonil es F, Cl o Br.

En una incorporación de este aspecto, R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno, metil, etil, hidroxilo, CF_3 o OCF_3. En una incorporación ulterior, al menos dos de R_{30}, R_{35}, R_{40}, R_{45} son hidrógeno. En una incorporación ulterior, R_{40} es CF_3. En otra incorporación más, R_{35} es CF_3. En una incorporación ulterior, R_{40} es CN. En otra incorporación más, R_{35} es CN. En una incorporación ulterior, R_{35} o R_{40} es hidroxilo.

En una incorporación de este aspecto , R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, -C(O)OR_{11}, -S(O_2)R_{10}, -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$ o C_2-C_6 alcanoil.

En una incorporación de este aspecto , R_{30} R_{35} o R_{35} R_{40} o R_{40} R_{45} son -OCH_2O- o -OCH_2CH_2O- en donde cada metileno de -OCH_2O- o -OCH_2CH_2O- es opcionalmente sustituido con uno o dos grupos C_1-C_4 alquilo.

En aún otra incorporación más de este aspecto, R_{11} es H.

En aún otra incorporación de este aspecto, uno de R_{10} R_{11} es CH_3.

En otra incorporación de este aspecto, R_{10} R_{11} junto con el nitrógeno al que están unidos pueden formar un anillo de 3-8 miembros, que opcionalmente incluye un adicional hetero átomo que es NH, NR_{12}, NR_{13}, O o S.

En aún otra incorporación de este aspecto , R_{10} y R_{11} en cada ocurrencia son independientemente fenil opcionalmente sustituido con 1 a 3 grupos que son independientemente halógeno , hidroxilo, C_1-C_6 alquilo , C_1-C_6 alcoxi , halo C_1-C_4 alquilo , halo C_1-C_4 alcoxi , CN o NO_2; y adicionalmente R_{11} puede ser H.

En otra incorporación de este aspecto , R_{10} R_{11} en cada ocurrencia son independientemente pirazolil, esoxazolil, esotiazolil, imidazolil o tiazolil, cada uno opcionalmente sustituido con 1 a 3 grupos que son independientemente halógeno , hidroxilo, C_1-C_6 alquilo , C_1-C_6 alcoxi , halo C_1-C_4 alquilo , halo C_1-C_4 alcoxi , CN o NO_2; y además R_{11} puede ser H.

En otra incorporación de este aspecto , R_{10} y R_{11} en cada ocurrencia son independientemente tiadiazolil, triazolil o oxadiazolil, cada de que es opcionalmente sustituido con 1 una 3 grupos que son independientemente halógeno , hidroxilo, C_1-C_6 alquilo , C_1-C_6 alcoxi , halo C_1-C_4 alquilo , halo C_1-C_4 alcoxi , CN o NO_2 y además R_{11} puede ser H.

En otro aspecto , aquí se proporcionan compuestos de Fórmula 4h, en donde R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno (*e.g.*, F), C_1-C_4 alquilo , $-C(O)OR_{11}$, $-S(O_2)R_{10}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ o $-O-C(O)NR_{11}R_{11}$.

En una incorporación de este aspecto , al menos dos de R_{30}, R_{35}, R_{40}, R_{45} son H, mientras otro es H, halógeno o C1-C4 alquilo , el otro es $-C(O)OR_{11}$, $-S(O_2)R_{10}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ o $-O-C(O)NR_{11}R_{11}$. En una incorporación ulterior, los grupos R51 pares que son alfa al anillo-B son ambos hidrógeno. En otra ulterior incorporación, al menos uno de el geminal R_{51} grupos que son alfa una el anillo-B es halógeno . En otra ulterior incorporación, los grupos R51 pares que son alfa al anillo-B son ambos halógenos . En aún otra ulterior

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incorporación, los grupos R51 pares que son alfa al anillo-B forman un grupo oxo. En otra incorporación más, los grupos R51 pares que son alfa al anillo-B forman un C_2-C_4 grupo alquenil. En otra incorporación más, los grupos R_{51} pares que son alfa al anillo-B forman un oxima o una C_1-C_4 alquilada oxima (*e.g.*, O- metil oxima).

En una incorporación de este aspecto , tres de R_{30}, R_{35}, R_{40}, R_{45} son H, mientras el otro es $-C(O)OR_{11}$, $-S(O_2)R_{10}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ o $-O-C(O)NR_{11}R_{11}$. En una incorporación ulterior, los grupos R51 pares que son alfa al anillo-B son ambos hidrógeno. En otra ulterior incorporación, al menos uno de los grupos R_{51} pares que son alfa al anillo-B es halógeno . En otra ulterior incorporación, los grupos R51 pares que son alfa al anillo-B son ambos halógeno . En aún otra ulterior incorporación, los grupos R51 pares que son alfa al anillo-B forman un grupo oxo. En otra incorporación más, los grupos R51 pares que son alfa al anillo-B forman un C_2-C_4 grupo alquenil. En otra incorporación más, los grupos R_{51} pares que son alfa al anillo-B forman una oxima o una C_1-C_4 alquilada oxima (*e.g.*, O- metil oxima).

En otra incorporación de este aspecto, tres de R_{30}, R_{35}, R_{40}, R_{45} son H, mientras el otro es $-NR_{11}R_{11}$. En una incorporación ulterior, los grupos R51 pares que son alfa al anillo-B son ambos hidrógeno. En otra ulterior incorporación, al menos uno de los grupos R_{51} pares que son alfa al anillo-B es halógeno . En otra ulterior incorporación, los grupos R51 pares que son alfa al anillo-B son ambos halógenos . En aún otra ulterior incorporación, los grupos R51 pares que son alfa al anillo-B forman un grupo oxo. En otra incorporación más, los grupos R51 pares que son alfa al anillo-B forman un C_2-C_4 grupo alquenil. En otra incorporación más, los grupos R_{51} pares que son alfa al anillo-B forman una oxima o una C_1-C_4 alquilada oxima (*e.g.*, O- metil oxima).

En otra incorporación de este aspecto, tres de R_{30}, R_{35}, R_{40}, R_{45} son H, mientras el otro es $-SO_2NR_{11}R_{11}$ o $-NR_{11}SO_2R_{10}$. En una incorporación ulterior,

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los grupos R51 pares que son alfa al anillo-B son ambos hidrógeno. En otra ulterior incorporación, al menos uno de los grupos R_{51} pares que son alfa al anillo-B es halógeno . En otra ulterior incorporación, los grupos R51 pares que son alfa al anillo-B son ambos halógenos . En aún otra ulterior incorporación, los grupos R51 pares que son alfa al anillo-B forman un grupo oxo. En otra incorporación más, los grupos R51 pares que son alfa al anillo-B forman un C_2-C_4 grupo alquenil. En otra incorporación más, los grupos R_{51} pares que son alfa al anillo-B forman un oxima o una C_1-C_4 alquilada oxima (*e.g.*, O- metil oxima).

En una incorporación de este aspecto , tres de R_{30}, R_{35}, R_{40}, R_{45} son H, mientras el otro es $-C(O)NR_{11}R_{11}$ o $-NR_{11}C(O)R_{10}$. En una incorporación ulterior, los grupos R51 pares que son alfa al anillo-B son ambos hidrógeno. En otra ulterior incorporación, al menos uno de los grupos R_{51} pares que son alfa al anillo-B es halógeno . En otra ulterior incorporación, los grupos R51 pares que son alfa al anillo-B son ambos halógenos . En aún otra ulterior incorporación, los grupos R51 pares que son alfa al anillo-B forman un grupo oxo. En otra incorporación más, los grupos R51 pares que son alfa al anillo-B forman un C_2-C_4 grupo alquenil. En otra incorporación más, los grupos R_{51} pares que son alfa al anillo-B forman una oxima o una C_1-C_4 alquilada oxima (*e.g.*, O- metil oxima).

En aún otra incorporación de este aspecto , tres de R_{30}, R_{35}, R_{40}, R_{45} son H, mientras el otra es $-O-C(O)NR_{11}R_{11}$. En una incorporación ulterior, los grupos R51 pares que son alfa al anillo-B son ambos hidrógeno. En otra ulterior incorporación, al menos uno de los grupos R_{51} pares que son alfa al anillo-B es halógeno . En otra ulterior incorporación, los grupos R51 pares que son alfa al anillo-B son ambos halógenos. En aún otra ulterior incorporación, los grupos R51 pares que son alfa al anillo-B forman un grupo oxo. En otra incorporación más, los grupos R51 pares que son alfa al anillo-B forman un C_2-C_4 grupo alquenil. En otra incorporación más, los grupos R_{51} pares que son alfa al anillo-B forman una oxima o una C_1-C_4 alquilada oxima (*e.g.*, O- metil oxima).

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En aún otra incorporación de este aspecto , dos de R_{30}, R_{35}, R_{40}, R_{45} son H, mientras uno es metil el otro es $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$ o $-NR_{11}C(O)R_{10}$. En una incorporación ulterior, los grupos R51 pares que son alfa al anillo-B son ambos hidrógeno. En otra ulterior incorporación, al menos uno de los grupos pares R_{51} que son alfa al anillo-B es halógeno . En otra ulterior incorporación, los grupos R51 pares que son alfa al anillo-B son ambos halógenos . En aún otra ulterior incorporación, los grupos R51 pares que son alfa al anillo-B forman un grupo oxo. En otra incorporación más, los grupos R51 pares que son alfa al anillo-B forman un C_2-C_4 grupo alquenil. En otra incorporación más, los grupos R_{51} pares que son alfa al anillo-B forman un oxima o una C_1-C_4 alquilada oxima (*e.g.*, O- metil oxima).

En una incorporación de este aspecto , tres de R_{30}, R_{35}, R_{40}, R_{45} son H, mientras el otra es $-C(O)OR_{11}$. En una incorporación ulterior, R_{11} es H o C_1-C_4 alquilo. En una incorporación ulterior, los grupos R51 pares que son alfa al anillo-B son ambos hidrógeno. En otra ulterior incorporación, al menos uno de los grupos R_{51} pares que son alfa al anillo-B es halógeno . En otra ulterior incorporación, los grupos R51 pares que son alfa al anillo-B son ambos halógenos . En aún otra ulterior incorporación, los grupos R51 pares que son alfa al anillo-B forman un grupo oxo. En otra incorporación más, los grupos R51 pares que son alfa al anillo-B forman un C_2-C_4 grupo alquenil. En otra incorporación más, los grupos R_{51} pares que son alfa al anillo-B forman un oxima o una C_1-C_4 alquilada oxima (*e.g.*, O- metil oxima).

En otro aspecto , aquí se proporcionan compuestos de Fórmula 4h, en donde R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno , C_1-C_4 alquilo , C_1-C_4 alcoxi , fenil oxi, C_2-C_6 alcanoil, oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil, tienil, fenil o fenil C_1-C_4 alquilo donde las porciones fenil de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquilo , C_1-C_6 alcoxi , C_1-C_4 halo alquilo (*e.g.* CF_3) o halógeno.

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En otra incorporación de este aspecto, al menos dos de R_{30}, R_{35}, R_{40}, R_{45} son H.

En aún otra incorporación de este aspecto, tres de R_{30}, R_{35}, R_{40}, R_{45} son H.

En aún otra incorporación de este aspecto, R_{30}, R_{35}, R_{40}, R_{45} son H.

En aún otra incorporación más de este aspecto, R_{30}, R_{35}, R_{40}, R_{45} son H; el anillo-B es no - sustituido pirazolil.

En aún otra incorporación de este aspecto , R_{30}, R_{35}, R_{40}, R_{45} son H; el anillo-B es no - sustituido pirazolil; los grupos R51 pares que son alfa al anillo-B forman un grupo oxo.

En aún otra incorporación de este aspecto , R_{30}, R_{35}, R_{40}, R_{45} son H; el anillo-B es no - sustituido pirazolil; los grupos R51 pares que son alfa al anillo-B forman un C_2-C_4 grupo alquenil.

En aún otra incorporación de este aspecto , R_{30}, R_{35}, R_{40}, R_{45} son H; el anillo-B es no - sustituido pirazolil; los grupos R51 pares que son alfa al anillo-B forman una oxima o una C_1-C_4 alquilada oxima (*e.g.*, O- metil oxima).

En aún otra incorporación de este aspecto , R_{30}, R_{35}, R_{40}, R_{45} son H; el anillo-B es no - sustituido pirazolil; los grupos R51 pares que son alfa al anillo-B son ambos H o uno es H el otra es F o OH.

En aún otra incorporación de este aspecto , R_{30} R_{45} son H; R_{35} R_{40} son independientemente halógeno (*e.g.*, F, Cl o Br), C_1-C_4 alquilo , C_1-C_4 alcoxi o C_2-C_6 alcanoil.

En aún otra incorporación de este aspecto , R_{30} R_{45} son H; R_{35} R_{40} junto al carbono al que están unidos forman un anillo heterocicloalquilo En una incorporación ulterior, el heterocicloalquilo es $-OCH_2O-$, $-OCH_2CH_2O-$ o $-OC(O)O-$. En otra incorporación más, los grupos R51 pares que son alfa al anillo-B son ambos H.

En aún otra incorporación de este aspecto , R_{30} R_{45} son H; R_{35} R_{40} son independientemente halógeno (*e.g.*, F, Cl o Br), C_1-C_4 alquilo , C_1-C_4 alcoxi o

C_2-C_6 alcanoil; los grupos R51 pares que son alfa al anillo-B forman un grupo oxo.

En aún otra incorporación de este aspecto , R_{30} R_{45} son H; R_{35} R_{40} son independientemente halógeno (*e.g.*, F, Cl o Br), C_1-C_4 alquilo , C_1-C_4 alcoxi o C_2-C_6 alcanoil; los grupos R51 pares que son alfa al anillo-B son ambos H.

En aún otra incorporación de este aspecto , R_{30} R_{45} son H; R_{35} R_{40} son independientemente halógeno (*e.g.*, F, Cl o Br), C_1-C_4 alquilo , C_1-C_4 alcoxi o C_2-C_6 alcanoil; los grupos R51 pares que son alfa al anillo-B son ambos halógenos. En otra incorporación, ambos grupos R_{51} pares que son alfa al anillo-B son F.

En aún otra incorporación de este aspecto , R_{30} R_{45} son H; R_{35} R_{40} son independientemente halógeno (*e.g.*, F, Cl o Br), los grupos R51 pares que son alfa al anillo-B son ambos halógenos.

En aún otra incorporación de este aspecto , R_{30} R_{45} son H; R_{35} R_{40} son independientemente halógeno (*e.g.*, F, Cl o Br), los grupos R51 pares que son alfa al anillo-B forman un C_2-C_4 grupo alquenil.

En aún otra incorporación de este aspecto , R_{30} R_{45} son H; R_{35} R_{40} son independientemente halógeno (*e.g.*, F, Cl o Br), los grupos R51 pares que son alfa al anillo-B forman una oxima o una C_1-C_4 alquilada oxima (*e.g.*, O-metil oxima).

En aún otra incorporación de este aspecto , R_{30} R_{45} son H; R_{35} R_{40} son independientemente halógeno (*e.g.*, F, Cl o Br), hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , C_2-C_6 alcanoil, fenil oxi, fenil o fenil C_1-C_4 alquilo , donde las porciones fenil de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquilo , C_1-C_6 alcoxi , C_1-C_4 halo alquilo (*e.g.* CF_3) o halógeno .

En aún otra incorporación de este aspecto , R_{30} R_{45} son H; R_{35} R_{40} son independientemente halógeno (*e.g.*, F, Cl o Br), C_1-C_4 alquilo , C_1-C_4 alcoxi ,

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C_2-C_6 alcanoil, oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil o tienil.

En aún otra incorporación de este aspecto , R_{35} R_{40} son H; R_{30} R_{45} son independientemente halógeno (*e.g.*, F, Cl o Br), hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi o C_2-C_6 alcanoil.

En aún otra incorporación más de este aspecto , R_{35} R_{40} son H; R_{30} R_{45} son independientemente halógeno (*e.g.*, F, Cl o Br), hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi o C_2-C_6 alcanoil; los grupos R51 pares que son alfa al anillo-B forman un grupo oxo. En una incorporación ulterior, uno de R_{30} o R_{45} es H, mientras el otra es F o Cl.

En aún otra incorporación de este aspecto , R_{35} R_{40} son H; R_{30} R_{45} son independientemente halógeno (*e.g.*, F, Cl o Br), hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi o C_2-C_6 alcanoil; los grupos R51 pares que son alfa al anillo-B son ambos hidrógeno. En una incorporación ulterior, uno de R_{30} o R_{45} es H, mientras el otro es F o Cl.

En aún otra incorporación de este aspecto , R_{35} R_{40} son H; R_{30} R_{45} son independientemente halógeno (*e.g.*, F, Cl o Br), hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi o C_2-C_6 alcanoil; los grupos R51 pares que son alfa al anillo-B forman un C_2-C_4 grupo alquenil.

En aún otra incorporación de este aspecto , R_{35} R_{40} son H; R_{30} R_{45} son independientemente halógeno (*e.g.*, F, Cl o Br), hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi o C_2-C_6 alcanoil; los grupos R51 pares que son alfa al anillo-B forman una oxima o una C_1-C_4 alquilada oxima (*e.g.*, O- metil oxima).

En aún otra incorporación de este aspecto , R_{35} R_{40} son H; R_{30} R_{45} son independientemente H, halógeno (*e.g.*, F, Cl o Br), C_1-C_4 alquilo , C_1-C_4 alcoxi o C_2-C_6 alcanoil; provisto que al menos uno de R_{30} R_{45} no es H. En otra incorporación, ambos grupos R_{51} pares que son alfa al anillo-B son F. En una incorporación ulterior, R_{30} es halógeno mientras R_{45} es H. En otra ulterior incorporación, R_{30} es H mientras R_{45} es halógeno . En una incorporación ulterior, los grupos R51 pares que son alfa al anillo-B son

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ambos hidrógeno. En otra ulterior incorporación, al menos uno de los grupos R_{51} pares que son alfa al anillo-B es halógeno . En otra ulterior incorporación, los grupos R51 pares que son alfa al anillo-B son ambos halógenos . En aún otra ulterior incorporación, los grupos R51 pares que son alfa al anillo-B forman un grupo oxo. En otra incorporación más, los grupos R51 pares que son alfa al anillo-B forman un C_2-C_4 grupo alquenil. En otra incorporación más, los grupos R_{51} pares que son alfa al anillo-B forman una oxima o una C_1-C_4 alquilada oxima (*e.g.*, O- metil oxima).

En aún otra incorporación de este aspecto , R_{35} R_{40} son H; R_{30} R_{45} son independientemente halógeno (*e.g.*, F, Cl o Br), metil o metoxi. En otra incorporación, ambos grupos R_{51} pares que son alfa al anillo-B son F. En una incorporación ulterior, R_{30} es halógeno . En otra ulterior incorporación, R_{45} es halógeno . En una incorporación ulterior, los grupos R51 pares que son alfa al anillo-B son ambos hidrógeno. En otra ulterior incorporación, al menos uno de los grupos R_{51} pares que son alfa al anillo-B es halógeno . En otra ulterior incorporación, los grupos R51 pares que son alfa al anillo-B son ambos halógenos . En aún otra ulterior incorporación, los grupos R51 pares que son alfa al anillo-B forman un grupo oxo. En otra incorporación más, los grupos R51 pares que son alfa al anillo-B forman un C_2-C_4 grupo alquenil. En otra incorporación más, los grupos R_{51} pares que son alfa al anillo-B forman un oxima o una C_1-C_4 alquilada oxima (*e.g.*, O- metil oxima).

En aún otra incorporación de este aspecto , R_{35} R_{40} son H; R_{30} R_{45} son independientemente halógeno (*e.g.*, F, Cl o Br), hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , C_2-C_6 alcanoil, fenil oxi, fenil o fenil C_1-C_4 alquilo . En una incorporación ulterior, los grupos R51 pares que son alfa al anillo-B son ambos hidrógeno. En otra ulterior incorporación, al menos uno de los grupos R_{51} pares que son alfa al anillo-B es halógeno . En otra ulterior incorporación, los grupos R51 pares que son alfa al anillo-B son ambos halógenos . En aún otra ulterior incorporación, los grupos R51 pares que son alfa al anillo-B forman un grupo oxo. En otra incorporación más, los grupos R51 pares que son alfa al anillo-B forman un C_2-C_4 grupo alquenil.

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En otra incorporación más, los grupos R_{51} pares que son alfa al anillo-B forman una oxima o una C_1-C_4 alquilada oxima (*e.g.*, O- metil oxima).

En aún otra incorporación de este aspecto , R_{35} R_{40} son H; R_{30} R_{45} son independientemente halógeno (*e.g.*, F, Cl o Br), hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , C_2-C_6 alcanoil, oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil o tienil.

En aún otra incorporación de este aspecto , R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno (*e.g.*, F, Cl o Br), C_1-C_4 alquilo o C_1-C_4 alcoxi ; un grupo R_{51} es halógeno o OH, mientras el otro grupo R_{51} es H. En otra incorporación más, el anillo-B es no - sustituido. En una incorporación ulterior, al menos dos de R_{30}, R_{35}, R_{40}, R_{45} son H. En otra incorporación más, R_{30}, R_{35}, R_{40}, R_{45} son H.

En aún otra incorporación de este aspecto , R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno (*e.g.*, F, Cl o Br), C_1-C_4 alquilo o C_1-C_4 alcoxi ; uno R_{51} grupo es halógeno o OH, mientras el otra R_{51} grupo es H. En otra incorporación más, el anillo-B es no - sustituido. En una incorporación ulterior, al menos uno de R_{30}, R_{35}, R_{40}, R_{45} es halógeno (*e.g.*, F, Cl o Br), C_1-C_4 alquilo o C_1-C_4 alcoxi. En otra incorporación más, dos de R_{30}, R_{35}, R_{40}, R_{45} son H.

En otra aspecto , aquí se proporcionan compuestos de Fórmula 4h, en donde R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno , C_1-C_4 alquilo , C_1-C_4 alcoxi , C_2-C_6 alcanoil; provisto que dos adyacentes carbonos de el fusionado anillo aril (el anillo al que los grupos R_{30}, R_{35}, R_{40} R_{45} están unidos) opcionalmente forman un anillo heterocicloalquilo o heteroaril, que es opcionalmente sustituido con 1, 2, 3 o 4 grupos que son independientemente C_1-C_4 alquilo , C_1-C_4 alcoxi , halógeno o C_1-C_4 alcanoil en donde el alcanoil es opcionalmente sustituido con hasta átomos 3 halógeno. En una incorporación ulterior, el anillo heterocicloalquilo es piperidinil, pirrolidinil o morfolinil, el heteroaril es pirazolil, imidazolil o piridinil, en donde cada heterocicloalquilo o heteroaril es opcionalmente sustituido con 1, 2, 3

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o 4 grupos que son independientemente C_1-C_4 alquilo , C_1-C_4 alcoxi , halógeno o C_2-C_4 alcanoil en donde el alcanoil es opcionalmente sustituido con hasta 3 átomos halógeno. En una incorporación ulterior, el anillo heterocicloalquilo es piperidinil o pirrolidinil, cada uno es opcionalmente sustituido con 1 o 2 grupos que son independientemente C_1-C_4 alquilo, C_1-C_4 alcoxi , halógeno o C_2-C_4 alcanoil en donde el alcanoil es opcionalmente sustituido con hasta 3 átomos halógeno. En una incorporación ulterior, el anillo heteroaril es pirazolil, imidazolil o piridinil, cada uno opcionalmente sustituido con 1 o 2 grupos que son independientemente C_1-C_4 alquilo , C_1-C_4 alcoxi , halógeno o C_2-C_4 alcanoil en donde el alcanoil es opcionalmente sustituido con hasta 3 átomos halógeno.

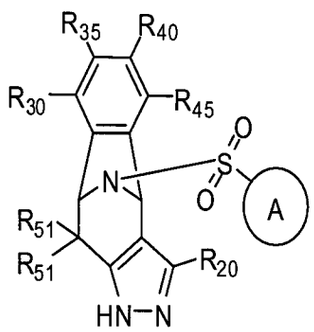
En otro aspecto , aquí se proporcionan compuestos de Fórmula 4h, en donde R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno , C_1-C_4 alquilo , C_1-C_4 alcoxi , C_2-C_6 alcanoil; provisto que dos adyacentes carbonos de el anillo aril fusionado forman un anillo benzo, que es opcionalmente sustituido con 1 a 4 grupos que son independientemente halógeno , hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , C_1-C_4 haloalquilo , C_1-C_4 haloalcoxi , CN o NO_2.

En una incorporación de este aspecto , R_{30} R_{45} son independientemente H, halógeno , hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , R_{35}, R_{40}, junto al carbono al que están unidos forman una anillo benzo, que es opcionalmente sustituido con 1 a 4 grupos que son independientemente halógeno , hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , C_1-C_4 haloalquilo , C_1-C_4 haloalcoxi , CN o NO_2. En una incorporación ulterior, el anillo benzo es no - sustituido.

En una incorporación de este aspecto , R_{30} R_{35} son independientemente H, halógeno , hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , R_{40}, R_{45}, junto al carbono al que están unidos forman una anillo benzo, que es opcionalmente sustituido con 1 a 4 grupos que son independientemente halógeno , hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , C_1-C_4 haloalquilo , C_1-C_4 haloalcoxi , CN o NO_2. En una incorporación ulterior, el anillo benzo es no - sustituido.

En una incorporación de este aspecto , R_{40} R_{45} son independientemente H, halógeno , hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , R_{30}, R_{35}, junto al carbono al que están unidos forman una anillo benzo, que es opcionalmente sustituido con 1 a 4 grupos que son independientemente halógeno , hidroxilo, C_1-C_4 alquilo , C_1-C_4 alcoxi , C_1-C_4 haloalquilo , C_1-C_4 haloalcoxi , CN o NO_2. En una incorporación ulterior, el anillo benzo es no - sustituido.

En otro aspecto, aquí se proporcionan compuestos o sales de Fórmula 4i, y.e., compuestos y/ o sales de Fórmula 4h teniendo la fórmula:



o farmacéuticamente aceptables solvatos, sales o mezclas de estos, en donde el anillo-A es como se define abajo y R_{30}, R_{35}, R_{40}, R_{45} R_{51} son como se definieron previamente, y R_{20} es H, C_1-C_4 alquilo , C_1-C_4 alcoxi , $-NR_{11}C(O)CH_3$, amino, C_1-C_4 alquilo amino, C_1-C_4 dialquilo amino, halo, CF_3, CN o $-NHC(O)CH_3$; donde R_{11} es H o C_1-C_6 alquilo . En una incorporación ulterior, R_{30}, R_{35}, R_{40}, R_{45} son independientemente H, halógeno , C_1-C_6 alquilo , C_1-C_6 haloalquilo , C_1-C_6 haloalcoxi , CN, hidroxilo, C_1-C_6 alcoxi , -C_1-C_3 alquilo -OH, -C_1-C_3 alquilo -alcoxi , fenil oxi, $-S(O_2)R_{10}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil, tienil, fenil o fenil C_1-C_4 alquilo , donde las porciones fenil de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquilo , C_1-C_6 alcoxi o halógeno
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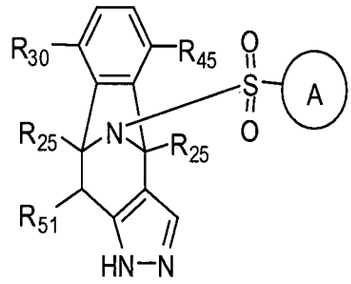
En otro aspecto, los compuestos de Fórmula 4i son compuestos o sales de Fórmula 4i1:



incluyendo estereoisómeros, tautómeros mezclas de estereoisómeros / o tautómeros, y / o farmacéuticas sales de éstos, en donde

R_{30} y R_{45} son independientemente H, halógeno , C_1-C_6 alquilo , C_1-C_6 haloalquilo , C_1-C_6 haloalcoxi , CN, hidroxilo, C_1-C_6 alcoxi , -C_1-C_3 alquilo -OH, -C_1-C_3 alquilo -alcoxi , fenil oxi, C_2-C_6 alquenil, C_2-C_6 alquinil, C_2-C_6 halo alquenil, C_2-C_6 halo alquilonil, -C(O)OR_{11}, -S(O_2)R_{10}, -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alcanoil, oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil, tienil, fenil o fenil C_1-C_4 alquilo , donde las porciones fenil de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquilo , C_1-C_6 alcoxi , C_1-C_4 halo alquilo (*e.g.*, CF_3) o halógeno ;

R_{51} es H, C_1-C_4 alquilo, F, Cl, Br, CN, amino, mono alquilo amino, dialquilo amino, OH o CF_3.

En una incorporación de este aspecto , R_{30} y R_{45} son independientemente H, halógeno , C_1-C_6 alquilo , hidroxilo, C_1-C_6 alcoxi , -C_1-C_3 alquilo -OH o -C_1-C_3 alquilo -alcoxi ; R_{51} es H, metil, etil, F, Cl, Br o CF_3.

En una incorporación de este aspecto , R_{30} y R_{45} son independientemente H, halógeno , C_1-C_6 alquilo , hidroxilo, C_1-C_6 alcoxi , -C_1-C_3 alquilo -OH o -C_1-C_3 alquilo -alcoxi ; R_{51} es CN, amino, mono alquilo amino, dialquilo amino.

En una incorporación de este aspecto, al menos uno de R_{30} y R_{45} es C_2-C_6 alquenil, C_2-C_6 alquinil, C_2-C_6 halo alquenil, C_2-C_6 halo alquilonil o -C(O)OR_{11}; R_{51}

es H, metil, etil, F, Cl, Br o CF_3. En una incorporación ulterior, R_{11} es H o C_1-C_4 alquilo.

En una incorporación de este aspecto , R_{30} y R_{45} son independientemente H, halógeno , C_1-C_4 alquilo , hidroxilo, C_1-C_4 alcoxi , -C_1-C_2 alquilo -OH o -C_1-C_2 alquilo - C_1-C_4 alcoxi ; R_{51} es H, metil, etil, F, Cl o CF_3.

En una incorporación de este aspecto, R_{30} y R_{45} son independientemente H, F o Cl; R_{51} es H, F, Cl o Br.

En aún otra incorporación de este aspecto, al menos uno de R_{30} R_{45} es F; R_{51} es H, F ó OH.

En otra incorporación de este aspecto, solo uno de R_{30} y R_{45} es F, mientras el otro es H; R_{51} es H, F o OH.

En otra incorporación de este aspecto, R_{30} y R_{45} son ambos H; R_{51} es H o F.

En otra incorporación de este aspecto, R_{30} y R_{45} son ambos H; R_{51} es F.

En otra incorporación de este aspecto, R_{30} y R_{45} son ambos H; R_{51} es OH.

En otra incorporación de este aspecto, uno de R_{30} R_{45} es H, mientras el otro es F, R_{51} es OH.

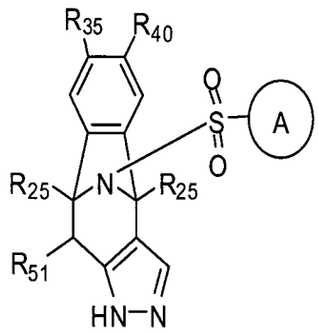
En otra incorporación de este aspecto, R_{30}, R_{45}, y R_{51} son H.

En aún otra incorporación de este aspecto, solo uno de R_{30}, R_{45}, R_{51} es F.

En aún otra incorporación de este aspecto, R_{30}, R_{45}, R_{51} son F.

En una incorporación de este aspecto , R_{30} y R_{45} son independientemente H, -C(O)OR_{11} , -S(O_2)R_{10}, -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$ o C_2-C_6 alcanoil; donde cada R_{11} es independientemente H o C_1-C_4 alquilo .

En otro aspecto, los compuestos de Fórmula 4i son compuestos de Fórmulas 4i2:



incluyendo estereoisómeros, tautómeros mezclas de estereoisómeros y / o tautómeros, y / o sales farmaceuticas de estos, en donde

R_{35} y R_{40} son independientemente H, halógeno , C_1-C_6 alquilo , C_1-C_6 haloalquilo , C_1-C_6 haloalcoxi , CN, hidroxilo, C_1-C_6 alcoxi , -C_1-C_3 alquilo -OH, -C_1-C_3 alquilo -alcoxi , fenil oxi, C_2-C_6 alquenil, C_2-C_6 alquinil, C_2-C_6 halo alquenil, C_2-C_6 halo alquilonil, -C(O)OR_{11}, -S(O_2)R_{10}, --$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alcanoil, oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil, tienil, fenil o fenil C_1-C_4 alquilo , en donde las porciones fenil de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquilo , C_1-C_6 alcoxi , C_1-C_4 halo alquilo (*e.g.* CF_3) o halógeno ; y

R_{51} es H, C_1-C_4 alquilo, F, Cl, Br, CN, CN, amino, mono alquilo amino, dialquilo amino, OH o CF_3.

En una incorporación de este aspecto , R_{35} y R_{40} son independientemente H, halógeno , C_1-C_6 alquilo , hidroxilo, C_1-C_6 alcoxi , -C_1-C_3 alquilo -OH o -C_1-C_3 alquilo -alcoxi ; R_{51} es H, metil, etil, F, Cl o CF_3.

En una incorporación de este aspecto , R_{35} y R_{40} son independientemente H, halógeno , C_1-C_6 alquilo , hidroxilo, C_1-C_6 alcoxi , -C_1-C_3 alquilo -OH o -C_1-C_3 alquilo -alcoxi ; R_{51} es CN, amino, mono alquiloamino, dialquiloamino.

En una incorporación de este aspecto, en al menos uno de R_{35} y R_{40} es C_2-C_6 alquenil, C_2-C_6 alquinil, C_2-C_6 halo alquenil, C_2-C_6 halo alquilonil o -C(O)OR_{11}; R_{51} es H, metil, etil, F, Cl, Br o CF_3. En una ulterior incorporación, R_{11} es H o C_1-C_4 alquilo.

En una incorporación de este aspecto, R_{35} y R_{40} son independientemente H, halogeno, C_1-C_4 alquilo, hidroxil, C_1-C_4 alkoxi, -C_1-C_2 alquilo-OH o -C_1-C_2 alquilo-C_1-C_4 alkoxi; R_{51} es H, metil, etil, F, Cl o CF_3.

En una incorporación de este aspecto, R_{35} y R_{40} son independientemente H, F o Cl; R_{51} es H, F o Cl.

En aún otra incorporación de este aspecto, en al menos uno de R_{35} R_{40} es F; R_{51} es H, F o OH.

En otra incorporación de este aspecto, solo uno de R_{35} R_{40} es F, mientras el otro es H; R_{51} es H, F o OH.

En otra incorporación de este aspecto, R_{35} R_{40} son ambos H; R_{51} es H, F, Cl o Br.

En otra incorporación de este aspecto, R_{35} R_{40} son ambos H; R_{51} es CN, amino, mono alquiloamino o dialquiloamino.

En otra incorporación de este aspecto, R_{35} R_{40} son ambos H; R_{51} es F.

En otra incorporación de este aspecto, R_{35} R_{40} son ambos H; R_{51} es OH.

En otra incorporación de este aspecto, uno de R_{35} y R_{40} es H, mientras el otro es F,y R_{51} es OH.

En otra incorporación de este aspecto, R_{35}, R_{40}, y R_{51} son H.

En otra incorporación más de este aspecto, solo uno de R_{35}, R_{40}, y R_{51} es F.

En otra incorporación más de este aspecto, R_{35}, R_{40}, y R_{51} son F.

En una incorporación de este aspecto, R_{35} y R_{40} son independientemente H, -$C(O)OR_{11}$, -$S(O_2)R_{10}$, -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$ o C_2-C_6 alcanoil; donde cada R_{11} es independientemente H o C_1-C_4 alquil.

En otro aspecto, se proporcionan aquí compuestos en donde el anillo-C es fenil sustituido con R_{30}, R_{35}, R_{40}, y R_{45}; o heteroaril, en donde el heteroaril, es opcionalmente sustituido con H, halógeno, C_1-C_6 alquil, C_1-C_6 haloalquil, C_1-C_6 haloalcoxi, CN, hidroxil, C_1-C_6 alcoxi, -C_1-C_3 alquil-OH, -C_1-C_3 alquil-alcoxi, feniloxi, -$S(O_2)R_{10}$, -$SO_2NR_{11}R_{11}$, -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil, tienil, fenil o fenil C_1-C_4 alquil, en donde las porciones fenil de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_4 haloalquil o halógeno;

R_{30}, R_{35}, R_{40}, y R_{45} son independientemente H, halógeno, C_1-C_6 alquil, C_2-C_6 alquenil, C_2-C_6 alquinil, C_2-C_8 haloalquenil, C_2-C_8 haloalquilnil, -$SO_2NR_{11}R_{11}$, arilalquil, cicloalquil, C_1-C_6 haloalquil, C_1-C_6 haloalcoxi, CN, NO_2, hidroxil, C_1-C_6 alcoxi, -C_1-C_6 alquil-OH, -C_1-C_6 alquil-C_1-C_6 alcoxi, ariloxi, -$S(O_2)R_{10}$, -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, hetero arilalquil, heteroaril, en donde cada grupo heteroaril es opcionalmente sustituido con un grupo C_1-C_6 alquil, heterociclo alquilalquil, heterociclo alquil, en donde cada grupo heterocicloalquil es opcionalmente sustituido *e.g.*, con uno o dos grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi o halógeno, aril, ariloxi o arilalquil, donde las porciones aril de arriba son opcionalmente sustituidas *e.g.*, con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi, hidroxil, C_1-C_4 haloalquil o halógeno; y

en donde cuando el anillo-C es aril o heteroaril, dos adyacentes carbonos del anillo-C opcionalmente forman un anillo heterocicloalquil o heteroaril, cada cual opcionalmente sustituido con uno o más grupos que son independientemente alquil, alcoxi, halógeno o C_2-C_4 alcanoil en donde el grupo alcanoil es opcionalmente ulteriormente sustituido con hasta 3 átomos halógeno; o dos adyacentes carbonos del anillo-C opcionalmente forman un anillo benzo el cual es opcionalmente sustituido *e.g.*, con 1 a 4 grupos que son independientemente halógeno, hidroxil, alquil, alcoxi, haloalquil, haloalcoxi, CN o NO_2.

En otro aspecto, se proporcionan aquí compuestos de Fórmulas 4j, i.e., compuestos de Fórmulas 4, 4a, 4b, 4c, y/o 4d, en donde el anillo-C es un anillo heteroaril o heterocicloalquil que es opcionalmente sustituido con uno o más grupos que son independientemente halógeno, C_1-C_6 alquil, C_1-C_6 haloalquil, C_1-C_6 haloalcoxi, C_2-C_8 alquenil, C_2-C_8 alquinil, C_2-C_8 haloalquenil, C_2-C_8 haloalquilnil, -C(O)OR_{11}, CN, hidroxil, C_1-C_6 alcoxi, -C_1-C_3 alquil-OH, -C_1-C_3 alquil-alcoxi, feniloxi, -S(O_2)R_{10}, -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alcanoil, oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil, tienill, fenil o fenil C_1-C_4 alquil, en donde las porciones fenil de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_4 haloalquil (*e.g.* CF_3) o halógeno. En una ulterior incorporación, el anillo-C es opcionalmente sustituido con C_1-C_4 alquil, C_1-C_4 alcoxi, halógeno, C_1-C_4 haloalquil (*e.g.* CF_3) o C_1-C_4 haloalcoxi (*e.g.*, OCF_3). En una más ulterior incorporación, el anillo-C es no-sustituido. En una incorporación, cada R_{10} y R_{11} es independientemente C_1-C_6 alquil o fenil; y adicionalmente R_{11} puede ser H.

En una ulterior incorporación de este aspecto, el anillo-C es a heteroaril sustituido en al menos un grupo que es halógeno, C_1-C_6 alquil, C_1-C_6 haloalquil, C_1-C_6 haloalcoxi, C_2-C_8 alquenil, C_2-C_8 alquinil, C_2-C_8 haloalquenil, C_2-C_8 haloalquilnil.

En una ulterior incorporación de este aspecto, el anillo-C es a heteroaril sustituido en al menos un grupo que es -C(O)OR_{11}, CN, hidroxilo, C_1-C_6 alcoxi, -C_1-C_3 alquil-OH, -C_1-C_3 alquil-alcoxi, feniloxi, -S(O_2)R_{10}, -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$ o C_2-C_6 alcanoil.

En una ulterior incorporación de este aspecto, el anillo-C es a heteroaril sustituido en al menos un grupo que es oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil, tienil, fenil o fenil C_1-C_4 alquil, en donde las porciones fenil de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_4 haloalquil (*e.g.* CF_3) o halógeno.

En una ulterior incorporación de este aspecto, el anillo-C es a heterocicloalquil sustituido en al menos un grupo que es halógeno, C_1-C_6 alquil, C_1-C_6 haloalquil,

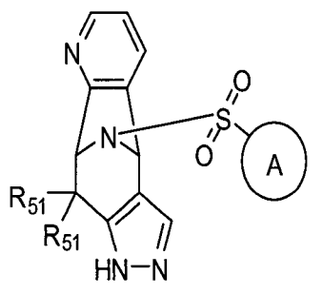
C_1-C_6 haloalcoxi, C_2-C_8 alquenil, C_2-C_8 alquinil, C_2-C_8 haloalquenil o C_2-C_8 haloalquilnil.

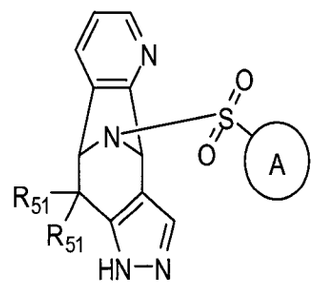
En una ulterior incorporación de este aspecto, el anillo-C es a heterocicloalquil sustituido con en least uno grupo que es -C(O)OR_{11}, CN, hidroxil, C_1-C_6 alcoxi, -C_1-C_3 alquil-OH, -C_1-C_3 alquil-alcoxi, feniloxi, -S(O_2)R_{10}, -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$ o C_2-C_6 alcanoil.

En una ulterior incorporación de este aspecto, el anillo-C es a heterocicloalquil sustituido en al menos un grupo que es oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil, tienill, fenil o fenil C_1-C_4 alquil, en donde las porciones fenil de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_4 haloalquil (*e.g.* CF_3) o halógeno.

En una incorporación de este aspecto, el anillo-C es un opcionalmente sustituido (como se describe arriba) anillo piridil. En una ulterior incorporación, el anillo-C es un no-sustituido anillo piridil. En una más ulterior incorporación, los grupos pares R_{51} que son alfa al Anillo-B son ambos H. En una ulterior incorporación, los grupos pares R_{51} que son alfa al Anillo-B son ambos halógenos. En otra incorporación, ambos grupos R_{51} que son alfa al Anillo-B son F. En una más ulterior incorporación, los grupos pares R_{51} que son alfa al Anillo-B forman un grupo oxo. En una más ulterior incorporación, los grupos pares R_{51} que son alfa al Anillo-B forman un grupo C_2-C_4 alquenil. En una más ulterior incorporación, los grupos pares R_{51} que son alfa al Anillo-B forman una oxima o a C_1-C_4 alquilada oxima (*e.g.*, O-metil oxima).

En otra incorporación de este aspecto, los compuestos de Fórmula 4j tienen las Fórmulas:





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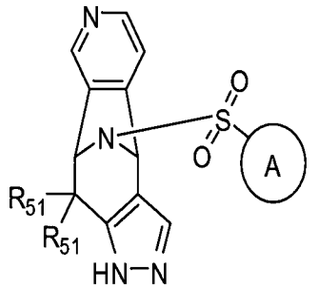
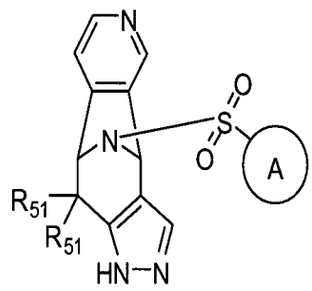
Fórmula 4c1



Fórmula 4c2



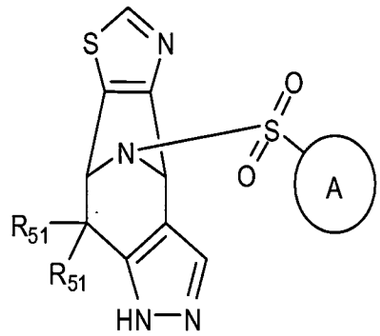
Fórmula 4c3

Fórmula 4c4

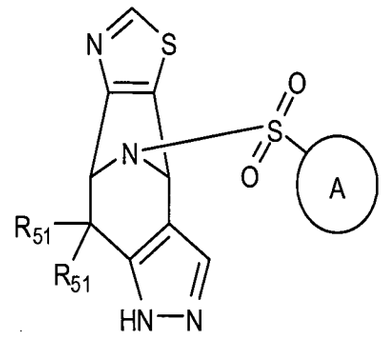
En donde cada R_{51} es H, C_1-C_4 alquil, F, Cl, Br, CN, amino, mono alquilamino o dialquilamino, OH, CF_3 o ambos grupos R_{51} forman un grupo oxo. En una incorporación, al menos uno de los grupos R_{51} es H. En otra incorporación, un grupo R_{51} es H mientras que el otro R_{51} es F o Cl. En otra incorporación, un R_{51} es H, y el otro R_{51} es OH. En otra incorporación más, ambos grupos R_{51} son halógeno (*e.g.*, F). En otra incorporación más, ambos grupos R_{51} forman un grupo oxo. En una más ulterior incorporación, los grupos pares R_{51} que son alfa al Anillo-B forman un grupo C_2-C_4 alquenil. En una más ulterior incorporación, los grupos pares R_{51} que son alfa al Anillo-B forman una oxima o a C_1-C_4 alquilada oxima (*e.g.*, O-metil oxima).

En una incorporación de este aspecto, el anillo-C es un opcionalmente sustituido (as described above) anillo tiazolil. En una más ulterior incorporación, los grupos pares R_{51} que son alfa al Anillo-B son ambos H. En otra ulterior incorporación, los grupos pares R_{51} que son alfa al Anillo-B son ambos halógenos. En otra incorporación, ambos grupos R_{51} que son alfa al Anillo-B son F. En una más ulterior incorporación, los grupos pares R_{51} que son alfa al Anillo-B forman un grupo oxo. En una más ulterior incorporación, los grupos pares R_{51} que son alfa al Anillo-B forman un grupo C_2-C_4 alquenil. En otra ulterior incorporación, los grupos pares R_{51} que son alfa al Anillo-B forman una oxima o una C_1-C_4 alquilada oxima (*e.g.*, O-metil oxima).

En otra incorporación de este aspecto, los compuestos de Fórmula 4j tienen las fórmulas:



Fórmula 4I1

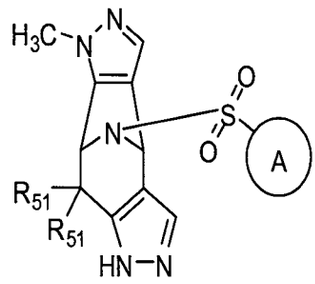


Fórmula 4I2

en donde cada R_{51} es H, C_1-C_4 alquil, F, Cl, Br, CN, amino, mono alquilamino o dialquilamino, OH, CF_3 o ambos grupos R_{51} forman un grupo oxo grupo. En una incorporación, al menos un R_{51} es H. En otra incorporación, un R_{51} es H y el otro R_{51} es F o Cl. En otra incorporación, un R_{51} es H, y el otro R_{51} es OH. En otra incorporación más, ambos grupos R_{51} son halógeno (*e.g.*, F). En otra incorporación más, ambos grupos R_{51} forman un grupo oxo. En una más ulterior incorporación, los grupos pares R_{51} que son alfa al Anillo-B forman un grupo C_2-C_4 alquenil. En una más ulterior incorporación, los grupos pares R_{51} que son alfa al Anillo-B forman una oxima o a C_1-C_4 alquilada oxima (*e.g.*, O-metil oxima).

En una incorporación de este aspecto, el anillo-C es un opcionalmente sustituido (como se describe arriba) anillo pirazolil. En una ulterior incorporación, el anillo-C es un no-sustituido anillo pirazolil. En una más ulterior incorporación, los grupos pares R_{51} que son alfa al Anillo-B son ambos H. En otra ulterior incorporación, los grupos pares R_{51} que son alfa al Anillo-B son ambos halógenos. En otra incorporación, ambos grupos R_{51} que son alpha al Anillo-B son F. En una más ulterior incorporación, los grupos pares R_{51} que son alfa al Anillo-B forman un grupo oxo. En una más ulterior incorporación, el anillo-C es sustituido con C_1-C_4 alquil. En otra incorporación de este aspecto, uno los grupos R_{51} es H, mientras que el otro es halógeno o OH.

En otra incorporación de este aspecto, los compuestos de Fórmula 4j tienen la fórmula:



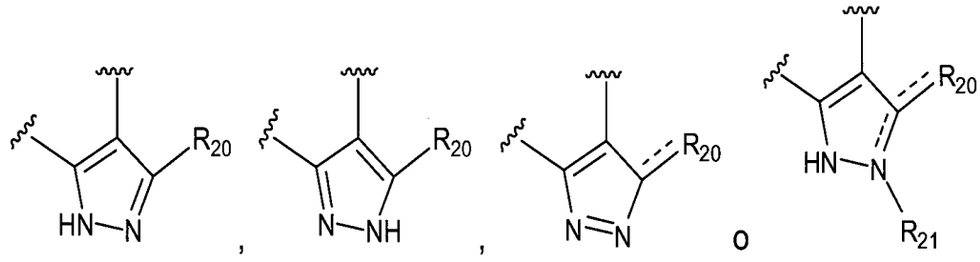
Fórmula 4m

En donde cada R_{51} es H, C_1-C_4 alquil, F, Cl, Br, CN, amino, mono alquilamino o dialquilamino, OH, CF_3 o ambos grupos R_{51} forman un grupo oxo. En una incorporación, al menos un R_{51} es H. En otra incorporación, un R_{51} es H mientras el otro es R_{51} es F o Cl. En otra incorporación, un R_{51} es H, mientras el otro R_{51} es OH. En otra incorporación más, both R_{51} grupos son halógeno (*e.g.*, F). En otra incorporación más, ambos grupos R_{51} forman un grupo oxo. En una más ulterior incorporación, los grupos pares R_{51} que son alfa al Anillo-B forman un grupo C_2-C_4 alquenil. En una más ulterior incorporación, los grupos pares R_{51} que son alfa al Anillo-B forman una oxima o a C_1-C_4 alquilada oxima (*e.g.*, O-metil oxime).

En una incorporación de este aspecto, el anillo-C es un opcionalmente sustituido (como se describe arriba) anillo tienil. En una ulterior incorporación, el anillo-C es una no-sustituido tienill ring. En una más ulterior incorporación, los grupos pares R_{51} que son alfa al Anillo-B son ambos H. En otra ulterior incorporación, los grupos pares R_{51} que son alfa al Anillo-B son ambos halógenos. En otra incorporación, ambos grupos R_{51} que son alfa al Anillo-B son F. En una más ulterior incorporación, los grupos pares R_{51} que son alfa al Anillo-B forman un grupo oxo. En una todavía más ulterior incorporación, el anillo-C es sustituido con C_1-C_4 alquil. En otra incorporación de este aspecto, uno de los grupos R_{51} es H, mientras el otro es halógeno o OH.

En otro aspecto, se proporcionan aquí compuestos de Fórmulas 1 (y aspectos e incorporaciones de estos), 2 (y aspectos e incorporaciones de estos), 3 (y

aspectos e incorporaciones de estos), y 4 (y aspectos e incorporaciones de estos), (siempre que el Anillo-B no sea definido de otra forma) en donde el Anillo-B es

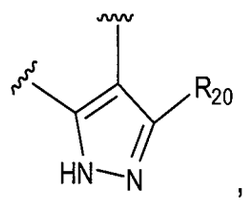


En donde la unión punteada representa una segunda unión opcional;

R_{20} es H, oxo (solo si hay un doble enlace al grupo R_{20}), C_1-C_6 alquil, C_1-C_6 alcoxi, amino, C_1-C_6 alquilamino, C_1-C_6 dialquilamino, -$NR_{11}C(O)R_{10}$, halo, CF_3 o –$NHC(O)CH_3$;

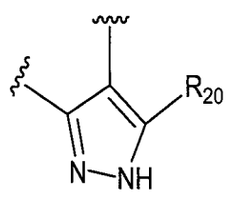
R_{21} es ausente o hidrógeno; previsto que cuando hay dos uniones punteadas en la fórmula del anillo solo una puede formaruna unión doble; más ulteriormente, R_{21} está ausente cuando la unión punteada al nitrógeno es una unión, y por lo tanto forma una doble unión.

En otra incorporación de este aspecto, el Anillo-B tiene la fórmula:



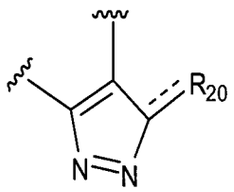
En donde R_{20} es H, C_1-C_4 alquil, C_1-C_4 alcoxi, amino, C_1-C_4 alquilamino, C_1-C_4 dialquilamino, -$NR_{11}C(O)R_{10}$, halo o CF_3. En una ulterior incorporación, R_{20} es H, C_1-C_4 alquil, C_1-C_4 alcoxi, amino, C_1-C_4 alquilamino, C_1-C_4 dialquilamino, halo o CF_3. En una ulterior incorporación, R_{20} es H.

En otra incorporación de este aspecto, el Anillo-B tiene la fórmula:



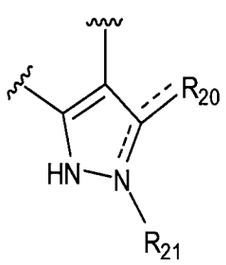
En donde R_{20} es H, C_1-C_4 alquil, C_1-C_4 alcoxi, amino, C_1-C_4 alquilamino, C_1-C_4 dialquilamino, $-NR_{11}C(O)R_{10}$, halo o CF_3. En una ulterior incorporación, R_{20} es H.

En otra incorporación de este aspecto, el Anillo-B tiene la fórmula:



en donde R_{20} es H, oxo (solo si hay un doble enlace al grupo R_{20}), C_1-C_4 alquil, C_1-C_4 alcoxi, amino, C_1-C_4 alquilamino, C_1-C_4 dialquilamino, $-NR_{11}C(O)R_{10}$, halo o CF_3; donde la unión punteada representa una segunda unión opcional. En una ulterior incorporación, R_{20} es oxo y la línea de puntos es una unión. En otra incorporación, R_{20} es H.

En otra incorporación de este aspecto, el Anillo-B tiene la fórmula:

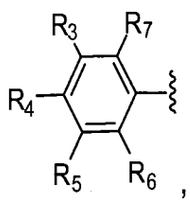


R_{20} es H, oxo (solo si hay un doble enlace en el grupo R_{20}), C_1-C_4 alquil, C_1-C_4 alcoxi, amino, C_1-C_4 alquilamino, C_1-C_4 dialquilamino, $-NR_{11}C(O)R_{10}$, halo o CF_3; y R_{21} está ausente o hidrógeno; y donde la unión punteada representa una opcional segunda unión; previsto que solo una de las dos uniones punteadas pueda seruna segunda unión, y por tanto formar una unión doble; más ulteriormente, R_{21} está ausente cuando la unión punteada al nitrógeno es una unión, y por tanto forma una doble unión al nitrógeno.

En otro aspecto, en los compuestos de Fórmulas 1 (y aspectos e incorporaciones de estos), 2 (y aspectos e incorporaciones de estos), 3 (y aspectos e incorporaciones de estos), y 4 (y aspectos e incorporaciones de estos), el Anillo-A es fenil o naftil (preferible fenil), el cual es opcionalmente sustituido en posiciones

sustituibles con halógeno, C_1-C_6 alquil, C_2-C_6 alquenil, C_2-C_6 alquinil, C_1-C_6 alcoxi, haloalquil, haloalcoxi, hidroxil, hidroxialquil, CN, feniloxi, -$S(O)_{0-2}$-(C_1-C_6 alquil), -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, C_0-C_3alquilCO_2R_{10}, piridil, tienill, furanil, pirrolil, pirrolidinil, piperidinil, piperazinil, fenil, fenil C_1-C_4 alquil, -OCH_2O-, -OCH_2CH_2O- o -$SO_2NR_{11}R_{11}$, en donde cada metileno de -OCH_2O- o -OCH_2CH_2O- es opcionalmente sustituido con uno o dos C_1-C_4 alquil grupos.

En una incorporación de este aspecto, el Anillo-A es fenil, y tiene la siguiente fórmula:



En donde,

R_3, R_4, R_5, R_6, R_7 son independientemente de cada otro H, halógeno, C_1-C_6 alquil, C_1-C_6 haloalquil, C_1-C_6 haloalcoxi, CN, hidroxil, C_1-C_6 alcoxi, -C_1-C_3 alquil-OH, -C_1-C_3 alquil-alcoxi, feniloxi, -$S(O_2)R_{10}$, -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil, tienill, fenil o fenil C_1-C_4 alquil, donde las porciones fenil de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_4 haloalquil (*e.g.* CF_3) o halógeno; o

R_4 y R_5 o R_5 y R_6 y el carbono al cual eli están unidos forman un anillo heterocicloalquil o heteroaril el cual es opcionalmente sustituido con 1, 2, 3 o 4 grupos que son independientemente C_1-C_4 alquil, C_1-C_4 alcoxi, halógeno o C_1-C_4 alcanoil en donde el alcanoil grupo es opcionalmente sustituido con hasta 3 átomos halógeno; o

R_4 y R_5 o R_5 y R_6 y los carbonos a los que están unidos forman un anillo benzo el cual es opcionalmente sustituido con 1 a 5 grupos opcionalmente sustituidos que

son independientemente halógeno, hidroxil, alquil, alcoxi, haloalquil, haloalcoxi, CN o NO_2.

En una incorporación de este aspecto, R_3 es H, halógeno, C_1-C_6 alquil, C_1-C_6 alcoxi, haloalquil o CN; R_4 es H, halógeno; C_1-C_6 alquil; C_1-C_6 alcoxi; C_1-C_6 haloalquil; haloalcoxi, CN, feniloxi, -SO_2-(C_1-C_6 alquil), -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alcanoil, oxazolil, pirazolil, tiazolil, piridil, furanil, tienill o fenil; y R_5 es H, C_1-C_6 alquil, -SO_2-$NR_{11}R_{11}$ o halógeno.

En una incorporación de este aspecto, R_3, R_4, R_5, R_6, R_7 son independientemente de cada otro H, halógeno, C_1-C_4 alquil, C_1-C_4 haloalquil (*e.g.*, CF_3), C_1-C_4 haloalcoxi (*e.g.*, OCF_3), CN, hidroxil, C_1-C_4 alcoxi, -C_1-C_3 alquil-OH, -C_1-C_3 alquil-C_1-C_4 alcoxi, feniloxi, -S(O_2)R_{10}, -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$ o C_2-C_4 alcanoil. En una ulterior incorporación, cada R_{10} y R_{11} es independientemente C_1-C_6 alquil o fenil; y adicionalmente R_{11} puede ser H.

En una incorporación de este aspecto, R_3, R_4, R_5, R_6, R_7 son independientemente de cada otro H, halógeno, C_1-C_4 alquil, oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil, tienill, fenil o fenil C_1-C_4 alquil, donde las porciones fenil de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_4 haloalquil (*e.g.* CF_3) o halógeno.

En una incorporación de este aspecto, R_6 y R_7 son independientemente H o metil.

En una incorporación de este aspecto, R_3 y R_5 son independientemente H, halo, CF_3, CHF_2 o metil.

En una incorporación de este aspecto, R_4, R_6 y R_7 son independientemente H, halo, CF_3, CHF_2 o metil.

En una incorporación de este aspecto, R_4 es H, halógeno (en un aspecto, i, Br, F o Cl), C_1-C_6 alquil opcionalmente sustituido con halógeno o hidroxil, C_1-C_6 alcoxi, OCF_3 o CN.

En una incorporación de este aspecto, R_4 es feniloxi, $-SO_2-(C_1-C_6$ alquil), $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, oxazolil, pirazolil, tiazolil, piridil, furanil, tienill o fenil.

En una incorporación de este aspecto, R_4 es $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$ o $-O-C(O)NR_{11}R_{11}$.

En una incorporación de este aspecto, R_4 es $-SO_2NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$ o $-NR_{11}SO_2R_{10}$.

En una incorporación de este aspecto, R_4 es $-SO_2NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$ o $-NR_{11}SO_2R_{10}$ y R_3, R_5, R_6, y R_7 son H.

En una incorporación de este aspecto, R_4 es $-C(O)NR_{11}R_{11}$.

En una incorporación de este aspecto, R_4 es $-C(O)NR_{11}R_{11}$, y R_3, R_5, R_6, y R_7 son H.

En una incorporación de este aspecto, R_4 es $-O-C(O)NR_{11}R_{11}$.

En una incorporación de este aspecto, R_4 es $-O-C(O)NR_{11}R_{11}$, y R_3, R_5, R_6, y R_7 son H.

En una incorporación de este aspecto, R_4 es $-NR_{11}R_{11}$.

En una incorporación de este aspecto, R_4 es $-NR_{11}R_{11}$, y R_3, R_5, R_6, y R_7 son H.

En una incorporación de este aspecto, R_3, R_4, R_5, R_6, y R_7 son H, halo, CF_3, CHF_2 o metil.

En una incorporación de este aspecto, R_3, R_5, R_6, y R_7 son H.

En una incorporación de este aspecto, R_4 es cloro.

En una incorporación de este aspecto, R_4 es cloro, y R_3, R_5, R_6, y R_7 son H.

En una incorporación de este aspecto, R_4 es trihalometil, y R_3, R_5, R_6, y R_7 son H. En una incorporación, R_4 es CCl_3 o CF_3. En otra incorporación, R_4 es CF_3.

En una incorporación de este aspecto, al menos uno de R_3, R_4 o R_5 es cloro, y R_6 y R_7 son H.

En una incorporación de este aspecto, R_3 es hidrógeno, halógeno, C_1-C_4 alquil, C_1-C_4 alcoxi, CF_3 o CN; R_4 es hidrógeno, halógeno, C_1-C_4 alquil, C_1-C_4 alcoxi, CF_3, OCF_3, CN, feniloxi, --SO_2-(C_1-C_4 alquil), -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$ o C_1-C_4 alcanoil, y R_5 es hidrógeno, C_1-C_4 alquil, -$SO_2NR_{11}R_{11}$ o halógeno. En una incorporación, R_6 y R_7 son H.

En una incorporación de este aspecto, R_4 es halógeno (en un aspecto, F o Cl), C_1-C_4 alquil, C_1-C_4 alcoxi, CF_3, OCF_3 o CN. En una ulterior incorporación, R_3, R_5 R_6, y R_7 son hidrógeno.

En una incorporación de este aspecto, R_4, R_5 R_6, y R_7 son hidrógeno.

En una incorporación de este aspecto, R_3 es hidrógeno, halógeno, C_1-C_4 alquil, C_1-C_4 alcoxi, CF_3 o CN; R_4 es oxazolil, pirazolil, tiazolil, piridil, furanil, tienill o fenil; y R_5 es hidrógeno, C_1-C_4 alquil, -$SO_2NR_{11}R_{11}$ o halógeno. En una incorporación de este aspecto, R_6 y R_7 son H.

En una incorporación de este aspecto, R_3 es -C(O)$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$ o -O-C(O)$NR_{11}R_{11}$, R_4 es H, C_1-C_4 alquil o halógeno, y R_5, R_6, y R_7 son H.

En una incorporación de este aspecto, R_4 es halógeno (en un aspecto, F o Cl), CH_3, OCH_3, CF_3 o OCF_3.

En una incorporación de este aspecto, R_3 es hidrógeno, halógeno, C_1-C_2 alquil, C_1-C_2 alcoxi, CF_3 o CN; R_4 es hidrógeno, halógeno, C_1-C_2 alquil, C_1-C_2 alcoxi, C_1-C_2 haloalquil, C_1-C_2 haloalcoxi, CN, -$NR_{11}R_{11}$, C_2-C_3 alcanoil, oxazolil, pirazolil, tiazolil, piridil, furanil o tienill; R_5 es hidrógeno, CH_3 o F; y R_6 y R_7 son independientemente hidrógeno o halógeno.

En una incorporación de este aspecto, R_4 es CF_3 u OCF_3. En una incorporación, R_6 y R_7 son H. En una ulterior incorporación, R_3 y R_5 son también H.

En una incorporación de este aspecto, R_4 y R_5 o R_5 y R_6 y el carbono al cual están unidos forman un anillo benzo el cual es opcionalmente sustituido con 1 ó 2 grupos opcionalmente sustituidos que son independientemente halógeno, hidroxil, C_1-C_4 alquil, C_1-C_4 alcoxi, C_1-C_3 haloalquil, C_1-C_3 haloalcoxi, CN o NO_2.

En una incorporación de este aspecto, R_4 y R_5 o R_5 y R_6 y el carbono al cual están unidos forman un anillo piridil, pirrolil, tienill, furanil, pirrolidinil, piperidinil, cada cual es opcionalmente sustituido con 1, 2 o 3 grupos que son independientemente C_1-C_4 alquil, C_1-C_4 alcoxi, halógeno o C_1-C_4 alcanoil en donde el alcanoil grupo es opcionalmente sustituido con hasta 3 átomos halógeno (*e.g.*, F).

En una incorporación de este aspecto, R_6 y R_7 son independientemente hidrógeno o metil.

En una incorporación de este aspecto, R_3 y R_5 son independientemente hidrógeno, halo o metil.

En una incorporación de este aspecto, R_3 y R_4 o R_5 y R_6 son $-OCH_2O-$, $-OCH_2CH_2O-$, en donde cada metileno de $-OCH_2O-$ o $-OCH_2CH_2O-$ es opcionalmente sustituido con uno o dos grupos C_1-C_4 alquil. En una incorporación, cada metileno es no-sustituido. En otra incorporación, al menos un metileno es sustituido con al menos un grupo C_1-C_4 alquil.

En una incorporación de este aspecto, R_{11} en cada ocurrencia es independientemente H o C_1-C_5 alquil. En una ulterior incorporación, R_{10} es C_1-C_4 alquil o fenil.

En otro aspecto, en los compuestos de Fórmulas 1 (y aspectos e incorporaciones de estos), 2 (y aspectos e incorporaciones de estos), 3 (y aspectos e incorporaciones de estos), y 4 (y aspectos y incorporaciones de estos), el Anillo-A es C_3-C_8 cicloalquil, el cual es opcionalmente sustituido en a sustituibles position con halógeno, C_1-C_6 alquil, C_2-C_6 alquenil, C_2-C_6 alquinil, C_1-C_6 alcoxi, haloalquil, haloalcoxi, hidroxil, hidroxialquil, CN, feniloxi, $-S(O)_{0-2}-(C_1$-C_6 alquil), $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, C_0-C_3alquilCO_2R_{10}, piridil, tienill, furanil, pirrolil, pirrolidinil, piperidinil, piperazinil, fenil, fenil C_1-C_4 alquil o $-SO_2NR_{11}R_{11}$, donde las porciones fenil de arriba son opcionalmente sustituido con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_4 haloalquil (*e.g.* CF_3) o halógeno.

En una incorporación de este aspecto, el C_3-C_8 cicloalquil es opcionalmente sustituido en sustituibles posiciones con halógeno, C_1-C_4 alquil, C_1-C_4 alcoxi, C_1-C_4

haloalquil, C_1-C_4 haloalcoxi, hidroxil o C_1-C_4hidroxialquil. En una incorporación, el grupo C_3-C_8 cicloalquil es sustituido con un grupo. En una incorporación, el C_3-C_8 cicloalquil grupo es sustituido con un grupo que es $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ o $-O-C(O)NR_{11}R_{11}$, donde R_{10} y R_{11} son independientemente C_1-C_4 alquil o fenil; y adicionalmente R_{11} puede ser H.

En otra incorporación de este aspecto, el C_3-C_8 cicloalquil es sustituido con uno o dos grupos que son independientemente metoxi, etoxi, metil, ethil o halógeno.

En una incorporación de este aspecto, el Anillo-A es no-sustituido ciclopropil.

En una incorporación de este aspecto, el Anillo-A es no-sustituido ciclobutil.

En una incorporación de este aspecto, el Anillo-A es no-sustituido ciclopentil.

En una incorporación de este aspecto, el Anillo-A es no-sustituido ciclohexil.

En una incorporación de este aspecto, el Anillo-A es no-sustituido cicloheptil.

En una incorporación de este aspecto, el Anillo-A es no-sustituido ciclooctil.

En otro aspecto, compuestos de Fórmulas 1 (y aspectos e incorporaciones de estos), 2 (y aspectos e incorporaciones de estos), 3 (y aspectos e incorporaciones de estos), y 4 (y aspectos e incorporaciones de estos), el Anillo-A es heteroaril, por ejemplo, piridil, pirimidil, piridazinil, pirazinil, tienill, furanil, pirrolil, pirazolil o imidazolil, cada uno opcionalmente sustituido en uno o más sustituibles posiciones con halógeno, C_1-C_6 alquil, C_2-C_6 alquenil, C_2-C_6 alquinil, C_1-C_6 alcoxi, haloalquil, haloalcoxi, hidroxil, hidroxialquil, CN, feniloxi, $-S(O)_{0-2}-(C_1$-C_6 alquil), $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, C_0-C_3alquilCO_2R_{10}, piridil, tienill, furanil, pirrolil, pirrolidinil, piperidinil, piperazinil, fenil, fenil C_1-C_4 alquil o $-SO_2NR_{11}R_{11}$, donde las porciones fenil de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_4 haloalquil (*e.g.* CF_3) o halógeno.

En una incorporación de este aspecto, el grupo heteroaril es piridil, el cual es opcionalmente sustituido en uno o más sustituibles posiciones con grupos que son independientemente halógeno, C_1-C_6 alquil, C_1-C_6 alcoxi, CF_3, OCF_3, hidroxil, CN, feniloxi, $-SO_2-(C_1$-C_6 alquil), $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$,

-O-C(O)$NR_{11}R_{11}$, C_2-C_6 alcanoil, piridil, fenil o -$SO_2NR_{11}R_{11}$, donde cada R_{10} y R_{11} es independientemente C_1-C_6 alquil o fenil; y adicionalmente R_{11} puede ser H. En algunas incorporaciones el grupo piridil es sustituido con uno halógeno, *e.g.* cloro. En una incorporación de este aspecto, el grupo piridil es sustituido con un grupo C_1-C_4 haloalquil (*e.g.*, CF_3). En una ulterior incorporación de este aspecto, el grupo piridil es 5-(trifluorometil)piridin-2-il o 6-(trifluorometil)piridin-3-il. En una más ulterior incorporación de este aspecto, el grupo piridil es 6-(trifluorometil) piridin-3-il. En otra incorporación, el grupo piridil es sustituido con uno o dos grupos que son independientemente halógeno, C_1-C_4 alquil o C_1-C_4 alcoxi. En otra incorporación más, el grupo piridil es sustituido con uno grupo que es -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10} o -O-C(O)$NR_{11}R_{11}$. En otra incorporación, el grupo piridil es sustituido con un grupo que es -SO_2-(C_1-C_6 alquil) o -$SO_2NR_{11}R_{11}$. En otra incorporación más, el grupo piridil es sustituido con uno o dos grupos que son independientemente C_1-C_4 alquil, C_1-C_4 alcoxi o hidroxil. En una ulterior incorporación, el grupo piridil es no-sustituido.

En una incorporación de este aspecto, el grupo heteroaril es pirimidil, el cual es opcionalmente sustituido en uno o más sustituibles posiciones con grupos que son independientemente halógeno, C_1-C_6 alquil, C_1-C_6 alcoxi, CF_3, OCF_3, hidroxil, CN, feniloxi, -SO_2-(C_1-C_6 alquil), -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alcanoil, piridil, fenil o -$SO_2NR_{11}R_{11}$, donde cada R_{10} y R_{11} es independientemente C_1-C_6 alquil o fenil; y adicionalmente R_{11} puede ser H. En algunas incorporaciones el grupo pirimidil es sustituido con un halógeno, *e.g.* cloro. En otra incorporación, el grupo pirimidil es sustituido con uno o dos grupos que son independientemente halógeno, C_1-C_4 alquil o C_1-C_4 alcoxi. En otra incorporación más, el grupo pirimidil es sustituido con un grupo que es -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, o -O-C(O)$NR_{11}R_{11}$. En otra incorporación, el grupo pirimidil es sustituido con un grupo que es -SO_2-(C_1-C_6 alquil) o -$SO_2NR_{11}R_{11}$. En otra incorporación más, el grupo pirimidil es sustituido con uno o dos grupos que son independientemente C_1-C_4 alquil, C_1-C_4 alcoxi o hidroxil. En una ulterior incorporación, el grupo pirimidil es no-sustituido.

En una incorporación de este aspecto, el grupo heteroaril es piridazinil, el cual es opcionalmente sustituido en uno o más sustituibles posiciones con grupos que son independientemente halógeno, C_1-C_6 alquil, C_1-C_6 alcoxi, CF_3, OCF_3, hidroxil, CN, feniloxi, -SO_2-(C_1-C_6 alquil), -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alcanoil, piridil, fenil o -$SO_2NR_{11}R_{11}$, donde cada R_{10} y R_{11} es independientemente C_1-C_6 alquil o fenil; y adicionalmente R_{11} pueden ser H. En algunas incorporaciones el grupo piridazinill es sustituido con uno halógeno, *e.g.* cloro. En otra incorporación, el grupo piridazinill es sustituido con uno o dos grupos que son independientemente halógeno, C_1-C_4 alquil o C_1-C_4 alcoxi. En otra incorporación más, el grupo piridazinill es sustituido con uno grupo que es -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10} o -O-C(O)$NR_{11}R_{11}$. en iet otra incorporación, el grupo piridazinill es sustituido con un grupo que es -SO_2-(C_1-C_6 alquil) o -$SO_2NR_{11}R_{11}$. En otra incorporación más, el grupo piridazinill es sustituido con uno o dos grupos que son independientemente C_1-C_4 alquil, C_1-C_4 alcoxi o hidroxilo. En una ulterior incorporación, el grupo piridazinill es no-sustituido.

En una incorporación de este aspecto, el grupo heteroaril es pirazinil, el cual es opcionalmente sustituido en uno o más sustituibles posiciones con grupos que son independientemente halógeno, C_1-C_6 alquil, C_1-C_6 alcoxi, CF_3, OCF_3, hidroxil, CN, feniloxi, -SO_2-(C_1-C_6 alquil), -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alcanoil, piridil, fenil o -$SO_2NR_{11}R_{11}$, donde cada R_{10} y R_{11} es independientemente C_1-C_6 alquil o fenil; y adicionalmente R_{11} puede ser H. En algunas incorporaciones el grupo pirazinill es sustituido con un halógeno, *e.g.* cloro. En otra incorporación, el grupo pirazinill es sustituido con uno o dos grupos que son independientemente halógeno, C_1-C_4 alquil o C_1-C_4 alcoxi. En otra incorporación más, el grupo pirazinill es sustituido con un grupo que es -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, o -O-C(O)$NR_{11}R_{11}$. En otra incorporación, el grupo pirazinill es sustituido con un grupo que es -SO_2-(C_1-C_6 alquil) o -$SO_2NR_{11}R_{11}$. En otra incorporación más, el grupo pirazinill es sustituido con uno o dos grupos que son independientemente C_1-C_4 alquil, C_1-C_4 alcoxi o hidroxil. En una ulterior incorporación, el grupo pirazinill es no-sustituido.

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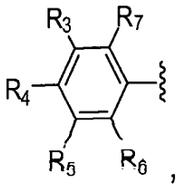
En una incorporación de este aspecto, el grupo heteroaril es tienill, el cual es opcionalmente sustituido en uno o más sustituibles posiciones con grupos que son independientemente halógeno, C_1-C_6 alquil, C_1-C_6 alcoxi, CF_3, OCF_3, hidroxil, CN, feniloxi, -SO_2-(C_1-C_6 alquil), -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, piridil, fenil o -$SO_2NR_{11}R_{11}$, donde cada R_{10} y R_{11} es independientemente C_1-C_6 alquil o fenil; y adicionalmente R_{11} pueden ser H. en algunas incorporaciones el grupo tienil es sustituido con uno halógeno, *e.g.* cloro. En una incorporación, el grupo tienil es sustituido en el 5-position con a Cl. en otra incorporación, el grupo heteroaril es 5-clorotiofen-2-il. En otra incorporación, el grupo tienil es sustituido con uno o dos grupos que son independientemente halógeno, C_1-C_4 alquil o C_1-C_4 alcoxi. En otra incorporación más, el grupo tienil es sustituido con uno grupo que es -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$ o -O-$C(O)NR_{11}R_{11}$. En otra incorporación, el grupo tienil es sustituido con un grupo que es -SO_2-(C_1-C_6 alquil) o -$SO_2NR_{11}R_{11}$. En otra incorporación más, el grupo tienil es sustituido con uno o dos grupos que son independientemente C_1-C_4 alquil, C_1-C_4 alcoxi o hidroxil. En una ulterior incorporación, el grupo tienil es no-sustituido.

En una incorporación de este aspecto, el grupo heteroaril es furanil, el cual es opcionalmente sustituido en uno o más sustituibles posiciones con grupos que son independientemente halógeno, C_1-C_6 alquil, C_1-C_6 alcoxi, CF_3, OCF_3, hidroxil, CN, feniloxi, -SO_2-(C_1-C_6 alquil), -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, piridil, fenil o -$SO_2NR_{11}R_{11}$, donde cada R_{10} y R_{11} es independientemente C_1-C_6 alquil o fenil; y adicionalmente R_{11} pueden ser H. En algunas incorporaciones el grupo furanil es sustituido con un halógeno, *e.g.* cloro. En otra incorporación, el grupo furanil es sustituido con uno o dos grupos que son independientemente halógeno, C_1-C_4 alquil o C_1-C_4 alcoxi. En otra incorporación más, el grupo furanil es sustituido con uno grupo que es -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, o -O-$C(O)NR_{11}R_{11}$. En otra incorporación, el grupo furanil es sustituido con un grupo que es -SO_2-(C_1-C_6 alquil) o -$SO_2NR_{11}R_{11}$. En otra incorporación más, el grupo furanil es sustituido con uno o dos grupos que son independientemente C_1-C_4 alquil, C_1-C_4 alcoxi o hidroxil. En una ulterior incorporación, el grupo furanil es no-sustituido.

En una incorporación de este aspecto, el grupo heteroaril es pirrolil, el cual es opcionalmente sustituido en una o más sustituibles posiciones con grupos que son independientemente halógeno, C_1-C_6 alquil, C_1-C_6 alcoxi, CF_3, OCF_3, hidroxil, CN, feniloxi, -SO_2-(C_1-C_6 alquil), -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alcanoil, piridil, fenil o -$SO_2NR_{11}R_{11}$, donde cada R_{10} y R_{11} es independientemente C_1-C_6 alquil o fenil; y adicionalmente R_{11} puede ser H. En algunas incorporaciones el grupo pirrolil es sustituido con uno halógeno, *e.g.* cloro. En otra incorporación, el grupo pirrolil es sustituido con uno o dos grupos que son independientemente halógeno, C_1-C_4 alquil o C_1-C_4 alcoxi. En otra incorporación más, el grupo pirrolil es sustituido con un grupo que es -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, o -O-C(O)$NR_{11}R_{11}$. En otra incorporación, el grupo pirrolil es sustituido con un grupo que es -SO_2-(C_1-C_6 alquil) o -$SO_2NR_{11}R_{11}$. En otra incorporación más, el grupo pirrolil es sustituido con uno o dos grupos que son independientemente C_1-C_4 alquil, C_1-C_4 alcoxi o hidroxil. En una ulterior incorporación, el grupo pirrolil es no-sustituido.

En otro aspecto, en compuestos de Fórmulas 1 (y aspectos e incorporaciones de éstos), 2 (y aspectos e incorporaciones de estos), 3 (y aspectos e incorporaciones de estos), y 4 (y aspectos incorporaciones de estos), el anillo-A es:



,

en donde,

R_3, R_4, R_5, R_6, R_7 son independientemente de cada otro H, halógeno, C_1-C_4 alquil, C_1-C_4 haloalquil, C_1-C_4 haloalcoxi, CN, hidroxilo, C_1-C_4 alcoxi, -C_1-C_3 alquil-OH, -C_1-C_3 alquil-C_1-C_4 alcoxi, feniloxi, -S(O_2)R_{10}, -$SO_2NR_{11}R_{11}$, -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$ o C_2-C_4 alcanoil; o

El Anillo-A es piridil, el cual es opcionalmente sustituido en uno o más sustituibles posiciones con grupos que son independientemente halógeno, C_1-C_6 alquil, C_1-C_6

alcoxi, CF_3, OCF_3, hidroxil, CN, feniloxi, $-SO_2-(C_1-C_6$ alquil), $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, piridil, fenil o $-SO_2NR_{11}R_{11}$, donde

Cada R_{10} y R_{11} es independientemente C_1-C_6 alquil o fenil; y adicionalmente R_{11} puede ser H.

En una ulterior incorporación de este aspecto, el Anillo-A es fenil o piridil, cada uno de los cuales es opcionalmente sustituido con halógeno o C_1-C_4 haloalquil (*e.g.*, CF_3 o CHF_2).

En una ulterior incorporación de este aspecto, el Anillo-A es fenil sustituido con R_3, R_4, R_5, R_6 y R_7, en donde R_4 es halógeno, C_1-C_4 alquil, C_1-C_4 alcoxi, CF_3, OCF_3 o CN; y R_3, R_5 R_6, y R_7 son hidrógeno.

En una ulterior incorporación de este aspecto, el Anillo-A es piridil, opcionalmente sustituido con un halógeno o CF_3.

En otro aspecto, en los compuestos de Fórmulas 1 (y aspectos e incorporaciones de estos), 2 (y aspectos e incorporaciones de estos), 3 (y aspectos e incorporaciones de estos), y 4 (y aspectos e incorporaciones de estos), el Anillo-A es heterocicloalquil que es pirrolidinil, piperidinil, piperazinil, morfolinil, tiomorfolinil o tiomorfolinil-S,S-dióxido, donde cada uno de los anillos de arriba es opcionalmente sustituido en sustituibles posiciones con halógeno, C_1-C_6 alquil, C_2-C_6 alquenil, C_2-C_6 alquinil, C_1-C_6 alcoxi, haloalquil, haloalcoxi, hidroxil, hidroxialquil, CN, feniloxi, $-S(O)_{0-2}-(C_1-C_6$ alquil), $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, C_0-C_3alquilCO_2R_{10}, piridil, tienill, furanil, pirrolil, pirrolidinil, piperidinil, piperazinil, fenil, fenil C_1-C_4 alquil o $-SO_2NR_{11}R_{11}$, donde las porciones fenil de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_4 haloalquil (*e.g.* CF_3) o halógeno.

En una incorporación de este aspecto, el grupo heterocicloalquil es pirrolidinil, el cual es opcionalmente sustituido en uno o más sustituibles posiciones con grupos que son independientemente halógeno, C_1-C_6 alquil, C_1-C_6 alcoxi, CF_3, OCF_3, hidroxil, CN, feniloxi, $-SO_2-(C_1-C_6$ alquil), $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$,

$-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, piridil, fenil o $-SO_2NR_{11}R_{11}$, donde cada R_{10} y R_{11} es independientemente C_1-C_6 alquil o fenil; y adicionalmente R_{11} puede ser H. En algunas incorporaciones el grupo pirrolidinil es sustituido con uno halógeno, *e.g.* cloro. En otra incorporación, el grupo pirrolidinil es sustituido con uno o dos grupos que son independientemente halógeno, C_1-C_4 alquil o C_1-C_4 alcoxi. En otra incorporación más, el grupo pirrolidinil es sustituido con un grupo que es $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, o $-O-C(O)NR_{11}R_{11}$. En otra incorporación, el grupo pirrolidinil es sustituido con un grupo que es $-SO_2$-(C_1-C_6 alquil) o $-SO_2NR_{11}R_{11}$. En otra incorporación más, el grupo pirrolidinil es sustituido con uno o dos grupos que son independientemente C_1-C_4 alquil, C_1-C_4 alcoxi o hidroxil. En una ulterior incorporación, el grupo pirrolidinil es no-sustituido.

En una incorporación de este aspecto, el grupo heterocicloalquil es piperidinil, el cual es opcionalmente sustituido en una o más sustituibles posiciones con grupos que son independientemente halógeno, C_1-C_6 alquil, C_1-C_6 alcoxi, CF_3, OCF_3, hidroxil, CN, feniloxi, $-SO_2$-(C_1-C_6 alquil), $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, piridil, fenil o $-SO_2NR_{11}R_{11}$, donde cada R_{10} y R_{11} es independientemente C_1-C_6 alquil o fenil; y adicionalmente R_{11} puede ser H. En algunas incorporaciones el grupo pirrolidinil es sustituido con un halógeno, *e.g.* cloro. En otra incorporación, el grupo pirrolidinil es sustituido con uno o dos grupos que son independientemente halógeno, C_1-C_4 alquil o C_1-C_4 alcoxi. En otra incorporación más, el grupo pirrolidinil es sustituido con un grupo que es $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, o $-O-C(O)NR_{11}R_{11}$. En otra incorporación, el grupo pirrolidinil es sustituido con un grupo que es $-SO_2$-(C_1-C_6 alquil) o $-SO_2NR_{11}R_{11}$. En otra incorporación más, el grupo pirrolidinil es sustituido con uno o dos grupos que son independientemente C_1-C_4 alquil, C_1-C_4 alcoxi o hidroxil. En una ulterior incorporación, el grupo pirrolidinil es no-sustituido.

En una incorporación de este aspecto, el grupo heterocicloalquil es piperazinil, el cual es opcionalmente sustituido en uno o más sustituibles posiciones con grupos que son independientemente halógeno, C_1-C_6 alquil, C_1-C_6 alcoxi, CF_3, OCF_3, hidroxil, CN, feniloxi, $-SO_2$-(C_1-C_6 alquil), $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, piridil, fenil o $-SO_2NR_{11}R_{11}$, donde

cada R_{10} y R_{11} es independientemente C_1-C_6 alquil o fenil; y adicionalmente R_{11} puede ser H. En algunas incorporaciones el grupo pirrolidinil es sustituido con uno halógeno, *e.g.* cloro. En otra incorporación, el grupo pirrolidinil es sustituido con uno o dos grupos que son independientemente halógeno, C_1-C_4 alquil o C_1-C_4 alcoxi. En otra incorporación más, el grupo pirrolidinil es sustituido con uno grupo que es $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, o $-O-C(O)NR_{11}R_{11}$. en iet otra incorporación, el grupo pirrolidinil es sustituido con uno grupo que es $-SO_2-(C_1-C_6$ alquil), $-NR_{11}SO_2R_{10}$ o $-SO_2NR_{11}R_{11}$. En otra incorporación más, el grupo pirrolidinil es sustituido con uno o dos grupos que son independientemente C_1-C_4 alquil, C_1-C_4 alcoxi o hidroxil. En una ulterior incorporación, el grupo pirrolidinil es no-sustituido.

En una incorporación de este aspecto, el grupo heterocicloalquil es morfolinil, el cual es opcionalmente sustituido en uno o más sustituibles posiciones con grupos que son independientemente halógeno, C_1-C_6 alquil, C_1-C_6 alcoxi, CF_3, OCF_3, hidroxil, CN, feniloxi, $-SO_2-(C_1-C_6$ alquil), $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, piridil, fenil o $-SO_2NR_{11}R_{11}$, donde cada R_{10} y R_{11} es independientemente C_1-C_6 alquil o fenil; y adicionalmente R_{11} pueden ser H. En algunas incorporaciones el grupo pirrolidinil es sustituido con uno halógeno, *e.g.* cloro. En otra incorporación, el grupo pirrolidinil es sustituido con uno o dos grupos que son independientemente halógeno, C_1-C_4 alquil o C_1-C_4 alcoxi. En otra incorporación más, el grupo pirrolidinil es sustituido con uno grupo que es $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$ $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, o $-O-C(O)NR_{11}R_{11}$. en iet otra incorporación, el grupo pirrolidinil es sustituido con uno grupo que es $-SO_2-(C_1-C_6$ alquil) o $-SO_2NR_{11}R_{11}$. En otra incorporación más, el grupo pirrolidinil es sustituido con uno o dos grupos que son independientemente C_1-C_4 alquil, C_1-C_4 alcoxi o hidroxil. En una ulterior incorporación, el grupo pirrolidinil es no-sustituido.

En una incorporación de este aspecto, el grupo heterocicloalquil es thiomorpholinil, el cual es opcionalmente sustituido en uno o más sustituibles posiciones con grupos que son independientemente halógeno, C_1-C_6 alquil, C_1-C_6 alcoxi, CF_3, OCF_3, hidroxil, CN, feniloxi, $-SO_2-(C_1-C_6$ alquil), $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, -

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$NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, piridil, fenil o $-SO_2NR_{11}R_{11}$, donde cada R_{10} y R_{11} es independientemente C_1-C_6 alquil o fenil; y adicionalmente R_{11} pueden ser H. En algunas incorporaciones el grupo pirrolidinil es sustituido con uno halógeno, *e.g.* cloro. En otra incorporación, el grupo pirrolidinil es sustituido con uno o dos grupos que son independientemente halógeno, C_1-C_4 alquil o C_1-C_4 alcoxi. En otra incorporación más, el grupo pirrolidinil es sustituido con uno grupo que es $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, o $-O-C(O)NR_{11}R_{11}$. En otra incorporación, el grupo pirrolidinil es sustituido con un grupo que es $-SO_2$-(C_1-C_6 alquil) o $-SO_2NR_{11}R_{11}$. En otra incorporación más, el pirrolidinil es sustituido con uno o dos grupos que son independientemente C_1-C_4 alquil, C_1-C_4 alcoxi o hidroxilo. En una ulterior incorporación, el pirrolidinil es no-sustituido.

En una incorporación de este aspecto, el grupo heterocicloalquil es tiomorfolinil-S,S-dioxido, el cual es opcionalmente sustituido en una o más sustituibles posiciones con grupos que son independientemente halógeno, C_1-C_6 alquil, C_1-C_6 alcoxi, CF_3, OCF_3, hidroxil, CN, feniloxi, $-SO_2$-(C_1-C_6 alquil), $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, piridil, fenil o $-SO_2NR_{11}R_{11}$, donde cada R_{10} y R_{11} es independientemente C_1-C_6 alquil o fenil; y adicionalmente R_{11} pueden ser H. En algunas incorporaciones el grupo pirrolidinil es sustituido con un halógeno, *e.g.* cloro. En otra incorporación, el grupo pirrolidinil es sustituido con uno o dos grupos que son independientemente halógeno, C_1-C_4 alquil o C_1-C_4 alcoxi. En otra incorporación más, el grupo pirrolidinil es sustituido con uno grupo que es $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, o $-O-C(O)NR_{11}R_{11}$. En otra incorporación, el grupo pirrolidinil es sustituido con uno grupo que es $-SO_2$-(C_1-C_6 alquil) o $-SO_2NR_{11}R_{11}$. En otra incorporación más, el grupo pirrolidinil es sustituido con uno o dos grupos que son independientemente C_1-C_4 alquil, C_1-C_4 alcoxi o hidroxil. En una ulterior incorporación, el grupo pirrolidinil es no-sustituido.

En otro aspecto, se proporcionanaquí compuestos de Fórmulas 1, 2, 3, y 4, así como también aspectos e incorporaciones de estos, en donde cada R_{25} es independientemente H, C_1-C_6 alquil, C_1-C_6 haloalquil, -C(O)OR_{11}, -C(O)$NR_{11}R_{11}$, -(C_1-C_6 alquil)-C(O)OR_{11}, C_1-C_6 alcoxi C_1-C_6 alquil, -CO$NR_{11}R_{11}$, CN, C_1-C_6 alquil-CN o hidroxi C_1-C_6 alquil. En una incorporación, los dos grupos R_{25} son iguales. En otra incorporación, los dos grupos R_{25} son diferentes.

En una incorporación de este aspecto, cada R_{25} es independientemente H, C_1-C_4 alquil, C_1-C_4 haloalquil, hidroxi C_1-C_4 alquil o C_1-C_4 alcoxialquil. En una ulterior incorporación, R_{25} es H o no-sustituido C_1-C_4 alquil (*e.g.*, CH_3). En una ulterior incorporación, R_{25} es H o hidroxi C_1-C_4 alquil (*e.g.*, hidroximetil). En una ulterior incorporación, R_{25} es H o C_1-C_4 alcoxi C_1-C_4 alquil. En una ulterior incorporación, R_{25} es H o C_1-C_4 haloalquil (*e.g.*, CF_3, CHF_2, CH_2F, CH_2Cl). En una ulterior incorporación, R_{25} es C_1-C_4 alquil o C_1-C_4 haloalquil (*e.g.*, CF_3, CHF_2, CH_2F, CH_2Cl). En una ulterior incorporación, R_{25} es C_1-C_4 alquil o hidroxi C_1-C_4 alquil (*e.g.*, hidroximetil). En una ulterior incorporación, R_{25} es C_1-C_4 alquil o C_1-C_4 alcoxi C_1-C_4 alquil.

En una incorporación de este aspecto, cada R_{25} es independientemente H, -C(O)OR_{11}, -(C_1-C_6 alquil)-C(O)OR_{11}. En una ulterior incorporación, R_{25} es H o -C(O)OR_{11}, -(C_1-C_6 alquil)-C(O)OR_{11}. En una ulterior incorporación, R_{13} es H o no-sustituido C_1-C_4 alquil. En una ulterior incorporación, R_{13} es H. en a más ulterior incorporación, R_{13} es C_1-C_4 alquil sustituido con en least uno grupo que es fenil, enaftil, hidroxil, C_1-C_6 alcoxi o halógeno, donde el fenil y enaftil grupos son no-sustituido. En una ulterior incorporación, R_{13} es C_1-C_4 alquil sustituido con fenil, en donde el fenil es sustituido con 1 a 5 grupos que son independientemente halógeno, hidroxil, C_1-C_4 alquil, C_1-C_4 alcoxi, C_1-C_4 haloalquil (*e.g.*, CF_3), C_1-C_4 haloalcoxi (*e.g.*, OCF_3), CN o NO_2.

En una incorporación de este aspecto, cada R_{25} es independientemente H, C_1-C_6 alquil-CN o CN.

En una ulterior incorporación de este aspecto, R_{25} es H, -C(O)OR_{11} o -CO$NR_{11}R_{11}$. en una ulterior incorporación, cada R_{11} es independientemente H, C_3-C_6 cicloalquil,

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heteroaril que es pirazolil, tiadiazolil (*e.g.*, 1,2,4-tiadiazolil o 1,3,4-tiadiazolil), triazolil (*e.g.*, 1,2,3-triazolil o 1,2,4-triazolil), isoxazolil, isotiazolil, imidazolil, tiazolil, oxadiazolil (*e.g.*, 1,2,4-oxadiazolil o 1,3,4-oxadiazolil), oxazolil, tetrazolil o piridil, heterocicloalquil que es seleccionado de tetrahidrofuranil, pirrolidinil, piperidinil, morfolinil, y imidazolidinil, fenil, C_2-C_6 alcanoil o C_1-C_6 alquil opcionalmente sustituido *e.g.*, con -C(O)OR_{11} o alcoxi, donde el alcoxi grupo es opcionalmente ulteriormente sustituido con -C(O)OR_{11}, y donde los grupos heteroaril y aril son opcionalmente sustituidos *e.g.*, con 1 a 3 grupos que son independientemente halógeno, hidroxil, C_1-C_4 alquil, C_1-C_4 alcoxi, C_1-C_4 haloalquil, C_1-C_4 haloalcoxi, CN o NO_2; o los dos grupos R_{11} junto con el nitrógeno al cual están unidos, forman un anillo de 3-8 miembros que opcionalmente contiene un adicional hetero átomo tal como *e.g.*, NH, NR_{12}, NR_{13}, O o S, y R_{13} es H o C_1-C_6 alquil.

En otra incorporación de este aspecto, cada R_{25} es independientemente H, C_1-C_4 alquil, C_1-C_4 haloalquil, hidroxi C_1-C_4 alquil, C_1-C_4 alcoxialquil, -C(O)OR_{11} o -C(O)$NR_{11}R_{11}$.

En otra incorporación de este aspecto, cada R_{11} es independientemente H o C_1-C_4 alquil opcionalmente sustituido con -C(O)OR_{11} o alcoxi, donde R_{11} es H o C_1-C_4 alquil.

En otra incorporación de este aspecto, cada R_{25} es independientemente H, hidroximetil, metil o -CO_2CH_3.

En otra incorporación de este aspecto, cada R_{25} es H.

Los compuestos de Fórmulas 1, 2, 3, y 4 comprenden derivados sulfonamido de la invención como es declarada, y/o farmacéuticamente aceptables sales, solvatos o polimorfos de tales compuestos. Además, compuestos de esta invención incluyen individuales isómeros estereoquímicos y geométricos, tautómeros, y mezclas de estos, producto de la selección de grupos sustitutos. Ciertos compuestos de esta invención pueden existir en formas isómeras. La invención contempla todos dichos estéreo isómeros, tanto en forma pura como en mezclas y mezclas racémicas.

Definiciones

Las definiciones y explicaciones a continuación son para los términos como son usados en todas las exposiciones de este documento, incluyendo la especificación y las reivindicaciones. A través de la especificación y las reivindicaciones anexas, una fórmula dada o nombre debe abarcar todos los isómeros de la misma, tales como estéreo – isómeros, isómeros geométricos, isómeros ópticos, tautómeros y mezclas de los mismos, donde dichos isómeros existan, así como sales farmacéuticamente aceptables y solvatos de las mismas, como por ejemplo, hidratos.

Debe señalarse que, como se usa en esta especificación y sus reivindicaciones anexas, las formas singulares "un", "una", "el" y "la" incluyen referencias plurales a menos que el contenido indique de forma explícita lo contrario. Así, por ejemplo, la referencia a una composición conteniendo "un compuesto" o "una composición" incluye una mezcla de dos o más compuestos o dos o más composiciones. Debe también señalarse que el término "o" es empleado de forma general en el sentido de "y / o" a menos que el contenido indique de forma clara lo contrario.

Cuando múltiples sustituyentes son indicados como unidos a una estructura, debe entenderse que los sustituyentes pueden ser iguales o diferentes. Así, por ejemplo, "R_m opcionalmente sustituido con grupos R_q 1, 2, 3 o 4" indica que R_m es sustituido con 1,2,3 o 4 grupos R_q, donde los grupos R_q pueden ser iguales o diferentes. Deberá entenderse por aquellas personas con destreza en el arte que cuando se hace referencia a cualquier grupo conteniendo uno o más sustituyentes, que dichos sustituyentes no tienen como intención introducir ninguna sustitución o patrones de sustitución que sean imprácticos de forma estérica y / o no logrables de forma sintética.

APP, proteína amiloide precursora, es definida como cualquier poli – péptido APP, incluyendo variantes APP, mutaciones e isomorfos, por ejemplo, como se muestra en la Patente de los Estados Unidos de América Número 5.766.846.

Un beta péptido beta – amiloide, es definido como cualquier péptido resultante a partir de división mediada por beta-secretasa de APP, incluyendo péptidos de los

amino – ácidos 39, 40, 41, 42 y 43 y extendiéndose a partir del sitio de división mediada por beta – secretasa a los amino – ácidos 39, 40, 41, 42 o 43.

"Forma farmacéuticamente aceptable" y "farmacéuticamente aceptable" se refiere a aquellas propiedades y / o sustancias que son aceptables para el paciente desde una perspectiva toxicológica y / o desde una perspectiva de seguridad.

Una cantidad terapéuticamente efectiva se define como una cantidad efectiva para reducir o minimizar al menos un síntoma de la enfermedad que está siendo tratada o para hacer más lenta la incidencia de uno o más marcadores clínicos o síntomas de la enfermedad.

Por "alcanoil" se quiere decir un radical alquilo Alc – C(O)-, donde Alc es un radical alquilo como se define aquí. Ejemplos de alcanoil incluyen acetil, propionil, butiril, iso – butiril, valeril, iso – valeril, 2 – metil, butiril, 2,2 – dimetilpropionil, valeril, hexanoil, heptanoil, octanoil y similares.

El término "alquil", por si mismo o como parte de otro sustituyente, significa que, al menos que se señale de otra forma, un radical hidrocarburo, que puede incluir radicales di – y multivalentes, teniendo el número de átomos de carbono designados (por ejemplo, C_1-C_{10} significa de uno a diez átomos de carbono). De forma típica, un grupo alquilo tendrá de 1 a 10 átomos de carbono, con aquellos grupos teniendo entre 1 a 8 átomos de carbono, a partir de 1 a 6 átomos, o entre 1 a 4 átomos de carbono siendo la incorporación preferida. Un grupo "alquil inferior" es un grupo alquil teniendo entre 1 a 4 átomos de carbono. El término "alquil" incluye "alquileno" cada vez que sea apropiado, por ejemplo, cuando la fórmula indica que el grupo alquil es divalente o cuando los sustituyentes son unidos para formar un anillo. Ejemplos de radicales alquilos incluyen, pero no están limitados a metil, etil, n – propiol, iso – propil, n – butil, tert – butil, iso – butil y sec – butil, así como homólogos e isómeros de, por ejemplo, n – pentil, n – hexil, n – heptil y n – octil.

El término "alquileno" por si mismo o como parte de otro sustituyente significa un grupo alquilo divalente (di - radical), donde alquil es como aquí se define. "Alquileno" es ejemplificado, pero no limitado, por - $CH_2CH_2CH_2CH_2$-. De forma

típica, un grupo "alquileno" tendrá de 1 a 24 átomos de carbono, con aquellos grupos teniendo 10 o menos átomos de carbono (por ejemplo, de 1 a 8 o de 1 a 6 átomos de carbono) siendo preferidos en la presente invención. Un "alquileno inferior" es un grupo alquileno teniendo entre 1 a 4 átomos de carbono.

Por "aril" se quiere decir un grupo carbo – cíclico aromático teniendo un único anillo o múltiples anillos condensados en los cuales al menos uno sea un hidrocarburo aromático, (por ejemplo, 1, 2, 3, 4-tetrahidronaftil, naftil). Donde el grupo "aril" incluye un anillo no – aromático (tal como en 1, 2, 3, 4 - tetrahidronaftil) o grupo heteroaril, donde el grupo "aril" está unido al núcleo/remanente de la molécula a través del anillo de hidrocarburo aromático. Ejemplos no limitativos de grupos aril incluyen al fenil, 1 – naftil, 2 – naftil, quinolina, indanil, indenil, di – hidronaftil, fluorenil, tetralinil, benzo [d][1,3]dioxolil o 6,7,8,9 – tetrahidro – 5H – benzo [a] cicloheptenil. Grupos "ariles" preferidos incluyen fenil, benzo [d] [1,3] dioxolil y naftil. La incorporación que resulta particularmente preferida es la que incluye fenil.

Por "ariloxi" se quiere decir el grupo – O – aril, donde aril es definido como se hace aquí. De forma más preferible, la porción aril del grupo ariloxi es fenil o natfil, de forma aún más preferible, fenil.

Por "arialquil" se quiere decir el grupo – alquil – aril, donde alquil y aril son como aquí se definen.

Por el término "halógeno" en la presente invención, se quiere decir fluorina, bromina, cloro y/o yodo

El término "alquenil" por si mismo o como parte de otro sustituyente se refiere a un radical hidrocarburo de cadena recta o ramificada teniendo de 2 a 12 átomos de carbono y al menos una doble unión de carbono a carbono. Un grupo alquenil típico tiene de 2 a 10 átomos de carbono y al menos una doble unión. Los grupos alquenil preferidos tienen de 2 a 8 átomos de carbono o entre 2 a 6 átomos de carbono y entre 1 a 3 doble uniones. Grupos "alqueniles" ejemplares incluyen vinil, 2 - propenil, 1 – but -3 – enil, crotil, 2 – (butadienil), 2, 4 – pentadienil, 3 – (1,4-pentadientil), 2 – isopentil, 1 – pent – 3 – enil, 1 – hex- 5 – enil y similares.

El término "alquinil" por si mismo o como parte de otro sustituyente se refiere a un radical hidrocarburo de cadena recta, saturada o poli - insaturada teniendo entre 2 a 12 átomos de carbono y al menos una triple unión. Un grupo "alquinil" tiene entre 2 a 10 átomos de carbono y al menos una triple unión. Los grupos "alquinil" preferidos tienen entre 2 a 6 átomos y al menos una triple unión. Grupos "alquinil" ejemplares incluyen al prop – 1 – inil, prop – 2 – inil (por ejemplo, propargil), etinil y 3 – butinil.

El término "cicloalquil" por si mismo o en combinación con otros términos, representa un radical carbo - cíclico saturado teniendo de 3 a 8 átomos de carbono, con esos grupos teniendo entre 3 a 6 átomos de carbono (por ejemplo, C_3 - C_6 cicloalquil) siendo preferidos. Ejemplos de cicloalquil incluyen, pero no están limitados a, ciclopropil, ciclobutil, ciclopentil, ciclohexil, cicloheptil, cicloheptil y similares. El término "cicloalquil" también incluye estructuras con puentes policíclicas (por ejemplo, bicíclicas), tales como norbonil, adamantil y biciclo [2.2.1] heptil. El grupo "cicloalquil" puede ser fusionado con al menos uno (por ejemplo, de 1 a 3) otros anillos seleccionados a partir de anillos aromáticos (por ejemplo, fenil), anillos heteroaromáticos (por ejemplo, piridil) o no – aromáticos (por ejemplo, heterocíclicos). Cuando el grupo "cicloalquil" es fusionado a un anillo aril, heteroaril o heterocíclico, entonces la porción "cicloalquil" del sistema de anillo fusionado es unida al núcleo / remanente de la molécula.

Por "oxo" se quiere decir el grupo =O.

Por "halógeno", en la presente invención, se quiere decir flúor, bromina, cloro y / o yodo.

Por "haloalquil", en la presente invención, se quiere decir un radical alquil teniendo el significado como se define arriba donde uno o más hidrógenos son reemplazados por un halógeno. Ejemplos de dichos haloalquilos incluyen al clorometil, 1 – bromoetil, fluorometil, difluorometil, trifluorometil, 1,1,1 – trifluorometil y similares.

El término "heteroaril" o "heteroaromático" se refiere a una porción poli – insaturadada, de 5 , 6 o 7 miembros conteniendo al menos un hetero – átomo (por

ejemplo, de 1 a 5 hetero – átomos, y de forma preferible de 1 – 3 hetero - átomos) seleccionados a partir de N, O, S, Si y B (de forma preferible N, O y S), donde los átomos de hidrógeno y sulfuro son oxidados de forma opcional y el (los) átomo (s) de nitrógeno son cuaternizados de forma opcional. El grupo "heteroaril" puede ser un único anillo o puede ser fusionado a otros anilos aril, heteroaril, cicloalquil, o heterocicloalquil (por ejemplo de 1 a 3 otros anillos). Cuando el grupo "heteroaril" incluye un anillo aril fusionado, cicloalquil o heteroalquil, entonces el grupo "heteroaril" es unido al núcleo / remanente de la molécula a través del anillo heteroaril. Un grupo heteroaril puede ser unido al remanente de la molécula a través de un carbono o un heteroátomo. Ejemplos no limitativos de grupos heteroariles incluyen piridil, pirimidil, quinolinil, benzotienil, indolil, indolinil, pridazinil, pirazinil, isoindolil, isoquinolil, quinazolinil, quinoxanilil, ftalazinil, imidazolil, isoxazolil, pirazolil, oxazolil, tiazolil, indolizinil, indazolil, benzotiazolil, benzimidazolil, benzofuranil, furanil, tienil, pirrolil, oxadiazolil, tiadiazolil, triazolil, tetrazolil, isotiazolil, naftiridinil, isocromanil, cromanil, tetrahidroisoquinolinil, isoindolinil, isobenztetrahidrofuranil, isobenzotetrahidrotienil, isobenzotienil, benzoxazolil, piridopiridil, benzotetrahidrofuranil, benzotetrahidrotienil, purinil, benzodioxolil, triazinil, teridinil, piridinil, benzotiazolil, imidazopiridil, imidazotiazolil, dihidrobenzisoxazinil, benzisoxazinil, benzoxazinil, dihidrobenzisotiazinil, benzopiranil, benzotiopiranil, cromonil, cromanonil, piridil – N – óxido, tetrahidroquinolinil, dihidroquinolinil, dihidroquinolinonil, dihidroisoquinolinonil, dihidrocumarinil, dihidroisocumarinil, isoindolinonil, benzodioxanil, benzoxazolinonil, N – óxido pirrolil, N – óxido pirimidinil, N – óxido piridazinil, N – óxido pirazinil, N – óxido quinolinil, N – óxido indolil, N – óxido indolinil, N – óxido isoquinolil, N – óxido quinazolinil, N – óxido quinoxalinil, N – óxido ftalazinil, N - óxido imidazolil, N – óxido isozazolil, N – óxido oxazolil, N – óxido tiazolil, N – óxido indolizinil, N – óxido indazolil, N – óxido benzotiazolil, N – óxido benzimidazolil, N – óxido pirrolil, N – óxido oxadiazolil, N – óxido tiadiazolil, N – óxido triazolil, N – óxido tetrazolil, S- óxido benzotiopiranil, S dióxido benzotiopiranil. Grupos heteroariles preferidos incluyen imidazolil, pirazolil, tiadiazolil, triazolil, isoxazolil, isotiazolil, imidazolil, tiazolil, oxadiozolil y piridil. Otros

grupos hetero ariles ejemplares incluyen 1 – pirrolil, 2 – pirrolil, 3 – pirrolil, 3 – pirazolil, 2 – imidazolil, 4 – imidazolil, pirazinil, 2 – oxazolil, 4 – oxazolil, 2 – fenil – 4 – oxazolil, 5 – oxazolil, 3 – isoxazolil, 4 – isoxazolil, isoxazolil, 2 - tiazolil, 4 - tiazoll, 5 -tiazolil, 2 - furil, 3 - furil, 2 - tienil, 3 - tienil, 2 - piridil, 3 - piridil, piridin - 4 - il, 2 - pirimidil, 4 - pirimidil, 5 - benzotiazolil, purinil, 2 - benzimidazolil, 5 - indolil, 1 - isoquinolil, 5 - isoquinolil, 2 - quinoxalinil, 5 - quinoxalinil, 3 -quinolil, y 6 – quinolil.

El término "hetero - cicloalquil", "hetero - cíclico", "hetero – ciclo" o "hetero - ciclil", por si mismo o en combinación con otros términos, representa a un anillo carbo – cíclico no – aromático (por ejemplo, un anillo compuestos por 3 a 8 miembros y, de forma preferible, un anillo de 4, 5, 6, o 7 miembros) conteniendo al menos uno hasta unos 5 hetero - átomos (por ejemplo, de 1 a 4 hetero – átomos seleccionados a partir de nitrógeno, oxígeno y sulfuro) o un sistema de anillos fusionados de anillos compuestos por 4 hasta 8 miembros, conteniendo al menos uno hasta 10 hetero – átomos (por ejemplo, de 1 a 5 hetero – átomos seleccionados a partir de nitrógeno, oxígeno y sulfuro) en combinaciones estables conocidas por todos aquellos con una destreza ordinaria en el arte. El grupo "hetero – cíclico" puede ser fusionado a un anillo aril, hetero – aril o ciclo – alquil más. En dichos sistemas de anillo fusionado, el grupo "hetero – cíclico" es unido al núcleo / remanente de la molécula a través del anillo hetero – cíclico saturado. Un hetero – átomo puede ocupar la posición en la cual el hetero – ciclo es unido al núcleo / remanente de la molécula. Grupos hetero – cicloalquil o hetero – cíclicos ejemplares de la presente invención incluyen al morfolinil, tiomorfolinil, S –óxido tiomorfolinil, tiomorfolinil S, S – dióxido, piperazinil, homopiperazinil, pirrolidinil, pirrolinil, imidazolidinil, tetrahidropiranil, piperidinil, tetra – hidrofuranil, tetra – hidrotienil, piperidinil, homo - piperidinil, homo – morfolinil, homo – tiomorftolinil, dioxanil, dioxolanil, dioxolan – 2 – onil, dihidrodioxinil, dioxol – 2 – onil, dioxolil, homotiomorfolinil S, S – dióxido, oxazolidinonil, dihidropirazolil, dihidropirrolil, dihidropirazolil, dihidropiridil, dihidropirimidinil, dihidrofuril, dihidropiranil, tetrahidrotienil S - óxido, tetrahidrotienil S, S -dióxido, homotiomorfolinil S - óxido, 1 - (1, 2, 5, 6 -tetrahidropiridil), 1 - piperidinil, 2 – piperidinil, 3 - piperidinil, 4 - morpholinil, 3 - morfolinil, tetrahidrofuran – 2 - yl, tetrahidrofuran – 3 - yl,

tetrahidrotien – 2 - yl, tetrahidrotien – 3 -yl, 1 - piperazinil, 2 – piperazinil y similares.

Los términos "hidrógeno" o "H" deben entenderse como que también abarcan a los isótopos deuterio y tritio. El hidrógeno (en lugar de deuterio o tritio) es preferido.

El término "enfermedades neurodegenerativas" incluye cualquier enfermedad o condición caracterizada por problemas de movimiento, tales como ataxia y condiciones que afecten las habilidades cognitivas (por ejemplo, la memoria) así como condiciones relacionadas, de forma general, como todos los tipos de demencia.

El término "enfermedades neurodegenerativas" puede ser asociado con la disminución o pérdida de habilidades cognitivas, pérdida potencial de habilidades cognitivas y / o inhabilitación o pérdida de células cerebrales. "Enfermedades neuro – degenerativas" ejemplares incluyen a la Enfermedad de Alzheimer, enfermedad de Parkinson, la esclerosis lateral amiotrófica (ALS), el síndrome de Down, la demencia, la demencia multi-infarto, la discapacidad cognitiva leve (MCI), la epilepsia, convulsiones, la enfermedad de Huntington, la neuro – degeneración inducida por infección viral (por ejemplo, SIDA, encefalopatías), las lesiones cerebrales traumáticas, así como la isquemia y la apoplejía.

A la mayor parte de los compuestos fue dado nombre usando Autonom 2000 4.01.305, el cual está disponible por parte de Beilstein Information Systems, Inc, Englewood, Colorado, ChemDraw v.10.0 (disponible a partir de Cambridgesoft en 100 Cambridge Park Drive, Cambridge, MA 02140) o ACD Name pro (por ejemplo, versión 12), el cual está disponible por parte de Advanced Chemistry Development, Inc., en 110 Yonge Street, piso 14, Toronto, Ontario, Canadá M5c 1T4. De forma alternativa, los nombres fueron generados basándose en las reglas IUPAC o fueron derivados a partir de nombres generados originalmente usando los programas de nomenclatura mencionados antes.

Los compuestos de esta invención pueden contener uno o más átomos de carbono asimétricos, de forma que los compuestos pueden existir en diferentes formas estéreo - isoméricas. Estos compuestos pueden ser, por ejemplo,

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compuestos racémicos, quirales no – racémicos o diastómeros. En estas situaciones, los enantiómeros simples, por ejemplo, formas ópticamente activas pueden ser obtenidas por síntesis asimétrica o por resolución de los racematos. La resolución de los racémicos puede ser lograda, por ejemplo, por medios convencionales tales como cristalización en la presencia de un agente resolvente; cromatografía, usando, por ejemplo, una columna quiral HPLC; o derivando la mezcla racémica con un agente resolvente para generar diasterómeros, separando los diasterómeros a través de cromatograía y removiendo el agente resolvente para generar el compuesto original en una forma enantioméricamente enriquecida. Cualquiera de los procedimientos de arriba puede ser repetido para incrementar la pureza enantiomérica de un compuesto.

Sales farmacéuticamente aceptables incluyen, pero no están limitadas a sales o ácidos inorgánicos tales como hidroclórico, sulfúrico, fosfórico, difosfórico, hidrobrómico y nítrico o sales de ácidos orgánicos tales como ácido fórmico, ácido cítrico, ácido málico, ácido maleico, ácido fumárico, ácido tartárico, ácido succínico, ácido acético, ácido láctico, ácido metanosulfónico, ácido p – toluenosulfónico, ácido 2 - hidroxietilsulfónico, ácido salicílico y ácido éstearico. Similarmente, los cationes que resultan farmacéuticamente aceptables incluyen, pero no están limitados a sodio, potasio, calcio, aluminio, litio y amonio. Aquellos con destreza en el arte reconocerán una amplia variedad de sales de adición no tóxicas que resulten farmacéuticamente aceptables. La invención también abarca pro - drogas de los compuestos de las fórmulas 1, 2, 3 y 4. Aquellos con destreza en el arte reconocerán varias metodologías sintéticas, las cuales pueden ser empleadas para preparar sales de adición no tóxicas que resulten farmacéuticamente aceptables y pro – drogas aciladas de los compuestos abarcados por las Fórmulas 1, 2, 3 y 4.

El término "grupo ácido pro – droga" denota a una fracción que es convertida in vivo en un compuesto activo de ácido carboxílico de las Fórmulas 1, 2, 3 y 4. Dichos grupos pro – droga son conocidos, de forma general, en el arte e incluyen a los grupos formadores de ésteres, para formar una pro – droga estérica, tal como benziloxi, di (C_1 - C_6) alquilaminoetiloxi, acetoximetil, pivaloiloximetil, ftalidoil,

etoxicarboniloxietil, 5 – metil – 2 – oxo - 1,3 – dioxol – 4 - il metil, y (C_1-C_6) alkoxi opcionalmente sustituido por N -morfolino y grupos formadores de amidas tales como di (C_1-C_6) alquilamino. Grupos pro – droga preferidos incluyen a C_1-C_6 alkoxi formando un éster, y $O.M_+$ donde M_+ representa un catión para formar una sal del ácido. Cationes preferidos incluyen al sodio, potasio y amonio. Otros cationes incluyen magnesio y calcio. Otros grupos pro – droga preferidos incluyen a $O^{=}M^{++}$ donde M^{++} es un catión divalente tal como magnesio o calcio.

Cuando los compuestos descritos aquí contienen uniones olefínicas dobles u otros centros de asimetría geométrica, y al menos que se especifique de otra forma, se tiene como intención que los compuestos incluyan las configuraciones cis, trans, Z – y E-. De forma similar, se tiene como intención que todas las formas tautoméricas sean también incluidas.

La invención también abarca las pro - drogas de los compuestos de las Fórmulas 1, 2, 3 y 4. Aquellos con destreza en el arte reconocerán varias metodologías sintéticas que pueden ser empleadas para preparar pro - drogas no – tóxicas que resulten farmacéuticamente aceptables de los compuestos abarcados por las Fórmulas 1, 2, 3 y 4. Aquellos con destreza en el arte reconocerán una amplia variedad de solvatos no – tóxicos que resulten farmacéuticamente aceptables, tales como agua, etanol, aceite mineral, aceite vegetal y dimetil - sulfóxido.

Composiciones Farmacéuticas

En una incorporación, la invención provee una composición farmacéutica comprendiendo al menos un compuesto de la invención (por ejemplo, aquellos de la Fórmula 1, Fórmula 2, Fórmula 3, Fórmula 4 o cualesquier aspecto e incorporaciones de los mismos) y al menos un portador que resulte farmacéuticamente aceptable. El término "portador farmacéuticamente aceptable" incluye todos los ingredientes que resulten farmacéuticamente aceptables conocidos para aquellos con destreza en el arte e incluye solventes, diluyentes sólidos o líquidos, vehículos, adyuvantes, excipientes, deslizantes, unidores, agentes granuladores, agentes dispersores, agentes suspensores, agentes humectantes, agentes lubricantes, desintegrantes, solubilizadores, estabilizadores,

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emulsificantes, rellenadores, preservantes (por ejemplo, anti - oxidantes), agentes saborizantes, agentes endulzantes, agentes espesantes, agentes amortiguadores, agentes para colorear y similares, así como cualesquier mezcla de los mismos. Portadores ejemplares (por ejemplo, excipientes) son descritos en, por ejemplo, el *Handbook of Pharmaceutical Manufacturing Formulations*, Vols. 1-6, Niazi, Sarfaraz K., Taylor & Francis Group 2005, que es incorporado aquí, a manera de referencia, de forma completa.

En una incorporación, la invención provee una composición farmacéutica comprendiendo al menos un compuesto de las Fórmulas 1 – 5 y aspectos e incorporaciones de cada uno de los anteriores y al menos un solvente farmacéuticamente aceptable, adyuvante, excipiente, portador, deslizador, unidor y / o desintegrante.

Los compuestos o composiciones de la invención pueden ser administrados de forma oral, tópica, parenteral, por inhalación o rociado o rectalmente en formulaciones de dosificación unitaria conteniendo portadores, adyuvantes y vehículos convencionales no – tóxicos que resulten farmacéuticamente aceptables.

El término parenteral como se usa aquí incluye a las técnicas percutáneas, subcutáneas, intravasculares (por ejemplo, intravenosas), intramusculares o intratecales o técnicas de infusión y similares. De forma adicional, se provee una formulación farmacéutica comprendiendo un compuesto de las Fórmulas generales 1, 2, 3 y 4 y un portador farmacéuticamente aceptable. Uno o más compuestos de las Fórmulas generales 1, 2, 3 y 4 pueden estar presentes en asociación con uno o más portadores no – tóxicos farmacéuticamente aceptables y / o diluyentes y / o adyuvantes, y si se desea, otros ingredientes activos. Las composiciones farmacéuticas conteniendo compuestos de las Fórmulas 1, 2, 3 y 4 pueden estar en una forma aceptable para el uso oral, por ejemplo, como tabletas, minitabletas, tabletas saborizadas, suspensiones acuosas o aceitosas, polvos que se puedan dispersar o gránulos, emulsión, cápsulas duras o suaves o jarabes o elíxires.

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Composiciones que tengan como intención el uso oral pueden ser preparadas de acuerdo a cualquier método conocido en el arte para la manufactura de composiciones farmacéuticas y dichas composiciones pueden contener uno o más agentes seleccionados a partir del grupo consistente de agentes endulzantes, agentes saborizantes, agentes para colorear y agentes preservantes a objeto de proveer preparaciones farmacéuticamente presentables y agradables al gusto. Tabletas que contengan el ingrediente activo en mezcla con excipientes no – tóxicos que resulten farmacéuticamente aceptables y sean apropiados para la manufactura de tabletas. Estos excipientes pueden ser, por ejemplo, diluyentes inertes, tales como el carbonato de calcio, el carbonato de sodio, la lactosa, el fosfato de calcio o el fosfato de sodio; agentes granuladores y desintegrantes, por ejemplo, almidón de maíz o ácido algínico; por ejemplo: almidón, gelatina o acacia, y agentes lubricantes, por ejemplo: estearato de magnesio, ácido esteárico o talco. Las tabletas pueden ser no cubiertas o cubiertas de acuerdo a técnicas conocidas. En algunos casos dichas cubiertas pueden ser preparadas por técnicas conocidas para demorar la desintegración y absorción en el tracto gastrointestinal y por tanto proveer una acción sostenida durante un período de tiempo. Por ejemplo, un material para demorar el proceso de desintegración en el tiempo, tal como el monoestearato de glicerilo o el diestearato de glicerilo puede ser empleado.

Formulaciones para el uso oral pueden también ser presentadas, como cápsulas duras de gelatina, donde el ingrediente activo es mezclado con un diluyente sólido inerte, por ejemplo, carbonato de calcio, fosfato de calcio o caolín, o como cápsulas de gelatina suave donde el ingrediente activo sea mezclado con agua o un medio acuoso, por ejemplo, aceite de maní, parafina líquida, o aceite de oliva.

Formulaciones para el uso oral también pueden ser presentadas como tabletas saborizadas.

Las suspensiones acuosas contienen los materiales activos en mezcla con los excipientes apropiados para la manufactura de suspensiones acuosas. Dichos excipientes son agentes de suspensión, por ejemplo, carboximetilcelulosa de sodio, metilcelulosa, hidropropil – metilcelulosa, alginato de sodio, poli- vinil –

pirrolidina, goma tragacanto, y goma acacia; agentes dispersores o humectantes pueden ser un fosfátido de ocurrencia natural, por ejemplo, lecitina o productos de condensación de un óxido alquileno con ácidos grasos, por ejemplo, estearato de polioxietileno o productos de condensación de óxido etileno con alcoholes alifáticos de cadena larga, por ejemplo, heptadecaetilenoxicetanol o productos de condensación de óxido etileno con ésteres parciales derivados a partir de ácidos grasos y un hexitol tal como un mono – oleato sorbitol polioxietileno o productos de condensación de óxido etileno con ésteres parciales derivados a partir de ácidos grasos y anhídridos de hexitol, por ejemplo mono – oleato sorbitan polietileno. Las suspensiones acuosas pueden también contener uno o más preservantes, por ejemplo etil o n – propil p – hidroxibenzoato, uno o más agentes para dar color, uno o más agentes para dar sabor y uno o más agentes para endulzar, como la sucrosa o la sacarina.

Las suspensiones oleosas pueden ser formuladas suspendiendo los ingredientes activos en un aceite vegetal, por ejemplo aceite de maní, aceite de oliva, aceite de sésamo o aceite de coco o en un aceite mineral tal como una parafina líquida. Las suspensiones oleosas pueden contener un agente para espesar, por ejemplo, cera de abejas, parafina dura o alcohol cetílico. Se pueden agregar agentes para endulzar o agentes para dar sabor para proveer preparaciones orales que sean agradables al gusto. Estas composiciones pueden ser preservadas por la adición de un anti – oxidante tal como el ácido ascórbico.

Polvos que puedan dispersarse y gránulos apropiados para la preparación de una suspensión acuosa a través de la adición de agua proveen el ingrediente activo en mezcla con un agente de dispersión o humectación, un agente de suspensión y uno o más preservantes. Agentes de dispersión o humectación o suspensión son ejemplificados por aquellos que ya han sido mencionados arriba en este documento. Excipientes adicionales, por ejemplo, agentes para endulzar, dar sabor o dar color, pueden también estar presentes.

Las composiciones farmacéuticas de la invención pueden también estar en la forma de emulsiones de aceite en agua. La fase en aceite puede también ser un

aceite vegetal o un aceite mineral o mezclas de los mismos. Agentes emulsificadores apropiados pueden ser gomas que ocurran de forma natural, por ejemplo goma de acacia o goma de tragacanto, fosfátidos de ocurrencia natural, por ejemplo, granos de soya, lecitina, y ésteres o ésteres parciales derivados a partir de ácidos grasos y hexitol; anhídridos, por ejemplo, mono- oleato de sorbitan y productos de condensación de dichos ésteres parciales con óxido etileno, por ejemplo, mono – oleato de sorbitan poli – oxietileno. Las emulsiones también pueden contener agentes para dar sabor y agentes para endulzar.

Jarabes y elíxires pueden ser formulados con agentes para endulzar, por ejemplo, glicerol, glicol propileno, sorbitol, glucosa o sucrosa. Dichas formulaciones pueden también contener un demulcente, un preservante, agentes para dar sabor y agentes para dar color. Las composiciones farmacéuticas pueden estar en la forma de una suspensión acuosa estéril inyectable o suspensión oleosa estéril inyectable. Esta suspensión puede ser formulada de acuerdo al arte conocido usando aquellos agentes de dispersión o humectación y suspensión que ya han sido mencionados antes en este documento. La preparación estéril inyectable puede también ser una solución estéril inyectable o suspensión en un diluyente o solvente no – tóxico que resulte parenteralmente aceptable, por ejemplo: una solución en 1, 3 – butanediol. Dentro de los vehículos y solventes aceptables que pueden ser empleados están el agua, la solución de Ringer y la solución isotónica de cloruro de sodio. De forma adicional, aceites fijos y estériles son empleados de forma convencional como solvente o como medio de suspensión. Para este propósito, cualquier aceite blando fijo puede ser empleado incluyendo mono o di – glicéridos sintéticos. De forma adicional, ácidos grasos tales como el ácido oleico pueden encontrar uso en la preparación de inyectables.

Los compuestos de las Fórmulas generales 1, 2, 3 y 4 también pueden ser administrados en la forma de supositorios, por ejemplo, para la administración rectal de la droga. Estas composiciones pueden ser preparadas mezclando la droga con un excipiente apropiado que resulte no irritante y que sea sólido a temperaturas ordinarias pero líquido a la temperatura rectal y que, por tanto, se

derrita en el recto para liberar la droga. Dichos materiales incluyen manteca de cacao y glicoles poli – etilenos.

Compuestos de las Fórmulas generales 1, 2, 3 y 4 pueden ser administrados de forma parenteral en un medio estéril. La droga, dependiendo del vehículo y la concentración usados, puede estar suspendida o disuelta en el vehículo. De forma ventajosa, adyuvantes tales como anestésicos locales, preservantes y agentes de amortiguación pueden ser disueltos en el vehículo.

Para desórdenes del ojo u otros tejidos externos, por ejemplo, la boca y la piel, las formulaciones son aplicadas de forma preferible como un gel tópico, a través de un rociador, ungüento o crema o como un supositorio, conteniendo los ingredientes activos en una cantidad total, de, por ejemplo, 0,075 hasta 30 por ciento p / p, de forma preferible de 0,2 hasta 20 por ciento p / p y de forma aún más preferible 0,4 hasta 15 por ciento p / p. Cuando se formula como un ungüento, los ingredientes activos pueden ser empleados con una base, bien sea de parafina o de ungüento miscible en agua.

De forma alternativa, los ingredientes activos pueden ser formulados en una crema con una base de crema de aceite en agua. Si se desea, la fase acuosa de la base de la crema puede incluir, por ejemplo, al menos 30 por ciento p / p de un alcohol poli – hídrico tal como glicol propileno, butano – 1, 3 – diol, manitol, sorbitol, glicerol, glicol polietileno y mezclas de los mismos. La formulación tópica puede incluir, de forma deseable un compuesto, el cual mejore la absorción o penetración del ingrediente activo a través de la piel u otras áreas afectadas. Ejemplos de dichos potenciadores de penetración dérmica incluyen al dimetil sulfóxido y análogos relacionados. Los compuestos de esta invención pueden ser administrados también a través de un dispositivo trans-dérmico. La administración tópica preferida será lograda usando un parche con una membrana de tipo reservorio y poroso o a través de la variedad de matriz sólida. En cualquier caso, el agente activo es administrado de forma continua a partir del reservorio o micro – cápsulas a través de una membrana en el adhesivo permeable con el agente activo, el cual está en contacto con la piel o la mucosa del recipiente. Si el agente

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activo es absorbido a través de la piel, un flujo controlado y pre – determinado del agente activo es administrado al recipiente. En el caso de microcápsulas, el agente encapsulador puede también funcionar como la membrana. El parche trans – dérmico puede incluir el compuesto en un sistema de solvente apropiado con un sistema adhesivo, tal como una emulsión acrílica y un parche de poliéster. La fase oleosa de las emulsiones de esta invención puede ser constituida, a partir de ingredientes conocidos, de una forma conocida. Aunque la fase puede comprender meramente un emulsificador, puede comprender una mezcla de al menos un emulsificador con una grasa o aceite o con tanto una grasa como un aceite. De forma preferible, un emulsificador hidrófilo es incluido junto con un emulsificador lipófilo, que actúe como un estabilizador. También se prefiere incluir tanto un aceite como una grasa. Juntos, el (los) emulsificador (es) con o sin estabilizador (es) hacen la así llamada cera emulsificadora, y la cera junto con el aceite y la grasa hacen la así llamada base emulsificadora de ungüento, la cual forma la fase aceitosa, dispersada de las formulaciones de crema. Emulsificadores y estabilizadores de emulsión apropiados para el uso en la formulación de la invención incluyen a Tween 60, Span 80, alcohol cetoestearil, alcohol miristil, gliceril monoestearato, y lauril sulfato de sodio, entre otros. La escogencia de aceites o grasas apropiadas para la formulación, está basada en lograr las propiedades cosméticas deseadas, debido que la solubilidad del compuesto activo en la mayor parte de los aceites que probablemente sean usados en las formulaciones de emulsiones farmacéuticas es muy baja. Así, la crema debe, de forma preferible, ser no – grasienta, no – manchadora y debe ser un producto lavable con consistencia apropiada para evitar el derrame de tubos u otros contenedores. Ésteres alquil mono- o di – básicos de cadena recta o ramificada tales como di – isoadipato, isocetil estearato, di – éster propilén glicol de ácidos grasos de coco, isopropil miristato, decil oleato, butil estearato, 2 – etilhexil palmitato o una mezcla de ésteres de cadenas ramificadas pueden ser usados. Estos pueden ser usados de forma exclusiva o en combinación dependiendo de las propiedades requeridas. De forma alternativa, lípidos con puntos de fusión

altos, tales como la parafina suave blanca y / o la parafina líquida u otros aceites minerales pueden ser usados.

Las formulaciones apropiadas para la administración ocular tópica también incluyen gotas oftálmicas donde los ingredientes activos están disueltos o suspendidos en un portador apropiado, de forma especial en un solvente acuoso para los ingredientes activos. Los ingredientes activos anti – inflamatorios están presentes, de forma preferible, en dichas formulaciones en una concentración de 0,5 a 20 por ciento, de forma ventajosa de 0,5 a 10 por ciento y particularmente un 1,5 p / p. Para propósitos terapéuticos, los compuestos activos de esta invención que se encuentran en combinación son ordinariamente combinados con uno o más adyuvantes apropiados para la ruta indicada de administración. Los compuestos pueden ser mezclados con lactosa, sucrosa, polvo de almidón, ésteres de celulosa o ácidos alcanoicos, alquil ésteres de celulosa, talco, ácido esteárico, estearato de magnesio, óxido de magnesio, sodio y sales de calcio de ácidos fosfórico y sulfúrico, gelatina, goma de acacia, alginato de sodio , poli – vinil – pirrolidona, y / o alcohol poli – vinil y luego llevada a forma de tabletas o cápsulas para una administración conveniente. Dichas cápsulas o tabletas pueden contener una formulación de liberación – controlada tal como puede ser provisto en una dispersión de compuesto activo en hidroxipropilmetil celulosa. Formulaciones para la administración parenteral pueden ser en forma de soluciones o suspensiones estériles isotónicas acuosas o no – acuosas. Estas soluciones y suspensiones pueden ser preparadas a partir de polvos estériles o gránulos teniendo uno o más de los cargadores o diluyentes mencionados para el uso en las formulaciones para administración oral. Los compuestos pueden ser disueltos en agua, polietilénglicol, propilénglicol, etanol, aceite de maíz, aceite de semilla de algodón, aceite de maní, aceite de sésamo, bencil alcohol, cloruro de sodio y / o varios amortiguadores. Otros adyuvantes y modos de administración son bien conocidos y ampliamente conocidos en el arte farmacéutico.

Niveles de dosificación en el rango de entre 0,1 mg hasta unos 140 mg por kilogramo de peso corporal por día, son útiles en el tratamiento de las condiciones que se han indicado arriba (entre 0,5 mg hasta unos 7 g por paciente por día). La

cantidad de ingrediente activo que puede ser combinada con los materiales portadores para producir una forma de dosificación única puede variar dependiendo del paciente tratado y el modo particular de administración. Las formas de dosificación generalmente contendrán entre un 1 mg hasta unos 500 mg de un ingrediente activo. La dosis diaria puede ser administrada en una a cuatro dosis por día. En el caso de existencia de problemas en la piel, es preferible aplicar una preparación tópica de compuestos de esta invención al área afectada de dos a cuatro veces por día.

Las formulaciones apropiadas para la inhalación o insuflación incluyen a las soluciones y suspensiones en solventes acuosos u orgánicos que sean farmacéuticamente aceptables o mezclas de los mismos y polvos. Las composiciones líquidas o sólidas pueden contener excipientes farmacéuticamente aceptables que sean apropiados, como se describe arriba. Las composiciones pueden ser administradas por ruta oral o nasal para lograr un efecto sistémico o local. Las composiciones pueden ser nebulizadas para el uso de gases inertes o vaporizadas e inhaladas de forma directa a partir del dispositivo de nebulización / vaporización o el dispositivo de nebulización puede ser unido a un dispositivo de máscara facial o máquina de respiración de presión positiva intermitente.

Deberá entenderse, sin embargo, que el nivel de dosificación específico para cualquier paciente dependerá de una variedad de factores que incluyen la actividad del compuesto específico que será empleado, la edad, el peso corporal, la salud general, el sexo, la dieta, el tiempo de administración, la ruta de administración y la rata de excreción, la combinación de droga y la severidad de la enfermedad particular que se esté tratando.
Para la administración a animales no – humanos, la composición puede también ser añadida a la comida del animal o al agua que beberá. Puede ser conveniente formular la composición de la comida del animal y el agua que beberá de forma que el animal ingiera éstos en una cantidad de la composición que resulte apropiada desde el punto de vista terapéutico, junto con su dieta. Puede también ser conveniente presentar la composición como una pre - mezcla para la adición a la comida o al agua que el animal beberá.

Las presentaciones en este documento de todos los artículos y referencias, incluyendo patentes, son incorporadas aquí, a manera de referencia, de forma completa.

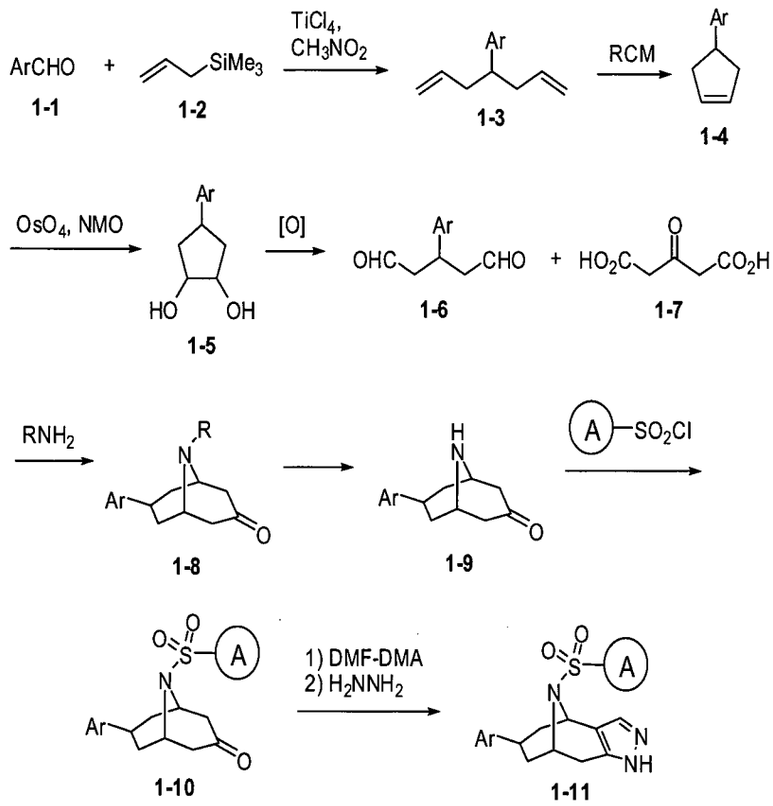
Procedimientos Sintéticos Generales

Los materiales iniciales y varios intermedios pueden ser obtenidos a partir de fuentes comerciales, preparados a partir de compuestos que están disponibles a partir de fuentes comerciales, y / o preparados usando métodos sintéticos conocidos.

Los compuestos de la invención pueden ser preparados usando métodos conocidos en el arte de la síntesis orgánica. Por ejemplo, los compuestos de la invención, así como todos sus intermedios, pueden ser sintetizados por procesos conocidos usando técnicas de fase de estado sólido o solución, como se muestra abajo. Procedimientos representativos para preparar compuestos de la invención son mencionados en los siguientes esquemas.

De forma adicional, será aparente para aquellos con destreza en el arte que grupos convencionalmente protectores pueden ser necesarios para prevenir que ciertos grupos funcionales sufran ciertas reacciones no deseables. Grupos de protección apropiados para varios grupos funcionales así como condiciones apropiadas para proteger y desproteger grupos funcionales particulares son bien conocidos en el arte. Por ejemplo, numerosos grupos protectores son descritos en T. W. Greene y G. M. Wuts, *Protecting Groups in Organic Synthesis*, Segunda Edición, Wiley, New York, 1991 y las referencias allí citadas.

<u>Esquema 1</u>



En el esquema anterior, el anillo-A es definido como se describe arriba, R es un grupo amino protector y Ar es un grupo aril.

Un método para obtener compuestos de la Fórmula 1 puede ser acoplar aldehído **1 - 1** con alilsilano **1 – 2** en presencia de tetracloruro de titanio para lograr el producto de doble alilación, **1 – 3**. La metátesis de cerradura de anillo de 1 – 3 puede lograr ciclopenteno **1 – 4** (ver: Durand, A-C; et al. *Synth. Commun.* **2005**, *35*(13), 1825). El tratamiento de 1 – 4 con OsO_4 / NMO puede lograr diol **1 – 5.** La división oxidativa del diol puede lograr dialdehído **1 – 6**. La condensación Mannich de **1 – 6** con acetona – 1, 3 – ácido dicarboxílico (1 - 7) y una amina puede lograr cetona bi – cíclica 1 – 8 (ver: Mach, R.H.; et al. *J. Med. Chem.* **1993**, *36*(23), 3707). La conversión de 1 – 8 a 1 – 9 puede ser efectuada usando condiciones familiares para aquellos de destreza ordinaria en el arte y las condiciones pueden ser variadas de acuerdo a la naturaleza de R. La sulfonilación de **1 – 9** con un sulfonilcloruro de la fórmula A - SO_2Cl, donde A está definido como se hace arriba, en la presencia de una base puede dar como resultado el compuesto **1 – 10**. El tratamiento de **1 – 10** con un agente acilante tal como DMF – DMA seguido por la

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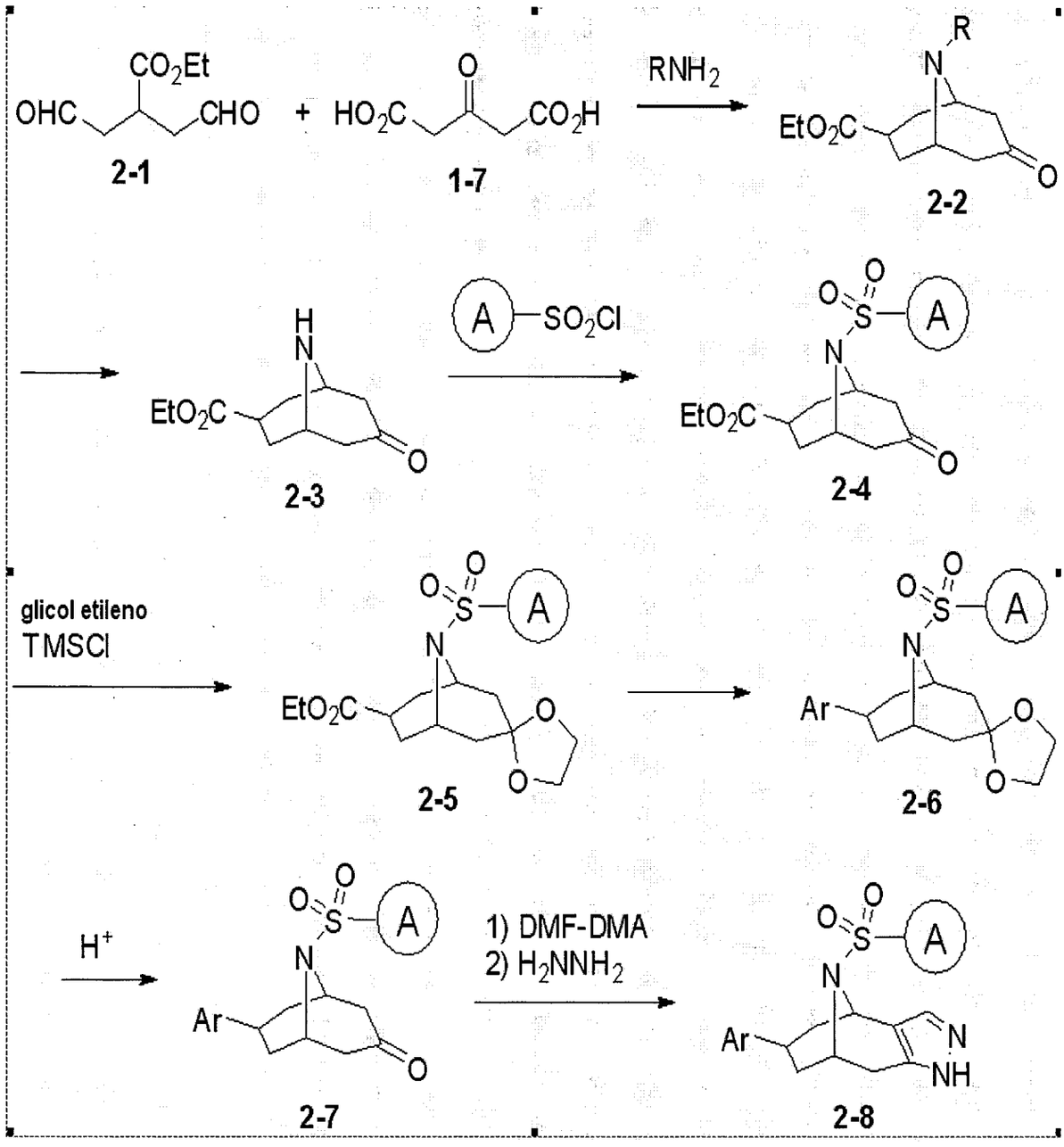
ciclización con hidracina puede dar como resultado compuestos de la fórmula **1 – 11**.

Esquema 2



En el esquema anterior, el anillo-A es definido como se describe arriba, R es un grupo protector y Ar es un grupo aril.

Otro método para obtener compuestos de la Fórmula 1 es preparar un azabicilo [3.2.1] nonano conteniendo un grupo alcoxicarbonil que pueda ser elaborado a grupo hetero – aromático como se muestra en el esquema arriba. La condensación Mannich de dialdehído **2 – 1** con ácido acetonedicarboxílico (**1 – 7**) y una amina puede lograr cetona bi – cíclica **2 – 2**. La conversión de **2 – 2** a **2 – 3**

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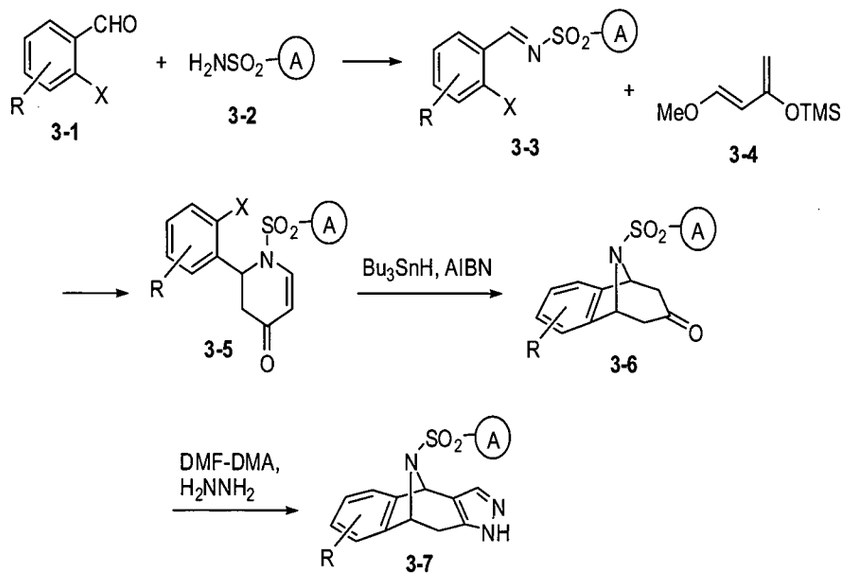
puede ser efectuada usando condiciones familiares para aquellos de destreza ordinaria en el arte y las condiciones pueden variar de acuerdo a la naturaleza de R. La sulfonilación de 2 – 3 con un sulfonil - cloruro de la fórmula A - SO_2Cl, donde A es como se define arriba, en la presencia de una base puede dar como resultado el compuesto **2 – 4**. La protección de la cetona puede ser lograda usando etilén glicol en presencia de un ácido Lewis para dar **2 – 5**. La conversión al grupo alcoxicarbonil de un anillo heteroaril puede ser lograda por numerosos métodos familiares para aquellos con destreza en el arte (ver: Gupta, R.R.; Kumar, M.; Gupta, V. *Heterocyclic Chemistry* Vol .I – Vol.III, Springer-Verlag: Berlin, 1999) para dar el compuesto **2 – 6**. La desprotección de la cetona seguida por el tratamiento con un agente acilante tal como DMF – DMA y una ciclización con hidracina puede dar los compuestos de las fórmulas **2 - 8**.

Esquema 3



En el esquema anterior, el anillo-A es definido como se describe arriba, R es equivalente a R_{30}, R_{35}, R_{40} y /o R_{45}, y X es un halógeno.

Un método para obtener compuestos de la invención es acoplar un 2 – halobenzaldehído tal como **3 – 1** con sulfonamida **3 – 2** para lograr sulfonimida **3 – 3** (ver, por ejemplo: Castellano, S.; et al. *J. Am. Chem. Soc.* **2007**, *129*(18), 5843). La cicloadición de **3 – 3** con un dieno tal como 3 – 4 puede formar dihidropiridona **3 – 5**. La ciclización radical de 3 – 5 con un reagente tal como Bu_3SnH/AIBN puede dar nortropanona 3 – 6. El tratamiento de 3 – 6 con un

agente acilante tal como DMF – DMA seguido por la ciclización con hidracina puede dar los compuestos de la fórmula **3 – 7**.

Ciertos compuestos de esta invención son preparados a partir de otros compuestos de esta invención a través de reacciones conocidas y transformaciones de grupos funcionales. Ejemplos de dichas transformaciones son la hidrólisis de éster, la formación de amidas y la alquilación reductiva; con ejemplos de éstas siendo descritos en las preparaciones a continuación. Los materiales iniciales son obtenidos a partir de fuentes comerciales o preparados por métodos conocidos como se describe en los ejemplos a continuación.

Métodos

Método de Tratamiento

En una incorporación, se proporciona aquí un método para tratar una enfermedad neuro – degenerativa comprendiendo la administración a un sujeto mamífero (por ejemplo, un sujeto humano) en necesidad de la misma, una cantidad farmacéuticamente aceptable de un compuesto o sal de las Fórmulas 1, 2, 3 ó 4 (o una incorporación de las mismas) de una composición farmacéutica comprendiendo al menos un compuesto de las Fórmulas 1, 2, 3 ó 4 (o cualquier incorporación de las mismas). En un ejemplo, la enfermedad neurodegenerativa es seleccionada a partir del grupo compuesto por la Enfermedad de Alzheimer, Enfermedad de Alzheimer corporal difusa tipo Lewy, enfermedad de Parkinson, síndrome de Down, demencia, discapacidad cognitiva leve (MCI), esclerosis lateral amiotrópica (ALS), lesiones cerebrales traumáticas, daño cerebral isquémico, apoplejía isquémica o hemorrágica, hemorragia cerebral hereditaria con amiloidosis del tipo holandés y angiopatía cerebral amiloide. En un ejemplo particular, la enfermedad neuro – degenerativa es la Enfermedad de Alzheimer, o la Enfermedad de Alzheimer corporal difusa de tipo Lewy. Así, en un ejemplo, la invención provee un método para tratar la Enfermedad de Alzheimer, o la Enfermedad de Alzheimer corporal difusa de tipo Lewy comprendiendo la administración de una cantidad terapéuticamente efectiva de un compuesto o sal de las Fórmulas 1, 2, 3 o 4 a un paciente en necesidad de dicho tratamiento.

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En otra incorporación, la invención provee un método para tratar una enfermedad seleccionada del grupo consistente de epilepsia, ataques, enfermedad de Huntington, esclerosis múltiple, cáncer, degeneración macular relacionada con la edad, retinopatía diabética y neuro – degeneración retiniana relacionada a glaucoma o trauma ocular, el método comprendiendo la administración a un sujeto mamífero (por ejemplo, un sujeto humano) en necesidad de ello, de una cantidad farmacéuticamente efectiva de un compuesto o sal de las Fórmulas 1, 2, 3 o 4 (o cualquier incorporación de las mismas) o una composición farmacéutica comprendiendo al menos un compuesto de las Fórmulas 1, 2, 3 ó 4 (o cualquier incorporación de las mismas). En una incorporación particular, la invención provee un método para tratar el cáncer seleccionado de médulo-blastoma (por ejemplo, con altos niveles del gen Notch2), cánceres colorectales tratados con compuestos de la invención solos o en conjunción con taxanos), cánceres pulmonares, leucemia linfoblástica aguda u otros cánceres hematológicos, sarcoma de Kaposi, cáncer de pecho y melanoma, el método comprendiendo la administración a un sujeto mamífero (por ejemplo, un sujeto humano) en necesidad de ello, de una cantidad farmacéuticamente efectiva de un compuesto o sal de las Fórmulas 1, 2 , 3, o 4 (o cualquier incorporación del mismo) de una composición farmacéutica comprendiendo al menos un compuesto de las Fórmulas 1, 2, 3 o 4 (o cualquier incorporación del mismo).

La invención además provee un método para tratar un estado de enfermedad en una célula, grupo de células (por ejemplo, tejido de mamífero) o un organismo (por ejemplo, humano), comprendiendo: la administración de un compuesto y / o sales de las Fórmulas 1, 2, 3 y/o 4, a la célula, grupo de células u organismo, donde la enfermedad es seleccionada del grupo consistente en cáncer, desórdenes intraoculares (por ejemplo, enfermedad macular relacionada con la edad), enfermedades relacionadas con la deposición de proteínas, síndrome de Down, hemorragia cerebral hereditaria con amiloidosis del tipo holandés, angiopatía amiloide cerebral, enfermedad de Parkinson, parálisis supra - nuclear progresiva, demencia asociada con degeneración basal cortical y enfermedad de Alzheimer corporal difusa del tipo Lewy.

Además, la invención proporciona un método para inhibir la angiogénesis en tejidos de mamífero o un organismo (por ejemplo, humano), comprendiendo la administración de una cantidad farmacéuticamente efectiva de un compuesto de la invención o una sal que resulte farmacéuticamente aceptable del mismo, al tejido o al organismo.

Además, se provee aquí un método para inhibir la angiogénesis en un tejido de mamífero u organismo, comprendiendo la administración de una cantidad farmacéuticamente efectiva de un compuesto de las Fórmulas 1, 2, 3 y/o 4 o sal (es) farmacéuticamente aceptable (s) del mismo, al tejido o al organismo, donde el compuesto (o composición farmacéutica) es administrado para prevenir, tratar o curar una condición tratable a través de la inhibición de la angiogénesis.

Métodos In Vitro

En una incorporación, los compuestos y composiciones de la invención pueden ser usados en un ensayo *in vitro* midiendo la actividad de gamma – secretasa. En un ejemplo, la actividad de gamma – secretasa es medida a través de la detección de división de un sustrato de gamma – secretasa (por ejemplo, APP o Notch). En otro ejemplo, los compuestos y composiciones de la invención pueden ser usados en un ensayo in vitro para identificar compuestos candidatos que sean capaces de inhibir la actividad de gamma – secretasa.

La invención también provee un método para la búsqueda de una sustancia que inicie o incremente la angiogénesis, comprendiendo: medir la actividad de una vía de gamma – secretasa en presencia de un compuesto candidato en un modelo apropiado; medir una actividad de una ruta gamma – 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, donde un cambio en la actividad indica que dicho candidato inicia o incrementa la angiogénesis.

EJEMPLOS

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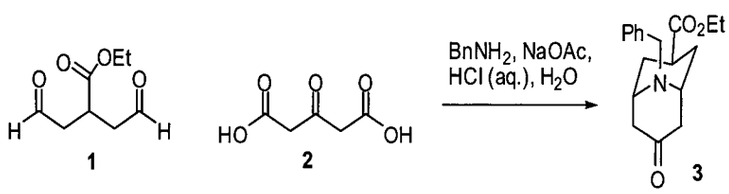
General

Reagentes y solventes obtenidos a partir de suplidores comerciales fueron usados sin pasar por un proceso de purificación adicional al menos que esto se indique aquí de forma explícita. Se realizó cromatografía de capa fina en bandejas percoladas de 0,25 mm de gel de silicio (E. Merck, gel de silicio, F254). La visualización fue lograda usando iluminación UV o realizando tinción con ácido fosfomolíbdico, ninhidrina u otros agentes de tinción comunes. La cromatografía flash fue realizada usando, o bien un sistema Biotage Flash 40 y columnas de silicio preempacadas, o columnas empacadas a mano (E. Merck gel de sílice 60, malla 230 – 400). El HPLC preparatorio fue realizado usando un cromatógrafo líquido de alto rendimiento Varian Prepstar. Los espectros ^{1}H NMR fueron registrados bien en un espectrómetro Varian Gemini de 300 MHz o en un espectrómetro Bruker Avance de 300 MHz. Los cambios químicos fueron reportados en ppm (δ) y fueron calibrados usando la resonancia de solvente no deuterado como estándar interno. El espectro de masa fue grabado en un espectrómetro de masa Agilent series 1100 conectado a un HPLC Agilent de series 1100.

Ejemplo 1

Síntesis de 9 – benzil – 7 – oxo – 9 – aza – biciclo [3.3.1] nonano – 3 – ácido etil éster carboxílico (3)

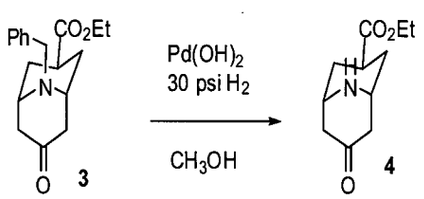


Acetona - 1, 3 – ácido dicarboxílico (**2**) (8,81 g, 60,36 mmol) y acetato de sodio (5,04 g, 61,5 mmol) fueron añadidos a una solución de 4 – oxo – 2- (2 – oxo - etil) – ácido etil éster butírico **(1)** (Patente Europea EP 0330788A1) (10,3 g, 60,36 mmol) en H_2O (75 mL). Bencilamina (6,59 mL, 60,36 mmol) fue disuelta en HCl acuoso (3 N, 41 mL) y fue subsecuentemente añadido a la solución de agitación del dialdehído y el ácido dicarboxílico por un período de 15 minutos.

La mezcla de reacción fue agitada por 3 días a temperatura ambiente, luego de lo cual el pH fue ajustado a 8 a través de la adición de carbonato de potasio. La solución resultante fue extraída con CH_2Cl_2 (4 × 50 mL), los extractos orgánicos secados (Na_2SO_4), filtrados y concentrados al vacío. El residuo resultante fue purificado por cromatografía de gel de silicio, (eluante hexano / EtOAc 9 / 1 a 1 / 1, v / v), para dar 7,43 gramos (40 por ciento) de 9 – benzil – 7 – oxo – 9 – aza – biciclo [3.3.1] nonano – 3 - ácido etil éster carboxílico (**3**) como un aceite marrón. El tiempo de retención (en minutos) = 0,963, método [1], MS(ESI) 302.2 (M+H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 - 7.10 (m, 5H), 4.10 (q, *J* = 7,1 Hz, 2H), 3,91 (s, 2H), 3.41-3.38 (m, 2H), 2.74 (dd, *J* = 16,5, 6,6 Hz, 2H), 2,61 – 2,48 (m, 1H), 2,30 (d, *J* = 16.5 Hz, 2H), 2.08 (dt, *J* = 3,8 Hz, *J* = 13,2 Hz, 2H), 1,81 – 1,72 (m, 2H), 1,22 (t, *J* = 7,1 Hz, 3H).

Ejemplo 2

Síntesis de 7 – oxo – 9 – aza – biciclo [3.3.1] nonano – 3 - ácido etil éster carboxílico (4)



se disolvió 9-Bencil-7-oxo-9-aza-biciclo[3.3.1]nonano-3-éster de ácido carboxílico (**3**) (11,1 gramos, 36,8 mmol) en MeOH (30 mL) y fue añadido a una suspensión de hidróxido paladio (1 gramo) en MeOH (10 mL) en una botella Parr. La botella Parr fue llenada con hidrógeno (30 psi) y evacuada tres veces. La botella Parr fue rellenada con hidrógeno (30 psi) y agitada por 12 horas. La suspensión fue filtrada a través de Celite y concentrada al vacío para dar 7,81 gramos (producción cuantitativa) de 7-oxo-9-aza-biciclo[3.3.1]nonano-3- ácido carboxílico etil éster como un aceite amarillo. El tiempo de retención (en minutos) = 0,369, método [1], MS (ESI) 212, 1 (M + H).

Ejemplo 3

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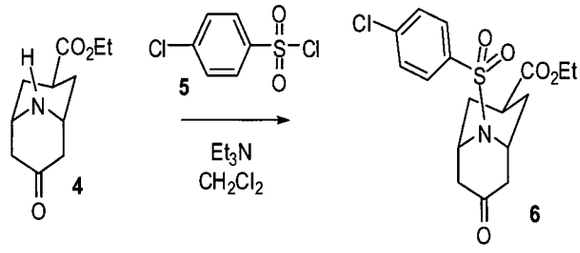
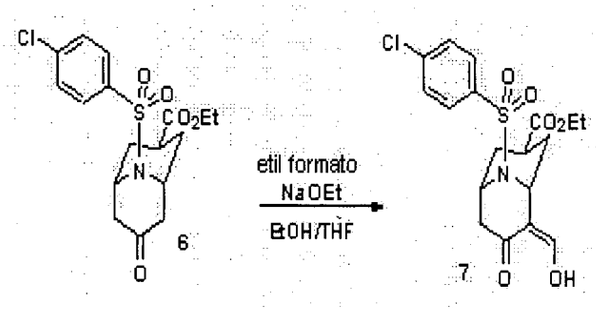
Síntesis de 9 - (4 – cloro - bencenosulfonil) – 7 – oxo – 9 – aza –biciclo [3.3.1] nonano – 3 – ácido etil éster carboxílico (6)



Se disolvió 7 – Oxo – 9 – aza – biciclo [3.3.1] nonano – 3 – ácido carboxílico etil éster (**4**) (5,91 g, 27,9 mmol) en CH_2Cl_2 (60 mL). Et_3N (7,76 mL, 55,9 mmol) y 4 – cloro benceno sulfonil (**5**) (7.08 g, 33.6 mmol) fueron añadidos a la mezcla y ésta fue agitada a temperatura ambiente por 2 horas. La mezcla de reacción fue diluida con CH_2Cl_2 (50 mL) y lavada con $NaHCO_3$ saturado (50 mL). La fase acuosa fue separada y extraída una vez con CH_2Cl_2 (50 mL). Las fases orgánicas combinadas fueron luego secadas (Na_2SO_4), filtradas, concentradas al vacío y el residuo purificado en una columna de gel de silicio (eluante hexano / EtOAc, 9 / 1 a 1 / 1 para dar 9,52 gramos (88 por ciento) de 9 – (4 – cloro - bencenosulfonil) – 7 – oxo – 9 – aza – biciclo [3.3.1] nonano – 3 – ácido etil ester carboxílico (6). Tiempo de retención (en minutos) = 2,100, método [1] MS (ESI) 408,1 (M + Na), ^{1}H NMR ($CDCl_3$) δ 7,81 (d, *J* = 8,2 Hz, 2H), 7,51 (d, *J* = 8,2 Hz, 2H), 4,61 – 4,57 (m, 2H), 4,09 (q, *J* = 7.1 Hz, 2H), 2,80 (dd, *J* = 17,0, 7,1 Hz, 2H), 2,67-2,51 (m, 1H), 2,41 (d, *J* = 16,4 Hz, 2H), 1,99-1,90 (m, 2H), 1,80 (dt, *J* = 13,2, 4,4 Hz, 2H), 1,20 (t, *J* = 7,1 Hz, 3H).

Ejemplo 4

Síntesis de 9 - (4-cloro-benzenosulfonil) - 6 - hidroximetileno- 7 -oxo - 9 - aza-biciclo [3.3.1] nonano - 3 - éster etil ácido carboxílico (7)



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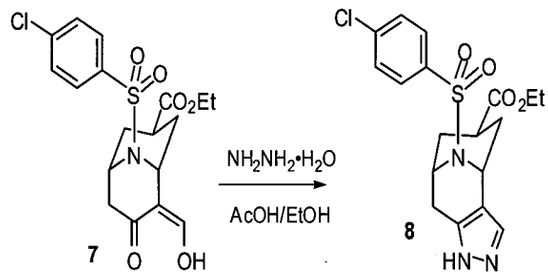
9 –(4-Cloro – benzenosulfonil)–7–oxo-9 aza – biciclo [3.3.1] nonano – 3 – éster etil ácido carboxílico (6) (2.49 g, 6.45 mmol) fue disuelto en THF/etanol (14 mL, 1/1, v/v). Etil formato (5.19 mL, 64.53 mmol) fue añadido seguido de etóxido de sodio (6.2 mL de 21% solución en etanol). La mezcla resultante fue calentada a 60 °C por 30 minutos después que la solución fue enfriada a temperatura ambiente y extinguida por la adición de solución acuosa saturada NH_4Cl (10 mL). La mezcla resultante fue extraída con EtOAc (2 x 20 mL) y las fases orgánicas combinadas fueron secadas (NA_2SO_4), filtrada y concentrada al vacío para producir 2.51 g (94%) de 9 – (4-cloro-benzenosulfonil)- 6 – hidroximetileno -7-oxo-9-aza-biciclo[3.3.1] nonano-3- éster etil ácido carboxílico (7) como un ácido amarillo. Tiempo de retención (min) = 2.017, método [1], MS (ESI) 414.0 (M+H).

Ejemplo 5

Síntesis de 12-(4-cloro-benzenosulfonil)-4, 5, 12-triaza-triciclo[6.3.1.$0_{2,6}$]dodeca-2(6),3-dieno-10- éster etil ácido carboxílico(8)

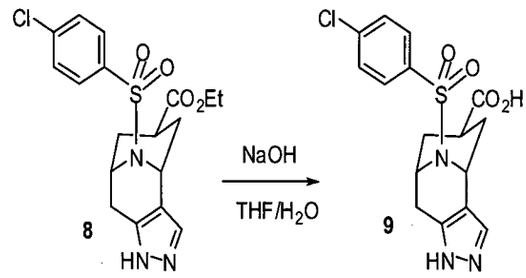


A una solución de 9-(4-cloro-benzenosulfonil)-6-hidroximetileno-7-oxo-9-aza-biciclo[3.3.1] nonano -3- éster etil ácido carboxílico (**7**) (2.48 g, 5.99 mmol) en etanol (10 mL) fue añadido ácido acético glacial (0.2 mL) seguido de mono hidrato de hidracina (2.9 mL, 59.9 mmol). La mezcla de reacción fue batida a temperatura ambiente por 1 h después de que $NaHCO_3$ (10 mL) saturada fue agregada. La solución resultante fue extraída con EtOAc (3 × 20 mL), los extractos orgánicos fueron combinados, secados (Na_2SO_4), filtrados, concentrados y purificados por cromatografía de color de columna de gel sílice (hexano eluante / EtOAc, 9/1 a 1/1) y preparativo HPLC para dar 12-(4-cloro-benzenosulfonil)-4, 5, 12-triaza-triciclo [6.3.1.$0_{2,6}$] dodeca-2 (6), 3-dieno- 10- éster etil ácido carboxílico (8) como un sólido blanco. Tiempo de retención (min) = 1.739, método [1], MS (ESI) 410.1

(M+H); ^{1}H NMR ($CDCl_3$) δ 7.66 (d, *J* = 8.2 Hz, 2H), 7.51 (s, 1H), 7.38 (d, *J* = 8.2 Hz, 2H), 5.37 (bs, 1H), 4.61-4.55 (m, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.04 (dd, *J* = 17.6, 7.1 Hz, 1H), 2.67 (d, *J* = 17.6 Hz, 1H), 2.48-2.31 (m, 1H), 2.11-1.91 (m, 4H), 1.20 (t, *J* = 7.1 Hz, 3H).

Ejemplo 6

Síntesis de 12-(4-Cloro-benzenosulfonil)-4, 5, 12-triaza-triciclo[6.3.1.0$_{2,6}$]dodeca-2(6),3-dieno-10-ácido carboxílico (9)



Hidróxido de sodio (0.5 mL, 3 N solución) fue agregado a una solución 12 -(4-cloro-benzenosulfonil)-4, 5, 12-triaza-triciclo[6.3.1.0$_{2,6}$]dodeca-2(6),3-dieno-10-éster etil ácido carboxílico (**8**) (321 mg, 0.783 mmol) en THF (2 mL). La mezcla resultante fue batida a temperatura ambiente por 4 h. La mezcla de reacción fue extraída con EtOAc (2 x 5 mL) y las fases orgánicas combinadas fueron secadas (NA_2SO_4), filtradas, concentradas y purificadas por preparativo HPLC para dar 12-(4-cloro-benzenosulfonil)-4, 5, 12-triaza-triciclo[6.3.1.0$_{2,6}$]dodeca-2(6),3-dieno-10-ácido carboxílico (**9**) como un sólido blanco. Tiempo de retención (min) = 1.316, método [1], MS(ESI) 382.0 (M+H); ^{1}H NMR ($CDCl_3$) δ 7.56 (d, *J* = 8.7 Hz, 2H), 7.30-7.22 (m, 3H), 5.30-5.25 (m, 1H), 4.54-4.45 (m, 1H), 2.80 (dd, *J* = 17.0, *J* = 7.7 Hz, 1H), 2.50 (d, *J* = 17.0 Hz, 1H), 2.42-2.30 (m, 1H), 2.24-1.85 (m, 4H).

Ejemplo 7

[12-(4-Cloro-benzenosulfonil)-4,5,12-triaza-triciclo[6.3.1.0$_{2,6}$]dodeca-2,5-dien-10-yl]-metanol (10)

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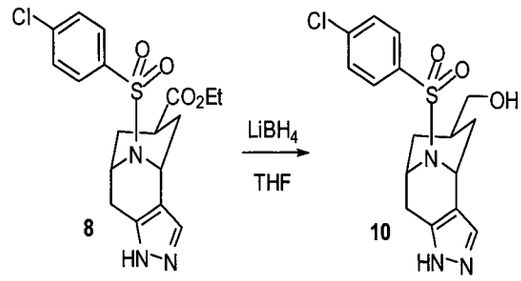

Borohidruro de litio (17 mg, 0.80 mmol) fue agregado a una solución de 12 -(4-cloro-benzenosulfonil)-4,5,12-triaza-triciclo[6.3.1.$0_{2,6}$]dodeca-2(6),3-dieno-10-éster etil ácido carboxílico (**8**) (328 mg, 0.80 mmol) in THF (3 mL). La solución resultante fue batida a temperatura ambiente por 18 h y luego calentada a 60 °C por 2 h. La reacción fue extinguida por la adición de agua (5 mL) y la mezcla resultante fue extraída con EtOAc (3 x 15 mL). Las fases orgánicas combinadas fueron secadas (Na_2SO_4), filtradas, concentradas y purificadas por cromatografía de color de columna de gel sílice (eluante hexano/EtOAc, 9/1 a 1/1) y preparativo HPLC para dar [12-(4-cloro-benzenosulfonil)-4, 5, 12-triaza-triciclo [6.3.1.$0_{2,6}$]dodeca-2,5-dien-10-yl]-metanol (**10**) como un sólido blanco. Tiempo de retención (min) = 1.242, método [1], MS(ESI) 368.0 (M+H); ^{1}H NMR ($CDCl_3$) □7.73 (d, *J* = 8.2 Hz, 2H), 7.58 (s, 1H), 7.38 (d, *J* = 8.2 Hz, 2H), 5.33 (s, 1H), 4.48 (d, *J* = 7.1 Hz, 1H), 3.41 (d, *J* = 2.7 Hz, 2H), 3.08 (dd, *J* = 17.6, 7.7 Hz, 1H), 2.62 (d, *J* = 17.6 Hz, 1H), 1.81-1.54 (m, 5H).

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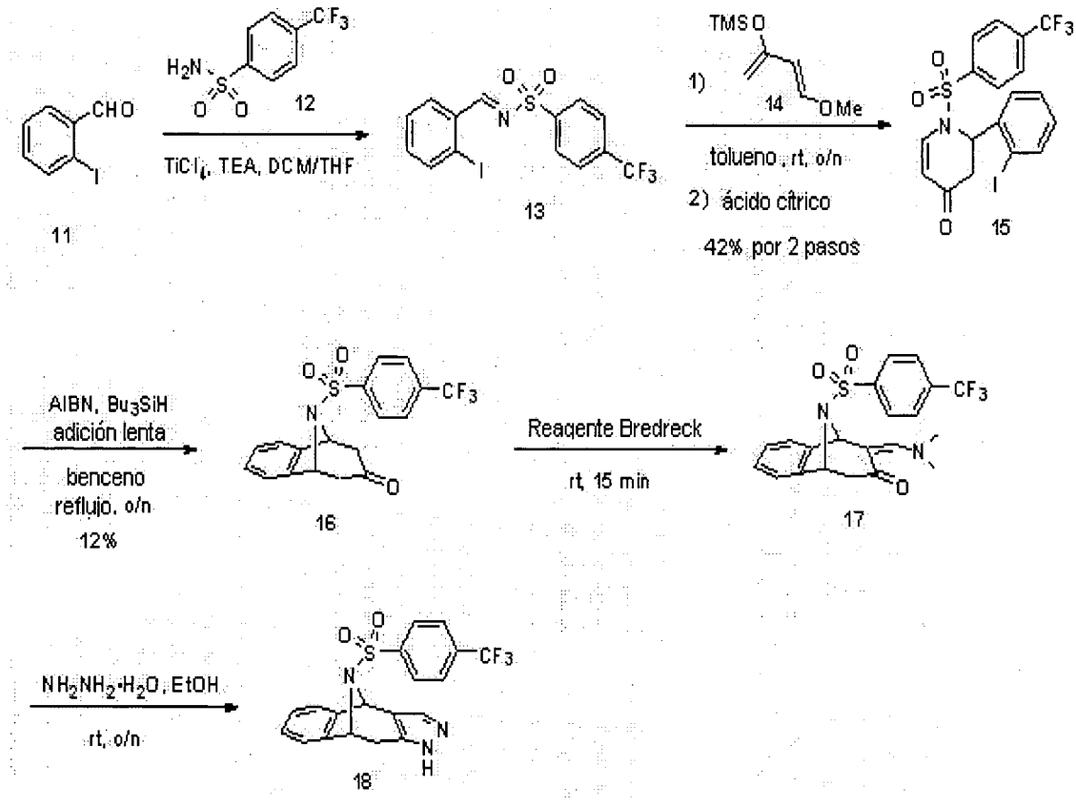
Ejemplo 8

Síntesis de (11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol) (18)



8.1. (*E*)-*N*-(2-yodobenzilideno)-4-(trifluorometil)benzeno-sulfonamida (13)

Para la mezcla de 2-yodobenzaldehido (**11**) (12.3 g, 53 mmol) y 4-trifluorometilbenzenosulfonamida (**12**) (12.15 g, 54 mmol) en CH_2Cl_2 (110 mL) y THF (27 mL) fue añadido trietilamina (22.5 mL) y cloruro de titanio (IV) (3 mL) a 0 °C. Después de batir a 0 °C por 2 h, el sólido fue separado via filtración Celite. El filtrado fue concentrado bajo presión reducida a secado, triturado con tolueno para dar 27 g de un sólido amarillo como el producto crudo **(3)** que fue usado sin una purificación ulterior.

8.2. 2-(2-Iodofenil)-1-(4-(trifluorometil)fenilsulfonil)-2,3-dihidropiridina-4(1H)-ona (15)

Para la suspensión de 27 g de **(3)** del paso 1 en tolueno (250 mL) fue agregado dieno de Danishefsky (**14**) (10 g) a temperatura ambiente. La suspensión fue batida a temperatura ambiente (se hizo clara en unos pocos minutos) por 2 horas. 2 N ácido cítrico (40 mL) fue agregado y la mezcla fue batida a temperatura

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ambiente por la noche. La capa orgánica fue separada y la capa acuosa fue extraída con EtOAc (2 x 50 mL). Las capas orgánicas fueron combinadas y concentradas bajo presión reducida para dar un aceite rojizo. Después de cromatografía flash en gel de sílice, un gel amarillo untuoso fue aislado como producto **(15)** (11g, 42 % en dos pasos). ^{1}H NMR ($CDCl_3$) □7.98 (d, *J* = 8.1 Hz, 1H), 7.77-7.71 (m, 3H), 7.56 (d, *J* = 8.7 Hz, 2H), 6.84-6.77 (m, 3H), 5.81 (d, *J* = 8.1 Hz, 1H), 5.47 (d, *J* = 8.1 Hz, 1H), 3.04 (dd, *J* = 8.1, 16.5 Hz, 1H), 2.61 (d, *J* = 16.5 Hz, 1H).

8.3. (10-{[4-(Trifluorometil) fenil] sulfonil}-5, 6, 8, 9-tetrahidro-7*H*-5, 9-epiminobenzo[7]anuleno-7-uno) (16)

Para una solución de compuesto **15** (1.65 g, 3.25 mmol) en benceno (300 mL) a 80 °C fue añadida una solución de AIBN (105 mg, 20% mol) y tri(n-butil)tin hidruro (0.86 mL, 3.25 mmol) en benceno (20 mL) por un período de 2 horas. La mezcla fue calentada a reflujo por 48 h. Después de evaporación del solvente, el residuo fue purificado vía cromatografía flash en gel de sílice para dar un sólido blanco como producto **(16)** (150 mg, 12 %). ^{1}H NMR ($CDCl_3$) □7.66 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.0-6.9 (m, 4H), 5.25 (dd, *J* = 3.3 Hz, 2H), 3.14 (dd, *J* = 4.5, 16.8 Hz, 2H), 2.58 (d, *J* = 16 Hz, 2H).

8.4. (6-[(Dimetilamino) metilideno]-10-{[4-(trifluorometil) fenil] sulfonil}-5,6,8,9-tetrahidro-7*H*-5,9-epiminobenzo[7]anuleno-7-ona) (17)

Compuesto **16** (15 mg, 0.04 mmol) fue mezclado con 0.3 mL de reagente de Bredreck y la mezcla fue batida a temperatura ambiente por 30 min. La reacción fue extinguida con agua (1 mL) y extraída con EtOAc. Después de la evaporación del solvente, el producto crudo fue obtenido como un aceite amarillo y usado sin purificación ulterior.

8.5. (11-{[4-(Trifluorometil) fenil] sulfonil}-1, 4, 9, 10-tetrahidro-4,9-epiminobenzo [4, 5]ciclohepta[1,2-c]pirazol) (18)

Compuesto **17** fue disuelto en EtOH (0.5 mL) y monohidrato de hidracina (6 □L) fue luego añadido. La mezcla fue batida a temperatura ambiente por la noche. El solvente fue removido bajo presión reducida y el producto crudo fue purificado por

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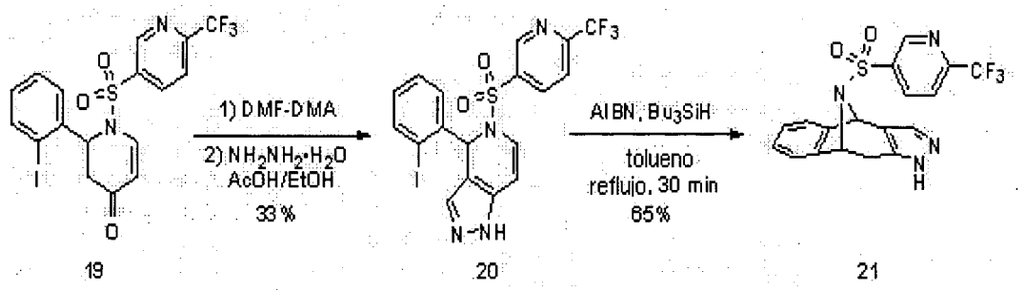
HPLC para dar un sólido blanco mientras el producto puro **(18)** (8 mg, 50 % en dos pasos). ^{1}H NMR ($CDCl_3$) □7.71 (d, *J* = 8.7 Hz, 2H), 7.45 (d, *J* = 8.7 Hz, 2H), 7.07-7.04 (m, 1H), 6.99-6.93 (m, 3H), 5.83 (s, 1H), 5.38 (d, *J* = 5.1 Hz, 1H), 3.53 (dd, *J* = 5.1, 16.2 Hz, 1H), 2.85 (d, *J* = 16.2 Hz, 1H).

Ejemplo 9

Síntesis de (11-{[6-(trifluorometil) piridina -3-yl]sulfonil}-1, 4, 9, 10-tetrahidro-4, 9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol) (21)



9.1. (4-(2-Iodofenil)-5-{[6-(trifluorometil) piridina-3-yl]sulfonil}-4, 5-dihidro-1*H*-pirazol[4,3-*c*] piridina) (20)

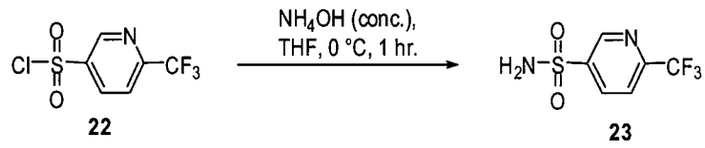
Compuesto **19** (200 mg, 0.39 mmol), similarmente preparado como es descrito para compuesto **15** en el Ejemplo 8 usando compuesto **23** en lugar de compuesto **12,** fue mezclado con complejo DMF-DMA (1.7 mL) y la mezcla fue calentada a 75 °C por 30 min. Después de la evaporación del exceso DMF-DMA, el residuo fue disuelto en AcOH/EtOH (2 mL, 1:1) y monohidrato de hidracina (0.11 mL) fue añadido. La mezcla fue batida a temperatura ambiente por 2 horas y concentrada bajo presión reducida a secado. El producto crudo fue purificado por cromatografía flash en gel de sílice para dar un sólido blanco como el producto puro **(20)** (69 mg, 33 %). ^{1}H NMR ($CDCl_3$) □8.95 (d, *J* = 2.4 Hz, 1H), 8.06 (dd, *J* = 2.1, 8.1 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 8.1 Hz, 1H), 7.50 (s, 1H), 7.20 (dd, *J* = 1.8, 7.8 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 6.96 (t, *J* = 7.8 Hz, 1H), 6.84-6.79 (m, 2H), 6.09 (d, *J* = 8.1 Hz, 1H).

9.2. (11-{[6-(Trifluorometil)piridina-3-yl]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol) (21)

Compuesto **20** (62 mg, 0.12 mmol) fue disuelto en tolueno (10 mL) y tratado con AIBN (8 mg) y Bu_3SnH (55 µL) secuencialmente 120 °C. La mezcla fue batida a 120 °C por 30 minutos. Después de la evaporación del solvente, el residuo fue purificado por cromatografía flash en gel de sílice para dar un sólido blanco como producto puro **(21)** (31 mg, 65%). ^{1}H NMR ($CDCl_3$) □8.86 (d, *J* = 1.5 Hz, 1H), 8.01 (dd, *J* = 1.5, 7.5 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.35 (s, 1H), 7.09-7.07 (m, 1H), 6.97-6.85 (m, 3H), 5.86 (s, 1H), 5.38 (d, *J* = 5.4 Hz, 1H), 3.45 (dd, *J* = 5.4, 16.5 Hz, 1H), 2.84 (d, *J* = 16.5 Hz, 1H).

Ejemplo 10

Síntesis de 6-(trifluorometil) piridina-3-sulfonamida (23)



Un frasco de fondo redondo de 2L con dos cuellos conteniendo una barra magnética de batido y ajustado con embudo de adición fue cargado con una solución acuosa concentrada de hidróxido de amonio (600 mL). La solución fue enfriada a 0 °C. El sulfonil cloruro, **22**, (54.4 g, 221 mmol) fue disuelto en THF (300 mL) y colocado en un embudo de adición. La solución de sulfonil cloruro fue agregada a la solución de hidróxido de amonio fría a 0 °C alrededor de 15-20 minutos. La reacción fue batida a 0 °C por 1 hr. La solución de reacción fue parcialmente concentrada al vacío con un baño de agua fría para proveer regulación de temperatura del frasco de evaporación durante 3 horas. (*Atención – el exceso de amoníaco es evaporado al vacío y en gran parte el vapor debe ser atrapado burbujeando con el conducto de salida del evaporador rotatorio a través de una solución.)* Una vez que el volumen de la solución de reacción fue reducido a aproximadamente a la mitad del volumen inicial, un sólido blanco fue formado en la solución acuosa. La suspensión fue extraída con EtOAc (500 mL) y la solución orgánica fue limpiada con solución de bicarbonato ($NaHCO_3$ acuoso.; 300 mL) y salmuera (300 mL). La solución orgánica fue secada sobre $MgSO_4$, filtrada sobre un pequeño tamizador de alúmina (200 mL), y concentrada al vacío. El sólido

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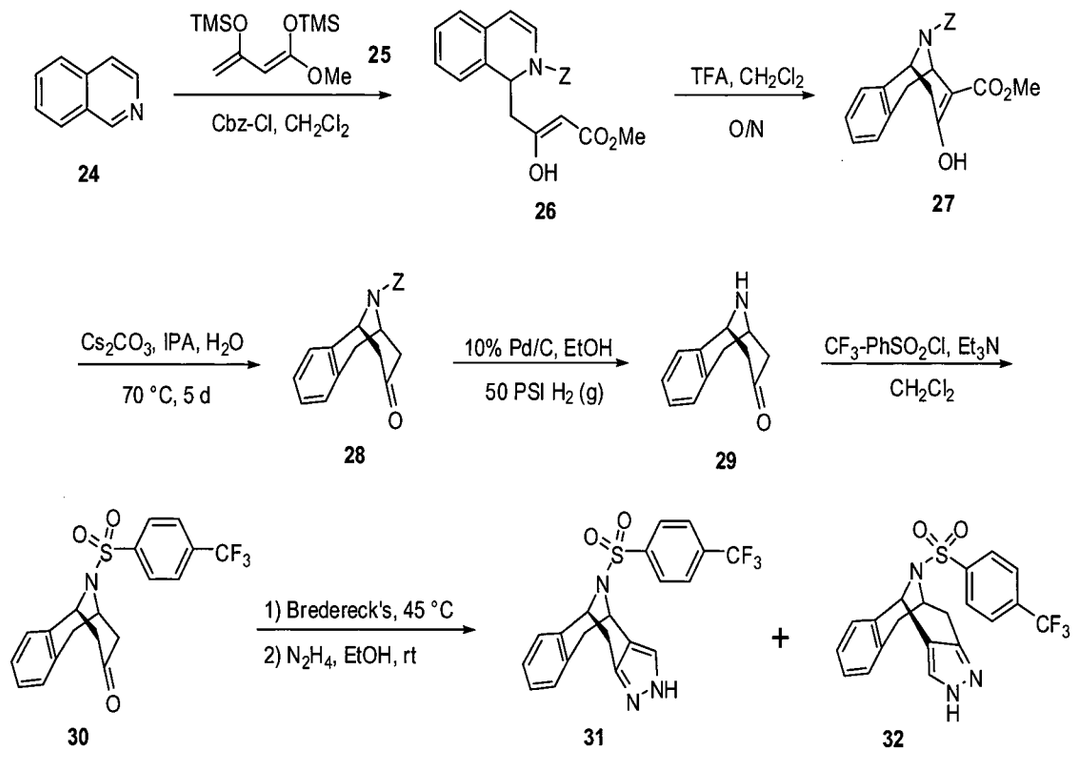
blanco fue secado al vacío durante la noche para producir 43.9 g de compuesto **23** (194 mmol, 87.8% de producción, m.p. 192-193 °C). ^{1}H NMR (DMSO-d_6) □9.16 (d, *J* =1.6 Hz, 1H), 8.48 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.18 (d, *J* = 8.3 Hz, 1H), 7.88 (s, 2H).

Ejemplo 11

Síntesis de 12-{[4-(trifluorometil)fenil]sulfonil}-4,5,10,11-tetrahidro-2*H*-4,10-epiminobenzo[5,6]cicloocta[1,2-*c*]pirazol (31) y 12-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,11-tetrahidro-2*H*-5,11-epiminobenzo[4,5]cicloocta[1,2-*c*]pirazol (32)



11.1. Benzil 1-(4-metoxi-2,4-dioxobutil) isoquinolina-2(1*H*)-carboxilato (26)

A una mezcla de isoquinolina **(24)** (2.05 g, 15.9 mmol) en 150 mL de CH_2CL_2 a 0 °C fue añadida (Z)-4-metoxi-2,2,8,8-tetrametil-6-metileno-3,7-dioxa-2,8-disilanon-4-ene (**25**) (8.29 g, 31.8 mmol), seguido de cloroformato de benzil (2.7 mL, 19.1 mmol). Después de batir a temperatura ambiente durante la noche, 100 mL de NH_4Cl (aq) fue añadida a la mezcla. La capa orgánica fue separada y la capa acuosa fue extraída con CH_2CL_2 (3 x 100 mL). Los extractos orgánicos combinados fueron secados con Na_2SO_4. Después que el secante fue retirado, los extractos orgánicos fueron concentrados bajo presión reducida para proveer **(26)**

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como un aceite amarillo (6.73 g). ^{1}H NMR indicado alrededor de 1:2 radio of ceto: enol tautómeros. Este aceite crudo fue usado en la siguiente reacción sin purificación ulterior.

11.2. 11-Benzil 8-metil-7-hidroxi-5, 6, 9, 10-tetrahidro-5, 9-epiminobenzo [8] anuleno -8, 11-dicarboxilato (27)

A una mezcla de éster (**26**) (6.73 g, 17.7 mmol) en 60 mL de CH_2Cl_2 a temperatura ambiente fue añadido ácido trifluoroacético (2.6 mL, 35.5 mmol). Esta mezcla fue batida a temperatura ambiente durante la noche. Ácido trifluoroacético adicional (2.6 mL, 35.5 mmol) fue añadido y la mezcla fue batida durante la noche a temperatura ambiente. Para esta mezcla fueron añadidos cuidadosamente 40 mL de sat. $NaHCO_3$ (ac.). Después que la efervescencia disminuyó, las capas fueron separadas y la capa acuosa fue extraída con CH_2Cl_2 (3 x 30 mL). Los extractos orgánicos combinados fueron secados sobre Na_2SO_4. Después que el secante fue retirado, los extractos orgánicos fueron concentrados bajos presión reducida para proveer (**27**) como un líquido amarillo (2.79 g). Este líquido crudo fue usado en la siguiente reacción sin purificación ulterior.

11.3. Benzil-7-oxo-5, 6, 7, 8, 9, 10-hexahidro-5, 9- epiminobenzo [8] anuleno-11-carboxilato (28)

A una mezcla de éster (**27**) (2.79 mg, 7.35 mmol) en 60 mL de isopropanol y 20 mL de agua fue añadida Cs_2CO_3 (47.9 g, 147 mmol) La suspensión fue calentada a 90 °C por 20 h. Cs_2CO_3 (47.9 g, 147 mmol) adicional fue añadido y la mezcla fue batida a 90 °C por 20 h. Cs_2CO_3 (47.9 g, 147 mmol) adicional fue añadido y la mezcla fue batida a 90 °C por otros dos días. La mezcla fue cuidadosamente extinguida con 100 mL de 6 N HCl. La solución acuosa fue extraída con EtOAc (3 x 100 mL). Los extractos orgánicos combinados fueron lavados con 10% de NaCl (aq) (250 mL) y secados sobre Na_2SO_4. Después el secante fue retirado, los extractos orgánicos fueron concentrados bajo presión reducida para proveer un aceite crudo. Después de la cromotografía flash en gel de sílice, un aceite espeso amarillo claro.(**28**) (1.13 g) fue obtenido.

11.4. 5, 8, 9, 10-Tetrahidro-5, 9-epiminobenzo [8] anuleno-7(6*H*)-uno (29)

A una mezcla de carbomato (**28**) (1.13 g) en 100 mL de MeOH en una botella Parr fue añadido 500 mg de 10% Pd/C. Esta suspensión fue batida bajo 50 psi de H_2 (g) a temperatura ambiente durante la noche. La mezcla fue filtrada a través de un tamizador de Celite y enjuagada con CH_2Cl_2 (2 x 100 mL). La solución fue concentrada a un aceite amarillo crudo (**29**) (130 mg) y usada en la siguiente reacción sin purificación ulterior.

11.5. 11-{[4-(Trifluorometil) fenil] sulfonil}-5,8,9,10-tetrahidro-5,9-epiminobenzo[8]anuleno-7(6*H*)-uno (30)

A una mezcla de amina (130 mg, 0.69 mmol) (**29**) en 7 mL de CH_2Cl_2 a temperatura ambiente fue añadido trietilamina (0.2 mL), seguido de 4-trifluorometilbenzenosulfonil cloruro (204 mg, 0.83 mmol). Esta mezcla fue batida a temperatura ambiente durante la noche. La mezcla fue concentrada bajo presión reducida a un aceite crudo. Después de cromatografía flash en gel de sílice, un sólido blanco (**30**) (290 mg) fue obtenido.

11.6. 12-{[4-(Trifluorometil)fenil]sulfonil}-4,5,10,11-tetrahidro-2*H*-4,10-epiminobenzo[5,6]cicloocta[1,2-*c*]pirazol (31) y 12-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,11-tetrahidro-2*H*-5,11-epiminobenzo[4,5]cicloocta[1,2-*c*]pirazol (32)

A cetona **30** (290 mg, 0.73 mmol) fue añadido *tert*-butoxibis(dimetilamino)metano (2.56 g, 14.67 mmol). Esta mezcla fue calentada a 45 °C por 1 h. La mezcla fue diluida con 50 mL de H_2O y extraída con EtOAc (3 x 50 mL). Los extractos orgánicos combinados fueron secados sobre Na_2SO_4. Después que el secante fue retirado, los extractos orgánicos fueron concentrados bajo presión reducida para proveer un aceite crudo. Este aceite crudo fue suspendido en 7 mL de EtOH. A esta solución fue añadido hidrato de hidracina (73.4 mg, 1.47 mmol). Esta mezcla fue batida a temperatura ambiente durante la noche. La mezcla fue diluida con agua (50 mL) y extraída con EtOAc (3 x 50 mL). Los extractos orgánicos combinados fueron lavados con 10% NaCl (aq) (100 mL) y secados sobre Na_2SO_4. Después que el secante fue retirado, los extractos orgánicos fueron concentrados bajo presión reducida para proveer un aceite crudo. Después de la cromatografía

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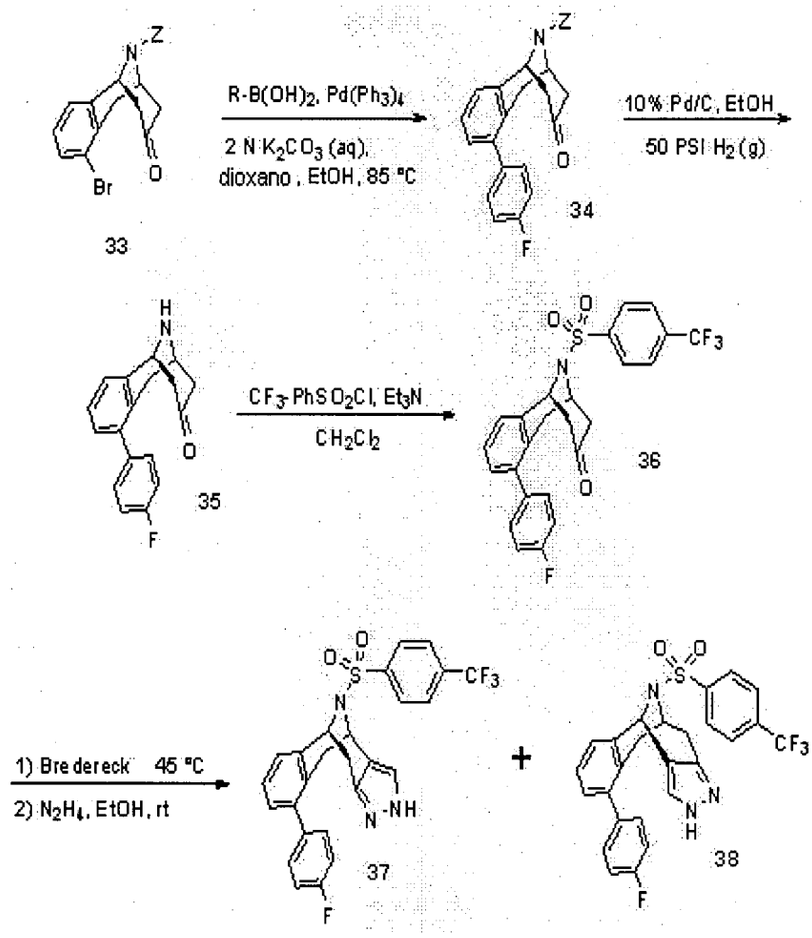
flash en gel de sílice, un sólido amarillo (**31**) (32.1 mg) ^{1}H NMR ($CDCl_3$) □7.90 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.40 (s, 1H), 7.19-7.09 (m, 3H), 6.93 (d, *J* = 7.7 Hz, 1H), 5.53 (d, *J* = 5.3 Hz, 1H), 5.49 (d, *J* = 5.2 Hz, 1H), 3.32 (dd, *J* = 16.5, 6.1 Hz, 1H), 3.16 (dd, *J* = 15.9, 5.7 Hz, 1H), 2.85 (d, *J* = 16.3 Hz, 1H), 2.73 (d, *J* = 16.4 Hz, 1H); y un sólido amarillo (**32**) (35.8 mg) ^{1}H NMR ($CDCl_3$) □7.62 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.33 (s, 1H), 7.15 (d, *J* = 7.4 Hz, 1H), 7.06 (d, *J* = 7.4 Hz, 1H), 6.95 (dt, *J* = 1.5, 7.5 Hz, 1H), 6.59 (d, *J* = 7.6 Hz, 1H), 6.01 (s, 1H), 4.88-4.84 (m, 1H), 3.24 (dd, *J* = 16.1, 6.1 Hz, 1H), 3.08 (d, *J* = 17.9, 9.6 Hz, 1H), 2.75 (dd, *J* = 17.3, 1.1 Hz, 1H); 2.46 (d, *J* = 17.9 Hz, 1H) fue obtenido.

Ejemplo 12

Síntesis de 6-(4-fluorofenil)-12-{[4-(trifluorometil)fenil]sulfonil}-4,5,10,11-tetrahidro-2*H*-4,10-epiminobenzo[5,6]cicloocta[1,2-*c*]pirazol (37) y 7-(4-fluorofenil)-12-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,11-tetrahidro-2*H*-5,11-epiminobenzo[4,5]cicloocta[1,2-*c*]pirazol (38)



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12.1 Benzil-1-(4-fluorofenil)-7-oxo-5, 6, 7, 8, 9, 10-hexahidro-5,9-epiminobenzo[8]anuleno-11-carboxilato (34)

A una mezcla de cetona **33** (243 mg, 0.61 mmol), preparada como es descrita para el compuesto **28** en el Ejemplo 11 usando 5-bromoisoquinolina, en 2M K_2CO_3 (aq) (6 mL), dioxano (6 mL), y EtOH (1.2 mL) fue añadido 4-fluorofenil ácido borónico (102 mg, 0.73 mmol), seguido de tetrakis paladio(trifenilfosfina) (35 mg, 0.03 mmol). Esta mezcla fue batida a 85 °C durante la noche. La mezcla fue filtrada a través de un tamizador de Celite y enjuagada con EtOAc (20 mL). La solución fue diluida con 30 mL de H_2O, y las capas fueron separadas. La capa acuosa fue extraída con EtOAc (3 x 50 mL). Los extractos orgánicos combinados fueron lavados con 10% NaCl (aq) (150 mL) y secados sobre Na_2SO_4. Después que el secante fue retirado, los extractos orgánicos fueron concentrados bajo presión reducida para proveer un aceite crudo. Después de cromatografía de flash en gel de sílice, una espuma amarilla (**34**) (148 mg) fue obtenida.

12.2. 1-(4-Fluorofenil)-5,8,9,10-tetrahidro-5,9-epiminobenzo[8]anuleno-7(6*H*)-uno (35)

A una mezcla de carbamato (**34**) (144 mg) en 100 mL de MeOH en una botella Parr fue añadido 35 mg de 10% Pd/C. Esta suspensión fue batida bajo 50 psi of H_2 (gas) a temperatura ambiente durante la noche. La mezcla fue filtrada a través de un tamizador de Celite y enjuagada con CH_2Cl_2 (2 x 100 mL). La solución fue concentrada a un aceite crudo (**35**) (110 mg) y usada en la siguiente reacción sin purificación ulterior.

12.3. (5*S*)-1-(4-Fluorofenil)-11-{[4-(trifluorometil) fenil] sulfonil}-5,8,9,10-tetrahidro-5,9-epiminobenzo[8]anuleno-7(6*H*)-uno (36)

A una mezcla de amina cruda (110 mg) (**35**) en 4 mL de CH_2Cl_2 a temperatura ambiente fue añadida trietilamina (0.1 mL) seguido de 4-trifluorometilbenzenosulfonil cloruro (101 mg, 0.42 mmol). Esta mezcla fue batida a temperatura ambiente durante la noche. La mezcla fue concentrada bajo presión reducida a un aceite crudo. Después de cromatografía flash en gel de sílice, un sólido ceroso blanco (**36**) (119 mg) fue obtenido.

12.4. 6-(4-Fluorofenil)-12-{[4-(trifluorometil)fenil]sulfonil}-4,5,10,11-tetrahidro-2*H*-4,10-epiminobenzo[5,6]cicloocta[1,2-*c*]pirazol (37) y 7-(4-fluorofenil)-12-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,11-tetrahidro-2*H*-5, 11-epiminobenzo[4,5]cicloocta[1,2-*c*]pirazol (38)

A cetona (119 mg, 0.24 mmol) (**36**) fue añadido *tert*-butoxibis(dimetilamino)metano (1 mL, 4.86 mmol). Esta mezcla fue calentada a 45 °C por 1 h. La mezcla fue diluida con 50 mL de H_2O y extraída con EtOAc (3 x 50 mL).Los extractos orgánicos combinados fueron secados sobre Na_2SO_4. Después que el secante fue retirado, los extractos orgánicos fueron concentrados bajo presión reducida para proveer un aceite crudo. Este aceite crudo fue suspendido en 2 mL de EtOH. A esta solución fue añadido hidrato de hidracina (24.3 mg, 0.49 mmol). Esta mezcla fue batida a temperatura ambiente durante la noche. La mezcla fue diluida con agua (30 mL) y extraída con EtOAc (3 x 30 mL). Los extractos orgánicos combinados fueron lavados con 10% NaCl (aq) (100 mL) y secados sobre Na_2SO_4. Después que el secante fue retirado, los extractos orgánicos fueron concentrados bajo presión reducida para proveer un aceite crudo. Después de cromatografía flash en gel de sílice, una sólido amarillo (**37**) (19.8 mg) ^{1}H NMR ($CDCl_3$) □7.90 (d, *J* = 8.2 Hz, 2H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.30 (s, 1H), 7.25-7.18 (m, 2H), 7.08-6.93 (m, 5H), 5.59 (d, *J* = 5.3 Hz, 1H), 5.44 (d, *J* = 5.5 Hz, 1H), 3.20 (dd, *J* = 5.7, 16.0 Hz, 1H), 3.04 (dd, *J* = 5.4, 16.3 Hz, 1H), 2.92 (d, *J* = 16.8 Hz, 1H), 2.42 (d, *J* = 15.7 Hz, 1H); y un sólido amarillo (**38**) (16.4 mg) ^{1}H NMR ($CDCl_3$) □7.61 (d, *J* = 7.9 Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 2H), 7.41 (s, 1H), 7.25 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.17 (t, *J* = 7.4 Hz,1H), 7.02 (t, *J* = 8.7 Hz, 2H), 6.89 (dd, *J* = 1.4, 7.5 Hz, 1H), 6.83-6.79 (m, 2H), 6.12 (s, 1H), 4.77-4.72 (m, 1H), 3.26 (dd, *J* = 5.6, 15.9 Hz, 1H), 2.87-2.81 (m, 1H), 2.75 (d, *J* = 16.9 Hz, 1H), 2.28 (d, *J* = 18.6 Hz, 1H) fueron obtenidos.

Ejemplo 13

Síntesis de 6-ciclopropil-12-{[6-(trifluorometil)piridina-3-yl]sulfonil}-4,5,10,11-tetrahidro-2*H*-4,10-epiminobenzo[5,6]cicloocta[1,2-*c*]pirazol (42) y 7-

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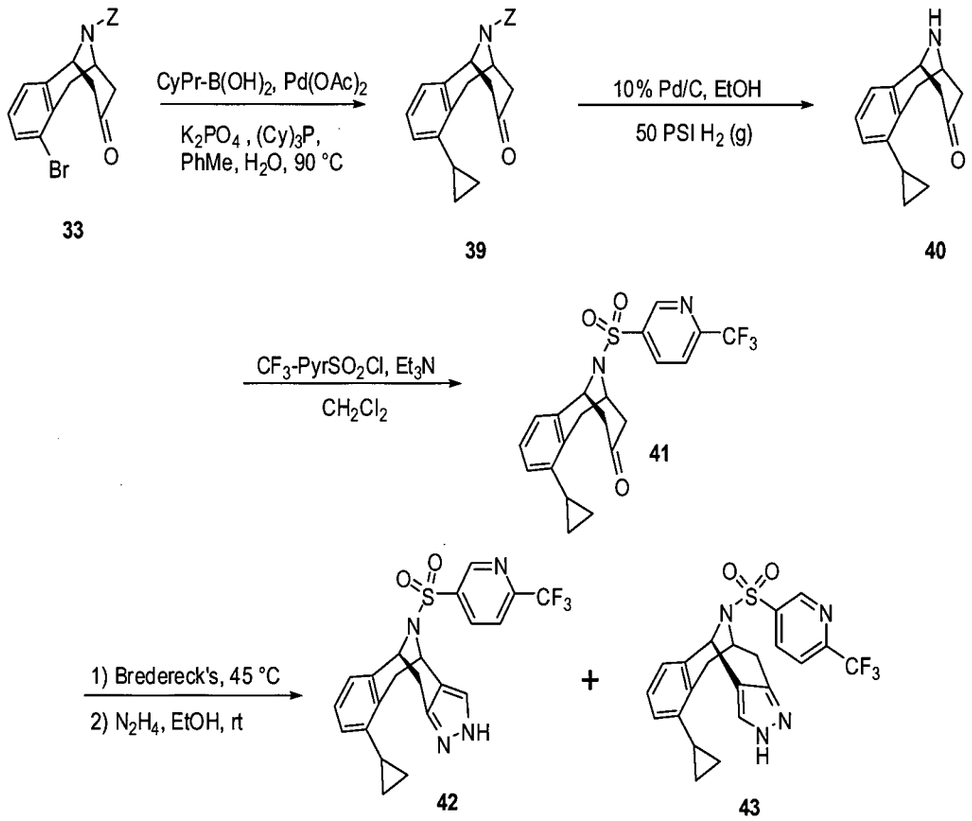
ciclopropil- 12-{[6-(trifluorometil)piridina-3-yl]sulfonil}-4,5,6,11-tetrahidro-2*H*-5,11- epiminobenzo[4,5]cicloocta[1,2-*c*]pirazol (43)



13.1. Benzil1-ciclopropil-7-oxo-5,6,7,8,9,10-hexahidro-5,9-epiminobenzo[8]anuleno-11-carboxilato (39)

A una mezcla de cetona (**33**) (400 mg, 1 mmol) en tolueno (4.5 mL), y H_2O (0.2 mL) fue añadido ácido ciclopropilborónico (112 mg, 1.3 mmol), fosfato de potasio (743 mg, 3.5 mmol), triciclohexilfosfina (28 mg, 0.1 mmol), y acetato de paladio (11 mg, 0.05 mmol). Esta mezcla fue batida a 90 °C durante la noche. La mezcla fue filtrada a través de un tamizador de Celite y enjuagada con EtOAc (20 mL). La solución fue diluida con 30 mL de H_2O, y las capas fueron separadas. La capa acuosa fue extraída con EtOAc (3 x 50 mL). Los extractos orgánicos combinados fueron lavados con 10% NaCl (aq) (150 mL) y secados sobre Na_2SO_4. Después que el secante fue retirado, los extractos orgánicos fueron concentrados bajo presión reducida para proveer un aceite crudo. Después de cromatografía flash en gel de sílice, un aceite amarillo (**39**) (330 mg) fue obtenido.

13.2. 1-Ciclopropil-5, 8,9,10-tetrahidro-5,9-epiminobenzo[8]anuleno-7(6*H*)-uno (40)

A una mezcla de carbamato (**39**) (330 mg) en 100 mL de MeOH en una botella Parr fueron añadidos 50 mg de 10% Pd/C. Esta suspensión fue batida bajo 50 psi de H_2 (gas) a temperatura ambiente durante la noche. La mezcla fue filtrada a través de un tamizador de Celite y enjuagada con CH_2Cl_2 (2 x 100 mL). La solución fue concentrada a un sólido crudo color canela (**40**) (192 mg) y usada en la siguiente reacción sin purificación ulterior.

13.3. 1-Ciclopropil-11-{[6-(trifluorometil)piridina-3-yl]sulfonil}-5,8,9,10-tetrahidro-5,9-epiminobenzo[8]anuleno-7(6*H*)-uno (41)

A una mezcla de amina cruda (192 mg) (**40**) en 8 mL de CH_2Cl_2 a temperatura ambiente fue añadida trietilamina (0.23 mL), seguido de 6-(trifluorometil) piridina-3-sulfonil cloruro (244 mg, 0.99 mmol). Esta mezcla fue batida a temperatura ambiente durante la noche. La mezcla fue concentrada bajo presión reducida. Después de cromatografía flash en gel de sílice, un sólido blanco (**41**) (281 mg) fue obtenido.

13.4. 6-Ciclopropil-12-{[6-(trifluorometil)piridina-3-il]sulfonil}-4,5,10,11-tetrahidro-2*H*-4,10-epiminobenzo[5,6]cicloocta[1,2-*c*]pirazol (42) y 7-Ciclopropil-12-{[6-(trifluorometil)piridina-3-il]sulfonil}-4,5,6,11-tetrahidro-2*H*-5,11- epiminobenzo[4,5]cicloocta[1,2-*c*]pirazol (43)

A cetona (278 mg, 0.64 mmol) (**41**) fue añadido *tert*-butoxibis(dimetilamino)metano (2.22 g, 12.74 mmol). Esta mezcla fue calentada a 45 °C por 1.5 h. La mezcla fue diluida con 50 mL de H_2O y extraída con EtOAc (3 x 50 mL). Los extractos orgánicos combinados fueron secados sobre Na_2SO_4. Después que el secante fue retirado, los extractos orgánicos fueron concentrados bajo presión reducida para proveer un aceite crudo. Este aceite crudo fue resuspendido en 6 mL de EtOH. A esta solución fue añadido hidrato - hidracina (61 mg, 1.22 mmol). Esta mezcla fue batida a temperatura ambiente durante la noche. La mezcla fue diluida con agua (30 mL) y extraída con EtOAc (3 x 30 mL). Los extractos orgánicos combinados fueron lavados con 10% NaCl (aq) (100 mL) y secados sobre Na_2SO_4. Después que el secante fue retirado, los extractos orgánicos fueron concentrados bajo presión reducida para proveer un aceite crudo. Después HPLC, un sólido

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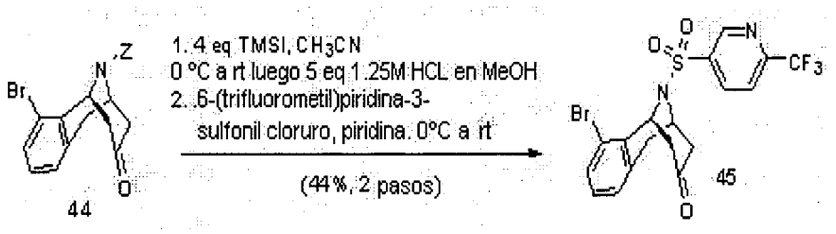
blanco (**42**) (17.9 mg) ^{1}H NMR ($CDCl_3$) □9.07 (d, *J* = 2.0 Hz, 1H), 8.20 (dd, *J* = 1.9, 8.2 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.54 (s, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 5.64 (d, *J* = 5.7 Hz, 1H), 5.53 (d, *J* = 5.1 Hz, 1H), 3.35 (dd, *J* = 6.3, 16.5 Hz, 1H), 3.16 (dd, *J* = 5.8, 17 Hz, 1H), 3.00 (d, *J* = 11.1 Hz, 1H), 2.94 (d, *J* = 11.4 Hz, 1H); 1.58-1.49 (m, 1H); 0.91-0.77 (m, 2H); 0.51-0.35 (m, 2H); y sólido blanco (**43**) (23.8 mg) ^{1}H NMR ($CDCl_3$) □8.88 (d, *J* = 1.9 Hz, 1H), 7.87 (dd, *J* = 1.9, 8.2 Hz, 1H), 7.50 (s, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.06 (t, *J* = 4.4 Hz, 1H), 6.76-6.71 (m, 1H), 6.06 (s, 1H), 5.05-5.00 (m, 1H), 3.42 (dd, *J* = 5.6, 16.5 Hz, 1H), 3.30 (dd, *J* = 9.9, 18.5 Hz, 1H), 2.95 (d, *J* = 16.5 Hz, 1H), 2.38 (d, *J* = 18.6 Hz, 1H); 1.32-1.23 (m, 1H); 0.84-0.72 (m, 2H), 0.46-0.37 (m, 1H), 0.30-0.24 (m, 1H) fueron obtenidos.

Ejemplo 14

Síntesis de 4-bromo-11-{[6-(trifluorometil)piridina-3-il]sulfonil}-5,8,9,10-tetrahidro-5,9-epiminobenzo[8]anuleno-7(6*H*)-uno (45)



A una solución enfriada con hielo de cetona **44** (706 mg, 1.76 mmol), preparada, como es descrito para el compuesto **28** en el Ejemplo 11 usando 8-bromoisoquinolina, en acetonitrilo (17 mL) fue añadido TMSI (960 □L, 7.05 mmol). La mezcla de reacción fue entibiada a temperatura ambiente alrededor de dos horas, tiempo en el cual el análisis LC/MC determinó que no quedaba material inicial alguno. La mezcla de reacción fue enfriada a 0 °C y tratada con 1.25 M HCl en MeOH (7 ml, 8.80 mmol) y entibiada a temperatura ambiente alrededor de 1.5 horas. La concentración produjo 530 mg de residuo grueso de color marrón que fue disuelto en piridina (9 mL), enfriado a 0 °C, y tratado con 6-(trifluorometil)piridina-3-sulfonil cloruro (1.07g, 4.37 mmol). Después de batir durante la noche a temperatura ambiente, el análisis LC/MS reveló la presencia de material inicial, así que la mezcla de reacción fue tratada con 6-

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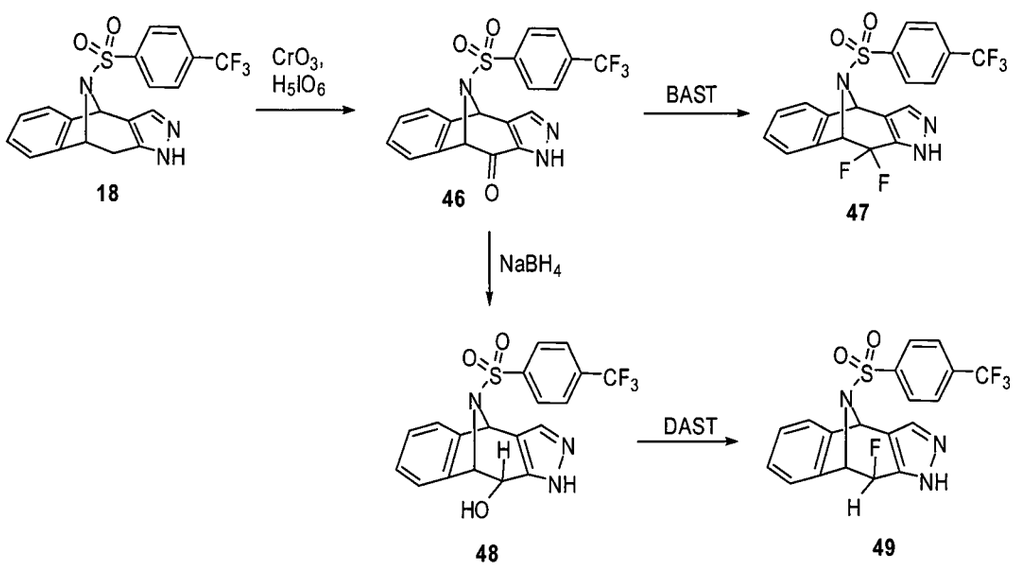
(trifluorometil)piridina-3-sulfonil cloruro (644 mg, 2.65 mmol) y batida a temperatura ambiente por cinco días. La mezcla de reacción fue luego diluida con EtOAc y agua (20 mL cada una). La porción orgánica fue lavada con 0.2 N ácido cítrico (6 x 35 mL), agua (1 x 20 mL), sat. ac. $NaHCO_3$ (3 x 25 mL), salmuera (1 x 20 mL), secada ($MgSO_4$), filtrada y concentrada. El producto crudo fue purificado por cromatografía de gel de sílice para producir 366 mg (44%) de compuesto **45**. ^{1}H NMR ($CDCl_3$) □9.05 (d, *J* = 2.1 Hz, 1H), 8.16 (dd, *J* = 8.0,1.0 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.39 (d, *J* = 8.4 Hz), 6.97 (t, *J* = 7.8 Hz, 1H), 6.77 (d, *J* = 7.2 Hz, 1H), 5.79 - 5.75 (m, 1H), 4.98 (t, *J* = 7.8 Hz, 1H), 3.07-2.93 (m, 3H), 2.78-2.64 (m, 2H), 2.46 (d, *J* = 15.0 Hz, 1H).

Ejemplo 15

Síntesis de 10-fluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol (49)



15.1. 11-{[4-(trifluorometil)fenil]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol-10(1*H*)-ona (46)

A una solución de ácido periódico (532 mg, 2.33 mmol) en acetonitrilo (6 mL) se añadió óxido de cromo (VI) (9 mg, 0.09 mmol). Luego de batir por 5 minutos, se añadió compuesto **18** (200 mg, 0.49 mmol) en acetonitrilo (6 mL). La resultante solución fue batida a temperature ambiente durante la noche. TLC análisis (1:1 EtOAc: hexanos) y LC/MS indicaron la completación de la reacción. La reacción fue entonces sofocada con agua (20 mL) y extraída con CH_2Cl_2 (30 mL x 3). Las

capas orgánicas combinadas fueron secadas sobre Na_2SO_4, filtradas y concentradas a presión reducida para dar el producto crudo. Purificación por cromatografía sobre gel de sílice, elucionando con 0 a 60% EtOAc en hexanos, dio el compuesto título (162 mg, 78% producción). ^{1}H NMR ($CDCl_3$) □7.77 (d, *J* = 8.3 Hz, 2H), 7.62 (s, 1H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.25-7.28 (m, 1H), 7.11-7.02 (m, 3H), 6.18 (s, 1H), 5.44 (s, 1H).

15.2. 10,10-difluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol (47)

Compuesto **46** (36 mg, 0.09 mmol) fue disuelto en bis(2-metoxietil)aminosulfuro trifluoruro (BAST) (0.5 mL) y calentado a80 °C por 30 minutos. LC/MS no mostró ningún material de inicio. La mezcla de reacción fue enfriada a temperatura ambiente y añadida gota a gota a una solución acuosa saturada de bicarbonato de sodio fría. Después de batir por 10 minutos la mezcla fue extraída con CH_2Cl_2 (3x), secada sobre Na_2SO_4, filtrada, y concentrada a presión reducida para dar el producto crudo. Purificación por preparativo HPLC dió el compuesto título (12 mg, 25% producción) como sal TFA. ^{1}H NMR ($CDCl_3$) □7.79 (d, 2H, *J* = 8.2 Hz), 7.52 (d, 2H, *J* = 8.3 Hz), 7.45 (s, 1H), 7.25-7.29 (m, 1H), 6.94-7.06 (m, 3H), 6.00 (s, 1H), 5.47 (d, 1H, *J* = 10.6 Hz).

15.3. 11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol-10-ol (48)

A una suspension del compuesto **46** (158 mg, 0.38 mmol) en MeOH (7 mL) fue añadido borohidruro de sodio (29 mg, 0.75 mmol). La mezcla fue batida a temperature ambiente por 30 minutos.El análisis TLC (1:1 EtOAc: hexanos) indicó la completación de la reacción. La reacción fue entonces sofocada con agua (20 mL) y extraída con CH_2Cl_2 (30 mL x 3).Las capas orgánicas combinadas fueron secadas sobre Na_2SO_4, filtradas, y concentradas a presión reducida para dar el producto crudo.Purificación por cromatografía flash sobre gel de sílice, elución con 0 a 80% EtOAc en hexanos, dio el compuesto título (137 mg, 86% producción). ^{1}H NMR ($CDCl_3$) □7.82 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.48 (s, 1H), 7.10-7.07 (m, 1H), 6.93-6.86 (m, 3H), 5.91 (s, 1H), 5.30-5.23 (m, 2H).

15.4. 10-fluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol (49)

A una solución de (dietilamino)sulfuro trifluoruro (DAST) (14 mg, 0.09 mmol) en CH_2Cl_2 (4 mL) a -78 °C fue añadida una solución del compuesto **48** (21 mg, 0.05 mmol) en CH_2Cl_2 (2 mL). La mezcla de reacción fue batida a esa temperature por 6h, a las 4h más DAST (14 mg, 0.09 mmol) fue añadido. La reacción fue sofocada con solución acuosa saturada de bicarbonato de sodio. (10 mL) y extraída con CH_2Cl_2 (20 mL x 3). Las capas orgánicas combinadas fueron secadas sobre Na_2SO_4, filtradas, y concentradas a presión reducida para dar el producto crudo.Purificación por cromatografía flash sobre gel de sílice, elución con 0 a 70% EtOAc en hexanos, dio el compuesto título (8.5 mg, 40% producción). ^{1}H NMR ($CDCl_3$) □7.80 (d, *J* = 8.3 Hz, 2H), 7.49 (d, *J* = 8.3 Hz, 2H), 7.40 (s, 1H), 7.19-7.16 (m, 1H), 7.03-6.94 (m, 3H), 6.01 (s, 1H), 5.61-5.44 (m, 2H).

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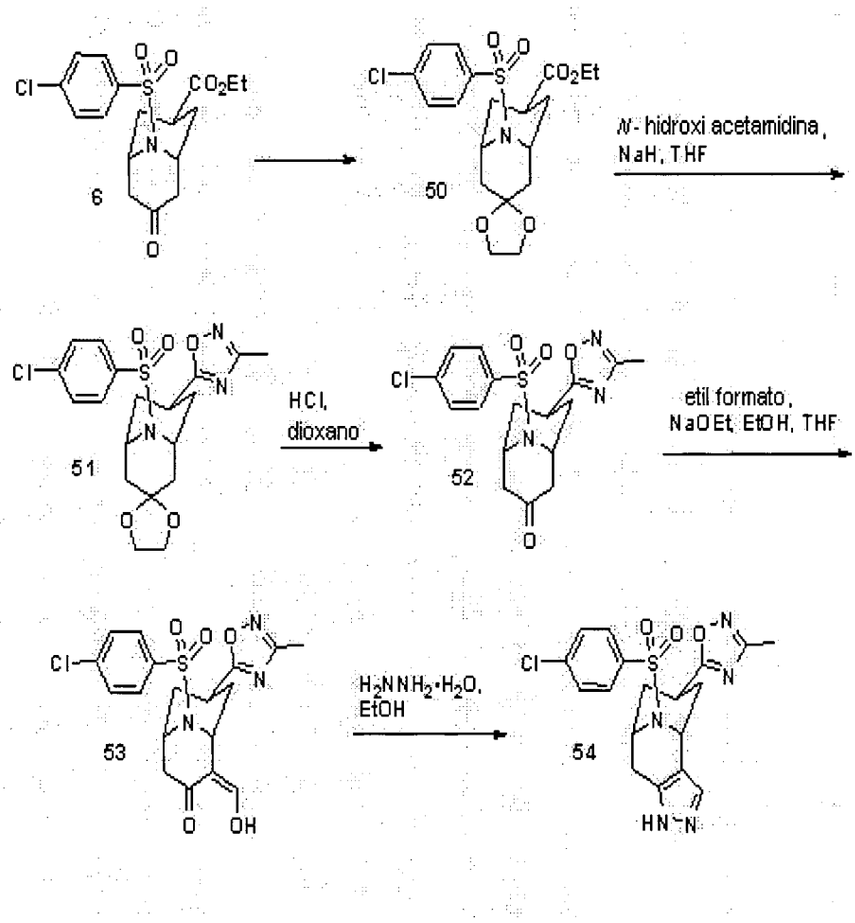
Ejemplo 16

Síntesis de 10-[(4-clorofenil)sulfonil]-6-(3-metil-1,2,4-oxadiazol-5-il)-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol (54)



16.1. Etill 9-[(4-clorofenil)sulfonil]spiro[9-azabiciclo[3.3.1]nonano-3,2'-[1,3]dioxolano]-7-carboxilato (50)

A una solución de 9-(4-cloro-benzenosulfonil)-7-oxo-9-aza-biciclo[3.3.1]nonano-3-ácido carboxílico etil ester (**6**) (1.62 g, 4.19 mmol) en CH_2Cl_2 (14 mL) fue añadido etilén glicol (0.94 mL, 16.7 mmol) y TMSCl (1.06 mL, 8.39 mmol). La solución resultante fue calentada a reflujo por 48 h y fue subsiguientemente lavada con solución acuosa saturada de $NaHCO_3$ (10 mL). La fase orgánica fue secada (Na_2SO_4), filtrada y concentrada al vacío para producir 1.62 g (90%) de compuesto **50**. MS(ESI) 430.1 (M+H).

16.2. 9-[(4-Clorofenil)sulfonil]-7-(3-metil-1,2,4-oxadiazol-5-il)spiro[9-azabiciclo[3.3.1]nonano-3,2'-[1,3]dioxolano] (51)

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Hidruro sódico (60% dispersion, 43 mg, 1.09 mmol) fue añadido a una solución de *N*-hidroxiacetamidina (81 mg, 1.09 mmol) en THF (2 mL) y la mezcla fue batida a 50 °C por 15 minutos. Etill 9-[(4-clorofenil)sulfonil]spiro[9-azabiciclo[3.3.1]nonano-3,2'-[1,3]dioxolano]-7-carboxilato (**50**) (0.394 g, 0.916 mmol) en THF (2 mL) fue añadido a la mezcla de reacción y la solución resultante fue batida a temperatura ambiente por 1 hora. La mezcla fue diluida con EtOAc y lavada con H_2O. La fase orgánica fue secada (Na_2SO_4), filtrada y concentrada al vacío para producir 0.40 g (quant.) de compuesto **51**. MS(ESI) 440.1 (M+H).

16.3. 9-[(4-Clorofenil)sulfonil]-7-(3-metil-1,2,4-oxadiazol-5-il)-9-azabiciclo[3.3.1]nonan-3-ona (52)

9-[(4-Clorofenil)sulfonil]-7-(3-metil-1,2,4-oxadiazol-5-il)spiro[9-azabiciclo[3.3.1]nonano-3,2'-[1,3] dioxolano] (**51**) (0.40 g, 0.916 mmol) fue cubierta con HCl en dioxano (4 N, 2 mL).La mezcla de reacción fue batida a temperatura ambiente por 2 h y luego fue diluida con EtOAc y lavada con hidróxido de sodio acuoso (1 N). La fase orgánica fue secada (Na_2SO_4), filtrada y concentrada al vacío para producir 0.36 g (quant.) de 9-[(4-clorofenil)sulfonil]-7-(3-metil-1,2,4-oxadiazol-5-il)-9-azabiciclo[3.3.1]nonan-3-ona (**52**). MS(ESI) 396.1 (M+H).

16.4. 9-[(4-Clorofenil)sulfonil]-2-(hidroximetilideno)-7-(3-metil-1,2,4-oxadiazol-5-il)-9-azabiciclo[3.3.1]nonan-3-ona (53)

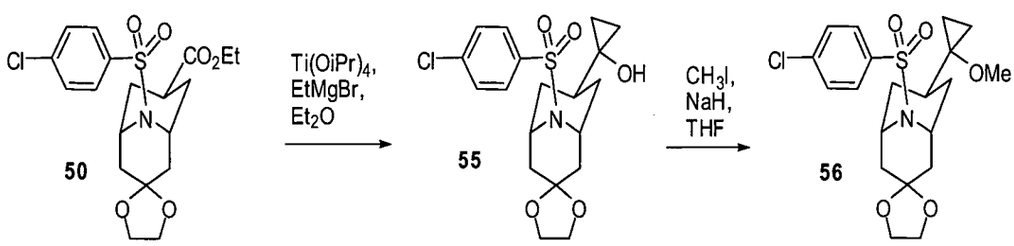
9-[(4-Clorofenil) sulfonil]-7-(3-metil-1,2,4-oxadiazol-5-il)-9-azabiciclo[3.3.1]nonan-3-ona (**52**) (0.357 g, 0.902 mmol) fue disuelto en THF/EtOH (2 mL, 1/1, v/v). Etill formato (0.725 mL, 9.02 mmol) fue añadido seguido de etóxido sódico (1.01 mL de 21% solución en EtOH). La mezcla fue batida a 50 °C por 1 hora y luego enfriada a temperatura ambiente y sofocada por la adición de solución acuosa saturada NH_4Cl. La mezcla fue extraída con EtOAc y las fases orgánicas combinadasfueron secadas (Na_2SO_4), filtradas y concentradas al vacío para dar 9 - [(4-clorofenil)sulfonil] -2- (hidroximetilideno) – 7 - (3-metil-1,2,4-oxadiazol-5-il) – 9 – azabiciclo [3.3.1] nonan - 3- ona (**53**). MS(ESI) 424.0 (M+H).

16.5. 10 - [(4-Clorofenil)sulfonil]-6-(3-metil-1,2,4-oxadiazol-5-il)-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol (54)

A una solución de 9-[(4-clorofenil) sulfonil]-2 - (hidroximetilideno)-7-(3-metil-1, 2, 4-oxadiazol-5-il)-9-azabiciclo[3.3.1]nonano-3-ona (**53**) (0.38 g, 0.902 mmol) en EtOH (5 mL) fue añadido ácido acético glacial (0.1 mL) seguido de monohidrato de hidrazina (0.44 mL, 9.02 mmol). La mezcla de reacción fue batida a temperatura ambiente por 2 h y luego a 50 °C por otras 2 h. La solución resultante fue diluida con EtOAc y lavada con H_2O. La fase orgánica fue secada (Na_2SO_4), filtrada, concentrada y purificada por cromatografía de columna de gel de sílice (eluante hexano/EtOAc, 9/1 a 2/8) y preparativo HPLC para dar 10-[(4-clorofenil)sulfonil]-6-(3-metil-1,2,4-oxadiazol-5-il)-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol (**54**). MS(ESI) 420.1 (M+H). ^{1}H NMR (300 MHz, $CDCl_3$) □7.67 (d, *J* = 8.8 Hz, 2H), 7.52 (s, 1H), 7.39 (d, *J* = 8.8 Hz, 2H), 5.43 (bs, 1H), 4.66 (bs, 1H), 3.06 (m, 1H), 2.72 (d, *J* = 17.6 Hz, 1H), 2.34 (s, 3H), 2.32-2.09 (m, 4H).

Ejemplo 17

Síntesis de 9-[(4-Clorofenil)sulfonil]-7-(1-metoxiciclopropil)spiro[9-azabiciclo[3.3.1]nonano-3,2'-[1,3] dioxolano] (56)



17.1. 1-{9-[(4-Clorofenil)sulfonil]spiro[9-azabiciclo[3.3.1]nonano-3,2'-[1,3]dioxolano]-7-il}ciclopropanol (55)

Etill 9-[(4-clorofenil)sulfonil]spiro[9-azabiciclo[3.3.1]nonano-3,2'-[1,3] dioxolano]-7-carboxilato (**50**) (395 mg, 0.918 mmol) fue disuelto en Et_2O (2 mL) y la solución resultante fue enfriada a -78 °C. Ti(O-*i*-Pr)$_4$ fue añadido seguido por EtMgBr gota a gota por 10 minutos. La mezcla de reacción fue entibiada a temperatura ambiente y batida por 18 h. La solución resultante fue diluida con EtOAc y lavada con solución acuosa saturada de NH_4Cl. La fase orgánica fue

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secada (Na_2SO_4), filtrada, y concentrada para dar 1-{9-[(4-clorofenil)sulfonil]spiro[9-azabiciclo[3.3.1]nonano-3,2'-[1,3]dioxolano]-7-il}ciclopropanol (**55**). MS(ESI) 414.1 (M+H).

17.2. 9-[(4-Clorofenil)sulfonil]-7-(1-metoxiciclopropil)spiro[9-azabiciclo[3.3.1]nonano-3,2'-[1,3] dioxolano] (56)

Hidruro sódico (60% dispersion en aceite mineral, 46 mg, 1.16 mol) fue añadido a una solución de 1-{9-[(4-clorofenil)sulfonil]spiro[9-azabiciclo[3.3.1]nonano-3,2'-[1,3]dioxolano]-7-il}ciclopropanol (**55**) (321 mg, 0.775 mmol) en THF (2 mL). La solución resultante fue batida por 10 minutos, y luego yodo metano (72 µL, 1.16 mmol) fue añadido.La mezcla de reacción fue batida a temperatura ambiente por 18 h y fue subsiguientemente diluida con EtOAc y lavada con salmuera. La fase orgánica fue secada (Na_2SO_4), filtrada, y concentrada para dar 9-[(4-clorofenil)sulfonil]-7-(1-metoxiciclopropil)spiro[9-azabiciclo[3.3.1]nonano-3,2'-[1,3] dioxolano] (**56**). MS(ESI) 428.1 (M+H).

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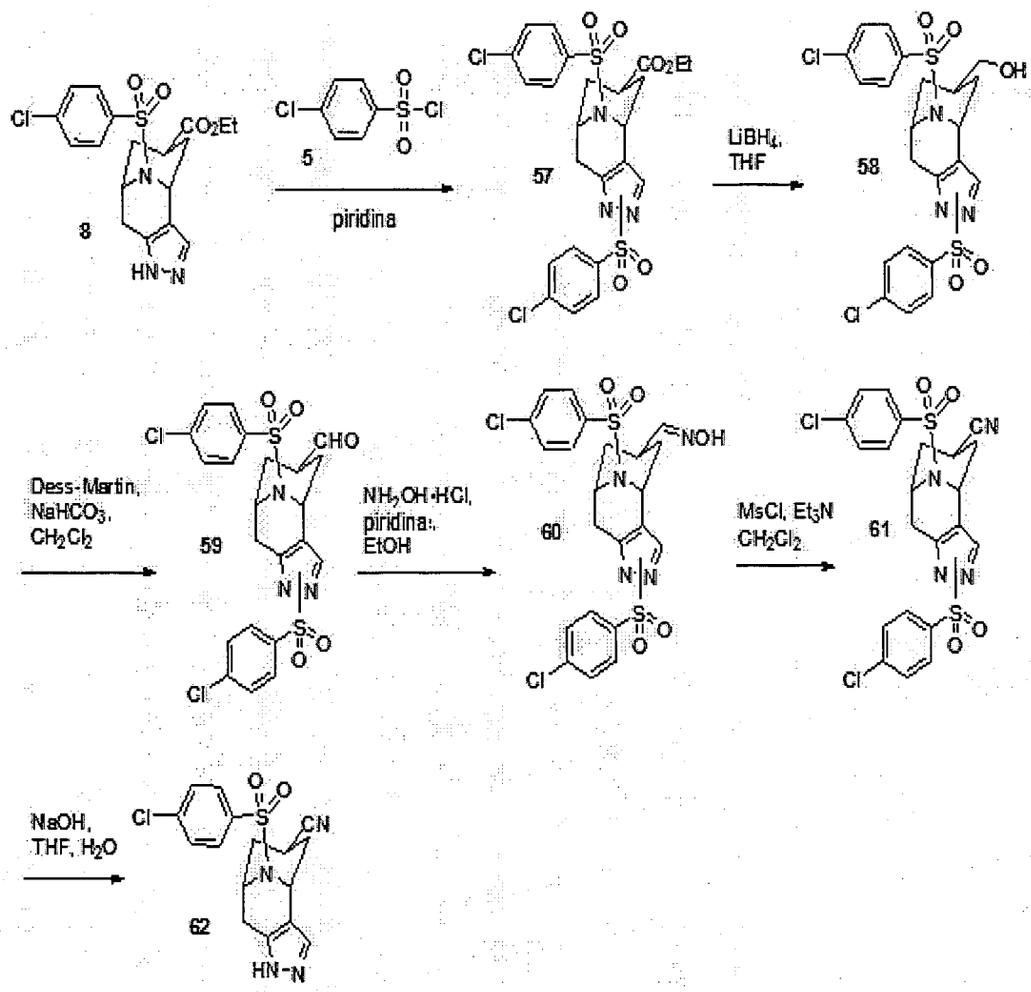
Ejemplo 18

Síntesis de 10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol-6-carbonitrilo (62)



18.1. Etill 1,10-bis[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol-6-carboxilato y etill 2,10-bis[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-2*H*-4,8-epiminociclooctа[*c*]pirazol-6-carboxilato (57)

4-Clorobenzensulfonl cloruro(0.315 g, 1.49 mmol) fue añadido a una solución de etill10-(4-clorofenil)sulfonil-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol-6-carboxilato (**8**) (0.51 g, 1.24 mmol) en piridina (5 mL) y la mezcla fue batida a temperatura ambiente por 1 h. La solución resultante fue diluida con CH_2Cl_2 y lavada con acuoso 1N HCl y luego con solución acuosa saturada $NaHCO_3$. La fase orgánica fue secada (Na_2SO_4), filtrada, concentrada y purificada por cromatografía de columna de gel de sílice (eluante hexano/EtOAc, 20/1 a 1/1)

para dar etill 1,10-bis[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol-6-carboxilato y etill 2,10-bis[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-2*H*-4,8-epiminociclooctа[*c*]pirazol-6-carboxilato (**57**) (0.721 mmol, 1.23 mmol, quant). MS(ESI) 584.0 (M+H).

18.2. {1,10-Bis[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol-6-il}metanol y {2,10-bis[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-2*H*-4,8-epiminociclooctа[*c*]pirazol-6-il}metanol (58)

Borohidruro de litio (10 mg, 0.516 mmol) fue añadido a una solución de etill 1,10-bis[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol-6-carboxilato y etill 2,10-bis[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-2*H*-4,8-epiminociclooctа[*c*]pirazol-6-carboxilato (**57**) (0.151 mg, 0.258 mmol) en THF (1 mL) y la solución resultante fue batida a temperatura ambiente por 2 h. La reaccionante mezcla fue diluida con EtOAc y lavada con agua. La fase orgánica fue secada (Na_2SO_4), filtrada y concentrada para dar {1,10-bis[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol-6-il}metanol y {2,10-Bis[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-2*H*-4,8-epiminociclooctа[*c*]pirazol-6-il}metanol (**58**). MS(ESI) 542.0 (M+H).

18.3. 1,10-Bis[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol-6-carbaldehyde y 2,10-bis[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-2*H*-4,8-epiminociclooctа[*c*]pirazol-6-carbaldehid (59)

Dess-Martin periodinano (128 mg, 0.304 mmol) fue añadido a una solución de {1,10-bis[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol-6-il}metanol y {2,10-Bis[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-2*H*-4,8-epiminociclooctа[*c*]pirazol-6-il}metanol (**58**) (110 mg, 0.202 mmol) conteniendo bicarbonato de sodio (76 mg, 0.912 mmol). La mezcla suspension fue batida a temperatura ambiente por 2 h y luego con una mezcla de solución acuosa saturada $NaHCO_3$ y solución acuosa saturada Na_2SO_4 (1/1, v/v) fue añadido. La fase orgánica fue secada (Na_2SO_4), filtrada, concentrada y purificada por cromatografía de columna de gel de sílice (eluante hexano

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/EtOAc, 4/1 a 1/1) para dar 1,10-bis[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol-6-carbaldehido y 2,10-bis[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-2*H*-4,8-epiminociclooctа[*c*]pirazol-6-carbaldehido (**59**) (95 mg, 0.175 mmol, 87%). MS(ESI) 540.0 (M+H).

18.4. 1-{1,10-Bis[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol-6-il}-*N*-hidroximetanimina y 1-{2,10-Bis[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol-6-il}-*N*-hidroximetanimina (60)

Hidroxilamina hidrocloruro (18 mg, 0.252 mmol) fue añadido a una solución de 1,10-bis[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol-6-carbaldehido y 2,10-bis[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-2*H*-4,8-epiminociclooctа[*c*]pirazol-6-carbaldehido (**59**) (91 mg, 0.168 mmol) en EtOH/piridina (2 ml, 1/1, v/v) y la solución resultante fue batida a temperatura ambiente por 2 h. La mezcla de reacción fue diluida con CH_2Cl_2 y lavada con solución acuosa saturada $NaHCO_3$. La fase orgánica fue secada (Na_2SO_4), filtrada y concentrada para dar 1-{1,10-bis[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol-6-il}-*N*-hidroximetanimina y 1-{2,10-bis[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol-6-il}-*N*-hidroximetanimina (**60**). MS(ESI) 555.0 (M+H).

18.5. 1,10-Bis[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol-6-carbonitrilo y 2,10-Bis[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-2*H*-4,8-epiminociclooctа[*c*]pirazol-6-carbonitrilo (61)

Metanosulfonil cloruro (30 µL, 0.390 mmol) y trietilamina (162 µL, 1.17 mmol) fueron añadidos a una solución de 1-{1,10-bis[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol-6-il}-*N*-hidroximetanimina y 1-{2,10-bis[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol-6-il}-*N*-hidroximetanimina (**60**) (73 mg, 0.130 mmol) en CH_2Cl_2 (1 mL) y la solución resultante fue batida a temperatura ambiente por 0.5 h. La mezcla de reacción fue diluida con CH_2Cl_2 y lavada con solución acuosa saturada $NaHCO_3$. La

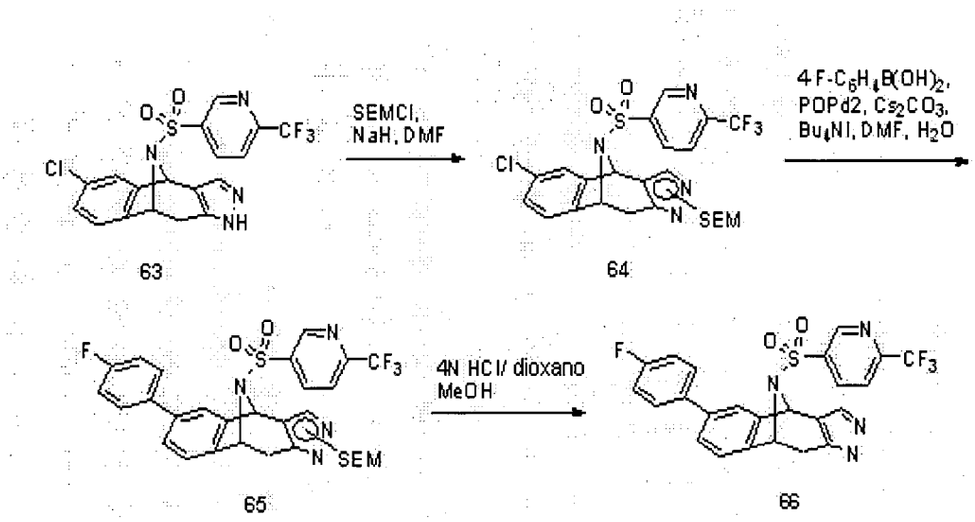
fase orgánica fue secada (Na_2SO_4), filtrada, y concentrada para dar 1,10-bis[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol-6-carbonitrilo y 2,10-bis[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-2*H*-4,8-epiminociclooctа[*c*]pirazol-6-carbonitrilo (**61**). MS(ESI) 537.0 (M+H).

18.6. 10-[(4-Clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol-6-carbonitrilo (62)

Hidróxido de sodio (130 µL de una solución acuosa 3N) fue añadido a una solución de 1,10-bis[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol-6-carbonitrilo y 2,10-bis[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-2*H*-4,8-epiminociclooctа[*c*]pirazol-6-carbonitrilo (**61**) (69 mg, 0.13 mmol) en THF (0.5 mL) y la solución resultante fue batida a temperatura ambiente por 5 h. La mezcla de reacción fue diluida con EtOAc y lavada con brine. La fase orgánica fue secada (Na_2SO_4), filtrada, concentrada y purificada por preparativo HPLC para dar 10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol-6-carbonitrilo (**62**). MS(ESI) 363.1 (M+H). ^{1}H NMR (300 MHz, $CDCl_3$) □7.62 (d, *J* = 8.8 Hz, 2H), 7.43 (s, 1H), 7.35 (d, *J* = 8.8 Hz, 2H), 5.38 (bs, 1H), 4.61-4.52 (m, 1H), 2.93 (dd, *J* = 17.0, 6.6 Hz, 1H), 2.71-2.52 (m, 2H), 2.32-1.98 (m, 4H).

Ejemplo 19

Síntesis de 6-(4-fluorofenil)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol (66)



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19.1. 6-Cloro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1-{[2-(trimetilsilil)etoxi]metil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol y 6-Cloro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-2-[2-(trimetilsilil)etoxi]-2,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol (64)

A una suspension de NaH (4.21 mmol, 0.17 g) en DMF (10 mL) a 0 °C fue añadido compuesto **63** (1.40 mmol, 0.62 g).La mezcla de reacción fue batida por 10 minutos antes de añadir 2-(trimetilsilil)etoximetil cloruro (4.21 mmol, 0.70 g). La mezcla de reacción fue batida por 2 h at 0 °C, y sofocada con solución acuosa saturada NH_4Cl (10 mL). La mezcla de reacción fue diluida con EtOAc (25 mL).Las dos capas fueron separadas. La capa orgánica fue secada con $MgSO_4$, filtrada y concentrada. La mezcla residual fue purificada por cromatografía flash (30% EtOAc en hexanos) para dar el compuesto **64** (0.57 g, 72%) como una regioisomérica mezcla de pirazoles alquilados.

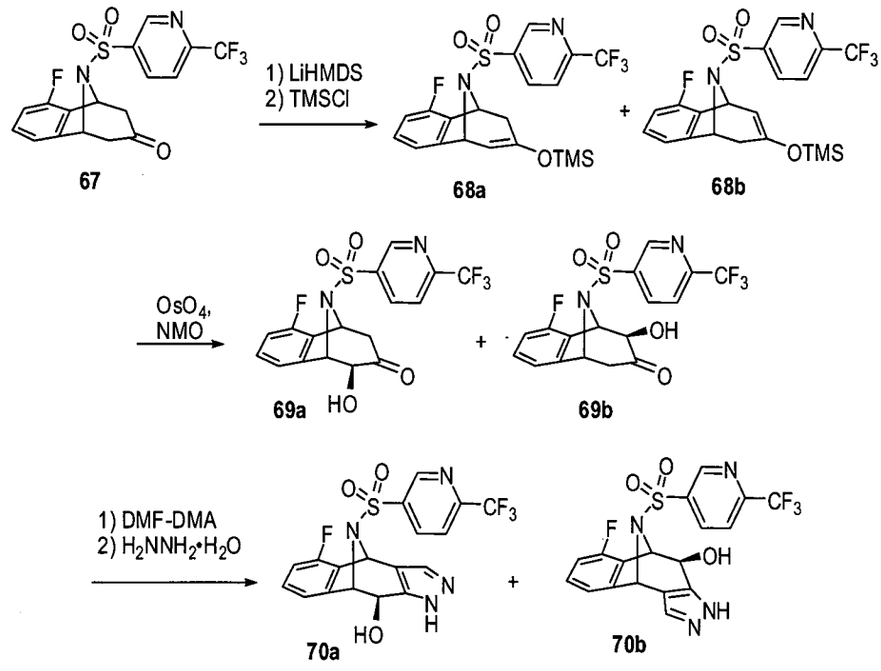
19.2. 6-(4-Fluorofenil)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol (66)

A una solución de **64** (0.26 mmol, 0.15 g) y ácido 4-fluorfenilborónico (1.31 mmol, 0.18 g) en THF (3mL) fue añadido dihidrogen di-ε-clorodiclorobis(di-tert-butyifosfinito-kP)dipaladato(2-) (0.008 mmol, 0.005 g), y Cs_2CO_3 (1.31 mmol, 0.43 g).La mezcla de reacción fue irradiada en el microondaspor 60 minutos a 145 °C (300W). La mezcla de reacción fue diluida con MeOH (5 mL) y filtrada en un paño de Celite. El filtrado fue concentrado, y la mezcla residual fue disuelta en MeOH (2 mL). La temperatura fue bajada a 0 °C y 4N HCl en dioxano (5 mL) fue añadido. La mezcla de reacción fue entibiada a temperatura ambiente y luego colocada en un baño de aceite a 60 °C y batida por 18 h. La mezcla de reacción fue enfriada a temperatura ambiente y concentrada. La mezcla residual fue disuelta en CH_2Cl_2 (5 mL) y la temperatura fue bajada a 0 °C. La mezcla de reacción fue diluida con solución acuosa saturada $NaHCO_3$ (5 mL) y batida por 5 minutos. Las dos capas fueron separadas. La capa orgánica fue secada con $MgSO_4$, filtrada y concentrada. La mezcla residual fue purificada

por cromatografía flash (70% EtOAc en hexanos) para dar el compuesto **66** (0.07 g, 54%).

Ejemplo 20

Síntesis de (10*S*)-5-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol-10-ol y (4*R*,10*R*)-8-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol-10-ol (70a y 70b)



20.1. 4-Fluoro-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-7-[(trimetilsilil)oxi]-6,9-dihidro-5*H*-5,9-epiminobenzo[7]anuleno y 1-Fluoro-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-7-[(trimetilsilil)oxi]-6,9-dihidro-5*H*-5,9-epiminobenzo[7]anuleno (68a y 68b)

A una solución de **67** (525 mg, 1.31 mmol) en THF (10 mL) at -78 °C fue añadido LiHMDS (1.0M en THF, 1.97 mL, 1.97 mmol) por 5 minutos. Luego la mezcla fue batida a -78 °C por 30 min, clorotrimetilsilano (500 □L, 3.94 mmol) fue añadido gota a gota y batida a esta temperatura por 60 minutos. La reacción fue extinguida con sat. acuoso $NaHCO_3$ (10 mL) y extraída con CH_2Cl_2 (3 x 50 mL). Las capas orgánicas fueron combinadas, secadas sobre Na_2SO_4, filtradas, y concentradas bajo reducida presión para dar una mezcla de regioisómeros (577 mg) consistente de racémicos **68a** y **68b**.

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20.2. (6*S*)-1-Fluoro-6-hidroxi-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-5,6,8,9-tetrahidro-7*H*-5,9-epiminobenzo[7]anuleno-7-ona y (8*R*)-1-Fluoro-8-hidroxi-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-5,6,8,9-tetrahidro-7*H*-5,9-epiminobenzo[7]anuleno-7-ona (69a y 69b)

A una solución de **68a** y **68b** (1.31 mmol) en THF (9 mL) fue añadido 4-metilmorfolina *N*-óxido (198 mg, 1.31 mmol), agua (4 mL), y tetróxido de osmio (4 peso% en agua, 253 □L, 0.04 mmol). La mezcla fue batida a una temperatura ambiente durante la noche, extinguida con una 10% solución acuosa de $Na_2S_2O_3$ (15 mL), y extraída con CH_2Cl_2 (3 x 50 mL). Las capas orgánicas combinadas fueron concentradas bajo reducida presión y el material fue purificado por cromatografía flash (elución con 0 a 50% EtOAc en hexano) para dar una mezcla de regioisómeros consistente de racémicos **69a** y **69b** (57 mg, 10% producción).

20.3. (10*S*)-5-Fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol-10-ol y (4*R*,10*R*)-8-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol-10-ol (70a y 70b)

La mezcla de arriba (**69a** y **69b**) (0.14 mmol) fue calentada con DMF-DMA (2 mL) a 100 °C por 60 min. La mezcla de reacción fue concentrada bajo reducida presión, secada en alto vacío y disuelto en ácido acético d (3 mL). La solución fue enfriada en un baño de hielo y tratada con hidrato de hidrazina (15 □L, 0.31 mmol). La mezcla fue batida a temperatura ambiente durante la noche. El solvente fue removido bajo reducida presión. El residuo fue purificado por cromatografía flash (carga sólida, 0 a 100% EtOAc en hexano) para dar una mezcla de regioisómeros consistente de racémicos **70a** y **70b**. Individuales estéreo isómeros fueron aislados por quiral HPLC.

Ejemplo 21

Síntesis de (+/-)-9-metil-11-{[4-(trifluorometil)fenil]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol-10(1*H*)-ona (82)

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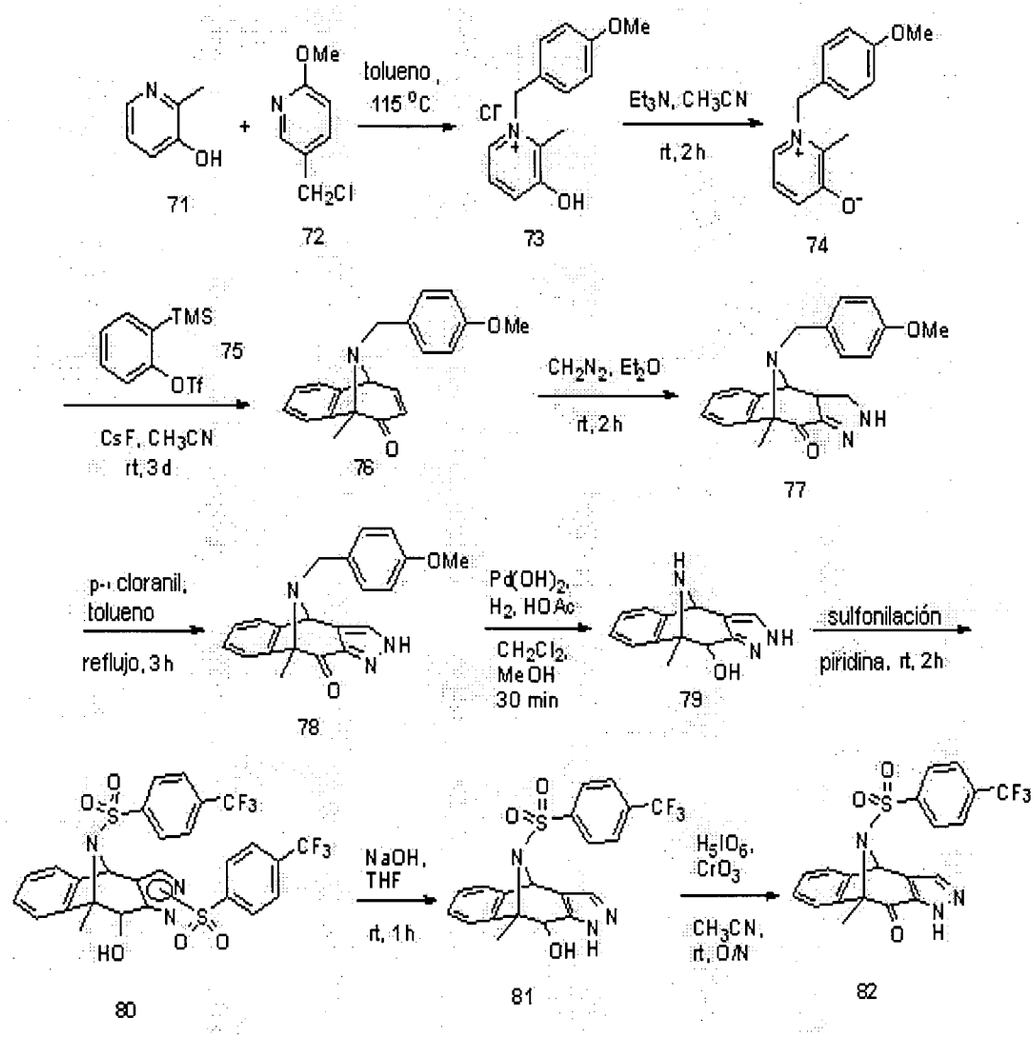

21.1. 3-Hidroxi-1-(4-metoxibencil)-2-metilpiridinio cloruro (73)

Una suspension de 2-metil-3-hidroxipiridina (**71**) (10g, 91.6 mmol) en tolueno (45 mL) fue añadido 4-metioxibencil cloruro (**72**) (12.4 mL, 1eq). La mezcla fue reflujada durante la noche. El solvente fue concentrado a alrededor de 1/3 de volúmen. Después de enfriado, el sólido fue aislado por filtración y lavado con una pequeña cantidad de tolueno para dar el producto deseado, que fue usado sin ulterior purificación. ^{1}H NMR (d_6-DMSO) □ 8.61 (d, 1H, J = 6 Hz), 8.16 (d, 1H, J = 8.4 Hz), 7.85 (t, 1H, J = 6.9 Hz), 7.28 (d, 2H, J = 8.1 Hz), 7.02 (d, 2H, J = 8.4 Hz), 5.82 (s, 2H), 3.79 (s 3H), 2.59 (s, 3H).

21.2. 1-(4-Metoxibencil)-2-metilpiridinio-3-olato (74)

A una suspension de compuesto **73** (23g) en CH_3CN (200 mL) fue añadido trietilamina (15 mL) y la mezcla fue batida a temperatura ambiente por 1.5 horas. El solvente fue concentrado a alrededor de 1/4 de volúmen. El sólido fue

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aislado via filtrado y lavado con una pequeña cantidad de CH_3CN para dar el producto deseado, que fue usado sin ulterior purificación. ^{1}H NMR (d_6-DMSO) □ 8.57 (d, 1H, J = 6 Hz), 8.08 (d, 1H, J = 8.1 Hz), 7.82 (t, 1H, J = 7.5 Hz), 7.25 (d, 2H, J = 8.7 Hz), 6.99 (d, 2H, J = 8.4 Hz), 5.78 (s, 2H), 3.74 (s 3H), 2.51 (s, 3H).

21.3. (+/-)-10-(4-Metoxibencil)-5-metil-5,9-dihidro-6*H*-5,9-epiminobenzo[7]anuleno-6-one (76)

A una suspension de compuesto **73** (11.97g) en CH_3CN (125 mL) fue añadido 2-(trimetilsilil) fenil trifluorometanosulfonato (**75**) (30g) y CsF (20g). La mezcla fue batida a temperatura ambiente por 3 días. Agua fue añadida para extinguir la reacción y la mayoría del CH_3CN fue removido via rotavaporizador. El residuo fue extraído con EtOAc, lavado con agua y salmuera, y secado sobre $MgSO_4$. Luego de la concentración del solvente, el producto crudo fue purificado por cromatografía de gel de sílice, elución con gradiente de 100% hexano a 80% EtOAc/hexano sobre 30 min. El producto puro fue aislado como un aceite marrón. ^{1}H NMR ($CDCl_3$) □ 7.30-7.24 (m 3H), 7.21-7.15 (m, 3H), 7.01 (dd, 1H, J = 5.1, 9.6 Hz), 6.87 (d, 2H, J = 8.7 Hz), 5.62 (d, 2H, J = 9.6 Hz), 4.31 (d, 1H, J = 5.1 Hz), 3.81 (s 3H), 1.65 (s, 3H).

21.4. (+/-)-11-(4-Metoxibencil)-9-metil-3,3a,4,9-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol-10(2*H*)-ona (77)

Diazometano en éter (75 mL) (preparado de 2.5g NMMG) fue añadido con precaución al compuesto **75** (2.6g) y la solución fue batida a temperatura ambiente por 2 horas. El diazometano en exceso fue extinguid por adición de HOAc. El solvente fue removido para dar el producto deseado en la forma de un sólido amarillo consistente de una mezcla de los dos regioisómeros. El producto fue usado sin ulterior purificación.

21.5. (+/-)-11-(4-Metoxibencil)-9-metil-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol-10(2*H*)-ona (78)

A una solución de compuesto **77** (3.6g) en tolueno (300 mL) fue añadido p-cloranil (7.66g) y la mezcla fue reflujada por 3 horas. El solvente fue removido y

el residuo fue purificado por cromatografía de gel de sílice, elución con 100% hexano a 50% EtOAc/hexano sobre 30 min.

21.6. (+/-)-9-Metil-2,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol-10-ol (79)

A una solución de compuesto **78** (104 mg) en $MeOH/CH_2Cl_2$ (2:1, 10 mL) fueron añadidas unas pocas gotas de 3N HCl y Pd/C (10%, 40 mg). Hidrogenación fue llevada a cabo en un batidor Parr a 50 psi de H_2 por 30 minutos. El catalizador fue eliminado por filtración y el solvente fue removido. El material crudo fue purificado por preparativo HPLC para dar el producto como un sólido blanco. ^1H NMR (CD_3OD) □ 7.73 (s 1H), 7.48-7.37 (m, 4H), 5.94 (s, 1H), 5.17 (s 1H), 2.00 (s, 3H).

21.7. (+/-)-9-Metil-1,11-bis{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol-10-ol y (+/-)-9-Metil-2,11-bis{[4-(trifluorometil)fenil]sulfonil}-2,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol-10-ol (80)

A una solución de compuesto **79** (34.2 mg) en piridina (0.6 mL) fue añadido 4-trifluorometilbenzenosulfonil cloruro (147.3 mg). La mezcla fue batida a temperatura ambiente por 2 horas.La reacción fue extinguida con agua y extraída con EtOAc. Las capas orgánicas fueron combinadas y lavadas con agua, sat. Acuoso $NaHCO_3$, HCl,salmuera y secada sobre $MgSO_4$. Luego de la remoción del solvente, la mezcla bis-sulfonilada de regioisómeros fue aislada como un aceite amarillo.

21.8. (+/-)-9-metil-11-{[4-(trifluorometil) fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol-10-ol (81)

A una solución de compuesto **80** (61 mg) en THF (3 mL) fue añadido 0.5 N NaOH (3 mL). La mezcla fue batida a temperatura ambiente por 1 hora y concentrada *en vacuo*. La mezcla acuosa fue then extraída con EtOAc. Las capas orgánicas fueron combinadas, secadas sobre $MgSO_4$, filtradas y el

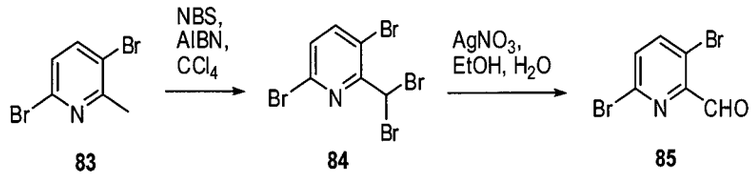
solvente fue removido para dar el producto en la forma de un sólido blanco opaco.

21.9. (+/-)-9-metil-11-{[4-(trifluorometil)fenil]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol-10(1*H*)-ona (82)

H_5IO_6 (153 mg) fue suspendido en CH_3CN (3.1 mL) y CrO_3 (6.1 mg) fue añadido a la mezcla. La mezcla fue batida a temperatura ambiente por 15 min al punto en que transformón en una solución homogénea. A esta solución fue añadida un a solución del compuesto **8b** (34 mg) en CH_3CN (5 mL) y se formó un precipitado amarillo. La mezcla fue batida a temperatura ambiente durante la noche. Agua y sat. Acuoso $NaHCO_3$ fueron añadidos para extinguir la reacción y el solvente fue concentrado para remover la mayría del CH_3CN. EtOAc fue añadido y la caoa orgánica fue lavada con agua, salmuera y secada sobre $MgSO_4$. Luego de evaporarse el solvente, se obtuvo un sólido blanco opaco como producto puro. ^{1}H NMR ($CDCl_3$) □ 7.83 (d, 2H, J = 8.4 Hz), 7.67 (s, 1H), 7.63 (d, 2H, J = 8.4 Hz), 7.29-7.17 (m, 4H), 6.28 (s, 1H), 1.92 (s, 3H).

Ejemplo 22

Síntesis de 3,6-Dibromopicolinaldehido (85)



22.1. 3,6-Dibromo-2-(dibromometil) piridina (84)

A una solución de 3,6-dibromo-2-metilpiridina (5.34 g, 21 mmol) en CCl_4 (50 mL) fue añadido *N*-bromosuccinimida (7.57 g, 42 mmol) y 2,2'-azobis(2-metilpropionitrilo) (0.70 g, 4.3 mmol).La mezcla fue calentada a 70 °C durante la noche y enfriada a temperatura ambiente. El sólido fue removido por filtración y el filtrado fue concentrado bajo reducida presión. El producto fue obtenido luego de cromatografía flash y elución con 0-10% EtOAc en hexano (8.17 g).

22.2. 3,6-Dibromopicolinaldehido (85)

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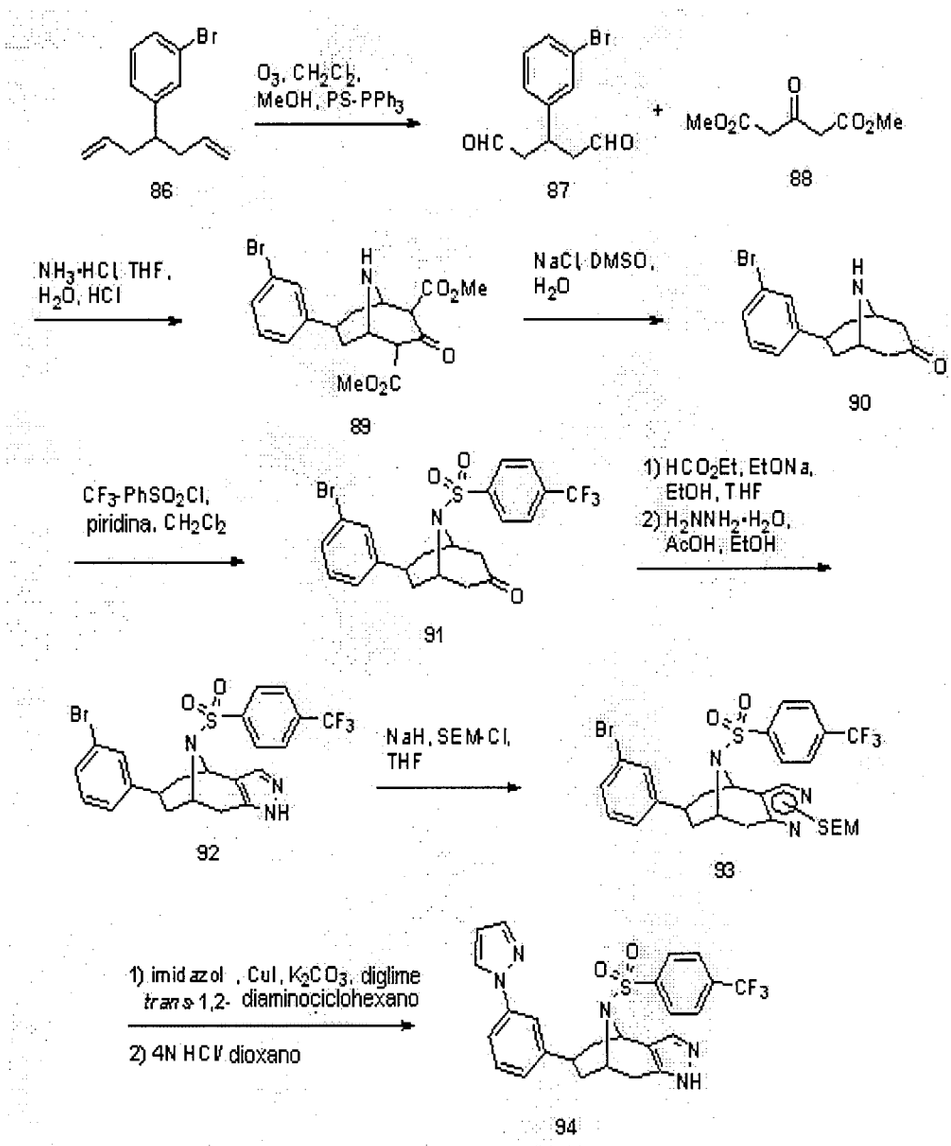
Una solución de nitrato de plata (8.5 g, 50 mmol) en agua (26 mL) fue añadida gota a gota a una solución de compuesto **84** (8.17 g, 20 mmol) a reflujo en EtOH (100 mL).La mezcla fue batida a 80 °C por 5 horas. Luego que la mezcla fue enfriada a temperatura ambiente, fue diluida con agua (100 mL), extraída con EtOAc (3 x), secada sobre Na_2SO_4, filtrada y concentrada bajo reducida presión. El producto fue obtenido por cromatografía de gel de sílice, elución con 0-40% EtOAc en hexano (2.85 g, 51% en dos pasos).

Ejemplo 23

Síntesis de 6-[3-(1*H*-Imidazol-1-il)fenil]-10-{[4-(trifluorometil)-fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol (94)



23.1. 3-(3-Bromofenil)pentanodial (87)

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Ozono fue burbujeado a través de una solución de 1-bromo-3-(hepta-1,6-dien-4-il) benzeno (6.14g, 24.4 mmol) en CH_3OH (10 ml) y CH_2Cl_2 (90 ml) a -78 °C por 30 min tiempo en el cual la solución se tornó a un color azul pálido. Nitrógeno fue entonces burbujeado a través de la solución por 5 min y la solución se tornó clara. Polímero de soporte, trifenilfosfina (20 g, 60.0 mmol) fue añadido y la solución batida a -78 °C por 30 min. El baño de hielo seco y acetona fue removido y la mezcla heterogénea fue batida por 1 h. La mezcla heterogénea fue filtrada por Celite y el filtrado fue concentrado para dar el compuesto **87**.

23.2. Dimetil 7-(3-bromofenil)-3-oxo-9-azabiciclo[3.3.1] nonano-2,4-dicarboxilato (89)

3-(3-Bromofenil) pentanodial (**87**), dimetil 3-oxopentanedioato (**88**) (5.78 g, 33.2 mmol), cloruro de amonio (14.42 g, 270 mmol) en THF (100 ml), 10% HCl acuoso (100 ml), y agua (100 ml) fueron batidos por 18 h. Acetato de sodio fue añadido hasta que el pH fue 4-5. Después de batir por 6 h, la solución fue extraída con EtOAc. Los extractos orgánicos combinados fueron lavados con solución acuosa saturada Na_2CO_3, secados sobre $MgSO_4$, filtrados y concentrados para dar el compuesto **89**.

23.3. 7-(3-Bromofenil)-9-azabiciclo[3.3.1]nonan-3-ona (90)

Dimetil 7-(3-bromofenil)-3-oxo-9-azabiciclo[3.3.1]nonano-2,4-dicarboxilato (**89**) y NaCl (61.22 g, 1.05 mol) en DMSO (200 ml) y agua (10 ml) fueron colocados en un baño de aceite precalentado a 160 °C. Luego de batir por 14 h, la solución fue enfriada a temperatura ambiental y exhaustivamente extraída con EtOAc. Los extractos orgánicos combinados fueron secados sobre $MgSO_4$, filtrados, y concentrados para dar el compuesto **90**.

23.4. 7-(3-Bromofenil)-9-{[4-(trifluorometil)fenil]sulfonil}-9-azabiciclo[3.3.1]nonan-3-one (91)

7-(3-Bromofenil)-9-azabiciclo[3.3.1]nonan-3-ona (**90**) y 4-(trifluorometil)benzeno-1-sulfonil cloruro (12.25 g, 50.1 mmol) en piridina (100 ml) y CH_2Cl_2 (100 ml) fueron batidos por 24 h. La solución fue concentrada y flash cromatografiada

con CH_2Cl_2 como eluente para producir 2.29 g (19% producción en 4 pasos) de compuesto **91** como un sólido rosado.

23.5. 6-(3-Bromofenil)-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol (92)

21% NaOEt (6 ml, 16.1 mmol) fue añadido a una solución de 7-(3-Bromofenil)-9-(4-(trifluorometil) fenilsulfonil)-9-azabiciclo[3.3.1]nonan-3-ona (**90**) (2.28 g, 4.54 mmol) y etill formato (6 ml, 74.5 mmol) en THF (20 ml). La solución fue colocada en un baño de aceite precalentado a 60°C. Luego de batir por 30 min, la solución fue enfriada a temperatura ambiente, diluida con solución acuosa saturada NH_4Cl, y extraída con EtOAc. Los extractos orgánicos combinados fueron secados sobre $MgSO_4$, filtrados , y concentrados para dar 7-(3-bromofenil)-2-(hidroximetileno)-9-(4-(trifluorometil)fenilsulfonil)-9-azabiciclo[3.3.1]nonan-3-ona. Hidrazina monohidratada (3 ml) fue añadida a una solución de 7-(3-bromofenil)-2-(hidroximetileno)-9-(4-(trifluorometil)fenilsulfonil)-9-azabiciclo[3.3.1]nonan-3-ona y ácido acético glacial (1 ml) en EtOH (20 ml). Luego de batir por 18 h, la solución fue concentrada para dar el compuesto **92**.

23.6. 6-(3-Bromofenil)-10-{[4-(trifluorometil)fenil]sulfonil}-1-{[2-(trimetilsilil)ethoxi]metil}-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа-[*c*]pirazol y 6-(3-Bromofenil)-10-{[4-(trifluorometil)fenil]sulfonil}-2-{[2-(trimetilsilil)ethoxi]metil}-4,5,6,7,8,9-hexahidro-2*H*-4,8-epiminociclooctа[*c*]-pirazol (93)

60% Hidruro sódico (0.41 g, 10.3 mmol) fue añadido a una solución de compuesto **92** en THF (50 mL). Luego de batir por 1 h, SEM-Cl (3.0 ml, 17.0 mmol) fue añadido. Luego de batir por 1 h, la solución fue diluida con solución acuosa saturada NH_4Cl, y extraída con CH_2Cl_2. Los extractos orgánicos combinados fueron secados sobre $MgSO_4$, filtrados, y concentrados. El residuo fue flash cromatografiado con 9:1, 4:1, 7:3, 3:2, 1:1, y 2:3 hexanos: EtOAc como eluente para producir 2.06 g (69% producción en 3 pasos) del producto como un aceite anaranjado.

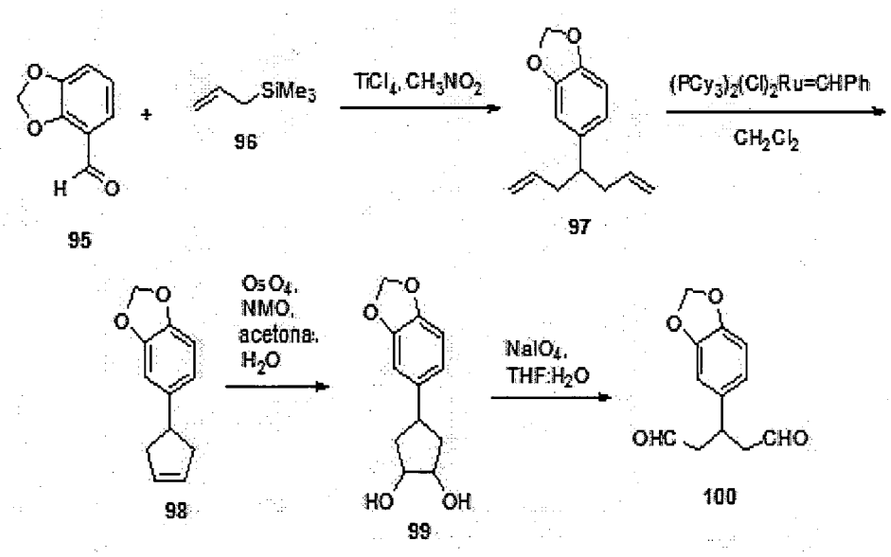
490

23.7. 6-[3-(1*H*-Imidazol-1-il)fenil]-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol (94)

A una solución de compuesto **93** (0.07 mmol, 0.05 g) y pirazol (1.52 mmol, 0.10 g) en dimetoxietano (1 mL) fue añadido yoduro de cobre (0.02 mmol, 0.004 g), *trans*-1,2-diaminociclohexano (0.02 mmol, 0.002 g), y carbonato de potasio (0.76 mmol, 0.11 g). La mezcla de reacción fue irradiada en un microondas por 35 minutos a 220 °C (300W). La mezcla de reacción fue diluida con MeOH (5 mL) y filtrada con un tamiz de Celite. El filtrado fue concentrado, y el residuo de mezcla fue disuelto en MeOH (2 mL). La temperatura fue bajada a 0 °C y 4N HCl en dioxano (3 mL) fue añadido. La mezcla de reacción fue entibiada a temperatura ambiente y colocada en un precalentado a 60 °C baño de aceite y batida por 18 h. La mezcla de reacción fue enfriada a temperatura ambiente y concentrada. The mezcla residue fue disuelto en CH_2Cl_2 (5 mL) y la temperatura fue bajada a 0 °C.la reacción mezcla fue diluida con solución acuosa saturada $NaHCO_3$ (5 mL) y batida por 5 minutos. Las dos capas fueron separadas y la capa orgánica fue secada con $MgSO_4$, filtrada y concentrada. La mezcla de residuo fue purificada por cromatografía de gel de sílice (5% MeOH en CH_2Cl_2) para obtener el compuesto **94** (0.04 g, 56%).

Ejemplo 24

Síntesis de 3-(benzo[d][1,3]dioxol-5-il)pentanodial (100)



24.1. 5-(Hepta-1,6-dien-4-il)benzo[d][1,3]dioxol (97)

A una solución de nitrometano (133.2 mmol, 7.15 g) y CH_2Cl_2 (100 mL) a -78 °C fueron añadidos $TiCl_4$ (56.61 mmol, 10.73 g) y aldehido **95** (33.10 mmol, 5.00 g). La mezcla de reacción fue batida por 20 minutos antes de la adición gota a gota de alliltrimetilsilano (**96**) (66.61 mmol, 7.61 g). La mezcla de reacción fue batida a -78 °C por 18 h. La mezcla de reacción fue vertida directamente en una solución acuosa saturada NaCl y entibiada a temperatura ambiente. Las dos capas fueron separadas y la capa orgánica fue secada con $MgSO_4$, filtrada y concentrada. El residuo resultante fue purificado por cromatografía de gel de sílice (10% EtOAc en hexanos) para obtener el compuesto **97** (1.49 g, 21%).

24.2. 5-(Ciclopent-3-enil)benzo[d][1,3]dioxol (98)

A una solución de Grubbs I (0.345 mmol, 0.284 g) en CH_2Cl_2 fue añadido dieno **97** (6.91 mmol, 1.49 g). La mezcla de reacción fue batida a temperatura ambiente por 48 h. La mezcla de reacción fue purificada por cromatografía flash (hexanos) para dar el compuesto **98** (0.42 g, 32%).

24.3. 4-(Benzo[d][1,3]dioxol-5-il)ciclopentano-1,2-diol (99)

A una solución de 4-metilmorfolina *N*-óxido (2.89 mmol, 0.339 g) y OsO_4 (0.013 mmol, 0.081 mL) en acetona (5 mL) y H_2O (1.5 mL) a 0 °C fue añadido ciclopenteno **98** (2.22 mmol, 0.42 g). La mezcla de reacción fue batida por 18 h a temperatura ambiente. La temperatura fue entonces bajada a 0 °C y la mezcla de reacción fue extinguida con solución acuosa saturada Na_2SO_3. La mezcla de reacción fue batida por 3 h mientra se calentaba a temperatura ambiente. La acetona fue removida por evapora ción rotatoria y la temperatura fue otra vez bajada a 0 °C. El pH fue ajustado a pH 2 añadiendo concentrado H_2SO_4. La mezcla de reacción fue lavada con EtOAc (3X, 25 mL). Las capas orgánicas combinadas fueron secadas con $MgSO_4$, filtradas y concentradas. El residuo de la mezcla fue purificado por cromatografía flash (EtOAc) para dar el compuesto **99** (0.42 g, 86%).

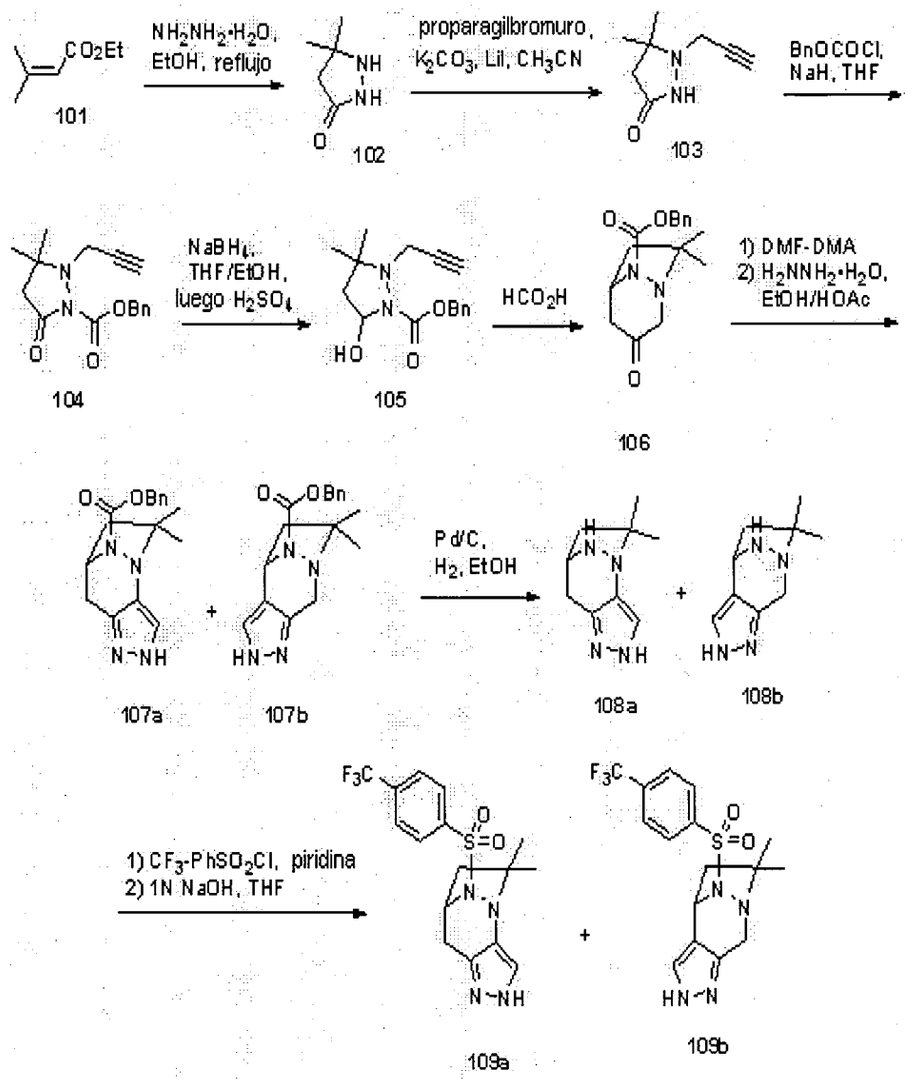
24.4. 3-(Benzo[d][1,3]dioxol-5-il)pentanodial (100)

A una solución de periodato de sodio (1.91 mmol, 0.41 g) en THF (3 mL) y H_2O (2 mL) a 0 °C fue añadido diol **99** (1.91 mmol, 0.42 g). La mezcla de reacción

fue batida a temperatura ambiente por 3 h. La mezcla de reacción fue filtrada, y la mezcla dialdehido **100** fue usada tal como es, una solución acuosa.

Ejemplo 25

Síntesis de 5,5-dimetil-9-{[4-(trifluorometil)fenil]sulfonil}-5,6,7,8-tetrahidro-2*H*-4,7-epiminopirazolo[4,3-*b*]azepina y 6,6-dimetil-9-{[4-(trifluorometil)fenil]sulfonil}-2,5,6,8-tetrahidro-4*H*-4,7-epiminopirazolo[3,4-*c*]azepina (109a y 109b)



25.1. 5,5-Dimetilpirazolidin-3-ona (102)

A una solución de hidrazina hidrato (4.4 g, 88 mmol) en EtOH (50 ml) fue añadido etill 3,3-dimetilacrilato (**101**) (10.0 g, 78 mmol) en EtOH (40 mL) gota a gota a temperatura ambiente por 1 h. La mezcla de reacción fue batida a temperatura ambiente por 1 h y luego calentada a reflujo por 4 hrs. Progreso de

la reacción fue monitoreado con TLC. Al consumirse por completo el material inicial, el solvente fue evaporado y el material crudo fue purificado por cromatografía de columna, elución con MeOH/ CH_2Cl_2 (1:25) para dar **2** (7.0 g) en 78 % de producción como un líquido incoloro, lentamente solidificado luego de un largo tiempo. ^{1}H NMR ($CDCl_3$) δ 6.95 (bs, 1H), 4.09 (bs, 1H), 2.33 (s, 2H), 1.31 (s, 6H).

25.2. 5,5-Dimetil-1-(prop-2-ynyl)pirazolidin-3-ona (103)

A una solución de **102** (10.0 g, 87.7 mmol) en acetonitrilo (100 mL) fueron añadidos K_2CO_3 (12.7 g, 92 mmol), LiI (0.59 g, 4.4 mmol) y propargil bromuro (11.0 g, 92 mmol). La mezcla de reacción fue reflujada por 24 h. Progreso de la reacción fue monitoreado con TLC. Al consumirse por completo el material inicial, la mezcla de reacción cruda fue filtrada en un pequeño tamiz de Celite y el solvente fue evaporado al vacío a temperatura ambiente. El material crudo fue pasado a través de elución de columna con EtOAc/hexano (3:7) para dar **103** (5.9 g) en 45% producción como un sólido amarillo pálido cristalino. ^{1}H NMR ($CDCl_3$) δ 7.45 (bs, 1H), 3.53 (d, J = 2.2 Hz, 2H), 2.46 (s, 2H), 2.29 (t, J = 2.6 Hz, 1H), 1.35 (s, 6H).

25.3. Bencil 3,3-dimetil-5-oxo-2-(prop-2-ynyl) pirazolidina-1-carboxilato (104)

A una suspension de NaH (1.7 g, 71 mmol) en THF fue añadido **103** (9.0 g, 59.2 mmol) gota a gota a 0 °C. La mezcla suspensión fue batida por 1 h adicional a 0 °C seguido por introduction de bencil cloroformato (30.4 g, 177.7 mmol) a la misma temperatura. La mezcla de reacción fue lentamente entibiada a temperatura ambiente y batida por otras 2 h. Al consumirse por completo el material inicial, monitoreado con TLC, la mezcla de reacción fue extinguida con saturado NH_4Cl. La mezcla de reacción fue extraída con EtOAc (50 × 2 mL), lavada con agua (30 mL), salmuera y secada sobre Na_2SO_4. Solvente fue evaporado al vacío a temperatura ambiente y el residuo crudo fue purificado por cromatografía de columna, elución con EtOAc/hexanos (1:10) para dar **104** (8.8 g) en 52% de producción como un aceite incoloro . ^{1}H NMR ($CDCl_3$) δ 7.48-7.27 (m, 5H), 5.35 (s, 2H), 3.85 (s, 2H), 2.79 (bs, 2H), 2.29 (s, 1H), 1.38 (s, 6H).

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25.4. Bencil 5-hidroxi-3,3-dimetil-2-(prop-2-inil)pirazolidina-1-carboxilato (105)

A una batida solución de **104** (3.0 g, 10.48 mmol) en THF (75 mL) y EtOH (50 mL), borohidruro de sodio (2.6 g, 68.1 mmol) fue añadido a -20 °C seguido de unas pocas gotas de conc. H_2SO_4 y batida por 3 h a -20 °C. La mezcla de reacció fue extinguida con sat. $NaHCO_3$ en solución a -20 °C y dejada en reposo a temperatura ambiente. La mezcla de reacción fue concentrada bajo reducida presión y el residuo fue disuelto en EtOAc. La capa orgánica fue lavada con agua, secada sobre Na_2SO_4 y concentrada bajo reducida presión para obtener un compuesto crudo que fue purificado por cromatografía de gel de sílice, elución con 15% EtOAc/hexanos para dar **105** (2.3 g, 76%). ^{1}H NMR ($CDCl_3$) δ 7.26-7.37 (m, 5H), 5.76 (m, 1H), 5.25 (s, 2H), 3.80-3.60 (m, 3H), 2.48-2.38 (m, 1H), 2.22 (m, 2H), 1.38 (s, 3H), 1.18 (s, 3H).

25.5. Bencil 7,7-dimetil-3-oxo-1,8-diazabiciclo[3.2.1]octane-8-carboxilato (106)

Una solución batida de **105** (2.5 g, 8.6 mmol) en ácido fórmico (10 mL) fue calentada a 100 °C por 5 h. Al consumirse por completo el **105** (monitoreado por TLC), el ácido fórmico fue evaporado bajo reducida presión. El residuo fue disuelto en EtOAc (100 mL) y lavado con saturado $NaHCO_3$ en solución (2 × 50 mL), agua (50 mL) y solución salmuera (50 mL). La capa orgánica fue secada sobre anhidro Na_2SO_4 y concentrada bajo reducida presión para dar el compuesto crudo que fue purificado con preparativo HPLC para dar **106** (0.52 g, 18%). ^{1}H NMR ($CDCl_3$) δ 7.30-7.40 (m, 5H), 5.25 (s, 2H), 3.62 (m, 1H), 2.76 (m, 1H), 2.42 (m, 1H), 2.20 (m, 1H), 2.09 (s, 1H), 1.65 (m, 1H), 1.22 (s, 3H), 1.13 (s, 3H).

25.6. Bencil 5,5-dimetil-5,6,7,8-tetrahidro-2*H*-4,7-epiminopirazolo[4,3-*b*]azepin-9-carboxilato y Bencil 6,6-dimetil-2,5,6,8-tetrahidro-4*H*-4,7-epiminopirazol[3,4-*c*]azepina-9-carboxilato (107a y 107b)

Una solución DMF-DMA (700 □L) de **106** (53 mg, 0.18 mmol) fue calentada a 100 °C por 2 horas, tiempo al cual el análisis LC/MS determinó que no quedaba

material inicial alguno. La mezcla de reacción fue enfriada y diluida con agua y EtOAc. La fase orgánica separada fue lavada con agua (2 x 20 mL), salmuera (1 x 20 mL), secada ($MgSO_4$) y filtrada y concentrada para dar 62 mg (0.18 mmol) de un aceite que fue disuelto en 25:1 EtOH/glacial HOAc (1 mL) y tratado con hidrazina hidrato (43 □L, 0.90 mmol). A las pocas horas, hidrazina hidrato adicional fue añadido (84 □L, 1.8 mmol) y la mezcla de reacción fue batida durante la noche a temperatura ambiente. La reacción fue entonces concentrada y el residuo fue disuelto en EtOAc y lavado con saturado $NaHCO_3$ (2 x 20mL), salmuera (1 x 20 mL), secado ($MgSO_4$), filtrado y concentrado para dar 34 mg de un aceite dorado que fue purificado por preparativo HPLC para dar **107a** y **107b** como una mezcla de aproximadamente 4:1 de regioisómeros pirazol como fue determinado por análisis HPLC.

25.7. 5,5-Dimetil-5,6,7,8-tetrahidro-2*H*-4,7-epiminopirazol[4,3-*b*]azepina y 6,6-Dimetil-2,5,6,8-tetrahidro-4*H*-4,7-epiminopirazol[3,4-*c*]azepin

(108a y 108b)

Una botella Parr fue cargada con **107** (132mg, 0.42 mmol) 10 peso % Pd/C (13 mg), y EtOH absoluto (5 mL) y colocada bajo 35 psi H_2. Luego de batir durante la noche, the reacción mezcla fue filtrada con un tamiz de Celite y concentrada para dar 81 mg (100%) de **108a** y **108b** como un aceite que fue usado sin purificación.

25.8. 5,5-dimetil-9-{[4-(trifluorometil)fenil]sulfonil}-5,6,7,8-tetrahidro-2*H*-4,7-epiminopirazolo[4,3-*b*]azepina y 6,6-dimetil-9-{[4-(trifluorometil)fenil]sulfonil}-2,5,6,8-tetrahidro-4*H*-4,7-epiminopirazolo[3,4-*c*]azepina (109a y 109b)

La mezcla regioisomérica mezcla de pirazoles **108a** y **108b** (81mg, 0.45 mmol) fueron disueltos en piridina (4.5 mL) y enfriados a 0 °C en un baño de hielo al cual fue añadido 4-(trifluorometil)benzenosulfonil cloruro (1.1 g, 4.54 mmol). La reacción fue entibiada a temperatura ambiente y batida durante la noche. Adicional 4-(trifluorometil) benzenosulfonil cloruro (444 mg, 1.82 mmol) fue añadido a la reacción y el batido fue continuado por 48 horas. La mezcla de reacción fue entonces diluida con EtOAc y agua. La porción orgánica fue

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lavada con agua (1 x 20 mL), 0.5 N HCL (3 x 15 mL), agua (1 x 10 mL), sat $NaHCO_3$ (3 x 20 mL) salmuera (1 x 20 mL), secada ($MgSO_4$), filtrada y concentrada a un aceite espeso amarillo. The crude product fue purificado por preparativo, cromatografía, elución con 3:1 hexanos/EtOAc para dar bis-sulfonilados pirazoles como un claro aceite espeso.I: $(MH)^+$ = 595.1. El producto purificado fue disuelto en THF (3 mL) al cual fue añadido 1N NaOH (1mL). La solución de dos fases fue rigurosamente batida durante la noche, tiempo al cual el análisis LC/MS determinó que no quedaba material inicial alguno. La mezcla de reacción fue concentrada y el residuo fue disuelto en EtOAc y lavado con agua (3 x 15), salmuera (1 x 10), secado ($MgSO_4$) filtrado y concentrado para dar 82 mg (85%) de **109a** y **109b** como una mezcla de pirazoles 5:1 . ^{1}H-NMR (Mayor pirazol regioisómero) ($CDCl_3$) □7.92 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.28 (s, 1H), 4.87(m, 1H), 3.09 (dd, J = 16.5, 4.8 Hz, 1H), 2.51 (d, J = 16.2 Hz, 1H), 2.40 (m, 1H), 1.55 (d, J = 12.0 Hz, 1H), 1.28 (s, 3H), 1.02 (s, 3H).

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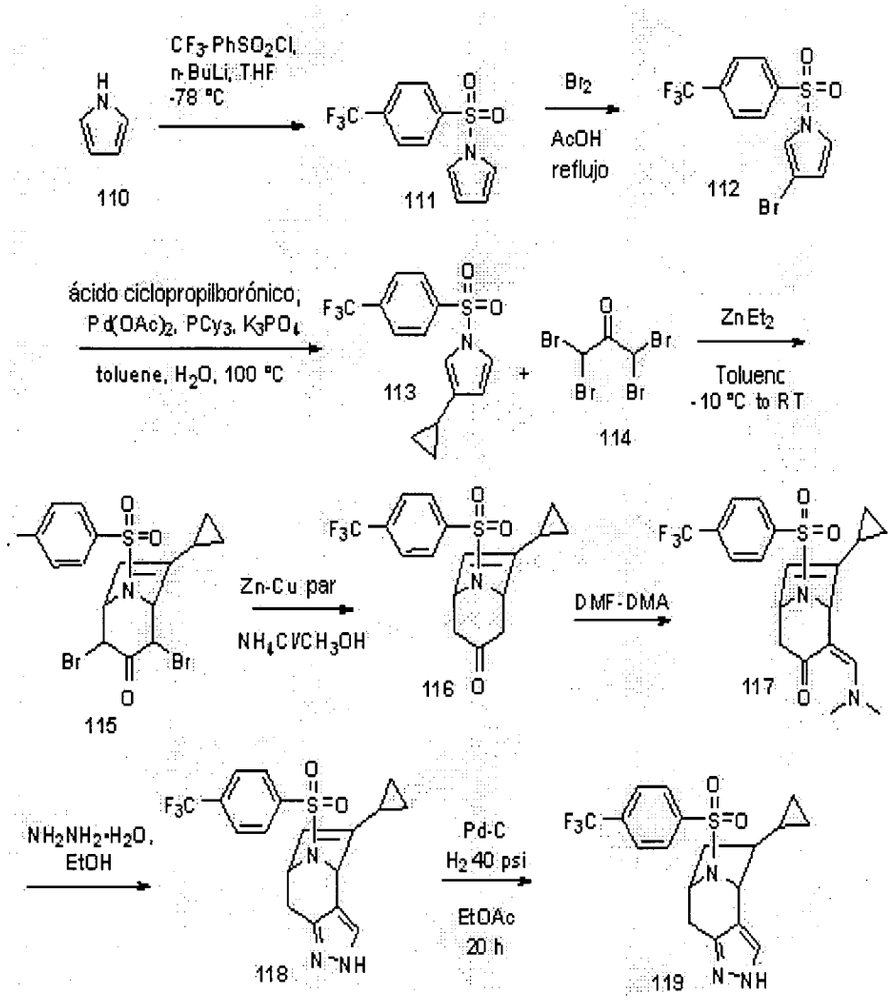
Ejemplo 26

Síntesis de 5-ciclopropil-9-{[4-(trifluorometil)fenil]sulfonil}-2,4,5,6,7,8-hexahidro-4,7-epiminociclohepta[*c*]pirazol (119).



26.1. 1-(4-(Trifluorometil)fenilsulfonil)-1*H*-pirrol (111)

n-BuLi (56 mL, 89.7 mmol) fue añadido a una solución de 1*H*-pirrol (6.02 g, 89.7 mmol) en THF (179 mL) a -78 °C por 10 minutos. 4-(trifluorometil)benzeno-1-sulfonil cloruro (26.3 g, 107.6 mmol) fue disuelto en THF (20 mL) y añadido a la mezcla de reacción durante 30 minutos. La reacción fue batida por 30 minutos y luego entibiada a temperatura ambiente y batida por 18 h. adicionales. La solución fue diluida con EtOAc, lavada con salmuera y la fase orgánica fue separada, secada (Na_2SO_4), filtrada y concentrada al vacío y purificada en columna de gel de silicio (eluante, hexano/EtOAc 99/1 a 4/1, v/v) para dar el compuesto **111** (21.4 g, 77.7 mmol, 87%). MS(ESI) 276.1 (M+H).

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26.2. 3-Bromo-1-(4-(trifluorometil)fenilsulfonil)-1*H*-pirrol (112)

Bromina (4.12 mL, 80.1 mmol) fue añadida a una solución de 1-(4-(trifluorometil)fenilsulfonil)-1*H*-pirrol (**111**) (21 g, 76.2 mmol) en ácido acético (254 mL) y la solución resultante fue calentada a 100 °C por 1 h. La mezcla fue diluida con CH_2Cl_2 y vertida lentamente sobre hidróxido sódico acuoso congelado (3 N). La solución fue ajustada a pH 7 con hidróxido sódico acuoso (3 N), extraída con CH_2Cl_2. La fase orgánica fue separada, secada (Na_2SO_4), filtrada y concentrada al vacío y purificada en columna de gel de silicio (eluante hexano/EtOAc, 4/1, v/v) para dar el compuesto **112** (20.4 g, 57.6 mmol, 75%). MS(ESI) 354.0 (M+H).

26.3. 3-Ciclopropil-1-(4-(trifluorometil)fenilsulfonil)-1*H*-pirrol(113)

Ácido ciclopropil borónico (1.6 g, 18.7 mmol), paladio (II)acetato (323 mg, 1.44 mmol), triciclohexilfosfina (808 mg, 2.88 mmol) y fosfato de potasio (10.7 g, 50.5 mmol) fueron añadidos a una solución de 3-bromo-1-(4-(trifluorometil)fenilsulfonil)-1*H*-pirrol (5.11 g, 14.4 mmol) en tolueno/H_2O (75 mL, 19/1). La mezcla suspension fue evacuada y purgada con nitrógeno tre veces y luego colocada en un baño de aceite precalentado a 100 °C. La reacción fue batida por 6 h y fue subsiguientemente concentrada al vacío. El residuo fue purificado en columna de gel de silicio (eluante hexano/EtOAc, 9/1, v/v) para dar el compuesto **113** (3.21 g, 10.1 mmol, 71%). MS(ESI) 316.1 (M+H).

26.4. 2,4-Dibromo-6-ciclopropil-8-(4-(trifluorometil)fenilsulfonil)-8-azabiciclo[3.2.1]oct-6-en-3-ona (115)

Dietil zinc (18.1 mL, 18.1 mmol de una 1M solución en hexano) fue añadido a una solución de 3-ciclopropil-1-(4-(trifluorometil)fenilsulfonil)-1*H*-pirrol (3.18 g, 10.1 mmol) y tetrabromoacetona (7.53 g, 20.1 mmol) en tolueno a -10 °C. La mezcla de reacción fue batida a temperatura ambiente por 17 h y fue subsiguientemente diluida con EtOAc y lavada con solución acuosa saturada de Na_2CO_3. . La fase orgánica fue separada, secada (Na_2SO_4), filtrada, concentrada al vacío y purificada en columna de gel de silicio (eluante

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hexano/EtOAc, 9/1 a 7/3, v/v) para dar compuesto el **115** (3.31 g, 6.25 mmol, 62%). MS(ESI) 530.0 (M+H).

26.5. 6-ciclopropil-8-{[4-(trifluorometil)fenil]sulfonil}-8-azabiciclo[3.2.1]oct-6-en-3-ona (116)

Zinc-cobre acoplados (3.21 g, 24.8 mmol) fueron añadidos a una solución de 2,4-dibromo-6-ciclopropil-8-(4-(trifluorometil)fenilsulfonil)-8-azabiciclo[3.2.1]oct-6-en-3-ona (3.29 g, 6.21 mmol) en una solución metanólica saturada de NH_4Cl (24 mL). La mezcla de reacción fue batida a temperatura ambiente por 4 h y fue subsiguientemente filtrada con Celite. El filtrado fue concentrado al vacío, re-disuelto en CH_2Cl_2 y lavado con solución acuosa saturada Na_2CO_3. La fase orgánica fue separada, secada (Na_2SO_4), filtrada, concentrada al vacío y purificada en columna de gel de silicio (eluante hexano/EtOAc, 9/1 a 1/1, v/v) para dar el compuesto **116** (1.68 g, 4.52 mmol, 73%). MS(ESI) 372.1 (M+H).

26.6. 7-ciclopropil-2-[(dimetilamino)metilideno]-8-{[4-(trifluorometil)fenil]sulfonil}-8-azabiciclo[3.2.1]oct-6-en-3-ona (117)

6-Ciclopropil-8-(4-(trifluorometil)fenilsulfonil)-8-azabiciclo[3.2.1]oct-6-en-3-ona (1.02 g, 2.74 mmol), fue disuelto en DMF-DMA (6 mL) y calentado a 100 °C por 4 h. La mezcla de reacción fue concentrada al vacío para dar el compuesto **117**. MS(ESI) 427.1 (M+H).

26.7. 5-ciclopropil-9-{[4-(trifluorometil)fenil]sulfonil}-2,4,7,8-tetrahidro-4,7-epiminociclohepta[*c*]pirazol (118)

7-Ciclopropil-2-((dimetilamino)metileno)-8-(4-(trifluorometil)fenilsulfonil)-8-azabiciclo[3.2.1]oct-6-en-3-ona (1.16 g, 2.74 mmol) fue disuelto en etanol (13 mL) y monohidrato de hidrazina (1.3 mL, 27.4 mmol) fue añadido. La solución resultante fue batida a temperatura ambiente por 1 h y luego EtOAc fue añadido. La solución fue lavada con salmuera, secada (Na_2SO_4), filtrada, concentrada al vacío y purificada en columna de gel de silicio (eluante hexano/EtOAc, 3/1 a 1/1) para dar el compuesto **118** como una mezcla de regioisómeros. MS(ESI) 395.1 (M+H).

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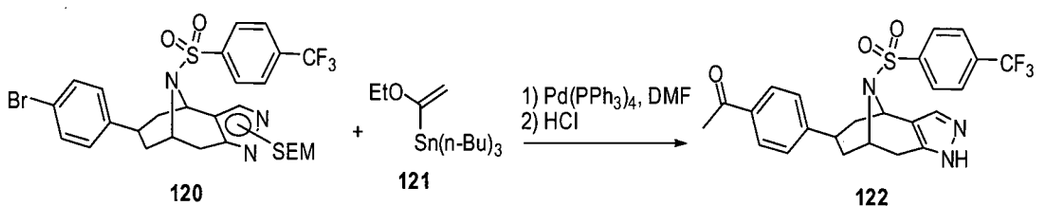
26.8. 5-ciclopropil-9-{[4-(trifluorometil)fenil]sulfonil}-2,4,5,6,7,8-hexahidro-4,7-epiminociclohepta[*c*]pirazol (119)

Una suspension de 7-ciclopropil-2-((dimetilamino)metileno)-8-(4-(trifluorometil)fenilsulfonil)-8-azabiciclo[3.2.1]oct-6-en-3-ona (107 mg, 0.27 mmol) y Pd/C (20 mg) en EtOAc (2 mL) fue batida bajo una atmósfera de hidrógeno (30 psi) por 18 h. La mezcla suspension fue filtrada a través de Celite y concentrada al vacío. El residuo fue purificado por preparativo HPLC para dar el compuesto **119**. MS(ESI) 398.1 (M+H).

Ejemplo 27

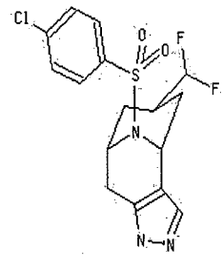
Síntesis de 1-[4-(10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol-6-il)fenil]etanona (122)

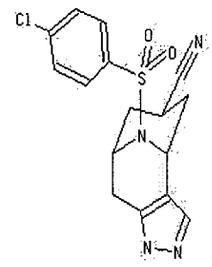
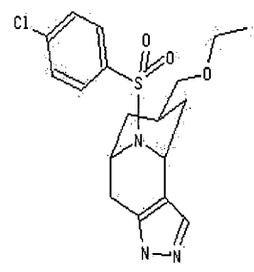


Tetrakis(trifenilfosfina)paladio (200 mg, 173 umol) fue añadido a una solución de compuesto **120** (170 mg, 324 umol) y tributil-(1-etoxi-vinil)-estanano (**121**) (610 mg, 1.69 mmol) en DMF (5 ml) y colocada en un baño de aceite precalentado a a 90°C. Luego de batir por 18 h, la solución fue enfriada a temperatura ambiente y 10% de HCl acuoso fue añadido. Luego de batir por otras18 h, la solución fue filtrada y el producto crudo fue purificado por HPLC para dar el compuesto título **122**.

Los compuestos en Tabla 1 fueron preparados esencialmente de acuerdo a los métodos y procedimientos arriba descritos.

Ex. No.	**Estructura / Nombre Compuesto / Masa Espec.** (M+H) / ^{1}**H-NMR** (300 MHz) / **Procedimientos Experimentales**	**γAPP** IC_{50} (nM)

28	etill 10-[(4-clorofenil)sulfonil]-1,4,5,7,8,9-hexahidro-6H-4,8-epiminopirazol[4,3-d]azocina-6-carboxilato; MS 411.0. Preparado por tratamiento de 10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminopirazol[4,3-d]azocina (WO2007/022502) con etill cloroformato seguido por hidrolisis del N-etilcarbamoilpirazol con NaOH.	C
29	 10-[(4-clorofenil)sulfonil]-6-(difluorometil)-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 388.0. Preparado por sulfonilación de etill 10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-carboxilato (WO2007/022502) con 4-clorobenzeno sulfonil cloruro seguido por reducción del éster con $LiBH_4$, oxidación con Dess-Martin periodinano, y tratamiento DAST. El N-sulfonilpirazol fue entonces hidrolizado con NaOH.	D
30	1-{10-[(4-clorofenil)sulfonil]-1,4,5,7,8,9-hexahidro-6H-4,8-epiminopirazol[4,3-d]azocin-6-il}propan-1-ona; MS 395.0. Preparado de 10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminopirazol[4,3-d]azocina (WO2007/022502) y anhídrido propiónico, e hidrolisis del N-propionoilpirazol con NaOH.	B

31	 (±)-10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-carbonitrilo; MS 363.1. ^{1}H NMR ($CDCl_3$) δ 7.62 (d, J = 8.8 Hz, 2H), 7.43 (s, 1H), 7.35 (d, J = 8.8 Hz, 2H), 5.38 (bs, 1H), 4.61-4.52 (m, 1H), 2.93 (dd, J = 17.0, 6.6 Hz, 1H), 2.71-2.52 (m, 2H), 2.32-1.98 (m, 4H). Preparado como se describe en Ejemplo 18.	D
32	2-metoxietil 10-[(4-clorofenil) sulfonil]-1,4,5,7,8,9-hexahidro-6H-4,8-epiminopirazol[4,3-d]azocina-6-carboxilato; MS 441.0. Preparado por tratamiento de 10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminopirazol[4,3-d] azocina (WO2007/022502) con 2-metoxietil cloroformato seguido por hidrólisis del N-metoxietilcarbamoil-pirazol con NaOH.	B
33	 10-[(4-clorofenil)sulfonil]-6-(etoximetil)-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 396.1. Preparado por protección de etill 10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-carboxilato (WO2007/022502) con SEM-Cl seguido por reducción del ester con LiBH4, y alquilación con etill yoduro y tratamiento con 4N HCl en dioxano.	D

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34	10-[(4-clorofenil)sulfonil]-6-(metoximetil)-4,5,6,7,8,9-hexahidro-1H-4,8-epiminocicloocta[c]pirazol; MS 382.1. Preparado por protección de etill 10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminocicloocta[c]pirazol-6-carboxilato (WO2007/022502) con SEM-Cl seguido por reducción del éster con LiBH4, y alquilación con metil yoduro y tratamiento con 4N HCl en dioxano.	D
35	propan-2-il 10-[(4-clorofenil)sulfonil]-1,4,5,7,8,9-hexahidro-6H-4,8-epiminopirazol[4,3-d]azocina-6-carboxilato; MS 425.0. Preparado por tratamiento de 10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminopirazol[4,3-d]azocina (WO2007/022502) con isopropil cloroformato seguido por hidrolisis del N-isopropil carbamoil pirazol con NaOH.	A
36	10-[(4-clorofenil) sulfonil]-6-(metilsulfonil)-4,5,6,7,8,9-hexahidro-1H-4,8-epimino pirazol[4,3-d] azocina; MS 417.0. Preparado por tratamiento de 10-[(4-clorofenil) sulfonil]-4,5,6,7,8,9-hexahidro-1H-4,8-epimino pirazol-[4,3-d]azocina (WO2007/022502) con metano sulfonil-cloruro seguido por hidrolisis de la mezcla N-sulfonilpirazol con NaOH.	A
37	(±)-10-[(4-clorofenil)sulfonil]-6-(3-metil-1,2,4-oxadiazol-5-il)-4,5,6,7,8,9-hexahidro-1H-4,8-epiminocicloocta[c] pirazol; MS 420.1. ^{1}H NMR ($CDCl_3$) δ 7.67 (d, J = 8.8 Hz, 2H), 7.52 (s, 1H), 7.39 (d, J = 8.8 Hz, 2H), 5.43 (bs, 1H), 4.66 (bs, 1H), 3.06 (m, 1H), 2.72 (d, J = 17.6 Hz, 1H), 2.34 (s, 3H), 2.32-2.09 (m, 4H). Preparado como se describe en Ejemplo 16.	D

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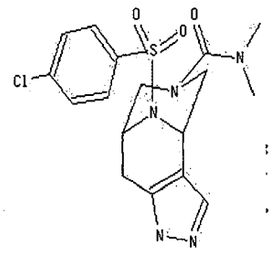
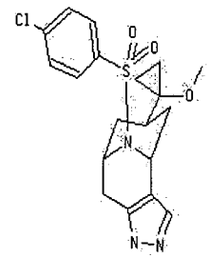
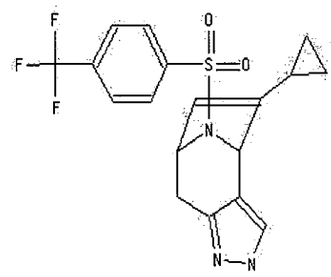
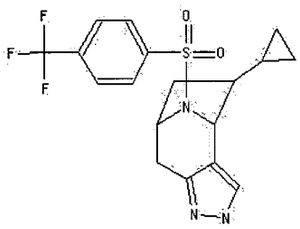
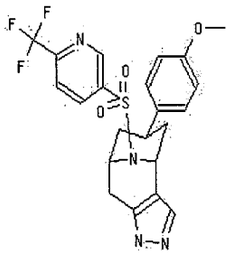
38	10-[(4-clorofenil) sulfonil]-6-(ciclopropilsulfonil)-4,5,6,7,8,9-hexahidro-1H-4,8-epiminopirazol[4,3-d]azocina; MS 453.0. Preparado por tratamiento de 10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1H-4,8-epimino-pirazol[4,3-d]azocina (WO2007/022502) con ciclopropanesulfonilcloruro seguido por hidrolisis del mezcla N-sulfonilpirazol con NaOH.	A
39	 10-[(4-clorofenil)sulfonil]-N,N-dimetil-1,4,5,7,8,9-hexahidro-6H-4,8-epiminopirazol[4,3-d]azocina-6-carboxamida; MS 410.1. ^{1}H NMR (CDCl3) δ 7.63 (d, J = 8.8 Hz, 2H), 7.36 (s, 1H), 7.34 (d, J = 8.8 Hz, 2H), 5.18 (s, 1H), 4.34 (s, 1H), 2.82 (d, J = 13.2 Hz, 1H), 3.46-3.33 (m, 2H), 3.21 (dd, J = 13, 3.2 Hz, 1H), 2.93-2.78 (m, 2H), 2.51 (s, 6H). Preparado por tratamiento de 10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminopirazol[4,3-d] azocina (WO2007/022502) con N,N-dimetilcarbamoilcloruro seguido por hidrolisis de la mezcla N,N-dimetilcarbamoilpirazol con NaOH.	C
40	10-[(4-clorofenil) sulfonil]-6-(etilsulfonil)-4,5,6,7,8,9-hexahidro-1H-4,8-epiminopirazol[4,3-d]azocina; MS 431.0. Preparado por tratamiento de 10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminopirazol-[4,3-d]azocina (WO2007/022502) con etanosulfonilcloruro seguido por hidrolisis de la mezcla N-sulfonilpirazol con NaOH.	A

41	(-)-10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclo octa[c]pirazol-6-carbonitrilo; MS 363.1. ^{1}H NMR ($CDCl_3$) δ 7.62 (d, J = 8.8 Hz, 2H), 7.43 (s, 1H), 7.35 (d, J = 8.8 Hz, 2H), 5.38 (bs, 1H), 4.61-4.52 (m, 1H), 2.93 (dd, J = 17.0, 6.6 Hz, 1H), 2.71-2.52 (m, 2H), 2.32-1.98 (m, 4H). Preparado como se describe en Ejemplo 18 seguido por quiral cromatográfica separación de estereoisómeros.	A
42	(+)-10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclo octa[c]pirazol-6-carbonitrilo; MS 363.1. ^{1}H NMR ($CDCl_3$) δ 7.62 (d, J = 8.8 Hz, 2H), 7.43 (s, 1H), 7.35 (d, J = 8.8 Hz, 2H), 5.38 (bs, 1H), 4.61-4.52 (m, 1H), 2.93 (dd, J = 17.0, 6.6 Hz, 1H), 2.71-2.52 (m, 2H), 2.32-1.98 (m, 4H). Preparado como se describe en Ejemplo 18 seguido por quiral cromatográfica separación de estereoisómeros.	D
43	 (±)-10-[(4-clorofenil)sulfonil]-6-(1-metoxiciclopropil)-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclo octa[c]pirazol; MS 408.1. ^{1}H NMR ($CDCl_3$) δ 7.62 (d, J = 8.6 Hz, 2H), 7.34 (s, 1H), 7.32 (d, J = 8.8 Hz, 2H), 5.35 (bs, 1H), 4.57 (d, J = 7.9 Hz, 1H)), 3.05 (s, 3H), 2.86 (dd, J = 17.1, 6.6 Hz, 1H), 2.51 (d J = 17.1, 1H), 1.75-1.61 (m, 5H), 0.66-0.63 (m, 2H), 0.33-0.29 (m, 2H). Preparado como se describe en Ejemplo 16 usando compuesto **56** de Ejemplo 17.	C

S06

44	 5-ciclopropil-9-{[4-(trifluorometil)fenil]sulfonil}-1,4,7,8-tetrahidro-4,7-epiminociclohepta[c]pirazol; MS 396.1. Isómero principal: ^{1}H NMR ($CDCl_3$) □ 8.01 (d, J = 8.7 Hz, 2H), 7.75 (d, J = 8.7 Hz, 2H), 7.49 (s, 1H), 5.36-5.31 (m, 1H), 5.05 (s, 1H), 4.94-4.92 (m, 1H), 3.24-3.21 (m, 1H), 2.65 (d, J = 16.5 Hz, 1H), 1.16-1.11 (m, 1H), 0.66-0.59 (m, 2H), 0.17-0.65 (m, 2H). Isómero menor: ^{1}H NMR ($CDCl_3$) □ 8.01 (d, J = 8.7 Hz, 2H), 7.75 (d, J = 8.7 Hz, 2H), 7.42 (s, 1H), 5.53-5.52 (m, 1H), 5.07-5.05 (m, 1H), 4.70 (d, J = 5.4 Hz,1H), 3.30-3.28 (m, 1H), 2.86 (d, J = 16.5 Hz, 1H), 1.16-1.11 (m, 1H), 0.66-0.59 (m, 2H), 0.17-0.65 (m, 2H). Preparado como se describe en Ejemplo 26.	D

507

45	 5-ciclopropil-9-{[4-(trifluorometil)fenil]sulfonil}-1,4,5,6,7,8-hexahidro-4,7-epiminociclohepta[c]pirazol; MS 398.1. Isómero principal: ^{1}H NMR ($CDCl_3$) δ 7.91 (d, J = 8.0 Hz, 2H), 7.68 (d, J = 8.0 Hz, 2H), 7.56 (s, 1H), 4.95 (d, J = 5.5 Hz,1H), 4.56-4.53 (m, 1H), 3.09 (dd, J = 16.7, 4.4 Hz, 1H), 2.65 (d, J = 16.7 Hz, 1H), 1.82-1.77 (m, 2H), 1.64-1.62 (m, 1H), 0.58-0.42 (m, 2H), 0.27-0.35 (m, 3H). Isómero menor: ^{1}H NMR ($CDCl_3$) δ 7.91 (d, J = 8.0 Hz, 2H), 7.68 (d, J = 8.0 Hz, 2H), 7.42 (s, 1H), 5.13 (d, J = 6.4 Hz,1H), 4.65-4.58 (m, 1H), 3.23 (d, J = 16.7, 1H), 2.52-2.46 (m, 1H), 1.82-1.77 (m, 2H), 1.64-1.62 (m, 1H), 0.58-0.42 (m, 2H), 0.27-0.35 (m, 3H). Preparado como se describe en Ejemplo 26.	D
46	 (±)-6-(4-metoxifenil)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 479.1 ^{1}H NMR ($CDCl_3$) δ 8.95 (s, 1H), 8.15 (d, J = 7.6 Hz, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.26 (d, J = 13.2 Hz, 1H), 7.01 (d, J = 8.2 Hz, 2H), 6.81 (d, J = 8.0 Hz, 2H), 5.41 (s, 1H), 4.68 (s, 1H), 3.76 (s, 3H), 2.76 (m, 3H), 2.12 (m, 2H), 1.87 (m, 2H). Preparado como se describe en Ejemplo 5 usando 3-(4-metoxifenil)-pentanodial y 6-(trifluorometil) piridina-3-sulfonil cloruro.	D

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47	5,5-dimetil-9-{[4-(trifluorometil)fenil]sulfonil}-5,6,7,8-tetra hidro-1H-4,7-epiminopirazol[4,3-b]azepina;y6,6-dimetil-9-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,8-tetrahidro-1H-4,7-epiminopirazol[3,4-c]azepina; MS 387.1. ^{1}H-NMR ($CDCl_3$) δ7.92 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.28 (s, 1H), 4.87(m, 1H), 3.09 (dd, J = 16.5, 4.8 Hz, 1H), 2.51 (d, J = 16.2 Hz, 1H), 2.40 (m, 1H), 1.55 (d, J = 12.0 Hz, 1H), 1.28 (s, 3H), 1.02 (s, 3H). Preparado como se describe en Ejemplo 25.	B
48	(±)-6-fenil-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminocicloocta[c]pirazol; MS 449.1. ^{1}H NMR ($CDCl_3$) δ 8.96 (d, J = 1.7 Hz, 1H), 8.16 (dd, J = 8.1, 1.7 Hz, 1H), 7.64, (d, J = 8.1 Hz, 1H), 7.23 (m, 4H), 7.08 (d, J = 6.9 Hz, 2H), 5.43 (s, 1H), 4.69 (s, 1H), 2.78 (m, 3H), 2.68 (d, J = 17.3 Hz, 1H), 2.21 (ddd, J = 12.8, 11.2, 3.8 Hz, 2H), 1.89 (m, 2H). Preparado como se describe en Ejemplo 5 usando 3-fenilglutar-aldehido y 6-(trifluorometil) piridina-3-sulfonil cloruro.	D
49	(±)-6-fenil-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminocicloocta[c]pirazol; MS 448.1. ^{1}H NMR ($CDCl_3$) δ 7.86 (d, J = 8.2 Hz, 2H), 7.62 (d, J = 8.3, 2H), 7.22, (m, 4H), 7.04 (m, 2H), 5.41 (s, 1H), 4.67 (s, 1H), 2.85 (dd, J = 17.1, 7.7 Hz, 1H), 2.76 (m, 1H), 2.65 (d, J = 17.1 Hz, 1H), 2.13 (m, 2H), 1.86 (m, 2H). Preparado como se describe en Ejemplo 5 usando 3-fenilglutaraldehido y 4-(trifluorometil)benzeno -1-sulfonil cloruro.	D

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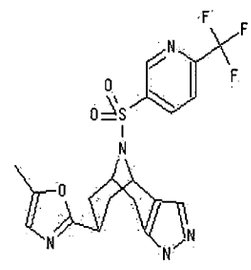
50	(±)-10-[(5-clorotiophen-2-il)sulfonil]-6-fenil-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 420.0. ^{1}H NMR ($CDCl_3$) δ 7.34 (s, 1H), 7.24 (m, 4H), 7.22, (m, 4H), 7.06 (m, 2H), 6.76 (d, J = 4.0, 1H), 5.38 (s, 1H), 4.67 (t, J = 5.5 Hz, 1H), 3.11 (dd, J = 17.0, 7.7 Hz 1H), 2.77 (m, 1H), 2.72 (d, J = 17.0 Hz , 2H), 2.15 (m, 2H), 1.86 (m, 2H). Preparado como se describe Ejemplo 5 usando 3-fenilglutaraldehido y 5-clorotiofeno-2-sulfonil cloruro.	D
51	6-(1-metil-1H-pirazol-3-il)-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol y 6-(1-metil-1H-pirazol-5-il)-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 452.1. ^{1}H NMR ($CDCl_3$) δ 7.83 (m, 2H), 7.58 (m, 2H), 7.35 (d, J = 1.8 Hz, 1H), 7.30 (s, 1H), 7.21 (s, 1H), 5.96 (d, J = 1.9 Hz, 1H), 5.94 (d, J = 2.1 Hz, 1H), 5.40 (s, 1H), 5.36 (s, 1H), 4.62 (m, 1H), 3.76 (s, 3H), 3.54 (s, 3H), 2.88 (m, 6H), 2.59 (dd, J = 17.1, 12.6 Hz, 2H), 2.02 (m, 8H).	C
52	(±)-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 452.1. ^{1}H NMR ($CDCl_3$) δ 7.71(d, J = 9 Hz, 2H), 7.46-7.44 (m, 3H), 7.06-6.99 (m, 1H), 6.98 – 6.93 (m, 3H), 5.83 (s, 1H), 5.38 (d, J = 5.1 Hz, 1H), 4.57 (bs, 1H), 3.53 (dd, J = 5.1, 16.2 Hz, 1H), 2.85 (d, J = 16.5 Hz, 1H). Preparado como se describe en Ejemplo 8.	D

53	(±)-exo-6-(4-fluorofenil)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 467.1. ^{1}H NMR ($CDCl_3$) δ 8.94 (s, 1H), 8.16 (dd, J = 8.1, 1.5 Hz, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.30 (s, 1H), 7.00 (m, 4H), 5.42 (s, 1H), 4.67 (s, 1H), 2.75 (m, 3H), 2.11 (m, 2H), 1.87 (m, 2H). Preparado como se describe en Ejemplo 5 usando 3-(4-fluorofenil) pentanodial y 6-(trifluorometil) piridina-3-sulfonil cloruro.	D
54	(±)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-6-[4-(trifluorometil)-1,3-tiazol-2-il]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 524.1. ^{1}H NMR ($CDCl_3$) δ 8.96 (s, 1H), 8.15 (d, 1H, *J* = 8.2 Hz), 7.66 (s, 1H), 7.64 (d, 1H, *J* = 8.2 Hz), 7.32 (s, 1H), 5.46 (s, 1H), 4.72 (br s, 1H), 3.31(br s, 1H), 2.76 (m, 2H), 2.26 (m, 4H).	D
55	 (±)-6-(5-metil-1,3-oxazol-2-il)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 454.1. ^{1}H NMR ($CDCl_3$) δ 8.9 (d, J = 1.6 Hz, 1H), 8.13 (dd, J = 8.2, 1.9 Hz, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.22 (s, 1H), 6.52 (s, 1H), 5.39 (s, 1H), 4.64 (s, 1H), 2.95 (m, 1H), 2.78 (dd, J = 17.3, 7.6 Hz, 1H), 2.62 (d, J = 17.3 Hz, 1H), 2.14 (m, 8H). Preparado como se describe en el Ejemplo usando 3-(5-metil-oxazol-2-il) pentanodial y 6-(trifluorometil) piridina-3-sulfonil cloruro.	D

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56	(±)-endo-6-(4-fluorofenil)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 467.1 ^{1}H NMR ($CDCl_3$) δ 9.0 (d, J = 1.9 Hz, 1H), 8.24 (dd, J = 8.2, 2.0 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.39 (s, 1H), 6.96 (m, 4H), 5.32 (d, J = 9.3 Hz, 1H), 4.73 (m, 1H), 2.89 (m, 1H), 2.68 (m, 2H), 2.58 (d, J = 15.9 Hz, 1H), 2.27 (m, 1H), 1.54 (m, 2H). Preparado como se describe en Ejemplo 5 usando 3-(4-fluorofenil) pentanodial y 6-(trifluorometil) piridina-3-sulfonil cloruro.	D
57	(±)-6-(5-metil-1,3-tiazol-2-il)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 470.1. ^{1}H NMR ($CDCl_3$) δ 8.99 (s, 1H), 8.18 (d, 1H, *J* = 8.0 Hz), 7.70 (d, 1H, *J* = 8.0 Hz), 7.46 (s, 1H), 7.40 (s, 1H), 5.46 (br s, 1H), 4.72 (br s, 1H), 3.38 (br s, 1H), 2.87 (m, 2H), 2.48 (s, 3H), 2.21 (m, 4H).	C
58	(±)-6-(1*H*-benzimidazol-2-il)-10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol; MS 454.1. ^{1}H-NMR (CD_3OD) δ 7.76 – 7.71 (m, 4H), 7.61 – 7.60 (m, 2H), 7.49 (s, 1H), 7.44 – 7.40 (m, 3H), 5.61 – 5.56 (m, 1H), 4.58 – 4.54 (m, 1H), 3.48 – 3.50 (m, 1H), 2.86 (dd, J = 17.6, 7.7 Hz, 1H), 2.70 (d, J = 18.1 Hz, 1H), 2.50 – 2.41 (m, 4H). Preparado por alquilación de metil 10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[c]pirazol-6-carboxilato (WO 2007022502) con trimetilsililetoximetil cloruro seguido por hidrolisis con KOH y formación de amidas usando 1,2-benzenodiamina, HBTU, e y-Pr_2EtN en DMF. La amida fue entonces tratada con TFA en EtOH a 120 °C en un reactor de microondas para dar el benzamidazol,que fue desalquilado usando 4N HCl/dioxano.	C

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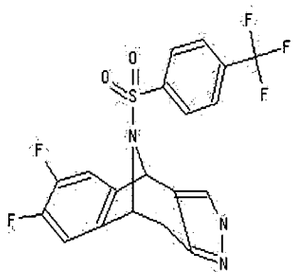
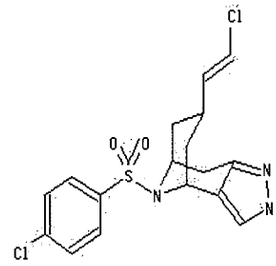
59	(±)-5-(4-fluorofenil)-9-{[4-(trifluorometil)fenil]sulfonil}-1,4,7,8-tetrahidro-4,7-epiminociclohepta[*c*]pirazol; MS 450.0. ^{1}H NMR ($CDCl_3$) δ 7.86 (d, 2H, J=8.2 Hz), 7.70 (d, 2H, J = 8.3 Hz), 7.41 (s, 1H), 7.05-7.10 (m, 2H), 6.92-6.98 (m, 2H), 5.76 (s, 1H), 5.64 (d, 1H, J = 2.6 Hz), 5.04-5.06 (m, 1H), 3.34 (dd, 1H, J = 16.4, 5.6 Hz), 2.73 (d, 1H, J = 16.3 Hz).	C
60	6-(4-fluorofenil)-9-{[4-(trifluorometil)fenil]sulfonil}-1,4,7,8-tetrahidro-4,7-epiminociclohepta[*c*]pirazol; MS 449.9. ^{1}H NMR ($CDCl_3$) δ 7.87 (d, 2H, J = 8.1 Hz), 7.60 (d, 2H, J = 8.3 Hz), 7.42 (s, 1H), 7.08-7.13 (m, 2H), 6.95-7.01(m, 2H), 6.24 (d, 1H, J = 2.4 Hz), 5.50 (d, 1H, J = 2.4 Hz), 5.34 (d, 1H, J = 5.5 Hz), 3.39 (dd, 1H, J = 16.6, 5.7 Hz), 2.89 (d, 1H, J = 16.7 Hz).	C
61	5-(4-fluorofenil)-9-{[4-(trifluorometil)fenil]sulfonil}-1,4,5,6,7,8-hexahidro-4,7-epiminociclohepta[*c*]pirazol; MS 452.1. ^{1}H NMR ($CDCl_3$) δ 7.95 (d, 2H, J = 8.2 Hz), 7.71 (d, 2H, J = 8.3 Hz), 6.80-6.95 (m, 3H), 6.77-6.82 (m, 2H), 5.12 (d, 1H, J = 5.5 Hz), 4.76-4.81 (m, 1H), 3.80-3.87 (m, 1H), 3.15 (dd, 1H, J = 16.5 Hz, J = 4.4 Hz), 2.73-2.82 (m, 2H), 1.77 (dd, 1H, J = 12.3 Hz, J=8.5 Hz).	D

S13

62	 (±)-6,7-difluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol; MS 442.1. ^{1}H NMR ($CDCl_3$) δ 7.78 (d, 2H, J = 8.3 Hz), 7.61 (d, 2H, J = 8.3 Hz), 7.50 (s, 1H), 6.94-7.01 (dd, 1H, J = 8.9, 6.9 Hz), 6.77-6.83 (dd, 1H, J = 8.8, 6.9 Hz), 5.84 (s, 1H), 5.39 (d, 1H, J = 5.3 Hz), 3.52 (dd, 1H, J = 16.6, 5.6 Hz), 2.86 (d, 1H, J = 16.6 Hz). Preparado como se describe en Ejemplo 8 usando 2-bromo-4, 5-difluorobenzaldehido.	D
63	6-(4-fluorofenil)-9-{[4-(trifluorometil)fenil]sulfonil}-1,4,5,6,7,8-hexahidro-4,7-epiminociclohepta[*c*]pirazol; MS 452.0. ^{1}H NMR ($CDCl_3$) δ 7.94 (d, 2H, J = 8.2 Hz), 7.71 (d, 2H, J = 8.3 Hz), 7.59 (s, 1H), 6.92-6.99 (m, 2H), 6.76-6.82 (m, 2H), 5.27 (d, 1H, J = 6.5 Hz), 4.68-4073 (m, 1H), 3.95-4.03(m, 1H), 2.75-2.89 (m, 2H), 2.13-2.26 (m, 2H).	B

514

64	 6-[(E)-2-cloroetenil]-10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 398.0. ^{1}H NMR ($CDCl_3$)δ 11.30 (ancho s, 1H), 7.66 (d, J=8.4 Hz, 2H), 7.50 (ancho s, 1H), 7.38 (d, J=8.4 Hz, 2H), 5.91 (d, J=13.2 Hz, 1H), 5.70 (dd, J=13.2 y 7.2 Hz, 1H), 5.34 (ancho s, 1H), 4.57 (ancho s, 1H), 2.95 (ancho s, 1H), 2.63 (ancho m, 1H), 2.22 (ancho m, 1H), 1.78 (ancho m, 4H). Preparado por protección de etill 10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа-[c]pirazol-6-carboxilato (WO2007/022502) con SEM-Cl seguido por reducción del éster con LiBH4, oxidación con Dess-Martin periodinano, y tratamiento con (clorometileno)trifenil-fosforano seguido por tratamiento con 4N HCl en dioxano y cromatográfica separación de isomeros.	D

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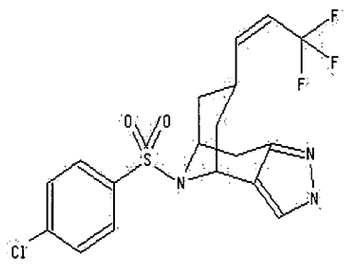
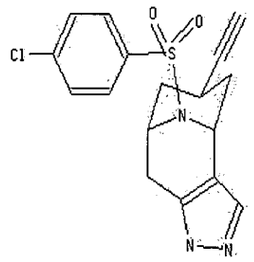
65	10-[(4-clorofenil)sulfonil]-6-[(1E)-3,3,3-trifluoroprop-1-en-1-il]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 432.0 ^{1}H NMR ($CDCl_3$)δ 8.40 (ancho s, 1H), 7.65 (d, J=8.4 Hz, 2H), 7.50 (ancho s, 1H), 7.37 (d, J=8.4 Hz, 2H), 6.19 (m, 1H), 5.54 (m, 1H), 5.39 (ancho s, 1H), 4.60 (ancho s, 1H), 2.95 (ancho s, 1H), 2.63 (ancho s, 1H), 2.31 (ancho s, 1H), 1.83 (ancho m, 4H). Preparado por protección de etill 10-[(4-clorofenil)-sulfonil]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]-pirazol-6-carboxilato (WO2007/022502) con SEM-Cl seguido por reducción del ester con LiBH4, oxidación con Dess-Martin periodinano, y tratamiento con difenil(2,2,2-trifluoroetil)fosfinóxido y TBAF en TF, seguido por tratamiento con 4N HCl en dioxano y cromatográfica separación de isómeros.	D

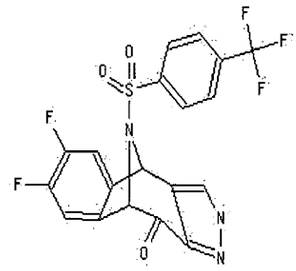
576

66	 10-[(4-clorofenil)sulfonil]-6-[(1Z)-3,3,3-trifluoroprop-1-en-1-il]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminocicloocta[c]pirazol; MS 432.0 ^{1}H NMR ($CDCl_3$) δ 7.62 (d, J=8.1 Hz, 2H), 7.32 (d, J=8.1 Hz, 3H), 5.75 (m, 1H), 5.59 (m, 1H), 5.34 (ancho s, 1H), 4.59 (ancho s, 1H), 4.34 (ancho s, 1H), 2.80 (ancho m, 2H), 2.58 (ancho s, 1H), 1.78 (ancho m, 4H). Preparado por protección de etill 10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminocicloocta[c]-pirazol-6-carboxilato (WO2007/022502) con SEM-Cl seguido por reducción del éster con LiBH4, oxidación con Dess-Martin periodinano, y tratamiento con difenil(2,2,2-trifluoroetil)-fosfinóxido y TBAF en TF, seguido por tratamiento con 4N HCl en dioxano y cromatográfica separación de isómeros.	D
67	6-[(Z)-2-cloroetenil]-10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminocicloocta[c]pirazol; MS 398.0. ^{1}H NMR ($CDCl_3$)δ 10.13 (ancho s, 1H), 7.65 (d, J=8.1 Hz, 2H), 7.38 (ancho s, 1H), 7.32 (d, J=8.1 Hz, 2H), 5.99 (d, J=7.2 Hz, 1H), 5.52 (t, J=7.2 Hz, 1H), 5.35 (ancho s, 1H), 4.59 (ancho s, 1H), 2.92 (ancho s, 1H), 2.70 (ancho m, 2H), 1.80 (ancho m, 4H). Preparado por protección de etill 10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminocicloocta[c]-pirazol-6-carboxilato (WO2007/022502) con SEM-Cl seguido por reducción del éster con LiBH4, oxidación con Dess-Martin periodinano, y tratamiento con (clorometilene)trifenilphosphorane seguido por tratamiento con 4N HCl en dioxano y cromatográfica separación de isómeros.	D

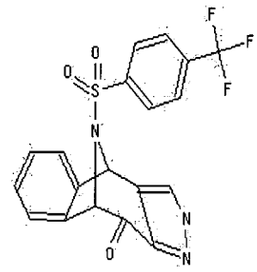
S17

68	 10-[(4-clorofenil)sulfonil]-6-etinil-4,5,6,7,8,9-hexahidro-1H-4,8-epiminocicloocta[c]pirazol; MS 362.1. ^{1}H NMR ($CDCl_3$) δ 7.66 (d, J = 8.0 Hz, 2H), 7.41 (bs, 1H), 7.38 (d, J = 8.0 Hz, 2H), 5.33 (s, 1H), 4.54 (s, 1H), 2.94-2.92 (m, 1H), 2.63-2.58 (m, 1H), 2.42-2.40 (m, 1H), 2.11-1.91 (m, 5H). Preparado por protección de etill 10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminocicloocta[c]pirazol-6-carboxilato (WO2007/022502) con SEM-Cl seguido por reducción del éster con LiBH4, y oxidación con Dess-Martin periodinano para dar 10-[(4-clorofenil)sulfonil]-1-{[2-(trimetilsilil)etoxi]metil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminocicloocta[c]pirazol-6-carbaldehido. El aldehido fue entonces tratado con dimetil (1-diazo-2-oxopropil)phosphonate y K2CO3 en C3CN para dar 10-[(4-clorofenil)sulfonil]-6-etinil-1-{[2-(trimetilsilil)etoxi]-metil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminocicloocta[c]pirazol que fue desprotegido con 4N HCl en dioxano.	D

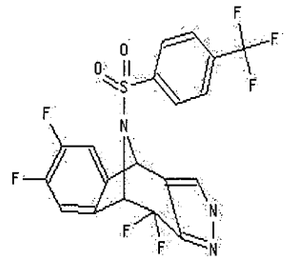
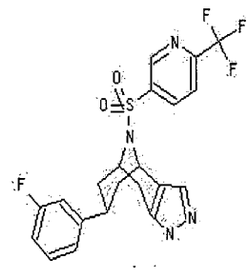
518

69	 (±)-6,7-difluoro-11-{[4-(trifluorometil)fenil]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol-10(1*H*)-ona; MS 456.1. ^{1}H NMR (CD_3OD) δ 7.89 (d, 2H, J = 8.2 Hz), 7.71 (s, 1H), 7.67 (d, 2H, J = 8.6 Hz), 7.22-7.28(m, 1H), 7.09-7.15 (m, 1H), 6.30 (s, 1H), 5.53 (s, 1H). Preparado por oxidación de 6,7-difluoro-11-{[4-(trifluorometil)fenil]-sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol usando el método descrito en Ejemplo 15.	D
70	(±)-6-(3-fluorofenil)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol; MS 467.1 ^{1}H NMR ($CDCl_3$) δ 8.94 (d, *J* = 1.9 Hz, 1H), 8.16 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.31 (s, 1H), 7.20 (m, 1H), 6.81 (m, 3H), 5.43 (s, 1H), 4.69 (s, 1H), 2.74 (m, 2H), 2.67 (d, *J* = 17.3 Hz, 1H), 2.14 (m, 2H), 1.88 (m, 2H). Preparado como se describe en Ejemplo 5 usando 3-(3-fluorofenil) pentanodial y 6-(trifluorometil) piridina-3-sulfonil cloruro.	D

S19

71	 (±)-11-{[4-(trifluorometil)fenil]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol-10(1*H*)-ona; MS 420.0 ^{1}H NMR ($CDCl_3$) δ 7.74 (d, 2H, J = 8.2 Hz), 7.65 (s, 1H), 7.48 (d, 2H, J = 8.3 Hz), 7.25-7.30 (m, 1H), 7.04-7.14 (m, 3H), 6.15 (s, 1H), 5.42 (s, 1H). Preparado como se describe en Ejemplo 15.	D
72	(-)-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol; MS 406.1. ^{1}H NMR ($CDCl_3$) δ 7.72 (d, 2H, J = 8.3 Hz), 7.46 (d, 2H, J = 8.3 Hz), 7.37 (s, 1H), 7.04-7.08 (m, 1H), 6.84-6.98 (m, 3H), 5.83 (s, 1H), 5.39 (d, 1H, J = 5.4 Hz), 3.50 (dd, 1H, J = 16.2, 5.5 Hz), 2.85 (d, 1H, J = 16.2 Hz). Preparado como se describe en Ejemplo 8 seguido por quiral cromatográfica separación de enantiomers.	A
73	(+)-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol; MS 406.1. ^{1}H NMR ($CDCl_3$) δ 7.72 (d, 2H, J = 8.3 Hz), 7.46 (d, 2H, J = 8.3 Hz), 7.37 (s, 1H), 7.04-7.08 (m, 1H), 6.84-6.98 (m, 3H), 5.83 (s, 1H), 5.39 (d, 1H, J = 5.4 Hz), 3.50 (dd, 1H, J = 16.2, 5.5 Hz), 2.85 (d, 1H, J = 16.2 Hz). Preparado como se describe en Ejemplo 8 seguido por quiral cromatográfica separación de enantiomers.	D

74	(±)-10,10-difluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol; MS 442.1 ^{1}H NMR ($CDCl_3$) δ 7.79 (d, 2H, J = 8.2 Hz), 7.52 (d, 2H, J = 8.3 Hz), 7.45 (s, 1H), 7.25-7.29 (m, 1H), 6.94-7.06 (m, 3H), 6.00 (s, 1H), 5.47 (d, 1H, J = 10.6 Hz). Preparado como se describe en Ejemplo 15.	D
75	(±)-7-fenil-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol; MS 448.1. ^{1}H-NMR ($CDCl_3$) δ 7.81 (d, 2H, *J* = 8.0 Hz), 7.56 (d, 2H, *J* = 8.0 Hz), 7.34 (m, 1H), 7.32 (d, 2H, *J* = 7.2 Hz), 7.26 (s, 1H), 7.18 (d, 2H, *J* = 7.2 Hz), 5.36 (m, 1H), 4.53 (m, 1H), 3.30 (m, 1H), 2.43-2.15 (m, 2H), 1.76 (m, 2H), 1.38-1.16 (m, 2H). Preparado como se describe en Ejemplo 5 usando 3-feniltetrahidro-2H-piran-2,6-diol y 4-trifluorometilbenzenesulfonil cloruro.	D
76	(±)-10-[(4-clorofenil)sulfonil]-6-(3-metilisoxazol-5-il)-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol; MS 419.0. ^{1}H NMR ($CDCl_3$) δ7.68 (d, *J* = 8.2 Hz, 2H), 7.56 (s, 1H), 7.41 (d, *J* = 8.2 Hz, 2H), 5.79 (s, 1H), 5.43 (s, 1H), 4.67-4.64 (m, 1H), 3.09 (dd, *J* = 18.3, 7.26 Hz, 1H),2.93-2.91 (m, 1H), 2.76 (d *J* = 18, 1H), 2.26 (s, 3H), 2.20-2.03 (m, 4H). Preparado por alquilación de 10-[(4-clorofenil)sulfonil]-6-etinil-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol con trimetilsililetoximetil cloruro seguido por tratamiento con acetaldehido oxime, NCS, y Et_3N en C_2Cl_2 y deprotección con 4N HCl/dioxano.	D

77	 (±)-6,7,10,10-tetrafluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol; MS 478.0 ^{1}H NMR ($CDCl_3$) δ 7.85 (d, 2H, J = 8.0 Hz), 7.64 (d, 2H, J = 8.2 Hz), 7.43 (s, 1H), 7.13-7.20 (m, 1H), 6.85-6.93 (m, 1H), 5.95 (s, 1H), 5.44 (d, 1H, J = 10.2 Hz). Preparado por fluorinación de 6,7-difluoro-11-{[4-(trifluorometil)-fenil]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona usando el método descrito en Ejemplo 15.	D
78	 (+)-6-(3-fluorofenil)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol; MS 467.1 ^{1}H NMR ($CDCl_3$) δ 8.94 (d, *J* = 1.9 Hz, 1H), 8.16 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.31 (s, 1H), 7.20 (m, 1H), 6.81 (m, 3H), 5.43 (s, 1H), 4.69 (s, 1H), 2.74 (m, 2H), 2.67 (d, *J* = 17.3 Hz, 1H), 2.14 (m, 2H), 1.88 (m, 2H). Preparado como se describe en Ejemplo 5 usando 3-(3-fluorofenil)-pentanodial y 6-(trifluorometil) piridina-3-sulfonil cloruro seguido por quiral cromatográfica separación de estereoisómeros.	D

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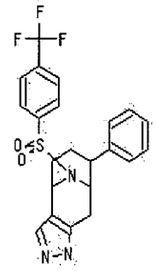
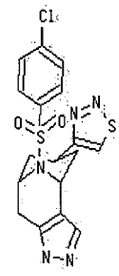
79	(-)-6-(3-fluorofenil)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol; MS 467.1 ^{1}H NMR ($CDCl_3$) δ 8.94 (d, *J* = 1.9 Hz, 1H), 8.16 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.31 (s, 1H), 7.20 (m, 1H), 6.81 (m, 3H), 5.43 (s, 1H), 4.69 (s, 1H), 2.74 (m, 2H), 2.67 (d, *J* = 17.3 Hz, 1H), 2.14 (m, 2H), 1.88 (m, 2H). Preparado como se describe arriba para el estereoisómero.	A
80	±)-6-(1,3-dimetil-1*H*-1,2,4-triazol-5-il)-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol; MS 467.1. ^{1}H NMR ($CDCl_3$) δ 7.86 (d, *J* = 8.3 Hz, 2H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.33 (s, 1H), 5.40 (s, 1H), 4.63 (t, *J* = 5.3 Hz, 1H), 3.52 (s, 3H), 2.92 (m, 2H), 2.65 (d, *J* = 15.9 Hz, 1H), 2.32 (m, 5H), 1.86 (m, 2H).	B
81	(±)-9-{[4-(trifluorometil)fenil]sulfonil}-1,4,7,8-tetrahidro-4,7-epiminociclohepta[*c*]pirazol; MS 322.1. ^{1}H NMR ($CDCl_3$) δ 7.75 (d, J = 8.6 Hz, 2H), 7.52 (d, J = 8.6 Hz, 2H), 7.41 (s, 1H), 6.10 (m, 1H), 5.58 (dd, J = 5.9, 2.3 Hz, 1H), 5.41 (d, J = 2.3 Hz, 1H), 4.66 (s, 1H), 3.09 (dd, J = 16.5, 5.8 Hz, 1H), 2.58 (d, J = 16.5 Hz, 1H).	C
82	(±)-6-(1H-1,2,4-triazol-3-il)-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 439.1 ^{1}H NMR ($CDCl_3$) δ 8.16 (s, 1H), 7.86 (d, 2H, J = 8.2 Hz, 2H), 7.64 (d, J = 8.3 Hz, 2H), 7.36 (s, 1H), 5.42 (m, 1H), 4.64 (m, 1H), 3.04-3.13 (m, 1H), 2.89-2.97 (m, 1H), 2.66-2.72 (m, 1H), 2.02-2.38 (m, 4H).	B

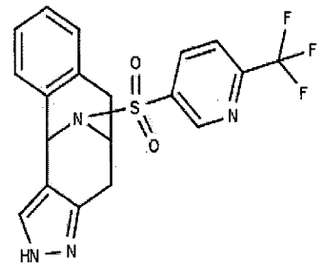
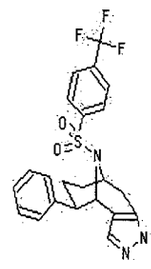
523

83	 (-)-7-fenil-10-{[4-(trifluorometil) fenil] sulfonil}-4, 5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 448.1. ^{1}H-NMR ($CDCl_3$) δ 7.82 (d, J = 8.2 Hz, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.37 (m, 1H), 7.33 (d, J = 7.3 Hz, 2H), 7.29 (s, 1H), 7.20 (d, J = 7.3 Hz, 2H), 5.37 (m, 1H), 4.54 (dd, J = 4.6, 7.6 Hz, 1H), 3.31 (m, 1H), 2.44-2.14 (m, 3H), 1.86-1.70 (m, 3H). Preparado como se describe en Ejemplo 5 usando 3-feniltetrahidro-2H-piran-2,6-diol y 4-trifluorometilbenzenesulfonil cloruro, seguido por quiral cromatográfica separación de estereoisómeros.	A
84	(+)-7-fenil-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 448.0 ^{1}H-NMR ($CDCl_3$) δ 7.82 (d, J = 8.2 Hz, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.37 (m, 1H), 7.33 (d, J = 7.3 Hz, 2H), 7.29 (s, 1H), 7.20 (d, J = 7.3 Hz, 2H), 5.37 (m, 1H), 4.54 (dd, J = 4.6, 7.6 Hz, 1H), 3.31 (m, 1H), 2.44-2.14 (m, 3H), 1.86-1.70 (m, 3H). Preparado como se describe arriba para el estereoisómero.	D
85	(±)-6-(5-metil-1H-1,2,4-triazol-3-il)-10-{[4-(trifluorometil)-fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 453.1. ^{1}H NMR ($CDCl_3$) δ 7.93 (d, J = 8.2 Hz, 2H), 7.69 (d, J = 8.3 Hz, 2H), 7.41 (s, 1H), 5.49 (s, 1H), 4.72 (m, 1H), 3.09 (m, 1H), 2.83 (dd, J = 17.4, 7.6 Hz, 1H), 2.63 (d, J = 17.4 Hz, 1H), 2.51 (s, 3H), 2.16 (m, 4H).	A

5271

86	10-[(4-clorofenil)sulfonil]-6-(prop-1-in-1-il)-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 376.0. ^{1}H NMR ($CDCl_3$) δ 7.68 (d, J = 8.4 Hz, 2H), 7.47 (s, 1H), 7.37 (d, J = 8.4 Hz, 2H), 5.29 (bs, 1H), 4.53-4.51 (m, 1H), 2.96 (dd, J = 17.6, 6.7 Hz, 1H), 2.61 (d, J = 17.6, 1H), 2.35 (bs, 1H), 2.03-1.74 (m, 4H), 1.73 (d, J = 2.1 Hz, 3H). Preparado por alquilación de 10-[(4-clorofenil)sulfonil]-6-etinil-1-{[2-(trimetilsilil)etoxi]-metil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol con metil-yoduro y LHMDS en TF seguido por deprotección con 4N HCl en dioxano.	D
87	 (±)-6-(1,2,3-tiadiazol-4-il)-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 422.0 ^{1}H-NMR ($CDCl_3$) δ 8.15 (s, 1H), 7.70 (d, J = 8.8 Hz, 2H), 7.54 (s, 1H), 7.40 (d, J = 8.8 Hz, 2H), 5.50 – 5.44 (m, 1H), 4.80 – 4.65 (m, 1H), 3.50 – 3.38 (m, 1H), 3.08 (dd, J = 17.6 Hz, 7.7 Hz, 1H), 2.78 (d, J = 17.6 Hz, 1H), 2.40 – 2.17 (m, 4H). Preparado por alquilación de metil 10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-carboxilato (WO 2007022502) con trimetilsililetoximetil cloruro seguido por tratamiento con metoximetilamina hidrocloruro y HATU en TF y Et_3N para dar la amida que fue convertida a cetona con metilmagnesio bromuro. La cetona fue secuencialmente tratada con tosilhidrazina/HOAc, tionil cloruro, y finalmente 4N HCl/dioxano.	D

525

88	 (±)-12-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,10,11-tetrahidro-1H-4,10-epiminobenzo[5,6]cicloocta[1,2-c]pirazol; MS 421.0. 1H NMR (CD_3OD) δ 8.82 (s, 1H), 8.11 (d, J = 8.3 Hz, 1H), 7.58 (d, J = 8.7 Hz, 1H), 7.47 (br, 1H), 7.26 (d, J = 6.4 Hz, 1H), 7.06 (t, J = 7.3 Hz, 1H), 6.91 (t, J = 7.5 Hz, 1H), 6.60 (d, J = 6.7 Hz, 1H), 6.07 (br, 1H), 5.04 - 4.98 (br, 1H), 3.20 – 3.10 (m, 2H), 2.77 (d, J = 19 Hz, 1H), 2.46 (d, J = 18 Hz, 1H). Preparado como se describe en Ejemplo 11 usando 6-(trifluorometil) piridina-3-sulfonil cloruro.	D
89	 5-fenil-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 448.1. ^{1}H-NMR ($CDCl_3$) (mezcla de isómeros) δ 7.68 (d, J = 8.2 Hz, 1H), 7.59-7.39 (m, 12H), 7.37-7.24 (m, 6H), 5.60 (s, 1H), 5.35 (m, 1H), 4.77 (d, J = 7.6 Hz, 1H), 5.37 (m, 1H), 4.48 (t, J = 6.2 Hz, 1H), 3.10-2.89 (m, 4H), 2.72 (d, J = 17.2 Hz, 1H), 2.60 (d, J = 17.2 Hz, 1H), 2.27 (m, 2H), 2.02-1.80 (m, 4H), 1.59 (m, 2H).	D

546

90	6-(piridin-3-il)-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 449.0. ^{1}H-NMR ($CDCl_3$) δ 8.44 (m,1H), 8.35 (s,1H), 7.92 (d, J = 6.0 Hz, 2H, mayor diast.), 7.86 (d, J = 9.0 Hz, 2H, menor diast.), 7.70 (d, J = 6.0 Hz, 2H, mayor diast.), 7.63 (d, J = 9 Hz, 2H, menor diast.), 7.41 - 7.30 (m, 1H), 2.71 - 7.16 (m, 2H), 5.46 (s, 1H menor diast.), 5.37 (d, J = 9 Hz, 1H, mayor diast.), 4.78 – 4.71(m, 1H), 2.96 – 2.82 (m, 1H), 2.78 – 2.71 (m, 2H), 2.69 – 2.46 (m, 1H), 2.37 – 2.27(m, 1H), 2.07 – 2.05 (m, 1H), 1.67 – 1.60 (m, 1H), 1.08 – 0.87 (m, 1H).	C
91	(±)-12-{[4-(trifluorometil)fenil]sulfonil}-1,4,10,11-tetrahidro-4,10-epimino[1,3]benzodioxolo[5',6':4,5]ciclohepta[1,2-c]pirazol; MS 449.9 ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.54 (s, 1H), 6.54 (s, 1H), 6.39 (s, 1H), 5.86 (s, 1H), 5.82 (s, 1H), 5.73 (s, 1H), 5.31 (d, J = 5.2 Hz, 1H), 3.54 (dd, J = 16.9, 5.5 Hz, 1H), 2.88 (d, J = 16.7 Hz, 1H). Preparado como se describe en Ejemplo 8 usando 6-bromo-3,4-(metilenedioxi)-benzaldehido.	D
92	(±)-10-[(4-clorofenil)sulfonil]-6-(5-metil-1,3,4-tiadiazol-2-il)-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 436.1 ^{1}H-NMR ($CDCl_3$) δ 7.66 (d, J = 7.7 Hz, 2H), 7.39 (d, J = 8.2 Hz, 2H), 7.26 (s, 1H), 5.60 – 5.40 (m, 1H), 4.70 – 4.60 (m, 1H), 3.97 – 3.86 (m, 1H), 3.40 – 3.25 (m, 2H), 2.75 (s, 3H), 2.36 – 2.13 (m, 4H). Preparado por alquilación de metil 10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-carboxilato (WO 2007022502) con trimetilsililetoximetil cloruro seguido por hidrólisis con $LiOH{\bullet}H_2O$ y formación de acilhidrazida usando acetilhidrazina y HATU. La acilhidrazida fue entonces tratada con reagente de Lawesson y $NaHCO_3$ en tolueno seguido por desalquilación con 4N HCl/dioxano.	B

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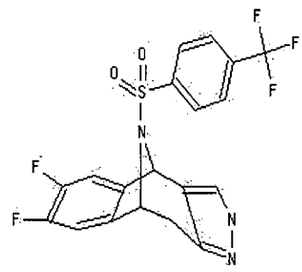
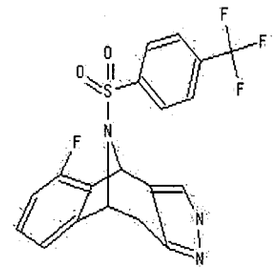
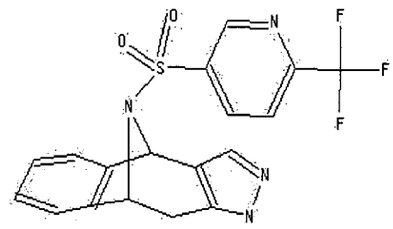
93	(±)-10-[(4-clorofenil)sulfonil]-6-(1H-1,2,3-triazol-4-il)-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 405.0. ^{1}H NMR ($CDCl_3$) δ 7.68 (d, J = 7.7 Hz, 2H), 7.46 (m, 2H), 7.37 (d, J = 7.7 Hz, 2H), 5.42-5.44 (m, 1H), 4.65-4.67 (m, 1H), 2.99 (dd, J = 17.7, 8.2, 1H), 2.81 (d, J = 17.7 Hz, 1H), 2.01-2.21 (m, 5H). Preparado por alquilación de 10-[(4-clorofenil)sulfonil]-6-etinil-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol con trimetilsililetoximetil cloruro seguido por tratamiento con azida sódica y $CuSO_4$ en DMF/H_2O seguido por desprotección con 4N HCl/dioxano.	D
94	 (-)-6,7-difluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 442.1. ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 8.1 Hz, 2H), 7.38 (s, 1H), 6.92-6.97 (m, 1H), 6.73-6.78 (m, 1H), 5.82 (s, 1H), 5.37 (d, J = 5.6 Hz, 1H), 3.47 (dd, J = 16.3, 5.7 Hz, 1H), 2.82 (d, J = 16.4 Hz, 1H). Preparado como se describe en Ejemplo 8 usando 2-bromo-4,5-difluorobenzaldehido seguido por quiral cromatográfica separación de enantiómeros.	A
95	(+)-6,7-difluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 442.1 ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 8.1 Hz, 2H), 7.38 (s, 1H), 6.92-6.97 (m, 1H), 6.73-6.78 (m, 1H), 5.82 (s, 1H), 5.37 (d, J = 5.6 Hz, 1H), 3.47 (dd, J = 16.3, 5.7 Hz, 1H), 2.82 (d, J = 16.4 Hz, 1H). Preparado como se describe arriba para el (-)-enantiómero.	D

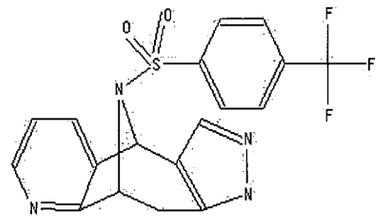
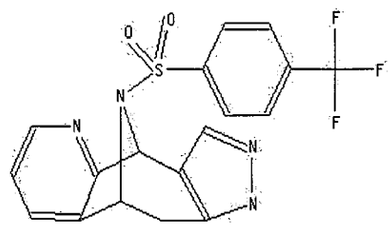
588

96	 (±)-5-fluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 424.0 ^{1}H NMR ($CDCl_3$) δ 7.76 (d, J = 7.7 Hz, 2H), 7.50 (d, J = 7.3 Hz, 2H), 7.43 (s, 1H), 6.90-6.97 (m, 1H), 6.84 (d, J = 7.2 Hz, 1H), 6.60 (t, J = 8.6 Hz, 1H), 6.03 (s, 1H), 5.41 (d, 1H, J = 5.6 Hz), 3.56 (dd, J = 16.3, 5.7 Hz, 1H), 2.87 (d, J = 16.2 Hz, 1H). Preparado como se describe en Ejemplo 8 usando 6-fluoro-2-iodobenzaldehido seguido por cromatográfica separación de regioisómeros.	D
97	(±)-8-fluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 424.0. ^{1}H NMR ($CDCl_3$) δ 7.75 (d, J = 7.9 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H), 7.38 (s, 1H), 6.87-6.97 (m, 1H), 6.55-6.70 (m, 2H), 5.85 (s, 1H), 5.57 (d, 1H, J = 4.5 Hz), 3.53 (dd, J = 16.3, 5.4 Hz, 1H), 2.92 (d, J = 16.5 Hz, 1H). Preparado como se describe en Ejemplo 8 usando 6-fluoro-2-yodobenzaldehido seguido por cromatográfica separación de regioisómeros.	D

S29

98	 (±)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 407.0. ^{1}H NMR ($CDCl_3$) δ 8.86 (d, J = 1.8 Hz, 1H), 8.00 (dd, J = 1.8, 7.8 Hz, 1H),7.48 (d, J = 8.4 Hz, 1H), 7.35 (s, 1H), 7.09-7.07 (m, 2H), 6.97-6.89 (m, 3H), 5.86 (s, 1H), 5.38 (d, 1H, J = 5.1 Hz), 3.45 (dd, J = 16.8, 5.7 Hz, 1H), 2.83 (d, J = 16.8 Hz, 1H). Preparado como se describe en Ejemplo 9.	D
99	(-)-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminopirazol[4',3':4,5]ciclohepta[1,2-b]piridina; MS 407.0 ^{1}H-NMR ($CDCl_3$) δ 8.03 (d, 1H, J = 5.0 Hz), 7.75 (d, J = 8.2 Hz, 1H), 7.50 (d, J = 8.2 Hz, 1H), 7.47 (s, 1H), 7.33 (d, J = 7.6 Hz, 1H), 6.83 (dd, J = 5.0, 7.6 Hz, 1H), 5.84 (s, 1H), 5.39 (d, J = 5.6 Hz, 1H), 3.55 (dd, J = 5.6, 16.4 Hz, 2H). Preparado como se describe en Ejemplo 8 usando 2-bromo-3-piridinacarbox-aldehido seguido por cromatográfica separación de regio y estereoisómeros.	A

530

100	 (+)-11-{[4-(trifluorometil) fenil] sulfonil}-1,4,9,10-tetrahidro-4,9-epiminopirazol[4',3':4,5]ciclohepta[1,2-b]piridina; MS 407.0. ^{1}H-NMR ($CDCl_3$) δ 8.03 (d, J = 5.0 Hz, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.50 (d, J = 8.2 Hz, 1H), 7.47 (s, 1H), 7.33 (d, J = 7.6 Hz, 1H), 6.83 (dd, J = 5.0, 7.6 Hz, 1H), 5.84 (s, 1H), 5.39 (d, J = 5.6 Hz, 1H), 3.55 (dd, J = 5.6, 16.4 Hz, 2H). Preparado como se describe en Ejemplo 8 usando 2-bromo-3-piridinacarboxaldehido seguido por cromatográfica separación de regio y estereoisómeros.	D
101	 (+)-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminopirazol[3',4':5,6]ciclohepta[1,2-b]piridina; MS 407.0. ^{1}H-NMR ($CDCl_3$) δ 8.15 (d, J = 5.0 Hz, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.52 (d, J = 8.2 Hz, 1H), 7.40 (s, 1H), 7.13 (d, J = 7.6 Hz, 1H), 6.81 (dd, J = 5.0, 7.6 Hz, 1H), 5.88 (s, 1H), 5.40 (d, J = 5.6 Hz, 1H), 3.53 (dd, J = 5.6, 16.4 Hz, 2H). Preparado como se describe en Ejemplo 8 usando 2-bromo-3-piridinacarboxaldehido seguido por cromatográfica separación de regio y estereoisómeros.	D

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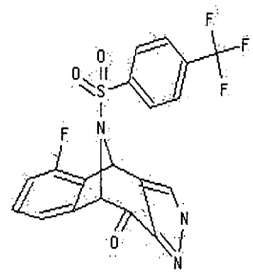
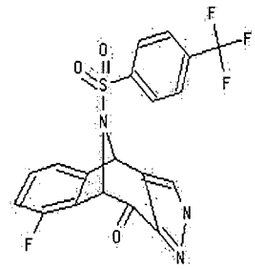
102	(-)-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminopirazol[3',4':5,6]ciclohepta[1,2-b]piridina; MS 407.0. ^{1}H-NMR ($CDCl_3$) δ 8.15 (d, J = 5.0 Hz, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.52 (d, J = 8.2 Hz, 1H), 7.40 (s, 1H), 7.13 (d, J = 7.6 Hz, 1H), 6.81 (dd, J = 5.0, 7.6 Hz, 1H), 5.88 (s, 1H), 5.40 (d, J = 5.6 Hz, 1H), 3.53 (dd, J = 5.6, 16.4 Hz, 2H). Preparado como se describe en Ejemplo 8 usando 2-bromo-3-piridinacarboxaldehido seguido por cromatográfica separación de regio y estereoisómeros.	B
103	 (±)-5-fluoro-11-{[4-(trifluorometil)fenil]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona; MS 438.1 ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 8.1 Hz, 2H), 7.72 (s, 1H), 7.52 (d, J = 8.3 Hz, 2H), 7.00-7.10 (m, 2H), 6.74 (t, J = 8.1 Hz, 1H), 6.35 (s, 1H), 5.47 (s, 1H). Preparado por oxidación de 5-fluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol usando el metodo descrito en Ejemplo 15.	D

532

104	 (±)-8-fluoro-11-{[4-(trifluorometil)fenil]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona; MS 438.0 ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 8.2 Hz, 2H), 7.72 (s, 1H), 7.52 (d, J = 8.3 Hz, 2H), 7.03-7.10 (m, 1H), 6.93 (d, J = 7.3 Hz, 1H), 6.73 (t, J = 8.3 Hz, 1H), 6.17 (s, 1H), 5.63 (s, 1H). Preparado por oxidación de 8-fluoro-11-{[4-(trifluorometil)fenil]-sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo-[4,5]ciclohepta[1,2-c]pirazol usando el metodo descrito en Ejemplo 15.	D
105	(±)-6,7-difluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 443.1 ^{1}H NMR ($CDCl_3$) δ 8.94 (s, 1H), 8.13 (dd, J = 8.3, 2.1 Hz, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.41 (s, 1H), 7.02 (dd, J = 8.8, 6.9 Hz, 1H), 6.84 (dd, J = 8.7, 6.8 Hz, 1H), 5.87 (s, 1H), 5.41 (d, J = 5.4 Hz, 1H), 3.41 (dd, J = 16.5, 5.6 Hz, 1H), 2.83 (d, J = 16.5 Hz, 1H). Preparado como se describe en Ejemplo 9 usando 5-(2-bromo-4,5-difluorofenil)-4-(6-(trifluorometil)piridin-3-ilsulfonil)ciclohex-2-enona, preparado como se describe en Ejemplo 8 usando 2-bromo-4,5-difluorobenzaldehido y sulfonamida **23**.	D

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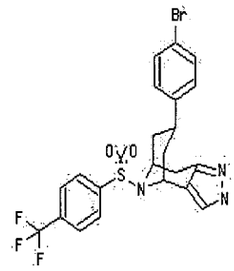
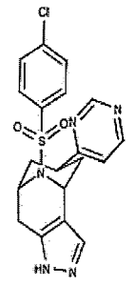
106	 (±)-6-(4-bromofenil)-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 528.0 ^{1}H NMR ($CDCl_3$) δ 7.88 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.37 (s, 1H), 6.96 (d, J = 8.4 Hz, 2H), 5.44 (s, 1H), 4.69 (s, 1H), 2.96 (dd, J = 17.4 y 7.5 Hz, 1H), 2.69 (m, 2H), 2.13 (m, 2H), 1.86 (m, 2H). Preparado como se describe en Ejemplo 23 usando 1-bromo-4-(hepta-1,6-dien-4-il) benceno.	D

S34

107	 (±)-10-[(4-clorofenil)sulfonil]-6-(piridin-4-il)-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 416.1. ^{1}H-NMR ($CDCl_3$) δ 9.11 (s, 1H), 8.66 (d, J = 5.5 Hz, 1H), 7.68 (d, J = 8.8 Hz, 2H), 7.49 (s, 1H), 7.39 (d, J = 8.24 Hz, 2H), 7.15 (d, J = 5.5 Hz, 1H), 5.52 – 5.43 (m, 1H), 4.75 – 4.64 (m, 1H), 3.04 (dd, J = 17.6, 7.7 Hz, 1H), 2.95 – 2.82 (m, 1H), 2.72 (d, J = 18.2 Hz, 1H), 2.33 – 2.19 (m, 2H), 2.03 – 1.95 (m, 2H). Preparado por alquilación de metil 10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-carboxilato (WO 2007022502) con trimetilsililetoximetil cloruro seguido por tratamiento con metoximetilamina hidrocloruro y HATU en TF y Et_3N para dar la amida que fue convertida a cetona con metilmagnesio bromuro. La cetona fue entonces tratada con etill formato y NaOEt en THF, formamidina hidrocloruro y NaOEt en EtOH, y 4N HCl/dioxano.	D

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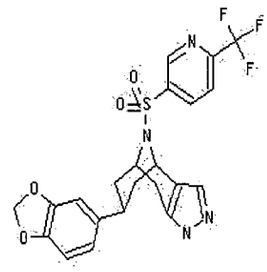
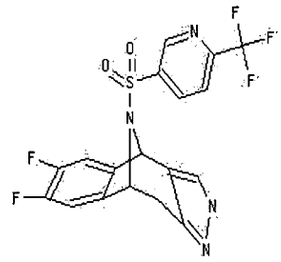
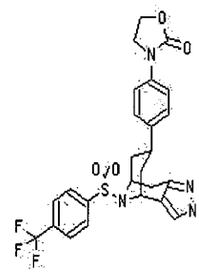
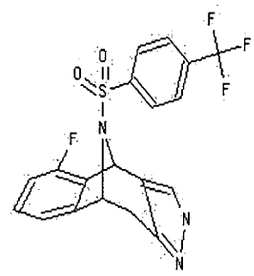
108	 (±)-6-(1,3-benzodioxol-5-il)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 493.1 ^{1}H NMR ($CDCl_3$) δ 8.94 (d, J = 1.9 Hz, 1H), 8.15 (dd, J = 8.2, 1.9 Hz, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.30 (s, 1H), 6.70 (d, J = 7.9 Hz, 1H), 6.58 (d, J = 1.6 Hz, 1H), 6.52 (dd, J = 8.0, 1.6 Hz, 1H), 5.90 (s, 2H), 5.41 (s, 1H), 4.67 (s, 1H), 2.71 (m, 3H), 2.10 (m, 2H), 1.86 (m, 2H). Preparado como se describe en Ejemplo 5 usando dialdehido **100**.	D
109	(±)-12-{[4-(trifluorometil)fenil]sulfonil}-1,4,10,11-tetrahidro-4,10-epimino[1,3]benzodioxolo[5',6':4,5]ciclohepta[1,2-c]pirazol-7-ona; MS 464.0. ^{1}H NMR ($CDCl_3$) δ 7.78 (d, J = 8.2 Hz, 2H), 7.54 (d, 2H, J = 8.2 Hz), 7.35 (s, 1H), 7.06 (s, 1H), 6.87 (s, 1H), 5.88 (s, 1H), 5.42 (d, J = 5.4 Hz, 1H), 3.38 (dd, J = 16.2, 5.6 Hz, 1H), 2.78 (d, J = 16.4 Hz, 1H).	>100

110	 (-)-6,7-difluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 443.0 ^{1}H NMR ($CDCl_3$) δ 8.94 (s, 1H), 8.13 (dd, J = 8.3, 2.1 Hz, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.41 (s, 1H), 7.02 (dd, J = 8.8, 6.9 Hz, 1H), 6.84 (dd, J = 8.7, 6.8 Hz, 1H), 5.87 (s, 1H), 5.41 (d, J = 5.4 Hz, 1H), 3.41 (dd, J = 16.5, 5.6 Hz, 1H), 2.83 (d, J = 16.5 Hz, 1H). Preparado como se describe en Ejemplo 9 usando 5-(2-bromo-4,5-difluorofenil)-4-(6-(trifluorometil)piridin-3-ilsulfonil)-ciclohex-2-enona, seguido por quiral cromatográfica separación de estereoisómeros.	A
111	(+)-6,7-difluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 443.0 ^{1}H NMR ($CDCl_3$) δ 8.94 (s, 1H), 8.13 (dd, J = 8.3, 2.1 Hz, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.41 (s, 1H), 7.02 (dd, J = 8.8, 6.9 Hz, 1H), 6.84 (dd, J = 8.7, 6.8 Hz, 1H), 5.87 (s, 1H), 5.41 (d, J = 5.4 Hz, 1H), 3.41 (dd, J = 16.5, 5.6 Hz, 1H), 2.83 (d, J = 16.5 Hz, 1H). Preparado como se describe arriba para el enantiómero.	D

112	 (±)-3-[4-(10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-il)fenil]-1,3-oxazolidin-2-ona; MS 533.0. ^{1}H NMR ($CDCl_3$) δ 7.88 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.7 Hz, 2H), 7.42 (s, 1H), 7.02 (d, J = 8.7 Hz, 2H), 5.45 (s, 1H), 4.69 (s, 1H), 4.50 (m, 2H), 4.05 (m, 2H), 2.96 (dd, J = 17.7 y 7.2 Hz, 1H), 2.69 (m, 2H), 2.00 (ancho m, 4H). Preparado como se describe en Ejemplo 23 usando 1-bromo-4-(hepta-1,6-dien-4-il) benceno y oxazolidin-2-ona.	D
113	(±)-6-[4-(1H-imidazol-1-il)fenil]-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 514.0. ^{1}H NMR ($CDCl_3$) δ 8.71 (s, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.48 (s, 1H), 7.39 (ancho m, 6H), 5.48 (s, 1H), 4.73 (s, 1H), 2.90 (dd, J = 17.1 y 7.8 Hz, 1H), 2.70 (m, 2H), 2.24 (m, 2H), 1.98 (m, 2H). Preparado como se describe en Ejemplo 23 usando 1-bromo-4-(hepta-1,6-dien-4-il)benceno e imidazol.	D

114	 (-)-5-fluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 424.1. ^{1}H NMR ($CDCl_3$) δ 7.76 (d, J = 7.7 Hz, 2H), 7.50 (d, J = 7.3 Hz, 2H), 7.43 (s, 1H), 6.90-6.97 (m, 1H), 6.84 (d, J = 7.2 Hz, 1H), 6.60 (t, J = 8.6 Hz, 1H), 6.03 (s, 1H), 5.41 (d, 1H, J = 5.6 Hz), 3.56 (dd, J = 16.3, 5.7 Hz, 1H), 2.87 (d, J = 16.2 Hz, 1H). Preparado como se describe en Ejemplo 8 usando 6-fluoro-2-yodobenzaldehido seguido por cromatográfica separación de regio- y estereoisómeros.	B
115	(+)-5-fluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 424.1. ^{1}H NMR ($CDCl_3$) δ 7.76 (d, J = 7.7 Hz, 2H), 7.50 (d, J = 7.3 Hz, 2H), 7.43 (s, 1H), 6.90-6.97 (m, 1H), 6.84 (d, J = 7.2 Hz, 1H), 6.60 (t, J = 8.6 Hz, 1H), 6.03 (s, 1H), 5.41 (d, 1H, J = 5.6 Hz), 3.56 (dd, J = 16.3, 5.7 Hz, 1H), 2.87 (d, J = 16.2 Hz, 1H). Preparado como se describe arriba para el enantiómero.	D

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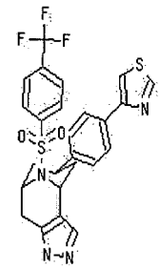
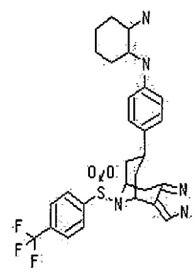
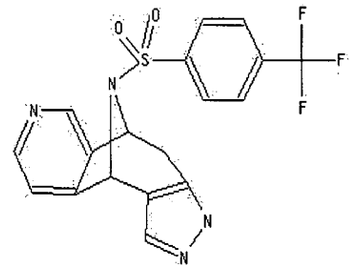
116	 (±)-6-[4-(1,3-tiazol-4-il)fenil]-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 531.1 ^{1}H NMR ($CDCl_3$) □ 8.99 (d, J = 2.2 Hz, 1H), 7.91 (d, J = 8.24 Hz, 2H), 7.80 (d, J = 8.24 Hz, 2H), 7.65 (d, J = 8.8 Hz, 2H), 7.55- 7.50 (m, 2H), 7.13 (d, J = 8.24 Hz, 2H), 5.47 (m, 1H), 4.80 – 4.70 (m, 1H), 3.07 (dd, J = 17.6, 7.7 Hz, 1H), 2.82 – 2.64 (m, 2H), 2.25 – 2.08 (m, 2H), 2.0 – 1.91 (m, 2H).	D
117	 N-[4-(10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-il)fenil]ciclohexano-1,2-diamine; MS 560.0. ^{1}H NMR (DMSO-d_6) δ 7.95 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 8.4 Hz, 4H), 7.33 (s, 1H), 6.74 (d, J = 8.4 Hz, 2H), 6.51 (d, J = 8.4 Hz, 2H), 5.28 (s, 1H), 4.53 (s, 1H), 1.70 (ancho m, 8H), 1.21 (m, 4H). Preparado como se describe en Ejemplo 23 usando 1-bromo-4-(hepta-1,6-dien-4-il)benzeno y ciclohexano-1,2-diamina.	A

540

118	 (+)-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminopirazol[4',3':4,5]ciclohepta[1,2-c]piridina; MS 407.0. ^{1}H NMR ($CDCl_3$) δ 8.40 (s, 1H), 8.20 (d, J = 5.0 Hz, 1H), 7.76 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 8.2 Hz, 2H), 7.36 (s, 1H), 6.85 (d, J = 5.0 Hz, 1H), 5.87 (s, 1H), 5.52 (d, J = 5.6 Hz, 1H), 3.51 (dd, J = 5.6, 16.2 Hz, 1H), 2.83 (d, J = 16.2 Hz, 1H). Preparado como se describe en Ejemplo 8 usando 3-bromo-4-piridina-carboxaldehido seguido por cromatográfica separación de regio- y estereoisómeros.	D
119	(+)-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminopirazol[3',4':5,6]ciclohepta[1,2-c]piridina; MS 407.0. ^{1}H NMR ($CDCl_3$) δ 8.26 (d, J = 5.0 Hz, 1H), 8.23 (s, 1H), 7.76 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 8.2 Hz, 2H), 7.37 (s, 1H), 7.06 (d, J = 5.0 Hz, 1H), 6.00 (s, 1H), 5.38 (d, J = 5.6 Hz, 1H), 3.49 (dd, J = 5.6, 16.2 Hz, 1H), 2.81 (d, J = 16.2 Hz, 1H). Preparado como se describe en Ejemplo 8 usando 3-bromo-4-piridinacarboxi-aldehido seguido por separación cromatográfica de regio- y estereoisómeros.	D

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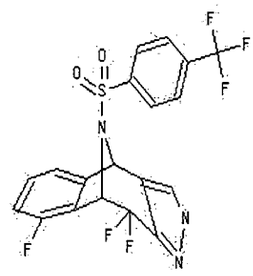
120	(-)-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminopirazol[3',4':5,6]ciclohepta[1,2-c]piridina; MS 407.0 ^{1}H NMR ($CDCl_3$) δ 8.26 (d, J = 5.0 Hz, 1H), 8.23 (s, 1H), 7.76 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 8.2 Hz, 2H), 7.37 (s, 1H), 7.06 (d, J = 5.0 Hz, 1H), 6.00 (s, 1H), 5.38 (d, J = 5.6 Hz, 1H), 3.49 (dd, J = 5.6, 16.2 Hz, 1H), 2.81 (d, J = 16.2 Hz, 1H). Preparado como se describe arriba para el enantiómero.	A
121	 (±)-8,10,10-trifluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 460.1 ^{1}H NMR ($CDCl_3$) δ 7.81 (d, J = 6.8 Hz, 2H), 7.56 (d, J = 7.7 Hz, 2H), 7.49 (s, 1H), 6.99-7.06 (m, 1H), 6.68-6.79 (m, 2H), 5.99 (s, 1H), 5.66 (d, J = 10.2 Hz, 1H). Preparado como se describe en Ejemplo 15 usando (±)-8-fluoro-11-{[4-(trifluorometil)fenil]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]-ciclohepta[1,2-c]pirazol-10(1H)-ona.	D

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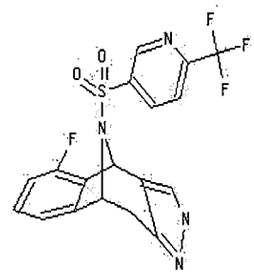
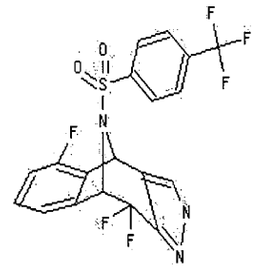
122	 (±)-5-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 425.0 ^{1}H NMR ($CDCl_3$) δ 8.90 (s, 1H), 8.10 (d, J = 8.3 Hz, 1H), 7.55 (d, J = 8.2 Hz, 1H), 7.44 (s, 1H), 6.96-7.03(m, 1H), 6.91 (d, J = 7.3 Hz, 1H), 6.66 (t, 1H, J = 8.4 Hz), 6.08 (s, 1H), 5.44 (d, J = 5.3 Hz, 1H), 3.50 (dd, J = 16.4, 5.7 Hz, 1H), 2.88 (d, J = 16.4 Hz, 1H). Preparado como se describe en Ejemplo 9 usando 5-(2-bromo-6-fluorofenil)-4-(6-(trifluorometil)piridin-3-ilsulfonil)ciclohex-2-enona preparado como se describe en Ejemplo 8 usando 6-fluoro-2-iodobenzaldehido y sulfonamida **23**.	D
123	 (±)-5,10,10-trifluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 460.0 ^{1}H NMR ($CDCl_3$) δ 7.82 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 8.2 Hz, 2H), 7.49 (s, 1H), 6.98-7.10 (m, 2H), 6.68 (t, J = 8.0 Hz, 1H), 6.18 (s, 1H), 5.49 (d, J = 10.6 Hz, 1H). Preparado por fluorinación de 5-fluoro-11-{[4-(trifluorometil)-fenil]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]-ciclohepta[1,2-c]pirazol-10(1H)-ona usando el metodo descrito en Ejemplo 15.	D

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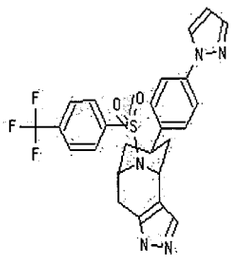
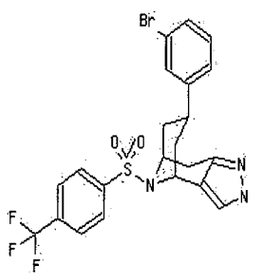
124	 (±)-6-[4-(1*H*-pirazol-1-il)fenil]-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 514.1 ^{1}H NMR ($CDCl_3$) δ 7.91-7.89 (m, 3H), 7.74-7.67 (m, 3H), 7.60 (d, J = 8.3 Hz, 2H), 7.46 (s, 1H), 7.15 (d, J = 8.6 Hz, 2H), 6.47 (dd, J = 2.0, 1.9 Hz, 1H), 5.46 (s, 1H), 4.72 (bs, 1H), 2.99 (dd, J = 17.8, 7.7 Hz, 1H), 2.77-2.69 (m, 2H), 2.22 (dd, J = 12.8, 4.5 Hz, 1H), 2.14 (dd, J = 12.8, 3.9 Hz, 1H), 1.96-1.87 (m, 2H). Preparado como se describe en Ejemplo 23 usando 1-bromo-4-(hepta-1,6-dien-4-il) benceno.	D
125	 (±)-6-(3-bromofenil)-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 526.0. ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H), 7.50 (s, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.21 (s, 1H), 1.16 (t, J = 7.8 Hz, 1H), 7.00 (d, J = 7.8 Hz, 1H), 5.46 (s, 1H), 4.71 (s, 1H), 2.96 (dd, J = 17.4 y 7.8 Hz, 1H), 2.70 (m, 2H), 2.17 (m, 2H), 1.90 (m, 2H). Preparado como se describe en Ejemplo 23.	D

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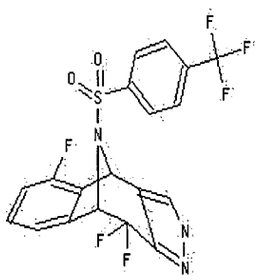
126	(±)-6-(1*H*-tetrazol-5-il)-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 440.1. ^{1}H NMR (MeOD) δ 7.93 (d, J = 8.2 Hz, 2H), 7.70 (d, J = 8.3 Hz, 2H), 7.48 (s, 1H), 5.50 (s, 1H), 4.74 (m, 1H), 3.23 (m, 1H), 2.86 (dd, J = 17.5, 7.6 Hz, 1H), 2.68 (d, J = 17.5 Hz, 1H), 2.18 (m, 1H).	A
127	 (-)-5,10,10-trifluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 460.1 ^{1}H NMR ($CDCl_3$) δ 7.82 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 8.2 Hz, 2H), 7.49 (s, 1H), 6.98-7.10 (m, 2H), 6.68 (t, J = 8.0 Hz, 1H), 6.18 (s, 1H), 5.49 (d, J = 10.6 Hz, 1H). Preparado por fluorination de 5-fluoro-11-{[4-(trifluorometil)-fenil]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona usando el metods described en Ejemplo 15 seguido por separación quiral cromatográfica de estereoisómeros.	D
128	(+)-5,10,10-trifluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 460.1 ^{1}H NMR ($CDCl_3$) δ 7.82 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 8.2 Hz, 2H), 7.49 (s, 1H), 6.98-7.10 (m, 2H), 6.68 (t, J = 8.0 Hz, 1H), 6.18 (s, 1H), 5.49 (d, J = 10.6 Hz, 1H). Preparado como se describe arriba para el enantiómero.	D

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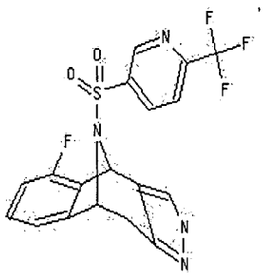
129	 (-)-5-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 425.1 ^{1}H NMR ($CDCl_3$) δ 8.90 (s, 1H), 8.10 (dd, J = 8.2, 1.7 Hz, 1H), 7.55 (dd, J = 8.2, 0.6 Hz, 1H), 7.46 (s, 1H), 6.96-7.03(m, 1H), 6.91 (d, 1H, J = 7.3 Hz), 6.66 (t, 1H, J = 8.43 Hz), 6.08 (s, 1H), 5.44 (d, 1H, J = 5.6 Hz), 3.50 (dd, J = 16.4, 5.7 Hz, 1H), 2.88 (d, J = 16.4 Hz, 1H). Preparado como se describe en Ejemplo 9 usando 5-(2-bromo-6-fluorofenil)-4-(6-(trifluorometil)piridin-3-ilsulfonil)ciclohex-2-enona la cual fue preparada como se describe en Ejemplo 8 usando 6-fluoro-2-yodobenzaldehido y sulfonamida **23** seguido por separación quiral cromatográfica de estereoisómeros.	>10
130	(+)-5-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 425.1 ^{1}H NMR ($CDCl_3$) δ 8.90 (s, 1H), 8.10 (dd, J = 8.2, 1.7 Hz, 1H), 7.55 (dd, J = 8.2, 0.6 Hz, 1H), 7.46 (s, 1H), 6.96-7.03(m, 1H), 6.91 (d, 1H, J = 7.3 Hz), 6.66 (t, 1H, J = 8.43 Hz), 6.08 (s, 1H), 5.44 (d, 1H, J = 5.6 Hz), 3.50 (dd, J = 16.4, 5.7 Hz, 1H), 2.88 (d, J = 16.4 Hz, 1H). Preparado como se describe arriba para el enantiómero.	D

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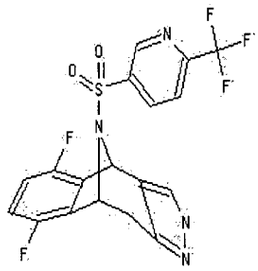
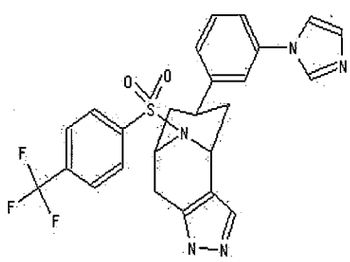
131	 (±)-5,8-difluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 443.0 ^{1}H NMR ($CDCl_3$) δ 8.93 (d, J = 1.7 Hz, 1H), 8.16 (dd, J = 8.3, 2.2 Hz, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.48 (s, 1H), 6.67 (t, J = 5.4 Hz, 2H), 6.08 (s, 1H), 5.61 (d, J = 5.6 Hz, 1H), 3.51 (dd, J = 16.6, 5.7 Hz, 1H), 2.95 (d, J = 16.6 Hz, 1H). Preparado como se describe en Ejemplo 9 usando 5-(2-bromo-3,6-difluorofenil)-4-(6-(trifluorometil)piridin-3-ilsulfonil)ciclohex-2-enona que fue preparada como se describe en Ejemplo 8 usando 2-bromo-3,6-difluorobenzaldehido y sulfonamida **23**.	D
132	 (±)-6-[3-(1H-imidazol-1-il)fenil]-10-{[4-(trifluorometil)fenil]-sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminocicloocta[c]pirazol; MS 514.1. ^{1}H NMR ($CDCl_3$) δ 7.84 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 8.3 Hz, 2H), 7.37 (m, 2H), 7.22 (m, 3H), 7.10 (m, 2H), 5.43 (s, 1H), 4.68 (m, 1H), 2.85 (2H), 2.65 (d, J = 17.1 Hz, 1H), 2.19 (m, 2H), 1.88 (m, 2H). Preparado como se describe en Ejemplo 23 usando imidazol.	D

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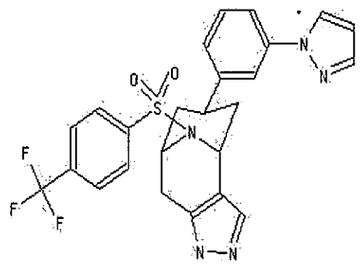
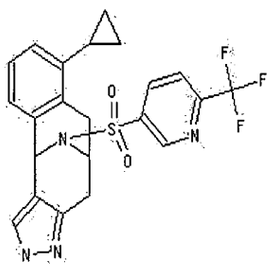
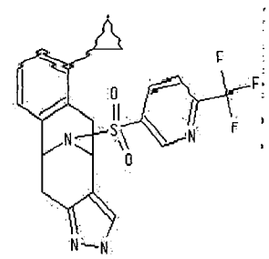
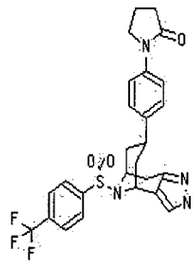
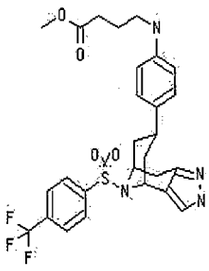
133	 (±)-6-[3-(1H-pirazol-1-il)fenil]-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 514.1 ^{1}H NMR ($CDCl_3$) δ 7.87 (m, 3H), 7.64 (m, 10H), 7.45 (m, 2H), 7.32 (m, 3H), 7.99 (m, 1H), 6.44 (m, 1H), 5.42 (s, 1H), 4.64 (m, 1H), 3.77 (m, 1H), 3.60 (m, 2H), 2.85 (m, 2H), 2.65 (d, J = 17.0 Hz, 1H), 2.16 (m, 2H), 1.88 (m, 2H). Preparado como se describe en Ejemplo 23.	D
134	 (±)-7-ciclopropil-12-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,6,11-tetrahidro-3H-5,11-epiminobenzo[4,5]ciclooctа[1,2-c]pirazol; MS 461.0 ^{1}H NMR ($CDCl_3$) δ 8.88 (d, *J* = 1.9 Hz, 1H), 7.87 (dd, *J* = 1.9, 8.2 Hz, 1H), 7.50 (s, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.06 (t, *J* = 4.4 Hz, 1H), 6.76-6.71 (m, 1H), 6.06 (s, 1H), 5.05-5.00 (m, 1H), 3.42 (dd, *J* = 5.6, 16.5 Hz, 1H), 3.30 (dd, *J* = 9.9, 18.5 Hz, 1H), 2.95 (d, *J* = 16.5 Hz, 1H), 2.38 (d, *J* = 18.6 Hz, 1H); 1.32-1.23 (m, 1H); 0.84-0.72 (m, 2H), 0.46-0.37 (m, 1H), 0.30-0.24 (m, 1H). Preparado como se describe en Ejemplo 13.	D

135	 (±)-6-ciclopropil-12-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,10,11-tetrahidro-1H-4,10-epiminobenzo[5,6]ciclooctа[1,2-c]pirazol; MS 461.0 ^{1}H NMR ($CDCl_3$) δ 9.07 (d, *J* = 2.0 Hz, 1H), 8.20 (dd, *J* = 1.9, 8.2 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.54 (s, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 5.64 (d, *J* = 5.7 Hz, 1H), 5.53 (d, *J* = 5.1 Hz, 1H), 3.35 (dd, *J* = 6.3, 16.5 Hz, 1H), 3.16 (dd, *J* = 5.8, 17 Hz, 1H), 3.00 (d, *J* = 11.1 Hz, 1H), 2.94 (d, *J* = 11.4 Hz, 1H); 1.58-1.49 (m, 1H); 0.91-0.77 (m, 2H); 0.51-0.35 (m, 2H). Preparado como se describe en Ejemplo 13.	D
136	(±)-10-[(4-clorofenil)sulfonil]-6-(1-metil-1H-1,2,3-triazol-5-il)-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 419.1 ^{1}H NMR ($CDCl_3$) δ 7.68 (d, J = 8.2 Hz, 2H), 7.44 (s, 1H), 7.37 (d, J = 8.2 Hz, 2H), 7.30 (s, 1H), 5.42-5.43 (m, 1H), 4.63-4.65 (m, 1H), 4.11 (s, 3H), 2.91-2.96 (m, 2H), 2.69 (d, J = 17.6 Hz, 1H), 1.96-2.16 (m, 4H).	D
137	10-[(4-clorofenil)sulfonil]-6-(1-metil-1H-1,2,3-triazol-4-il)-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol (enantiomer A); MS 419.1 ^{1}H NMR ($CDCl_3$) δ 7.68 (d, J = 8.0 Hz, 2H), 7.51 (s, 1H), 7.46 (s, 1H), 7.38 (d, J = 8.0 Hz, 2H), 5.45-5.47 (m, 1H), 4.66-4.69 (m, 1H), 3.96 (s, 3H), 2.98-3.07 (m, 2H), 2.67 (d, J = 17.6 Hz, 1H), 1.92-2.16 (m, 4H). Preparado de la mezcla racémica por quiral separación.	A

138	10-[(4-clorofenil)sulfonil]-6-(1-metil-1H-1,2,3-triazol-4-il)-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol (enantiómero B); MS 419.1 ^{1}H NMR ($CDCl_3$) δ 7.67 (d, J = 8.3 Hz, 2H), 7.45 (s, 1H), 7.37 (s, 1H), 7.36 (d, J = 8.3 Hz, 2H), 5.45-5.47 (m, 1H), 4.65-4.68 (m, 1H), 3.85 (s, 3H), 2.87-2.97 (m, 2H), 2.62 (d, J = 17.1 Hz, 1H), 1.88-2.18 (m, 4H). Preparado de la mezcla racémica por quiral separación.	B
139	(-)-10-[(4-clorofenil)sulfonil]-6-(2-metil-2H-1,2,3-triazol-4-il)-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 419.1 ^{1}H NMR ($CDCl_3$) δ 7.64 (d, J = 8.9 Hz, 2H), 7.28-7.33 (m, 3H), 7.22 (s, 1H) 5.40-5.43 (m, 1H), 4.61-4.63 (m, 1H), 4.07 (s, 3H), 3.05-3.08 (m, 1H), 2.85 (dd, J = 17.2, 7.8 Hz, 1H), 2.62 (d, J = 17.2 Hz, 1H), 2.00-2.18 (m, 4H).	>300
140	(+)-10-[(4-clorofenil)sulfonil]-6-(2-metil-2H-1,2,3-triazol-4-il)-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 419.1 ^{1}H NMR ($CDCl_3$) δ 7.70 (d, J = 8.2 Hz, 2H), 7.55 (s, 1H), 7.41 (d, J = 8.2 Hz, 2H), 7.30 (s, 1H) 5.41-5.43 (m, 1H), 4.63-4.65 (m, 1H), 4.08 (s, 3H), 3.01-3.08 (m, 2H), 2.80 (d, J = 17.8 Hz, 1H), 2.03-2.15 (m, 4H).	C

SS0

141	 (±)-1-[4-(10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-il)fenil]pirrolidin-2-ona; MS 531.0 ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.46 (s, 1H), 7.06 (d, J = 8.4 Hz, 2H), 5.44 (s, 1H), 4.69 (s, 1H), 3.85 (t, J = 7.2 Hz, 2H), 3.00 (dd, J = 17.4 y 7.5 Hz, 1H), 2.68 (m, 4H), 2.18 (m, 4H), 1.87 (m, 2H). Preparado como se describe en Ejemplo 23 usando 1-bromo-4-(hepta-1,6-dien-4-il) benzeno y pirrolidin-2-ona.	D
142	 (±)-metil 4-{[4-(10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8epiminociclooctа[c]pirazol6il)fenil]amino}butanoato; MS 563.0. ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.43 (s, 1H), 6.98 (d, J = 7.8 Hz, 2H), 6.87 (d, J = 7.8 Hz, 2H), 5.43 (s, 1H), 4.67 (s, 1H), 3.69 (s, 3H), 3.26 (m, 2H), 2.96 (dd, J = 16.5 y 7.2 Hz, 1H), 2.66 (m, 2H), 2.45 (m, 2H), 2.04 (m, 4H), 1.94 (m, 2H). Preparado como se describe en Ejemplo 23 usando 1-bromo-4-(hepta-1,6-dien-4-il) benceno y metil 4-aminobutanoato.	D

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143	(±)-4-[4-(10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-il)fenil]morpholin-3-ona; MS 547.0 ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.40 (s, 1H), 7.23 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 5.45 (s, 1H), 4.69 (s, 1H), 4.35 (s, 2H), 4.04 (m, 2H), 3.74 (m, 2H), 2.96 (m, 1H), 2.73 (m, 2H), 2.13 (m, 2H), 1.86 (m, 2H). Preparado como se describe en Ejemplo 23 usando 1-bromo-4-(hepta-1,6-dien-4-il)benceno y morfolin-3-ona.	B
144	(±)-metil (2-{[4-(10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-il)fenil]amino}-etoxi)acetate; MS 579.0. ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 8.1 Hz, 2H), 7.68 (d, J = 8.1 Hz, 2H), 7.47 (s, 1H), 7.00 (s, 4H), 5.44 (s, 1H), 4.68 (s, 1H), 4.19 (s, 2H), 3.87 (t, J = 4.8 Hz, 2H), 3.80 (s, 3H), 3.45 (t, J = 4.5 Hz, 2H), 3.00 (dd, J = 17.7 y 7.8 Hz, 1H), 2.65 (m, 2H), 2.12 (m, 2H), 1.86 (m, 2H). Preparado como se describe en Ejemplo 23 usando 1-bromo-4-(hepta-1,6-dien-4-il) benceno y metil 2-(2-aminoetoxi)acetato.	A
145	(±)-(2-{[4-(10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-il)fenil]amino}etoxi)acetic acid; MS 565.0. ^{1}H NMR (DMSO-d_6) δ 8.68 (s, 1H), 7.93 (d, J = 8.1 Hz, 2H), 7.68 (d, J = 8.1 Hz, 2H), 7.34 (s, 1H), 6.80 (d, J = 8.1 Hz, 2H), 6.60 (d, J = 8.1 Hz, 2H), 5.39 (s, 1H), 4.68 (s, 1H), 2.70 (m, 2H), 1.77 (m, 4H). Preparado como se describe en Ejemplo 23 usando 1-bromo-4-(hepta-1,6-dien-4-il) benzen y 2-(2-aminoetoxi) ácido acético.	D

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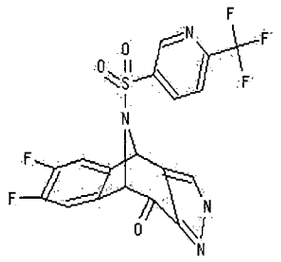
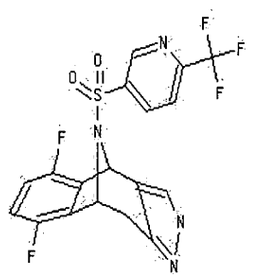
146	(±)-metil N-[4-(10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-il)fenil]-b-alaninate; MS 549.0. ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.33 (s, 1H), 6.95 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 5.44 (s, 1H), 4.69 (s, 1H), 3.72 (s, 3H), 3.52 (t, J = 6.3 Hz, 2H), 3.00 (dd, J = 17.7 y 7.8 Hz, 1H), 2.70 (m, 4H), 2.12 (m, 2H), 1.86 (m, 2H). Preparado como se describe en Ejemplo 23 usando 1-bromo-4-(hepta-1,6-dien-4-il)benceno y metil 3-aminopropanoato.	D
147	(±)-6-[4-(1H-1,2,4-triazol-1-il)fenil]-10-{[4-(trifluorometil)fenil]-sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol; MS 515.0. ^{1}H NMR ($CDCl_3$) δ 8.63 (s, 1H), 8.16 (s, 1H), 7.89 (d, J = 8.1 Hz, 2H), 7.70 (d, J = 8.1 Hz, 2H), 7.61 (d, J = 8.7 Hz, 2H), 7.51 (s, 1H), 7.23 (d, J = 8.7 Hz, 2H), 5.49 (s, 1H), 4.74 (s, 1H), 3.00 (dd, J = 17.4 y 7.5 Hz, 1H), 2.80 (m, 2H), 2.19 (m, 2H), 1.94 (m, 2H). Preparado como se describe en Ejemplo 23 usando 1-bromo-4-(hepta-1,6-dien-4-il) benceno y 4H-1,2,4-triazol.	C

148	 (±)-6,7-difluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona; MS 457.0 ^{1}H NMR ($CDCl_3$) δ 8.93 (d, J = 1.5 Hz, 1H), 8.15 (dd, J = 8.2, 1.7 Hz, 1H), 7.71 (s, 1H), 7.63 (d, J = 8.3 Hz, 1H), 7.21-7.28 (m, 1H), 7.09 (dd, J = 8.4, 6.9 Hz, 1H), 6.21 (s, 1H), 5.43 (s, 1H). Preparado por oxidación de 6,7-difluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epimino-benzo-[4,5]ciclohepta[1,2-c]pirazol usando el metodo descrito en Ejemplo 15.	D
149	 (-)-5,8-difluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 443.1 ^{1}H NMR ($CDCl_3$) δ 8.93 (d, J = 1.7 Hz, 1H), 8.16 (dd, J = 8.3, 2.2 Hz, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.48 (s, 1H), 6.67 (t, J = 5.4 Hz, 2H), 6.08 (s, 1H), 5.61 (d, J = 5.6 Hz, 1H), 3.51 (dd, J = 16.6, 5.7 Hz, 1H), 2.95 (d, J = 16.6 Hz, 1H). Preparado como se describe en Ejemplo 9 usando 5-(2-bromo-3,6-difluorofenil)-4-(6-(trifluorometil)piridin-3-ilsulfonil)ciclohex-2-enona, seguido por quiral cromatográfica separación de estereoisómeros.	C

150	(+)-5,8-difluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 443.1 ^{1}H NMR ($CDCl_3$) δ 8.93 (d, J = 1.7 Hz, 1H), 8.16 (dd, J = 8.3, 2.2 Hz, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.48 (s, 1H), 6.67 (t, J = 5.4 Hz, 2H), 6.08 (s, 1H), 5.61 (d, J = 5.6 Hz, 1H), 3.51 (dd, J = 16.6, 5.7 Hz, 1H), 2.95 (d, J = 16.6 Hz, 1H). Preparado como se describe arriba para el enantiómero.	D
151	(±)-7-fluoro-5-metil-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 439.1. ^{1}H NMR ($CDCl_3$) δ 8.90 (s, 1H), 8.07 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.40 (s, 1H), 6.91 (d, J = 6.5 Hz, 1H), 6.62 (d, J = 8.5 Hz, 1H), 5.83 (s, 1H), 5.33 (d, J = 5.4 Hz, 1H), 3.44 (dd, J = 16.4, 5.6 Hz, 1H), 2.83 (d, J = 16.4 Hz, 1H). Preparado como se describe en Ejemplo 9 usando 5-(2-bromo-4-fluoro-6-metilfenil)-4-(6-(trifluorometil)piridin-3-ilsulfonil)ciclohex-2-enona,que fue preparada como se describe en Ejemplo 8 usando 2-bromo-4-fluoro-6-metilbenzaldehido y sulfonamida **23**.	D
152	(±)-N-[4-(10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-il)fenil]acetamide; MS 505.0 ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 8.7 Hz, 2H), 7.70 (d, J = 8.7 Hz, 2H), 7.46 (s, 1H), 7.40 (d, J = 9.0 Hz, 2H), 7.18 (s, 1H), 7.01 (d, J = 9.0 Hz, 2H), 5.44 (s, 1H), 4.69 (s, 1H), 3.00 (dd, J = 17.1, 7.2 Hz, 1H), 2.66 (m, 2H), 2.18 (s, 3H), 2.20 (m, 2H), 1.87 (m, 2H). Preparado como se describe en Ejemplo 23 usando 1-bromo-4-(hepta-1,6-dien-4-il) benzeno y acetamida.	D

SSS

153	(±)-1-[4-(10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-il)fenil]azetidin-2-ona; MS 517.0 ^{1}H NMR (CD_3OD) δ 7.94 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H), 7.38 (s, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 5.45 (s, 1H), 4.70 (s, 1H), 3.66 (t, J = 4.5 Hz, 2H), 3.10 (t, J = 4.5 Hz, 2H), 2.85 (m, 3H), 2.10 (m, 2H), 1.87 (m, 2H). Preparado como se describe en Ejemplo 23 usando 1-bromo-4-(hepta-1,6-dien-4-il) benzeno y azetidin-2-ona.	D
154	(±)-1-[4-(10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-il)fenil]etanona; MS 490.0. ^{1}H NMR ($CDCl_3$) δ 7.87 (m, 4H), 7.64 (d, J = 8.7 Hz, 2H), 7.38 (s, 1H), 7.17 (d, J = 8.7 Hz, 2H), 5.46 (s, 1H), 4.71 (s, 1H), 2.87 (m, 2H), 2.66 (m, 1H), 2.60 (s, 3H), 2.20 (m, 2H), 1.90 (m, 2H). Preparado como se describe en Ejemplo 27.	C
155	(±)-6-(trifluorometil)-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 474.0 ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.1 Hz, 2H), 7.50-7.47 (m, 3H), 7.34 (s, 1H), 7.24 (d, J = 7.2 Hz, 1H), 7.01 (d, J = 7.2 Hz, 1H), 5.90 (s, 1H), 5.45 (d, J = 6.0 Hz, 1H), 3.58 (dd, J = 6.0, 16.5 Hz, 1H), 2.90 (d, J = 16.5 Hz, 1H). Preparado como se describe en Ejemplo 8 usando 2-bromo-5-(trifluorometil) benzaldehido, seguido por cromatográfica separación de regioisómeros.	D

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156	(±)-7-(trifluorometil)-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 474.1 ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.1 Hz, 2H), 7.50-7.47 (m, 3H), 7.28-7.26 (m, 1H), 7.20 (d, J = 7.8 Hz, 1H), 7.15 (s, 1H), 5.91 (s, 1H), 5.45 (d, J = 5.7 Hz, 1H), 3.58 (dd, J = 5.4, 16.5 Hz, 1H), 2.89 (d, J = 16.5 Hz, 1H). Preparado como se describe en Ejemplo 8 usando 2-Bromo-5-(trifluorometil)benzaldehido seguido por cromatográfica separación de regioisómeros.	D
157	(±)-6,7,10,10-tetrafluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 479.0. ^{1}H NMR ($CDCl_3$): δ 9.01 (s, 1H), 8.22 (d, J = 8.3 Hz, 1H), 7.72 (d, J = 8.3 Hz, 1H), 7.52 (s, 1H), 7.30-7.20 (m, 1H), 7.02-6.96 (m, 1H), 6.05 (s, 1H), 5.52 (d, J = 10.1 Hz, 1H). Preparado por fluorinación de 6,7-difluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo-[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona usando el método descrito en Ejemplo 15.	D

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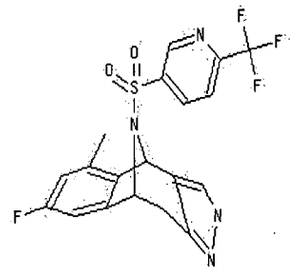
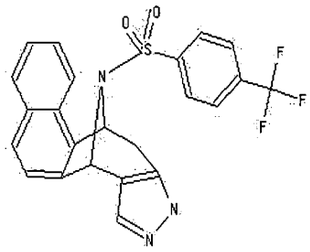
158	 (-)-7-fluoro-5-metil-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 439.1. ^{1}H NMR ($CDCl_3$): δ 8.90 (s, 1H), 8.07 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 8.23 Hz, 1H), 7.40 (s, 1H), 6.91 (d, *J* = 6.5 Hz, 1H), 6.62 (d, *J* = 8.5 Hz, 1H), 5.83 (s, 1H), 5.33 (d, *J* = 5.4 Hz, 1H), 3.44 (dd, *J* = 16.4, 5.6 Hz, 1H), 2.83 (d, *J* = 16.4 Hz, 1H). Preparado como se describe en Ejemplo 9 usando 5-(2-bromo-4-fluoro-6-metilfenil)-4-(6-(trifluorometil)piridin-3-ilsulfonil)ciclo-hex-2-enona, seguido por quiral cromatográfica separación de estereoisómeros.	>10
159	(+)-7-fluoro-5-metil-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 439.1. ^{1}H NMR ($CDCl_3$): δ 8.90 (s, 1H), 8.07 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 8.23 Hz, 1H), 7.40 (s, 1H), 6.91 (d, *J* = 6.5 Hz, 1H), 6.62 (d, *J* = 8.5 Hz, 1H), 5.83 (s, 1H), 5.33 (d, *J* = 5.4 Hz, 1H), 3.44 (dd, *J* = 16.4, 5.6 Hz, 1H), 2.83 (d, *J* = 16.4 Hz, 1H). Preparado como se describe arriba para el enantiómero.	D

160	 13-{[4-(trifluorometil)fenil]sulfonil}-7,10,11,12-tetrahidro-7,12-epiminonafto[2',1':4,5]ciclohepta[1,2-c]pirazol; MS 456.1. ^{1}H-NMR ($CDCl_3$) (Diastereómeros) δ 7.71-7.60 (m, 2H), 7.67 (m, 2H), 7.62 (d, *J* = 8.2 Hz, 4H), 7.51 (t, *J* = 7.2 Hz, 2H), 7.45-7.37 (m, 2H), 7.46 (d, *J* = 8.6 Hz, 1H), 7.43 (s, 1H), 7.41 (m, 1H), 7.39 (s, 1H), 7.17 (d, *J* = 8.6 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 4H), 7.02 (d, *J* = 8.6 Hz, 1H), 6.27 (s, 1H), 5.93 (s, 1H), 5.85 (d, *J* = 5.5 Hz, 1H), 5.52 (d, *J* = 5.5 Hz, 1H), 3.60 (dd, *J* = 5.5, 16.0 Hz, 1H), 3.58 (dd, *J* = 5.5, 16.0 Hz, 1H), 2.98 (d, *J* = 16.0 Hz, 1H) 2.90 (d, *J* = 16.0 Hz, 1H). Preparado como se describe en Ejemplo 8 usando 1-bromo-2-naftaleno-carboxaldehido.	D
161	(-)-5-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona; MS 439.0. ^{1}H NMR ($CDCl_3$): δ 8.96 (d, *J* = 1.8 Hz, 1H), 8.21 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.77 (s, 1H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.13-7.02 (m, 2H), 6.74 (t, *J* = 8.2 Hz, 1H), 6.51 (s, 1H), 5.57 (s, 1H). Preparado por oxidación de 5-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol usando el método descrito en el Ejemplo 15.	D

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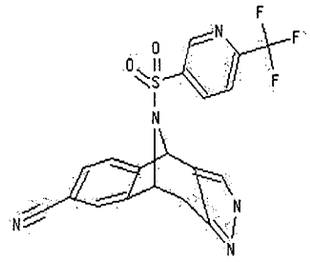
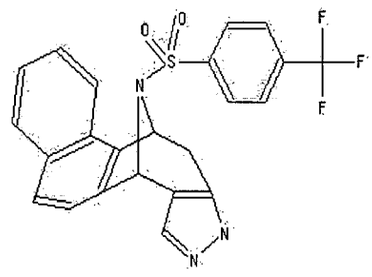
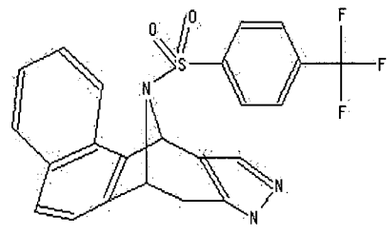
162	(±)-7-(4-fluorofenil)-12-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,11-tetrahidro-3H-5,11-epiminobenzo[4,5]cicloocta[1,2-c]pirazol; MS 514.1. ^{1}H NMR ($CDCl_3$) δ 7.61 (d, *J* = 7.9 Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 2H), 7.41 (s, 1H), 7.25 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.17 (t, *J* = 7.4 Hz,1H), 7.02 (t, *J* = 8.7 Hz, 2H), 6.89 (dd, *J* = 1.4, 7.5 Hz, 1H), 6.83-6.79 (m, 2H), 6.12 (s, 1H), 4.77-4.72 (m, 1H), 3.26 (dd, *J* = 5.6, 15.9 Hz, 1H), 2.87-2.81 (m, 1H), 2.75 (d, *J* = 16.9 Hz, 1H), 2.28 (d, *J* = 18.6 Hz, 1H). Preparado como se describe en Ejemplo 12.	D
163	(±)-12-{[4-(trifluorometil)fenil]sulfonil}-4,5,10,11-tetrahidro-1H-4,10-epiminobenzo[5,6]cicloocta[1,2-c]pirazol; MS 419.9. ^{1}H NMR ($CDCl_3$) δ 7.90 (d, J = 8.1 Hz, 2H), 7.64 (d, J = 8.2 Hz, 2H), 7.40 (s, 1H), 7.19-7.09 (m, 3H), 6.93 (d, J = 7.7 Hz, 1H), 5.53 (d, J = 5.3 Hz, 1H), 5.49 (d, J = 5.2 Hz, 1H), 3.32 (dd, J = 6.1, 16.5 Hz, 1H), 3.16 (dd, J = 5.7, 15.9 Hz, 1H), 2.85 (d, J = 16.3 Hz, 1H), 2.73 (d, J = 16.4 Hz, 1H). Preparado como se describe en Ejemplo 11.	D
164	(±)-12-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,11-tetrahidro-3H-5,11-epiminobenzo[4,5]cicloocta[1,2-c]pirazol; MS 419.9. ^{1}H NMR ($CDCl_3$) δ 7.62 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.33 (s, 1H), 7.15 (d, *J* = 7.4 Hz, 1H), 7.06 (d, *J* = 7.4 Hz, 1H), 6.95 (dt, *J* = 1.5, 7.5 Hz, 1H), 6.59 (d, *J* = 7.6 Hz, 1H), 6.01 (s, 1H), 4.88-4.84 (m, 1H), 3.24 (dd, *J* = 6.1, 16.1 Hz, 1H), 3.08 (d, *J* = 9.6, 17.9 Hz, 1H), 2.75 (dd, *J* = 1.1, 17.3 Hz, 1H); 2.46 (d, *J* = 17.9 Hz, 1H). Preparado como se describe en Ejemplo 11.	D

165	(±)-6-(4-fluorofenil)-12-{[4-(trifluorometil)fenil]sulfonil}-4,5,10,11-tetrahidro-1H-4,10-epiminobenzo[5,6]cicloocta[1,2-c]pirazol; MS 514.1 ^{1}H NMR ($CDCl_3$) δ 7.90 (d, *J* = 8.2 Hz, 2H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.30 (s, 1H), 7.25-7.18 (m, 2H), 7.08-6.93 (m, 5H), 5.59 (d, *J* = 5.3 Hz, 1H), 5.44 (d, *J* = 5.5 Hz, 1H), 3.20 (dd, *J* = 5.7, 16.0 Hz, 1H), 3.04 (dd, *J* = 5.4, 16.3 Hz, 1H), 2.92 (d, *J* = 16.8 Hz, 1H), 2.42 (d, *J* = 15.7 Hz, 1H). Preparado como se describe en Ejemplo 12.	D
166	5,10,10-trifluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 461.0. ^{1}H NMR ($CDCl_3$): δ 8.96 (s, 1H), 8.18 (d, *J* = 8.3 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.57 (s, 1H), 7.18-7.07 (m, 2H), 6.82-6.76 (m, 1H), 6.23 (s, 1H), 5.54 (d, *J* = 10.4 Hz, 1H). Preparado por fluorinación de 5-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo-[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona usando el método descrito en Ejemplo 15.	D

167	 (±)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-7-carbonitrilo; MS 432.0 ^{1}H NMR ($CDCl_3$): δ 8.92 (d, *J* = 2.0 Hz, 1H), 8.13 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.49 (s, 1H), 7.41 (s, 1H), 7.38 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 6.00 (s, 1H), 5.49 (d, *J* = 5.3 Hz, 1H), 3.42 (dd, *J* = 16.6, 5.7 Hz, 1H), 2.83 (d, *J* = 16.6 Hz, 1H). Preparado como se describe en Ejemplo 9 usando 3-bromo-4-(5-oxo-2-(6-(trifluorometil)piridin-3-ilsulfonil)ciclohex-3-enil)benzonitrilo, que fue preparado como se describe en Ejemplo 8 usando 2-bromo-4-cianobenzaldehido y sulfonamida **23**.	D
168	 (+)-13-{[4-(trifluorometil)fenil]sulfonil}-7,10,11,12-tetrahidro-7,12-epiminonaphto[2',1':4,5]ciclohepta[1,2-c]pirazol; MS 456.1. ^{1}H-NMR ($CDCl_3$) δ 7.67 (m, 2H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.51 (t,*J* = 7.2 Hz, 1H), 7.45-7.37 (m, 2H), 7.39 (s, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 7.02 (d, *J* = 8.6 Hz, 1H), 5.93 (s, 1H), 5.85 (d, *J* = 5.5 Hz, 1H), 3.60 (dd, *J* = 5.5, 16.0 Hz, 1H), 2.98 (d, *J* = 16.0 Hz, 1H). Preparado como se describe en Ejemplo 8 usando 1-bromo-2-naftalenecarboxaldehido, seguido por cromatográfica separación de regio- y estereoisómeros.	D

169	(-)-13-{[4-(trifluorometil)fenil]sulfonil}-7,10,11,12-tetrahidro-7,12-epiminonafto[2',1':4,5]ciclohepta[1,2-c]pirazol; MS 456.1. ^{1}H-NMR ($CDCl_3$) δ 7.67 (m, 2H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.51 (t,*J* = 7.2 Hz, 1H), 7.45-7.37 (m, 2H), 7.39 (s, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 7.02 (d, *J* = 8.6 Hz, 1H), 5.93 (s, 1H), 5.85 (d, *J* = 5.5 Hz, 1H), 3.60 (dd, *J* = 5.5, 16.0 Hz, 1H), 2.98 (d, *J* = 16.0 Hz, 1H). Preparado como se describe arriba para el enantiómero.	C
170	 (+)-13-{[4-(trifluorometil)fenil]sulfonil}-7,8,9,12-tetrahidro-7,12-epiminonafto[1',2':4,5]ciclohepta[1,2-c]pirazol; MS 456.1. ^{1}H-NMR ($CDCl_3$) δ 7.71-7.60 (m, 2H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.46 (d, *J* = 8.6 Hz, 1H), 7.43 (s, 1H), 7.41 (m, 1H), 7.17 (d, *J* = 8.6 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 6.27 (s, 1H), 5.52 (d, *J* = 5.5 Hz, 1H), 3.58 (dd, *J* = 5.5, 16.0 Hz, 1H), 2.90 (d, *J* = 16.0 Hz, 1H). Preparado como se describe en Ejemplo 8 usando 1-bromo-2-naftalenocarboxaldehido, seguido por cromatográfica separación de regio- y estereoisómeros.	D
171	(-)-13-{[4-(trifluorometil)fenil]sulfonil}-7,8,9,12-tetrahidro-7,12-epiminonafto[1',2':4,5]ciclohepta[1,2-c]pirazol; MS 456.1. ^{1}H-NMR ($CDCl_3$) δ 7.71-7.60 (m, 2H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.46 (d, *J* = 8.6 Hz, 1H), 7.43 (s, 1H), 7.41 (m, 1H), 7.17 (d, *J* = 8.6 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 6.27 (s, 1H), 5.52 (d, *J* = 5.5 Hz, 1H), 3.58 (dd, *J* = 5.5, 16.0 Hz, 1H), 2.90 (d, *J* = 16.0 Hz, 1H). Preparado como se describe arriba para el enantiómero.	C

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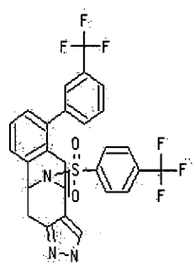
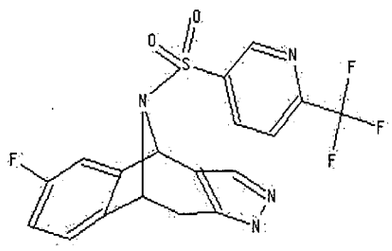
172	(-)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-7-carbonitrilo; MS 432.0 ^{1}H NMR ($CDCl_3$): δ 8.92 (d, *J* = 2.0 Hz, 1H), 8.13 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.49 (s, 1H), 7.41 (s, 1H), 7.38 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 6.00 (s, 1H), 5.49 (d, *J* = 5.3 Hz, 1H), 3.42 (dd, *J* = 16.6, 5.7 Hz, 1H), 2.83 (d, *J* = 16.6 Hz, 1H). Preparado como se describe en Ejemplo 9 usando 3-bromo-4-(5-oxo-2-(6-(trifluorometil)piridin-3-ilsulfonil)ciclohex-3-enil)benzonitrilo, seguido por quiral cromatográfica separación de estereoisómeros.	A
173	(-)-11-{[4-(trifluorometil)fenil]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona; MS 420.1. ^{1}H NMR ($CDCl_3$): □ 7.77 (d, *J* = 8.3 Hz, 2H), 7.62 (s, 1H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.25-7.28 (m, 1H), 7.11-7.02 (m, 3H), 6.18 (s, 1H), 5.44 (s, 1H). Preparado como se describe en Ejemplo 15 seguido por quiral cromatográfica separación de estereoisómeros.	D
174	(+)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-7-carbonitrilo; MS 432.0. ^{1}H NMR ($CDCl_3$): □ 8.92 (d, *J* = 2.0 Hz, 1H), 8.13 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.49 (s, 1H), 7.41 (s, 1H), 7.38 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 6.00 (s, 1H), 5.49 (d, *J* = 5.3 Hz, 1H), 3.42 (dd, *J* = 16.6, 5.7 Hz, 1H), 2.83 (d, *J* = 16.6 Hz, 1H). Preparado como se describe en Ejemplo 9 usando 3-bromo-4-(5-oxo-2-(6-(trifluorometil)piridin-3-ilsulfonil)ciclohex-3-enil)benzonitrilo que fue preparado como se describe en Ejemplo 8 usando 2-bromo-4-cianobenzaldehido y sulfonamida **23** seguido por quiral cromatográfica separación de estereoisómeros.	D

175	(+)-endo-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10-ol; MS 422.1. ^{1}H NMR ($CDCl_3$): δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.48 (s, 1H), 7.10-7.07 (m, 1H), 6.93-6.86 (m, 3H), 5.91 (s, 1H), 5.30-5.23 (m, 2H). Preparado como se describe en Ejemplo 15.	D
176	(±)-6-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 425.1. ^{1}H-NMR ($CDCl_3$) δ 8.96 (s, 1H), 8.08 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 8.6 Hz, 1H) 7.36 (s, 1H), 7.08 (m, 1H), 6.67 (m, 2H), 6.86 (s, 1H), 5.38 (d, *J* = 5.5 Hz, 1H), 3.40 (dd, *J* = 5.5, 16.0 Hz, 1H), 2.77 (d, *J* = 16.0 Hz, 1H). Preparado como se describe en Ejemplo 9 usando 5-(2-bromo-5-fluorofenil)-4-(6-(trifluoro-metil)piridin-3-ilsulfonil)ciclohex-2-enona que fue preparada como se describe en Ejemplo 8 usando 2-bromo-5-fluorobenzaldehido y sulfonamida **23**.	D
177	 (±)-6-[3-(trifluorometil)fenil]-12-{[4-(trifluorometil)fenil]sulfonil}-4,5,10,11-tetrahidro-1H-4,10-epiminobenzo[5,6]cicloocta[1,2-c]pirazol; MS 564.1. ^{1}H NMR ($CDCl_3$) δ 7.91 (d, *J* = 8.2 Hz, 2H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.63-7.57 (m, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.30 (s, 1H), 7.26-7.20 (m, 3H), 7.03 (dd, *J* = 1.6, 7.1 Hz, 1H), 5.60 (d, *J* = 5.3 Hz, 1H), 5.47 (d, *J* = 5.5 Hz, 1H), 3.25 (dd, *J* = 5.6, 16.0 Hz, 1H), 3.08 (dd, *J* = 5.8, 16.5 Hz, 1H), 2.93 (d, *J* = 15.4 Hz, 1H), 2.38 (d, *J* = 17.8 Hz, 1H). Preparado como se describe en Ejemplo 12 usando 3-trifluorometilfenil ácido borónico.	D

178	(±)-7-[3-(trifluorometil)fenil]-12-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,11-tetrahidro-3H-5,11-epiminobenzo[4,5]cicloocta[1,2-c]pirazol; MS 564.1. ^{1}H NMR ($CDCl_3$) δ 7.62 (d, *J* = 8.3 Hz, 2H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.46 (d, *J* = 8.7 Hz, 2H), 7.44-7.41 (m, 1H), 7.40 (s, 1H), 7.17 (t, *J* = 7.5 Hz, 2H), 7.09 (s, 1H), 7.02 (d, *J* = 7.1 Hz, 1H), 6.87 (dd, *J* = 1.4, 7.6 Hz, 1H), 6.12 (s, 1H), 4.77-4.74 (m, 1H), 3.24 (dd, *J* = 5.6, 16.0 Hz, 1H), 2.83 (dd, *J* = 9.5, 18 Hz, 1H), 2.73 (d, *J* = 16.4 Hz, 1H), 2.23 (d, *J* = 17.8 Hz, 1H). Preparado como se describe en Ejemplo 12 usando 3-trifluorometilfenil ácido borónico.	D
179	 (-)-6-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 425.1 ^{1}H-NMR ($CDCl_3$) δ 8.96 (s, 1H), 8.08 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 8.6 Hz, 1H) 7.36 (s, 1H), 7.08 (m, 1H), 6.67 (m, 2H), 6.86 (s, 1H), 5.38 (d, *J* = 5.5 Hz, 1H), 3.40 (dd, *J* = 5.5, 16.0 Hz, 1H), 2.77 (d, *J* = 16.0 Hz, 1H). Preparado como se describe en Ejemplo 9 usando 5-(2-bromo-5-fluorofenil)-4-(6-(trifluorometil)piridin-3-ilsulfonil)ciclohex-2-enona, seguido por quiral cromatográfica separación de estereoisómeros.	B

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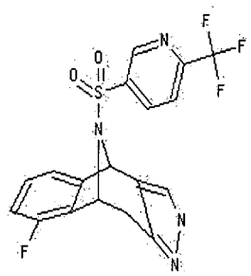
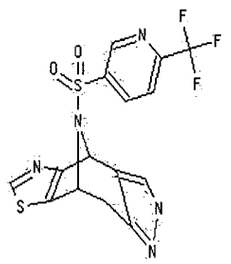
180	(+)-6-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 425.1 ^{1}H-NMR ($CDCl_3$) δ 8.96 (s, 1H), 8.08 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 8.6 Hz, 1H) 7.36 (s, 1H), 7.08 (m, 1H), 6.67 (m, 2H), 6.86 (s, 1H), 5.38 (d, *J* = 5.5 Hz, 1H), 3.40 (dd, *J* = 5.5, 16.0 Hz, 1H), 2.77 (d, *J* = 16.0 Hz, 1H). Preparado como se describe arriba para el enantiómero.	D
181	(±)-9-fluoro-12-{[4-(trifluorometil)fenil]sulfonil}-4,5,10,11-tetrahidro-1H-4,10-epiminobenzo[5,6]cicloocta[1,2-c]pirazol; MS 438.0 ^{1}H NMR ($CDCl_3$) δ 7.92 (d, *J* = 8.2 Hz, 2H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.41 (s, 1H), 7.11 (dt, *J* = 5.9, 8.0 Hz, 1H), 6.89 (t, *J* = 9.2 Hz, 1H), 6.75 (d, *J* = 7.7 Hz, 1H), 5.70 (d, *J* = 5.7 Hz, 1H), 5.56 (d, *J* = 5.6 Hz, 1H), 3.32 (dd, *J* = 5.8, 16.6 Hz, 1H), 3.07 (dd, *J* = 5.6, 16.3 Hz, 1H), 2.89 (d, *J* = 16.3 Hz, 1H), 2.76 (d, *J* = 16.2 Hz, 1H). Preparado como se describe en Ejemplo 11 usando 8-fluoroisoquinolina.	D
182	(±)-10-fluoro-12-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,11-tetrahidro-3H-5,11-epiminobenzo[4,5]cicloocta[1,2-c]pirazol; MS 438.0 ^{1}H NMR ($CDCl_3$) δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.39 (s, 1H), 6.93 (dt, *J* = 5.9, 8.0 Hz, 1H), 6.77 (t, *J* = 8.5 Hz, 1H), 6.50 (d, *J* = 7.6 Hz, 1H), 6.37 (s, 1H), 4.95-4.90 (m, 1H), 3.28-3.17 (m, 2H), 2.71 (d, *J* = 16.3 Hz, 1H), 2.76 (d, *J* = 17.9 Hz, 1H). Preparado como se describe en Ejemplo 11 usando 8-fluoroisoquinolina.	D

183	 (±)-8-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 424.9 ^{1}H NMR ($CDCl_3$): δ 8.90 (s, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.42 (s, 1H), 7.02-6.94 (m, 1H), 6.75-6.64 (m, 2H), 5.90 (s, 1H), 5.60 (d, *J* = 5.4 Hz, 1H), 3.49 (dd, *J* = 16.5, 5.6 Hz, 1H), 2.94 (d, *J* = 16.5 Hz, 1H). Preparado como se describe en Ejemplo 9 usando 5-(2-bromo-3-fluorofenil)-4-(6-(trifluorometil)-piridin-3-ilsulfonil)ciclohex-2-enona, quefue preparada como se describe en Ejemplo 8 usando 2-bromo-3-fluorobenzaldehido y sulfonamida **23**.	D
184	(-)-8-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 425.1 ^{1}H NMR ($CDCl_3$): δ 8.90 (s, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.42 (s, 1H), 7.02-6.94 (m, 1H), 6.75-6.64 (m, 2H), 5.90 (s, 1H), 5.60 (d, *J* = 5.4 Hz, 1H), 3.49 (dd, *J* = 16.5, 5.6 Hz, 1H), 2.94 (d, *J* = 16.5 Hz, 1H). Preparado como se describe arriba para la mezcla racémica, seguido por quiral cromatográfica separación de estereoisómeros.	B

185	(+)-8-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 425.1 ^{1}H NMR ($CDCl_3$): δ 8.90 (s, 1H), 8.10 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.42 (s, 1H), 7.02-6.94 (m, 1H), 6.75-6.64 (m, 2H), 5.90 (s, 1H), 5.60 (d, *J* = 5.4 Hz, 1H), 3.49 (dd, *J* = 16.5, 5.6 Hz, 1H), 2.94 (d, *J* = 16.5 Hz, 1H). Preparado como se describe arriba para la mezcla racémica, seguido por quiral cromatográfica separación de estereoisómeros.	D
186	(+)-exo-10-fluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 424.0 ^{1}H NMR ($CDCl_3$): δ 7.80 (d, *J* = 8.3 Hz, 2H), 7.49 (d, *J* = 8.3 Hz, 2H), 7.40 (s, 1H), 7.19-7.16 (m, 1H), 7.03-6.94 (m, 3H), 6.01 (s, 1H), 5.61-5.44 (m, 2H). Preparado como se describe en Ejemplo 15.	D
187	 (±)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,8,9-tetrahidro-4,8-epiminopirazol[3',4':5,6]ciclohepta[1,2-d][1,3]tiazole; MS 414.0 ^{1}H NMR ($CDCl_3$): δ 8.97 (d, *J* = 2.2 Hz, 1H), 8.45 (s, 1H), 8.16 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.57 (s, 1H), 5.97 (s, 1H), 5.60 (d, *J* = 5.2 Hz,. 1H), 3.53 (dd, *J* = 16.6, 5.5 Hz, 1H), 2.90 (d, *J* = 16.6 Hz, 1H). Preparado como se describe en Ejemplo 9 usando 2-(5-bromotiazol-4-il)-1-(6-(trifluorometil)piridin-3-ilsulfonil)-2,3-dihidropiridin-4(1H)-onaque fue preparada como se describe en Ejemplo 8 usando 5-bromotiazol-4-carbaldehido y sulfonamida **23**.	C

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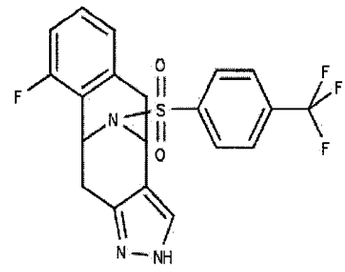
188	(-)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,8,9-tetrahidro-4,8-epiminopirazol[3',4':5,6]ciclohepta[1,2-d][1,3]tiazol; MS 414.0 ^{1}H NMR ($CDCl_3$ con a drop de CD_3OD): δ 8.93 (s, 1H), 8.41 (s, 1H), 8.14 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.44 (s, 1H), 5.92 (s, 1H), 5.56 (d, *J* = 5.3 Hz, 1H), 3.41 (dd, *J* = 16.4, 5.5 Hz, 1H), 2.81 (d, *J* = 16.4 Hz, 1H). Preparado como se describe arriba para la mezcla racémica, seguido por quiral cromatográfica separación de estereoisómeros.	A
189	(+)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,8,9-tetrahidro-4,8-epiminopirazol[3',4':5,6]ciclohepta[1,2-d][1,3]tiazol; MS 414.0 ^{1}H NMR ($CDCl_3$ con a drop de CD_3OD): δ 8.93 (s, 1H), 8.41 (s, 1H), 8.14 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.44 (s, 1H), 5.92 (s, 1H), 5.56 (d, *J* = 5.3 Hz, 1H), 3.41 (dd, *J* = 16.4, 5.5 Hz, 1H), 2.81 (d, *J* = 16.4 Hz, 1H). Preparado como se describe arriba para la mezcla racémica, seguido por quiral cromatográfica separación de estereoisómeros.	C

190	 (-)-9-fluoro-12-{[4-(trifluorometil)fenil]sulfonil}-4,5,10,11-tetrahidro-1H-4,10-epiminobenzo[5,6]cicloocta[1,2-c]pirazol; MS 438.1 ^{1}H NMR ($CDCl_3$) δ 7.92 (d, *J* = 8.2 Hz, 2H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.41 (s, 1H), 7.11 (dt, *J* = 5.9, 8.0 Hz, 1H), 6.89 (t, *J* = 9.2 Hz, 1H), 6.75 (d, *J* = 7.7 Hz, 1H), 5.70 (d, *J* = 5.7 Hz, 1H), 5.56 (d, *J* = 5.6 Hz, 1H), 3.32 (dd, *J* = 5.8, 16.6 Hz, 1H), 3.07 (dd, *J* = 5.6, 16.3 Hz, 1H), 2.89 (d, *J* = 16.3 Hz, 1H), 2.76 (d, *J* = 16.2 Hz, 1H). Preparado como se describe en Ejemplo 11 usando 8-fluoroisoquinolina seguido por quiral cromatográfica separación de estereoisómeros (QuiralPak AD 20 x 250 nm column).	D
191	(+)-9-fluoro-12-{[4-(trifluorometil)fenil]sulfonil}-4,5,10,11-tetrahidro-1H-4,10-epiminobenzo[5,6]cicloocta[1,2-c]pirazol; MS 438.1 ^{1}H NMR ($CDCl_3$) δ 7.92 (d, *J* = 8.2 Hz, 2H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.41 (s, 1H), 7.11 (dt, *J* = 5.9, 8.0 Hz, 1H), 6.89 (t, *J* = 9.2 Hz, 1H), 6.75 (d, *J* = 7.7 Hz, 1H), 5.70 (d, *J* = 5.7 Hz, 1H), 5.56 (d, *J* = 5.6 Hz, 1H), 3.32 (dd, *J* = 5.8, 16.6 Hz, 1H), 3.07 (dd, *J* = 5.6, 16.3 Hz, 1H), 2.89 (d, *J* = 16.3 Hz, 1H), 2.76 (d, *J* = 16.2 Hz, 1H). Preparado como se describe arriba para el enantiómero.	D

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192	(-)-8-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona; MS 439.0 ^{1}H NMR ($CDCl_3$ con a drop de CD_3OD): δ 8.84 (s, 1H), 8.13 (d, *J* = 8.3 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.56 (s, 1H), 7.15-7.08 (m, 1H), 6.97 (d, *J* = 7.5 Hz, 1H), 6.81-6.74 (m, 1H), 6.18 (s, 1H), 5.62 (s, 1H). Preparado por oxidación de 8-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol usando el método descrito en Ejemplo 15, seguido por quiral cromatográfica separación de estereoisómeros.	D
193	(+)-8-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona; MS 439.0 ^{1}H NMR ($CDCl_3$): δ 8.93 (s, 1H), 8.17 (d, *J* = 7.7 Hz, 1H), 7.72 (s, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.15-7.05 (m, 1H), 7.00-6.94 (m, 1H), 6.80-6.72 (m, 1H), 6.27 (s, 1H), 5.69 (s, 1H). Preparado como se describe arriba para el enantiómero.	B
194	(±)-metil 11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-6-carboxilato; MS 465.1. ^{1}H-NMR ($CDCl_3$) δ 8.88 (s, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H) 7.58 (s, 1H), 7.50 (d, *J* = 8.4 Hz ,1H), 7.40 (s, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 5.90 (s, 1H), 5.47 (d, *J* = 5.5 Hz, 1H), 3.86 (s, 3H), 3.48 (dd, *J* = 5.5, 16.4 Hz, 1H), 2.86 (d, *J* = 16.4 Hz, 1H). Preparado como se describe en Ejemplo 9 usando metil 4-bromo-3-(5-oxo-2-(6-(trifluorometil)piridin-3-ilsulfonil)ciclohex-3-enil)benzoato que fue preparado como se describe en Ejemplo 8 usando metil 4-bromo-3-formilbenzoato y sulfonamida **23**.	A

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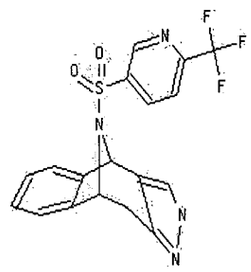
195	(±)-exo-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10-ol; MS 422.1. ^{1}H NMR ($CDCl_3$): δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.38 (s, 1H), 7.10-7.05 (m, 1H), 6.95-6.85 (m, 3H), 5.88 (s, 1H), 5.26 (s, 1H), 4.81 (s, 1H). Preparado como se describe en Ejemplo 20 usando compuesto 16.	C
196	 (-)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 407.1. ^{1}H NMR ($CDCl_3$ con a drop de CD_3OD): δ 8.88 (s, 1H), 8.03 (d, *J* = 7.7 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.39 (s, 1H), 7.14-7.07 (m, 1H), 7.03-6.90 (m, 3H), 5.87 (s, 1H), 5.40 (d, *J* = 3.9 Hz, 1H), 3.48 (dd, *J* = 16.2, 4.7 Hz, 1H), 2.87 (d, *J* = 16.3 Hz, 1H). Preparado como se describe en Ejemplo 9 seguido por quiral cromatográfica separación de estereoisómeros.	>30
197	(+)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 407.1. ^{1}H NMR ($CDCl_3$ con a drop de CD_3OD): δ 8.88 (s, 1H), 8.03 (d, *J* = 7.7 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.39 (s, 1H), 7.14-7.07 (m, 1H), 7.03-6.90 (m, 3H), 5.87 (s, 1H), 5.40 (d, *J* = 3.9 Hz, 1H), 3.48 (dd, *J* = 16.2, 4.7 Hz, 1H), 2.87 (d, *J* = 16.3 Hz, 1H). Preparado como se describe en Ejemplo 9 seguido por quiral cromatográfica separación de estereoisómeros.	D

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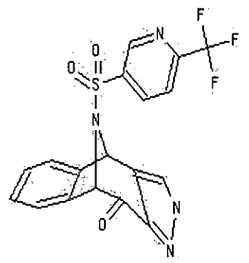
198	(±)-exo-10-fluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 424.0 ^{1}H NMR ($CDCl_3$ con a drop de CD_3OD): δ 7.76 (d, *J* = 7.6 Hz, 2H), 7.46 (d, *J* = 7.6 Hz, 2H), 7.36 (s, 1H), 7.18-7.13 (m, 1H), 6.98-6.88 (m, 3H), 5.96 (s, 1H), 5.60-5.39 (m, 2H). Preparado como se describe en Ejemplo 15.	D
199	endo-5-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10-ol; MS 441.0 ^{1}H NMR (CD_3OD): δ 8.96 (s, 1H), 8.31 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.58 (s, 1H), 7.01-6.93 (m, 2H), 6.69-6.60 (m, 1H), 6.17 (s, 1H), 5.40-5.30 (m, 2H). Preparado por reducción de 5-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona usando el método descrito en el Ejemplo 15.	D

200	 (-)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona ; MS 421.0 ^{1}H NMR ($CDCl_3$): δ 8.95 (s, 1H), 8.14 (d, *J* = 8.3 Hz, 1H), 7.69 (s, 1H), 7.58 (d, *J* = 8.3 Hz, 1H), 7.32-7.27 (m, 1H), 7.15-7.02 (m, 3H), 6.31 (s, 1H), 5.52 (s, 1H). Preparado por oxidación de 11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol usando el metodo descrito en el Ejemplo 15 seguido por quiral cromatográfica separación de estereoisómeros.	D
201	(+)-6-(3-metil-1,2,4-oxadiazol-5-il)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 489.1. ^{1}H-NMR ($CDCl_3$) δ 8.90 (s, 1H), 8.10 (d, *J* = 8.6 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 1H) 7.70 (s, 1H), 7.53 (d, *J* = 8.2 Hz ,1H), 7.40 (s, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 5.97 (s, 1H), 5.50 (d, *J* = 5.5 Hz, 1H), 3.46 (dd, *J* = 5.5, 16.4 Hz, 1H), 2.86 (d, *J* = 16.4 Hz, 1H), 2.44 (s, 3H). Preparado por tratamiento de (±)-metil 11-{[6-(trifluorometil)-piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-6-carboxilato con N-hidroxiacetamidina como se describe para el compuesto 51 en Ejemplo 16 seguido por quiral cromatográfica separación de estereoisómeros.	A

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202	(-)-6-(3-metil-1,2,4-oxadiazol-5-il)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 489.1. ^{1}H-NMR ($CDCl_3$) δ 8.90 (s, 1H), 8.10 (d, *J* = 8.6 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 1H) 7.70 (s, 1H), 7.53 (d, *J* = 8.2 Hz ,1H), 7.40 (s, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 5.97 (s, 1H), 5.50 (d, *J* = 5.5 Hz, 1H), 3.46 (dd, *J* = 5.5, 16.4 Hz, 1H), 2.86 (d, *J* = 16.4 Hz, 1H), 2.44 (s, 3H). Preparado como se describe arriba para el enantiómero (+)-.	A
203	(-)-metil 11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-6-carboxilato; MS 465.1 ^{1}H-NMR ($CDCl_3$) δ 8.88 (s, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H) 7.58 (s, 1H), 7.50 (d, *J* = 8.4 Hz ,1H), 7.40 (s, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 5.90 (s, 1H), 5.47 (d, *J* = 5.5 Hz, 1H), 3.86 (s, 3H), 3.48 (dd, *J* = 5.5, 16.4 Hz, 1H), 2.86 (d, *J* = 16.4 Hz, 1H). Preparado como se describe en Ejemplo 9 usando metil 4-bromo-3-(5-oxo-2-(6-(trifluorometil)piridin-3-ilsulfonil)ciclohex-3-enil)benzoato, seguido por quiral cromatográfica separación de estereoisómeros.	A
204	(±)-7-metil-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,7,8,9-tetrahidro-1H-4,8-epiminociclohepta[1,2-c:5,4-c']dipirazol; MS 411.0 ^{1}H-NMR ($CDCl_3$) δ 8.89 (s, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.53 (s, 1H), 7.50 (d, *J* = 8.4 Hz ,1H), 7.34 (s, 1H), 5.96 (s, 1H), 5.52 (d, *J* = 5.5 Hz, 1H), 3.63 (s, 3H), 3.41 (dd, *J* = 5.5, 16.4 Hz, 1H), 2.90 (d, *J* = 16.4 Hz, 1H).	D

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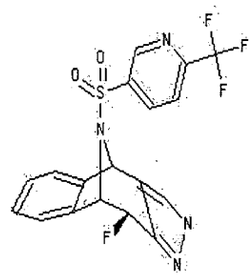
205	(+)-metil 11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-6-carboxilato; MS 465.1. ^{1}H-NMR ($CDCl_3$) δ 8.88 (s, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H) 7.58 (s, 1H), 7.50 (d, *J* = 8.4 Hz ,1H), 7.40 (s, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 5.90 (s, 1H), 5.47 (d, *J* = 5.5 Hz, 1H), 3.86 (s, 3H), 3.48 (dd, *J* = 5.5, 16.4 Hz, 1H), 2.86 (d, *J* = 16.4 Hz, 1H). Preparado como se describe en Ejemplo 9 usando metil 4-bromo-3-(5-oxo-2-(6-(trifluorometil)piridin-3-ilsulfonil)ciclohex-3-enil)benzoate, seguido por quiral cromatográfica separación de estereoisómeros.	C
206	 exo-10-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 425.1 ^{1}H NMR (CD_3OD): δ 8.94 (d, *J* = 1.9 Hz, 1H), 8.26 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.60 (s, 1H), 7.30-7.27 (m, 1H), 7.02-6.91 (m, 3H), 6.13 (s, 1H), 5.70 (dd, *J* = 10.6, 1.6 Hz, 1H), 5.25 ((dd, *J* = 52.0, 1.9 Hz, 1H). Preparado por fluorinación de 11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10-ol usando el método descrito en el Ejemplo 15.	D

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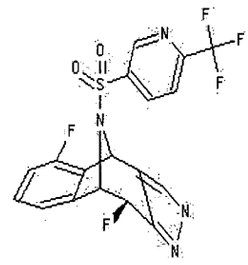
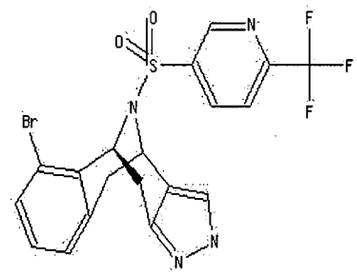
207	 (+)-exo-5,10-difluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 443.1. ^{1}H NMR (CD_3OD): δ 8.98 (s, 1H), 8.33 (d, *J* = 8.2 Hz, 1H), 7.73 (d, *J* = 8.2 Hz, 1H), 7.66 (s, 1H), 7.15 (d, *J* = 7.4 Hz, 1H), 7.08-7.00 (m, 1H), 6.73-6.66 (m, 1H), 6.34 (s, 1H), 5.78 (d, *J* = 10.4 Hz, 1H), 5.55 ((dd, *J* = 51.7, 1.9 Hz, 1H). Preparado por fluorinación de 5-fluoro-11-{[6-(trifluorometil)-piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]-ciclohepta[1,2-c]pirazol-10-ol usando el método descrito en el Ejemplo 15.	D
208	endo-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10-ol; MS 423.1. ^{1}H NMR ($CDCl_3$ con a drop de CD_3OD): δ 8.84 (s, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.33 (s, 1H), 7.17-7.10 (m, 1H), 6.95-6.85 (m, 3H), 5.78 (s, 1H), 5.35-5.23 (m, 2H). Preparado por reducción de 11-{[6-(trifluoro-metil)piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]-ciclo-hepta[1,2-c]pirazol-10(1H)-ona usando el método descrito en Ejemplo 15.	D

575

209	(±)-11-[(4-clorofenil)sulfonil]-5-fluoro-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 390.4. ^{1}H NMR ($CDCl_3$) δ 7.54 (m, 3H), 7.22 (m, 2H), 7.01 (m, 1H), 6.86 (m, 1H), 6.66 (t, J = 8.4 Hz, 1H), 6.01 (s, 1H), 5.42 (d, J = 5.4 Hz, 1H), 3.58 (dd, J = 16.7, 5.4 Hz, 1H), 2.85 (d, J = 16.6 Hz, 1H). Preparado como se describe en Ejemplo 9 usando 2-(2-bromo-6-fluorofenil)-1-(4-clorofenilsulfonil)-2,3-dihidropiridin-4(1H)-onaque fue preparada como se describe en el Ejemplo 8 usando 2-bromo-6-fluorobenzaldehido y 4-cloro benceno sulfonamida.	D
210	(±)-5-fluoro-11-[(4-fluorofenil)sulfonil]-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 374.0. ^{1}H NMR ($CDCl_3$) δ 7.62 (m, 3H), 6.96 (m, 4H), 6.67 (t, J = 8.4 Hz, 1H), 6.02 (s, 1H), 5.44 (d, J = 5.2 Hz, 1H), 3.57 (dd, J = 16.9, 5.6 Hz, 1H), 2.94 (d, J = 16.7 Hz, 1H). Preparado como se describe en Ejemplo 9 usando 2-(2-bromo-6-fluorofenil)-1-(4-fluorofenilsulfonil)-2,3-dihidropiridin-4(1H)-onaque fue preparada como se describe en Ejemplo 8 usando 2-bromo-6-fluorobenzaldehido y 4-fluoro benceno sulfonamida.	D
211	(±)-5-fluoro-11-{[5-(trifluorometil)piridin-2-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 425.1 ^{1}H NMR ($CDCl_3$) δ 8.56 (s, 1H), 7.90 (s, 2H), 7.35 (s, 1H), 6.91 (m, 2H), 6.59 (at, J = 8.0 Hz, 1H), 6.13 (s, 1H), 5.57 (d, J = 5.5 Hz, 1H), 3.57 (dd, J = 16.2, 5.7 Hz, 1H), 2.85 (d, J = 16.1 Hz, 1H). Preparado como se describe en Ejemplo 9 usando 2-(2-bromo-6-fluorofenil)-1-(4-fluorofenilsulfonil)-2,3-dihidropiridin-4(1H)-onaque fue preparada como se describe en Ejemplo 8 usando 2-bromo-6-fluorobenzaldehido y 5-(trifluorometil)-2-piridinasulfonamida.	D

579

212	 (+)-9-bromo-12-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,10,11-tetrahidro-1H-4,10-epiminobenzo[5,6]cicloocta[1,2-c]pirazol; MS 499.0 ^{1}H-NMR ($CDCl_3$) δ 9.08 (d, J = 2.1 Hz, 1H), 8.24 (dd, J = 6.5, 2.1 Hz, 1H), 7.68 (d, J = 8.1 Hz, 1H), 7.45-7.42 (m, 2H), 7.02 (t, J = 7.8 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 5.69 (d, J = 4.8 Hz, 1H), 5.50 (d, J = 5.4 Hz, 1H), 3.36 (dd, J = 16, 5.7 Hz, 1 H), 3.16-3.11 (m, 2H), 2.79 (d, J = 16 Hz, 1H). Preparado como se describe en Ejemplo 13 usando compuesto 45 seguido por quiral cromatográfica separación de estereoisómeros.	D
213	(-)-9-bromo-12-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,10,11-tetrahidro-1H-4,10-epiminobenzo[5,6]cicloocta[1,2-c]pirazol; MS 499.0 ^{1}H NMR ($CDCl_3$) δ 9.08 (d, J = 2.1 Hz, 1H), 8.24 (dd, J = 6.5, 2.1 Hz, 1H), 7.68 (d, J = 8.1 Hz, 1H), 7.45-7.42 (m, 2H), 7.02 (t, J = 7.8 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 5.69 (d, J = 4.8 Hz, 1H), 5.50 (d, J = 5.4 Hz, 1H), 3.36 (dd, J = 16, 5.7 Hz, 1 H), 3.16-3.11 (m, 2H), 2.79 (d, J = 16 Hz, 1H). Preparado como se describe en Ejemplo 13 usando compuesto 45 seguido por quiral cromatográfica separación de estereoisómeros.	C

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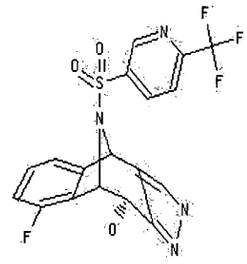
214	exo-8,10-difluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 443.1 ^{1}H NMR ($CDCl_3$ con gota de CD_3OD): δ 8.96 (d, *J* = 1.9 Hz, 1H), 8.18 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.60 (d, *J* = 8.2 Hz, 1H), 7.42 (s, 1H), 7.06-6.99 (m, 1H), 6.83 (d, *J* = 7.4 Hz, 1H), 6.71 (t, *J* = 8.4 Hz, 1H), 6.09 (s, 1H), 5.77 (dd, *J* = 10.0, 1.3 Hz, 1H), 5.55 (dd, *J* = 51.2, 1.7Hz, 1H). Preparado por fluorinacion de 8-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10-ol usando el mètodo descrito en Ejemplo 15.	D
215	(+)-8,10,10-trifluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 461.1 ^{1}H NMR (CD_3OD): δ 9.02 (s, 1H), 8.37 (d, *J* = 6.4 Hz, 1H), 7.76-7.70 (m, 2H), 7.10-7.00 (m, 1H), 6.95-6.87 (m, 1H), 6.80-6.68 (m, 1H), 6.28 (s, 1H), 5.90 (d, *J* = 8.0 Hz, 1H). Preparado por fluorinación de 8-fluoro-11-{[6-(tri-fluorometil)piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]-ciclohepta[1,2-c]pirazol-10(1H)-ona usando el método del Ejemplo 15.	D

S 81

216	 endo-8-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10-ol; MS 441.1 ^{1}H NMR (CD_3OD): δ 8.94 (s, 1H), 8.30-8.25 (m, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.55 (s, 1H), 7.00-6.90 (m, 1H), 6.83-6.79 (m, 1H), 6.67-6.60 (m, 1H), 6.05 (s, 1H), 5.56-5.52 (m, 1H), 5.38-5.30 (m, 1H). Preparado por reducción de 8-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]-ciclohepta[1,2-c]pirazol-10(1H)-ona usando el método descrito en el Ejemplo 15.	C

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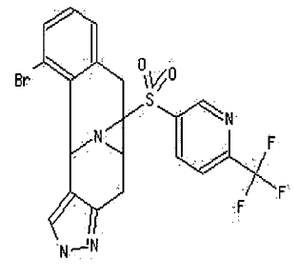
217	 (-)-10-bromo-12-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,6,11-tetrahidro-3H-5,11-epiminobenzo[4,5]cicloocta[1,2-c]pirazol; MS 499.0 ^{1}H NMR ($CDCl_3$) δ 8.89 (d J = 1.5 Hz, 1H), 7.98 (dd, J = 6.0, 2.1 Hz, 1H,) 7.64 (s, 1H), 7.46 (d, J = 8.1 Hz, 1H), 7.30 (d, J = 9.3 Hz, 1H), 6.83 (t, J = 8.4 Hz, 1H), 6.60 (d, J = 6.0 Hz, 1H), 6.49 (s, 1H), 4.98, (t, J = 7.2 Hz, 1H), 3.31 (dd, J = 16, 6.3 Hz, 1H), 3.18 (dd, J = 16, 9.9 Hz, 1 H) 2.67 (d, J = 15 Hz, 1H), 2.51 (d, J = 18 Hz, 1H). Preparado como se describe en Ejemplo 11 usando el compuesto **45**, seguido por quiral cromatográfica separación de estereoisómeros.	D
218	(+)-10-bromo-12-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,6,11-tetrahidro-3H-5,11-epiminobenzo[4,5]cicloocta[1,2-c]pirazol; MS 499.0 ^{1}H NMR ($CDCl_3$) δ 8.89 (d J = 1.5 Hz, 1H), 7.98 (dd, J = 6.0, 2.1 Hz, 1H,) 7.64 (s, 1H), 7.46 (d, J = 8.1 Hz, 1H), 7.30 (d, J = 9.3 Hz, 1H), 6.83 (t, J = 8.4 Hz, 1H), 6.60 (d, J = 6.0 Hz, 1H), 6.49 (s, 1H), 4.98, (t, J = 7.2 Hz, 1H), 3.31 (dd, J = 16, 6.3 Hz, 1H), 3.18 (dd, J = 16, 9.9 Hz, 1 H) 2.67 (d, J = 15 Hz, 1H), 2.51 (d, J = 18 Hz, 1H). Preparado como se describe arriba para el enantiómero.	D

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219	(±)-6-cloro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 441.1 ^{1}H NMR ($CDCl_3$) δ 8.90 (s, 1H), 8.06 (dd, J = 8.2, 2.0 Hz, 1H), 7.55 (d, J = 8.2 Hz, 1H), 7.35 (s, 1H), 6.97 (m, 3H), 5.83 (s, 1H), 5.39 (d, J = 5.3 Hz, 1H), 3.39 (dd, J = 16.4, 5.6 Hz, 1H), 2.79 (d, J = 16.3 Hz, 1H). Preparado como se describe en Ejemplo 9 usando 5-(2-bromo-5-clorofenil)-4-(6-(trifluorometil)piridin-3-ilsulfonil)ciclohex-2-enona que fue preparada como se describe en Ejemplo 8 usando 2-bromo-5-clorobenzaldehido y sulfonamida **23**.	D
220	(±)-metil 11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-8-carboxilato; MS 465.1. ^{1}H NMR ($CDCl_3$) δ 8.84 (s, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 1H) 7.40 (s, 1H), 7.10 (m, 2H), 6.02 (d, *J* = 5.4 Hz, 1H), 7.02 (d, *J* = 8.6 Hz, 1H), 5.91 (s, 1H), 3.95 (s, 3H), 3.49 (dd, *J* = 5.4, 16.8 Hz, 1H), 3.01 (d, *J* = 16.8 Hz, 1H). Preparado como se describe en Ejemplo 9 usando metil 2-bromo-3-(5-oxo-2-(6-(trifluorometil)piridin-3-ilsulfonil)ciclohex-3-enil)benzoato (preparado como se describe en Ejemplo 8 de metil 2-bromo-3-formilbenzoato y sulfonamida **23**).	D

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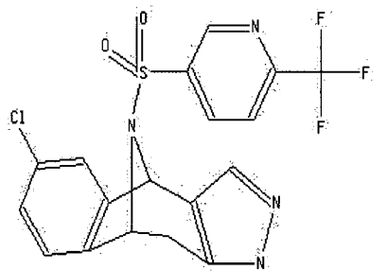
221	 (-)-6-cloro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 441.1 ^{1}H NMR ($CDCl_3$) δ 8.90 (s, 1H), 8.06 (dd, J = 8.2, 2.0 Hz, 1H), 7.55 (d, J = 8.2 Hz, 1H), 7.35 (s, 1H), 6.97 (m, 3H), 5.83 (s, 1H), 5.39 (d, J = 5.3 Hz, 1H), 3.39 (dd, J = 16.4, 5.6 Hz, 1H), 2.79 (d, J = 16.3 Hz, 1H). Preparado como se describe en Ejemplo 9 usando 5-(2-bromo-5-clorofenil)-4-(6-(trifluorometil)piridin-3-ilsulfonil)-ciclohex-2-enona, seguido por separación cromatográfica de estereoisómeros.	C
222	(+)-6-cloro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 441.1 ^{1}H NMR ($CDCl_3$) δ 8.90 (s, 1H), 8.06 (dd, J = 8.2, 2.0 Hz, 1H), 7.55 (d, J = 8.2 Hz, 1H), 7.35 (s, 1H), 6.97 (m, 3H), 5.83 (s, 1H), 5.39 (d, J = 5.3 Hz, 1H), 3.39 (dd, J = 16.4, 5.6 Hz, 1H), 2.79 (d, J = 16.3 Hz, 1H). Preparado como se describe arriba para el enantiómero.	D

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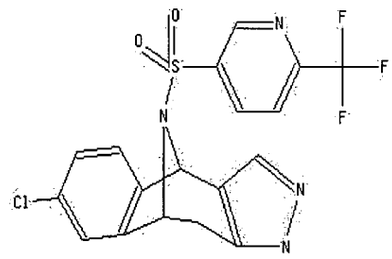
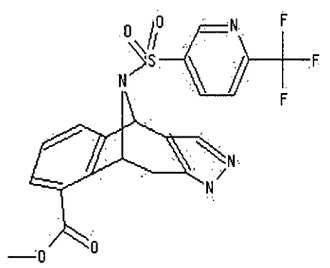
223	 (-)-7-cloro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 441.1 ^{1}H NMR ($CDCl_3$) δ 8.89 (s, 1H), 8.08 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.24 (s, 1H), 6.95 (m, 3H), 5.88 (s, 1H), 5.38 (d, *J* = 5.3 Hz, 1H), 3.41 (dd, *J* = 16.4, 5.6 Hz, 1H), 2.82 (d, *J* = 16.3 Hz, 1H). Preparado como se describe en el Ejemplo 8 usando 2-bromo-5-clorobenzaldehido y sulfonamida **23** seguido por separación cromatográfica de regio- y estereoisómeros.	B
224	(+)-7-cloro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 441.1 ^{1}H NMR ($CDCl_3$) δ 8.89 (s, 1H), 8.08 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.24 (s, 1H), 6.95 (m, 3H), 5.88 (s, 1H), 5.38 (d, *J* = 5.3 Hz, 1H), 3.41 (dd, *J* = 16.4, 5.6 Hz, 1H), 2.82 (d, *J* = 16.3 Hz, 1H). Preparado como se describe en Ejemplo 8 usando 2-bromo-5-clorobenzaldehido y sulfonamida **23** seguido por cromatográfica separación de regio- y estereoisómeros.	D

225	(±)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-6-ol; MS 423.1. ^{1}H NMR (CD_3OD) δ 8.90 (s, 1H), 8.22 (dd, J = 8.2; 2.0 Hz, 1H), 7.66 (d, J = 8.2 Hz, 1H), 7.54 (s, 1H), 6.91 (d, J = 8.0 Hz , 3H), 6.32 (m, 2H), 5.88 (s, 1H), 5.43 (d, J = 5.0 Hz, 1H), 4.95 (s, 1H), 3.34 (dd, J = 16.4, 5.4 Hz, 1H), 2.80 (d, J = 16.3 Hz, 1H). Preparado como se describe en Ejemplo 9 usando 5-(2-bromo-5-hidroxifenil)-4-(6-(trifluorometil)piridin-3-ilsulfonil)ciclohex-2-enonala cual fue preparada como se describe en el Ejemplo 8 usando 2-bromo-5-hidroxibenzaldehido y sulfonamida **23**.	D
226	 (+)-metil 11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-8-carboxilato; MS 465.1. ^{1}H NMR ($CDCl_3$) δ 8.84 (s, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 1H) 7.40 (s, 1H), 7.10 (m, 2H), 6.02 (d, *J* = 5.4 Hz, 1H), 7.02 (d, *J* = 8.6 Hz, 1H), 5.91 (s, 1H), 3.95 (s, 3H), 3.49 (dd, *J* = 5.4, 16.8 Hz, 1H), 3.01 (d, *J* = 16.8 Hz, 1H). Preparado como se describe en el Ejemplo 9 usando metil 2-bromo-3-(5-oxo-2-(6-(trifluorometil)piridin-3-ilsulfonil)ciclohex-3-enil)benzoato seguido por quiral cromatográfica separación de enantiómeros.	D

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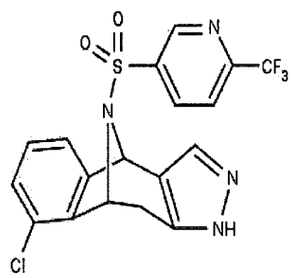
227	(-)-metil 11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-8-carboxilato; MS 465.1 ^{1}H NMR ($CDCl_3$) δ 8.84 (s, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 1H) 7.40 (s, 1H), 7.10 (m, 2H), 6.02 (d, *J* = 5.4 Hz, 1H), 7.02 (d, *J* = 8.6 Hz, 1H), 5.91 (s, 1H), 3.95 (s, 3H), 3.49 (dd, *J* = 5.4, 16.8 Hz, 1H), 3.01 (d, *J* = 16.8 Hz, 1H). Preparado como se describe en Ejemplo 9 usando metil 2-bromo-3-(5-oxo-2-(6-(trifluorometil)piridin-3-ilsulfonil)ciclohex-3-enil)benzoato, seguido por quiral cromatográfica separación de enantiómeros.	C
228	 (+)-8-cloro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 441.0 ^{1}H NMR (CD_3OD) □ 8.86 (s, 1H), 8.08, (d, J = 8.2 Hz, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.38 (s, 1H), 6.89 (m, 2H), 6.81 (m, 1H), 5.89 (s, 1H), 5.49 (d J = 5.5 Hz, 1H), 3.47 (dd J = 16.5, 5.6 Hz, 1H), 2.98 (d J = 16.4 Hz, 1H). Preparado como se describe en Ejemplo 9 usando 6-(2-bromo-3-clorofenil)-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-1H-pirazol[4,3-c]piridina, seguido por cromatográfica separación de regio- y estereoisómeros.	D

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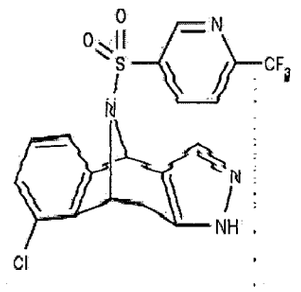
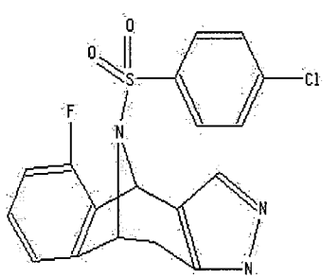
229	 (-)-8-cloro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 441.0 ^{1}H NMR (CD_3OD) □ 8.87 (d, J = 2.0 Hz, 1H), 8.08, (dd, J = 8.2, 1.7 Hz, 1H), 7.54 (dd, J = 8.2, 0.5 Hz, 1H), 7.46 (s, 1H), 6.89 (m, 2H), 6.91 (m, 3H), 5.96 (s, 1H), 5.45 (d J = 5.4 Hz, 1H), 3.52 (dd J = 16.4, 5.6 Hz, 1H), 2.87 (d J = 15.9 Hz, 1H). Preparado como se describe en Ejemplo 9 usando 6-(2-bromo-3-clorofenil)-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-1H-pirazol[4,3-c]piridina, seguido por cromatográfica separación de regio- y estereoisómeros.	C
230	 (-)-11-[(4-clorofenil)sulfonil]-5-fluoro-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 390.1. ^{1}H NMR (CD_3OD) □ 7.54 (m, 3H), 7.20, (m, 2H), 7.01 (m, 1H), 6.88 (d, J = 7.32 Hz, 1H), 6.66 (t, J = 8.5 Hz, 1H), 6.01 (s, 1H), 5.42 (d J = 5.4 Hz, 1H), 3.58 (dd J = 16.4, 5.6 Hz, 1H), 2.91 (d J = 15.9 Hz, 1H). Preparado como se describe en Ejemplo 9 usando 6-(2-bromo-6-fluorofenil)-5-(6-(trifluorometil)piridin-3-ilsulfonil)-4,5-dihidro-1H-pirazol[4,3-c]piridina, seguido por cromatográfica separación de regio- y estereoisómeros.	A

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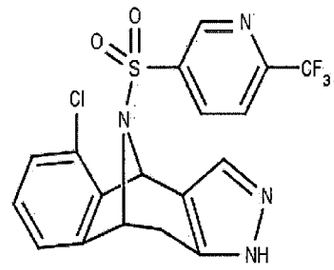
231	(+)-11-[(4-clorofenil)sulfonil]-5-fluoro-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 390.1. ^{1}H NMR (CD_3OD) □ 7.54 (m, 3H), 7.20, (m, 2H), 7.01 (m, 1H), 6.88 (d, J = 7.32 Hz, 1H), 6.66 (t, J = 8.5 Hz, 1H), 6.01 (s, 1H), 5.42 (d J = 5.4 Hz, 1H), 3.58 (dd J = 16.4, 5.6 Hz, 1H), 2.91 (d J = 15.9 Hz, 1H). Preparado como se describe arriba para el (-)-estereoisómero.	D
232	 (-)-5-cloro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 441.0 ^{1}H NMR (CD_3OD) □ 8.86 (s, 1H), 8.08, (d, J = 8.2 Hz, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.38 (s, 1H), 6.89 (m, 2H), 6.81 (m, 1H), 5.89 (s, 1H), 5.49 (d J = 5.5 Hz, 1H), 3.47 (dd J = 16.5, 5.6 Hz, 1H), 2.98 (d J = 16.4 Hz, 1H). Preparado como se describe en Ejemplo 9 usando 6-(2-bromo-6-clorofenil)-5-(6-(trifluoro-metil)piridin-3-ilsulfonil)-4,5-dihidro-1H-pirazol[4,3-c]piridina, seguido por cromatográfica separación de regio- y estereoisómeros.	B
233	(+)-5-cloro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 441.0 ^{1}H NMR (CD_3OD) □ 8.86 (s, 1H), 8.08, (d, J = 8.2 Hz, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.38 (s, 1H), 6.89 (m, 2H), 6.81 (m, 1H), 5.89 (s, 1H), 5.49 (d J = 5.5 Hz, 1H), 3.47 (dd J = 16.5, 5.6 Hz, 1H), 2.98 (d J = 16.4 Hz, 1H). Preparado como se describe arriba para el (-)-estereoisómero.	D

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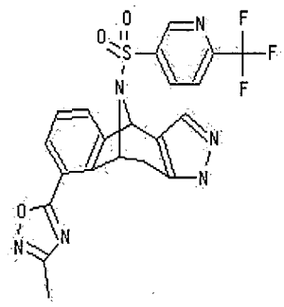
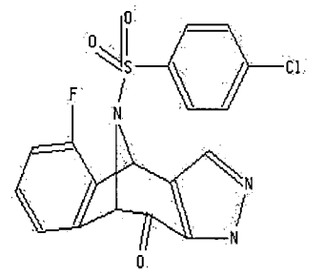
234	 (+)-8-(3-metil-1,2,4-oxadiazol-5-il)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 489.1. ^{1}H NMR (CD_3OD) □ 8.85 (d, J = 1.9 Hz, 1H), 8.01, (dd, J = 8.1, 1.9 Hz, 1H), 7.71 (m, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.41 (s, 1H), 7.15 (m, 2H), 6.16 (d, J = 5.7 Hz, 1H), 5.95 (s, 1H), 3.51 (dd J = 16.8, 5.9 Hz, 1H), 3.06 (d, J = 16.6 Hz, 1H), 2.53 (s, 3H). Preparado por condensación de una mezcla de metil 11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1-{[2-(trimetilsilil)etoxi]metil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]-ciclohepta[1,2-c]pirazol-8-carboxilato y metil 11-{[6-(trifluorometil)-piridin-3-il]sulfonil}-2-{[2-(trimetilsilil)etoxi]metil}-2,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-8-carboxilato,que fue preparado por alquilación de metil 11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-8-carboxilato como se describe en Ejemplo 19, con *N*-hidroxiacetamidina como se describe en Ejemplo 16 seguido por des-alquilación con 4N HCl/dioxano y cromatográfica separación de estereoisómeros.	D

235	(-)-8-(3-metil-1,2,4-oxadiazol-5-il)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 489.1. ^{1}H NMR (CD_3OD) □ 8.85 (d, J = 1.9 Hz, 1H), 8.01, (dd, J = 8.1, 1.9 Hz, 1H), 7.71 (m, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.41 (s, 1H), 7.15 (m, 2H), 6.16 (d, J = 5.7 Hz, 1H), 5.95 (s, 1H), 3.51 (dd J = 16.8, 5.9 Hz, 1H), 3.06 (d, J = 16.6 Hz, 1H), 2.53 (s, 3H). Preparado como se describe arriba para el (+)-estereoisómero.	C
236	 (±)-11-[(4-clorofenil)sulfonil]-5-fluoro-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona; MS 404.0 ^{1}H NMR (CD_3OD) □ 7.64 (s, 1H), 7.57, (m, 2H), 7.24 (m, 2H), 7.05 (m, 2H), 6.74 (m, 1H), 6.34 (s, 1H), 5.43 (s, 1H). Preparado por oxidación de (±)-11-[(4-clorofenil)sulfonil]-5-fluoro-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]-ciclohepta[1,2-c]pirazol usando el método descrito en el Ejemplo 15.	D

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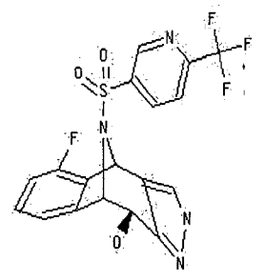
237	 (-)-(10S)-5-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10-ol; MS 441.1 ^{1}H NMR ($CDCl_3$ con a drop de CD_3OD) □ 8.89 (s, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.40 (s, 1H), 6.95-6.90 (m, 2H), 6.64-6.58 (m, 1H), 6.07 (s, 1H), 5.28 (s, 1H), 4.71 (s, 1H). Preparado como se describe en Ejemplo 20.	A
238	(+)-(10S)-5-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10-ol; MS 441.0 ^{1}H NMR ($CDCl_3$ con a drop de CD_3OD) □ 8.89 (s, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.40 (s, 1H), 6.95-6.90 (m, 2H), 6.64-6.58 (m, 1H), 6.07 (s, 1H), 5.28 (s, 1H), 4.71 (s, 1H). Preparado como se describe en Ejemplo 20.	D

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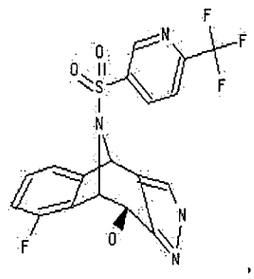
239	 (-)-(10S)-8-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10-ol; MS 441.1 ^{1}H NMR ($CDCl_3$ con a drop de CD_3OD) □ 8.90 (s, 1H), 8.13 (d, J = 8.3 Hz, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.37 (s, 1H), 6.98-6.90 (m, 1H), 6.74 (d, J = 7.4 Hz, 1H), 6.63 (t, J = 8.4 Hz,1H), 5.91 (s, 1H), 5.44 (s, 1H), 4.79 (s, 1H). Preparado como se describe en Ejemplo 20.	A
240	(+)-(10S)-8-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10-ol; MS 441.1 ^{1}H NMR ($CDCl_3$ con a drop de CD_3OD) □ 8.90 (s, 1H), 8.13 (d, J = 8.3 Hz, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.37 (s, 1H), 6.98-6.90 (m, 1H), 6.74 (d, J = 7.4 Hz, 1H), 6.63 (t, J = 8.4 Hz,1H), 5.91 (s, 1H), 5.44 (s, 1H), 4.79 (s, 1H). Preparado como se describe en Ejemplo 20.	C

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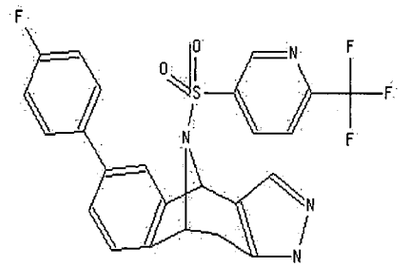
241	 (±)-6-(4-fluorofenil)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 501.1. ^{1}H NMR (CD_3OD) □ 8.94 (d, J = 1.8 Hz, 1H), 8.07 (dd, J = 8.1, 1.8 Hz, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.26 (m, 2H), 7.08 (m, 5H), 5.97 (s, 1H), 5.45 (d, J = 5.3 Hz, 1H), 3.47 (dd, J = 16.3, 5.6 Hz, 1H), 2.86 (d, J = 16.1 Hz, 1H). Preparado como se describe en Ejemplo 19.	D
242	(-)-11-[(4-clorofenil)sulfonil]-5-fluoro-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona; MS 404.0 ^{1}H NMR (CD_3OD) □ 7.68 (s, 1H), 7.56, (m, 2H), 7.22 (m, 2H), 7.05 (m, 2H), 6.75 (m, 1H), 6.33 (s, 1H), 5.43 (s, 1H). Preparado por oxidación de (±)-11-[(4-clorofenil)sulfonil]-5-fluoro-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]-ciclohepta[1,2-c]pirazol usando el metodo descrito en Ejemplo 15 seguido por quiral cromatográfica separación de estereoisómeros.	D
243	(+)-11-[(4-clorofenil)sulfonil]-5-fluoro-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona; MS 404.0 ^{1}H NMR (CD_3OD) □ 7.68 (s, 1H), 7.56, (m, 2H), 7.22 (m, 2H), 7.05 (m, 2H), 6.75 (m, 1H), 6.33 (s, 1H), 5.43 (s, 1H). Preparado como se describe arriba para el (-)-estereoisómero.	C

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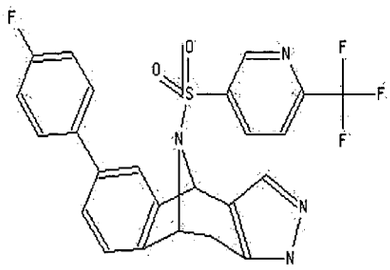
244	 (-)-6-(4-fluorofenil)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 501.0. ^{1}H NMR (CD_3OD) □ 8.91 (d, J = 2.0 Hz, 1H), 8.04 (dd, J = 8.1, 1.8 Hz, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.28 (m, 2H), 7.09 (m, 5H), 5.89 (s, 1H), 5.45 (d, J = 5.3 Hz, 1H), 3.48 (dd, J = 16.3, 5.6 Hz, 1H), 2.86 (d, J = 16.1 Hz, 1H). Preparado como se describe en Ejemplo 19 seguido por quiral cromatográfica separación de estereoisómeros.	A
245	(+)-6-(4-fluorofenil)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 501.0. ^{1}H NMR (CD_3OD) □ 8.91 (d, J = 2.0 Hz, 1H), 8.04 (dd, J = 8.1, 1.8 Hz, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.28 (m, 2H), 7.09 (m, 5H), 5.89 (s, 1H), 5.45 (d, J = 5.3 Hz, 1H), 3.48 (dd, J = 16.3, 5.6 Hz, 1H), 2.86 (d, J = 16.1 Hz, 1H). Preparado como se describe en Ejemplo 19 seguido por quiral cromatográfica separación de estereoisómeros.	C

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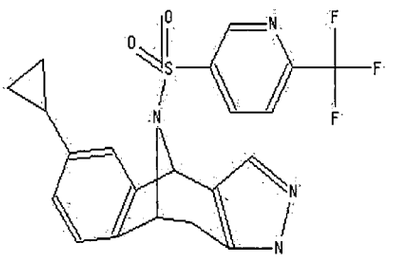
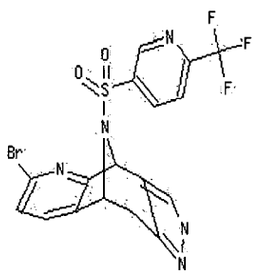
246	 (-)-6-ciclopropil-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 447.0 ^{1}H NMR (CD_3OD) □ 8.86 (d, *J* = 2.0 Hz, 1H), 7.99 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.36 (s, 1H), 6.92 (d, *J* = 7.7 Hz, 1H), 6.61 (m, 2H), 5.76 (s, 1H), 5.34 (d, *J* = 5.3 Hz, 1H), 3.44 (dd, *J* = 16.3, 5.6 Hz, 1H), 2.80 (d, *J* = 16.1 Hz, 1H), 1.67 (m, 1H), 0.87 (m, 2H), 0.47 (m, 2H). Preparado como se describe en Ejemplo 19 usando ácido ciclopropilborónico seguido por cromatográfica separación de estereoisómeros.	A
247	(+)-6-ciclopropil-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 447.0 ^{1}H NMR (CD_3OD) □ 8.86 (d, *J* = 2.0 Hz, 1H), 7.99 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.36 (s, 1H), 6.92 (d, *J* = 7.7 Hz, 1H), 6.61 (m, 2H), 5.76 (s, 1H), 5.34 (d, *J* = 5.3 Hz, 1H), 3.44 (dd, *J* = 16.3, 5.6 Hz, 1H), 2.80 (d, *J* = 16.1 Hz, 1H), 1.67 (m, 1H), 0.87 (m, 2H), 0.47 (m, 2H). Preparado como se describe en Ejemplo 19 usando ácido ciclopropilborónico seguido por cromatográfica separación de estereoisómeros.	D

597

248	 (+)-6-bromo-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminopirazol[3',4':5,6]ciclohepta[1,2-b]piridina; MS 488.0. ^{1}H NMR ($CDCl_3$) □ 8.93 (s, 1H), 8.15 (d, J = 8.2 Hz, 1H), 7.65 (d, J = 8.2 Hz, 1H), 7.54 (s, 1H), 7.35 (d, J = 7.9 Hz, 1H), 7.15 (d, J = 7.9 Hz, 1H), 5.84 (s, 1H), 5.46 (d, J = 5.0 Hz, 1H), 3.49 (dd, J = 16.6, 5.4 Hz, 1H), 2.84 (d, J = 16.6 Hz, 1H). Preparado como se describe en Ejemplo 9 usando 2-(3,6-dibromopiridin-2-il)-1-(6-(trifluorometil)piridin-3-ilsulfonil)-2,3-dihidropiridin-4(1H)-ona la cual fue preparada como se describe en Ejemplo 8 usando sulfonamida **23** y 3,6-dibromopicolinaldehido, que fue preparado como se describe en el Ejemplo 22, seguido por quiral cromatográfica separación de estereoisómeros.	D
249	(-)-6-bromo-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminopirazol[3',4':5,6]ciclohepta[1,2-b]piridina; MS 488.0. ^{1}H NMR ($CDCl_3$) □ 8.93 (s, 1H), 8.15 (d, J = 8.2 Hz, 1H), 7.65 (d, J = 8.2 Hz, 1H), 7.54 (s, 1H), 7.35 (d, J = 7.9 Hz, 1H), 7.15 (d, J = 7.9 Hz, 1H), 5.84 (s, 1H), 5.46 (d, J = 5.0 Hz, 1H), 3.49 (dd, J = 16.6, 5.4 Hz, 1H), 2.84 (d, J = 16.6 Hz, 1H). Preparado como se describe arriba para el (+)-estereoisómero.	A

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250	(+)-6-bromo-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 484.9 ^{1}H NMR ($CDCl_3$) □ 8.89 (d, J = 2.1 Hz, 1H), 8.05 (dd, J = 2.4, 8.4 Hz, 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.38 (s, 1H), 7.14 (dd, J = 1.8, 8.1 Hz, 1H), 7.08 (s, 1H), 7.00 (d, J = 7.8 Hz, 1H), 5.83 (s, 1H), 5.37 (d, J = 5.4 Hz, 1H), 3.42 (dd, J = 5.4, 16.5 Hz, 1H), 2.80 (d, J = 16.5 Hz, 1H). Preparado como se describe en el Ejemplo 9 usando 2-(2,5-dibromofenil)-1-(6-(trifluorometil)piridin-3-ilsulfonil)-2,3-dihidropiridin-4(1H)-ona que fue preparada como se describe en el Ejemplo 8 usando 2,5-dibromobenzaldehido y sulfonamida **23** seguido por cromatográfica separación de estereoisómeros.	D
251	(-)-6-bromo-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 484.9 ^{1}H NMR ($CDCl_3$) □ 8.89 (d, J = 1.5 Hz, 1H), 8.05 (dd, J = 1.8, 8.1 Hz, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.38 (s, 1H), 7.14 (dd, J = 1.2, 7.8 Hz, 1H), 7.08 (s, 1H), 7.00 (d, J = 8.1 Hz, 1H), 5.83 (s, 1H), 5.37 (d, J = 4.8 Hz, 1H), 3.42 (dd, J = 5.4, 16.5 Hz, 1H), 2.80 (d, J = 16.5 Hz, 1H). Preparado como se describe arriba para el (+)-estereoisómero.	C

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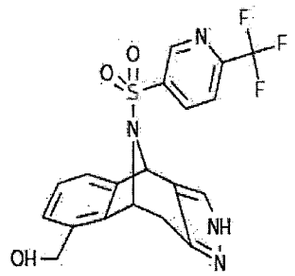
252	 (±)-(11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-8-il)metanol; MS 437.1 ^{1}H NMR (CD_3OD con una gota de DMSO-d_6) □ 8.92 (s, 1H), 8.22 (d, J = 8.2 Hz, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.53 (s, 1H), 6.92-6.88 (m, 3H), 6.00 (s, 1H), 5.73 (d, J = 5.4 Hz, 1H), 4.56 (s, 2H), 3.40 (dd, J = 16.5, 5.4 Hz, 1H), 3.03 (d, J = 16.5 Hz, 1H). Preparado por $LiAlH_4$ reducción de (±)-metil 11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-8-carboxilato.	D
253	metil (±)-11-{[6-(trifluorometil)-1,2-dihidropiridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-8-carboxilato; MS 467.1. ^{1}H NMR ($CDCl_3$) □ 7.83 (d, J = 7.8 Hz, 1H), 7.41-7.35 (m, 2H), 7.25 (d, J = 7.6 Hz, 1H), 6.95 (d, J = 5.5 Hz, 1H), 5.91 (d, J = 5.8 Hz, 1H), 5.83 (s, 1H), 5.78 (d, J = 4.8 Hz, 1H), 4.99 (s, 1H), 3.96 (s, 3H), 3.54 (dd, J = 16.6, 5.9 Hz, 1H), 3.06 (d, J = 16.6 Hz, 1H), 2.89 (s, 2H).	D

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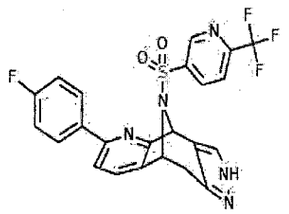
254	 (+)-6-(4-fluorofenil)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminopirazol[3',4':5,6]ciclohepta[1,2-b]piridina; MS 502.1. ^{1}H NMR ($CDCl_3$) □ 8.95 (d, J = 2.1 Hz, 1H), 8.13 (dd, J = 8.2, 1.8 Hz, 1H), 7.77-7.72 (m, 2H), 7.56 (s, 1H), 7.50 (t, J = 8.1 Hz, 2H), 7.25 (d, J = 7.9 Hz, 1H), 7.13 (t, J = 8.7 Hz, 2H), 5.91 (s, 1H), 5.50 (d, J = 5.4 Hz, 1H), 3.54 (dd, J = 16.4, 5.6 Hz, 1H), 2.90 (d, J = 16.4 Hz, 1H). Preparado por Pd-mediado acoplamiento de (+)-6-bromo-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminopirazol-[3',4':5,6]ciclohepta-[1,2-b]piridina con ácido 4-fluorofenil borónico como se describe en el Ejemplo 13.	C
255	(+)-6-ciclopropil-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminopirazol[3',4':5,6]ciclohepta[1,2-b]piridina; MS 448.1. ^{1}H NMR ($CDCl_3$) □ 8.88 (s, 1H), 8.08 (d, J = 7.6 Hz, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.51 (s, 1H), 7.24 (d, J = 7.8 Hz, 1H), 6.67 (d, J = 7.8 Hz, 1H), 5.73 (s, 1H), 5.40 (d, J = 5.2 Hz, 1H), 3.51 (dd, J = 16.4, 5.5 Hz, 1H), 2.83 (d, J = 16.4 Hz, 1H), 1.86-1.82 (m, 1H), 0.97-0.73 (m, 4H). Preparado por Pd-mediado acoplamiento de (+)-6-bromo-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminopirazol[3',4':5,6]ciclohepta-[1,2-b]piridina con ácido ciclopropillboronico como se describe en Ejemplo 13, seguido por quiral cromatográfica separación de estereoisómeros.	C

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256	(-)-6-ciclopropil-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminopirazol[3',4':5,6]ciclohepta[1,2-b]piridina; MS 448.1. ^{1}H NMR ($CDCl_3$) □ 8.88 (s, 1H), 8.08 (d, J = 7.6 Hz, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.51 (s, 1H), 7.24 (d, J = 7.8 Hz, 1H), 6.67 (d, J = 7.8 Hz, 1H), 5.73 (s, 1H), 5.40 (d, J = 5.2 Hz, 1H), 3.51 (dd, J = 16.4, 5.5 Hz, 1H), 2.83 (d, J = 16.4 Hz, 1H), 1.86-1.82 (m, 1H), 0.97-0.73 (m, 4H). Preparado como se describe arriba para el (+) -estereoisómero.	A
257	(±)-8-(fluorometil)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 439.1 ^{1}H NMR ($CDCl_3$) □ 8.89 (s, 1H), 8.04 (d, J = 8.2 Hz, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.42 (s, 1H), 7.00-6.85 (m, 3H), 5.89 (s, 1H), 5.63 (d, J = 5.5 Hz, 1H), 5.40 (d, J = 2.5 Hz, 1H), 5.25 (d, J = 2.5 Hz, 1H), 3.51 (dd, J = 16.5, 5.7 Hz, 1H), 2.95 (d, J = 16.5 Hz, 1H). Preparado por fluorinación de (±)-(11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-8-il)metanol usando DAST como se describe en el Ejemplo 15.	D
258	(±)-7-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminopirazol[3',4':5,6]ciclohepta[1,2-b]piridina; MS 426.1. ^{1}H NMR (CD_3OD) □ 8.97 (s, 1H), 8.31 (d, J = 8.3 Hz, 1H), 7.94 (s, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.61 (s, 1H), 7.49 (d, J = 8.1 Hz, 1H), 5.92 (s, 1H), 5.65 (d, J = 5.4 Hz, 1H), 3.40 (dd, J = 16.5, 5.3 Hz, 1H), 2.83 (d, J = 16.3 Hz, 1H). Preparado como se describe en Ejemplo 9 usando 2-(3-bromo-5-fluoropiridin-2-il)-1-(6-(trifluorometil)piridin-3-ilsulfonil)-2,3-dihidropiridin-4(1H)-onala cual fue preparada como se describe en Ejemplo 8 usando 3-bromo-5-fluoropicolinaldehido y sulfonamida **23**.	D

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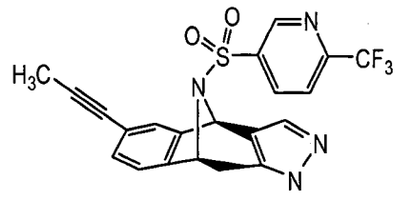
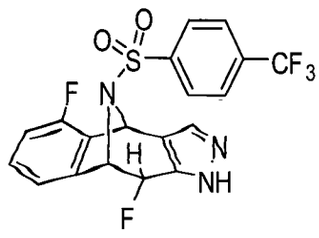
259	(-)-7-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-2,4,9,10-tetrahidro-4,9-epiminopirazol[3',4':5,6]ciclohepta[1,2-b]piridina; MS 426.1. ^{1}H NMR (CD_3OD) □ 8.97 (s, 1H), 8.31 (d, J = 8.3 Hz, 1H), 7.94 (s, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.61 (s, 1H), 7.49 (d, J = 8.1 Hz, 1H), 5.92 (s, 1H), 5.65 (d, J = 5.4 Hz, 1H), 3.40 (dd, J = 16.5, 5.3 Hz, 1H), 2.83 (d, J = 16.3 Hz, 1H). Preparado como se describe en Ejemplo 9 usando 2-(3-bromo-5-fluoropiridin-2-il)-1-(6-(trifluorometil)piridin-3-ilsulfonil)-2,3-dihidropiridin-4(1H)-ona,la cual fue preparada como se describe en Ejemplo 8 usando 3-bromo-5-fluoropicolinaldehido y sulfonamida **23,** seguido por quiral cromatográfica separación de estereoisómeros.	A
260	(+)-7-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-2,4,9,10-tetrahidro-4,9-epiminopirazol[3',4':5,6]ciclohepta[1,2-b]piridina; MS 426.0. ^{1}H NMR (CD_3OD) □ 8.97 (s, 1H), 8.31 (d, J = 8.3 Hz, 1H), 7.94 (s, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.61 (s, 1H), 7.49 (d, J = 8.1 Hz, 1H), 5.92 (s, 1H), 5.65 (d, J = 5.4 Hz, 1H), 3.40 (dd, J = 16.5, 5.3 Hz, 1H), 2.83 (d, J = 16.3 Hz, 1H). Preparado como se describe arriba para el (-)-estereoisómero.	D

261	 (4R,9S)-6-(prop-1-in-1-il)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 445.0. ^{1}H NMR ($CDCl_3$) □ 8.90 (d, J = 1.8 Hz, 1H), 8.00 (dd, J = 1.8, 8.1 Hz, 1H), 7.52 (d, J = 8.1 Hz, 1H), 7.44 (s, 1H), 7.02 (bs, 2H), 6.93 (s, 1H), 5.82 (s, 1H), 5.38 (d, J = 4.8 Hz, 1H), 3.48 (dd, J = 16.5, 5.1 Hz, 1H), 2.85 (d, J = 16.5 Hz, 1H), 1.98 (s, 3H). Preparado por alquilación de 6-bromo-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol con SEM-Cl seguido por acoplamiento Stille con tributilpropinilestanano en tolueno en presencia de $Pd(PPh_3)_4$.	C
262	 (-)-exo-5,10-difluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 442.1 ^{1}H NMR ($CDCl_3$) □ 7.83 (d, J = 8.2 Hz, H), 7.53 (d, J = 8.2, 2H), 7.45 (s, 1H), 6.93 (m, 2H), 6.60 (m, 1H), 6.18 (s, 1H), 5.59 (m, 1H), 5.43 (d, J = 1.9 Hz, 1H). Preparado como se describe en Ejemplo 15 usando (±)-5-fluoro-11-{[4-(trifluorometil)fenil]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]-ciclohepta[1,2-c]pirazol-10(1H)-ona seguido por quiral cromatográfica separación de estereoisómeros.	A

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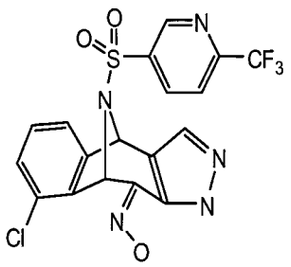
263	(+)-5,10-difluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 442.1 ^{1}H NMR ($CDCl_3$) □ 7.82 (d, J = 8.2 Hz, 1H), 7.54 (d, J = 8.2, 2H), 7.46 (s, 1H), 6.97 (m, 2H), 6.64 (m, 1H), 6.14 (s, 1H), 5.58 (m, 1H), 5.42 (d, J = 1.9 Hz, 1H). Preparado como se describe arriba para el (-)-estereoisómero.	D
264	(±)-8-cloro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona; MS 455.1 ^{1}H NMR ($CDCl_3$) □ 8.86 (s, 1H), 8.20 (d, J = 8.2 Hz, 1H), 7.68 (d, J = 8.2, 1H), 7.62 (s, 1H), 7.04 (m, 3H), 6.29 (s, 1H), 5.58 (s, 1H). Preparado por oxidación de 8-cloro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol usando el método descrito en el Ejemplo 15.	D
265	 (±)-8-cloro-N-hidroxi-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-imina; MS 470.0. ^{1}H NMR ($CDCl_3$) □ 14.8 (s, 1H), 9.34 (s, 1H), 9.15 (s, 1H), 8.37 (dd, J = 8.2, 1.6 Hz, 1H), 7.71 (d, J = 8.2 Hz, 1H), 7.64 (s, 1H), 6.92 (m, 4H), 6.63 (s, 1H). Preparado por tratamiento de (±)-8-cloro-11-{[6-(trifluorometil)-piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona con hidroxilamina hidrocloruro y $NaHCO_3$ en C_3CN/H2O (3:1).	65 D

266	(±)-8-(4-fluorofenil)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 501.1. ^{1}H NMR ($CDCl_3$) □ 8.79 (d, J = 2.0 Hz, 1H), 8.00 (dd, J = 8.2, 1.8 Hz, 1H), 7.51 (d, J = 8.1 Hz, 1H), 7.41 (s, 1H), 7.19 (m, 4H), 6.95 (m, 3H), 5.92 (s, 1H), 5.39 (d, J = 5.5 Hz, 1H), 3.38 (dd, J = 16.4, 5.7 Hz, 1H), 2.85 (d, J = 16.4 Hz, 1H). Preparado como se describe en Ejemplo 19 usando 8-cloro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol.	D
267	(4S,9S,10R)-5,10-difluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 443.1. ^{1}H NMR ($CDCl_3$) □ 10.36 (s, 1H), 8.92 (d, J = 2.1 Hz, 1H), 8.11 (dd, J = 8.2, 2.2 Hz, 1H), 7.57 (d, J = 8.3 Hz, 1H), 7.49 (s, 1H), 6.97-7.04 (m, 2H), 6.65-6.71 (m, 1H), 6.14 (dd, J = 52.8, 6.3 Hz, 1H), 6.07 (s, 1H), 5.53 (d, J = 6.2 Hz, 1H). Preparado como el menor componente de fluorinación de 5-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10-ol usando el método descrito en el Ejemplo 15, seguido por quiral cromatográfica separación de estereoisómeros.	D
268	(4R,9R,10R)-5,10-difluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 443.1. ^{1}H NMR ($CDCl_3$) □ 10.27 (s, 1H), 8.97 (d, J = 1.9 Hz, 1H), 8.20 (dd, J = 8.3, 1.8 Hz, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.51 (s, 1H), 7.05-7.11 (m, 2H), 6.74-6.81 (m, 1H), 6.23 (s, 1H), 5.65 (d, J = 10.4 Hz, 1H), 5.52 (dd, J = 52.1, 1.8 Hz, 1H). Preparado por fluorinación de 5-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10-ol usando el método descrito en el Ejemplo 15 seguido por quiral cromatográfica separación de estereoisómeros.	A

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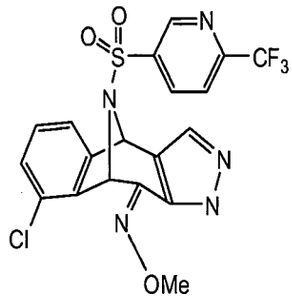
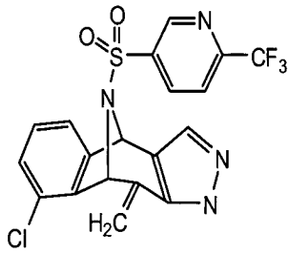
269	 (±)-8-cloro-N-metoxi-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-imina; MS 484.2. ^{1}H NMR ($CDCl_3$) □ 8.89 (d, J = 2.1 Hz, 0.3H), 8.83 (d, J = 2.1 Hz, 1H), 8.04 (dd, J = 8.2, 1.8 Hz, 1H), 7.94 (dd, J = 8.2, 1.8 Hz, 0.3H), 7.56 (s, 1H), 7.52 (m, 1H), 7.49 (s, 1H), 7.05 (s, 1), 7.02 (s, 3H), 6.65 (s, 1H), 6.03 (m, 1.3H), 4.12 (s, 3H), 4.08 (s, 1H). Preparado por tratamiento de (±)-8-cloro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona con metoxilamina hidrocloruro y $NaHCO_3$ en EtOH/TF (1:1).	D
270	(±)-8-ciclopropil-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 447.0 ^{1}H NMR ($CDCl_3$) □ 8.87 (d, J = 1.9 Hz, 1H), 7.99 (dd, J = 8.2, 2.0 Hz, 1H), 7.44 (d, J = 8.2 Hz, 1H), 7.38 (s, 1H), 6.84 (t, J = 7.5 Hz, 1H), 6.72 (d, J = 7.3 Hz, 1H), 6.41 (d, J = 7.7 Hz, 1H), 5.85 (s, 1H), 5.56 (d, J = 5.5 Hz, 1H), 3.51 (dd, J = 16.2, 5.6 Hz, 1H), 2.99 (d, J = 15.7 Hz, 1H), 1.66 (m, 1H), 0.98 (m, 2H), 0.60 (m, 2H). Preparado como se describe en el Ejemplo 19 usando ácido ciclopropilborónico y 8-cloro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]-ciclohepta[1,2-c]pirazol.	D

271	exo-10-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-2,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 425.0 ^{1}H NMR (CD_3OD) □ 8.94 (s, 1H), 8.25 (d, J = 8.2 Hz, 1H), 7.62 (m, 2H), 7.27 (d, J = 6.9 Hz, 1H), 6.94 (m, 3H), 6.15 (s, 1H), 5.71 (d, J = 10.6 Hz, 1H), 5.55 (d, J = 52.1 Hz, 1H). Preparado como se describe en Ejemplo 15 usando (-)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]-ciclohepta[1,2-c]pirazol.	A
272	 (±)-8-cloro-10-metilidene-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 453.1. ^{1}H NMR ($CDCl_3$) □ 8.78 (d, J = 2.1 Hz, 1H), 8.11 (dd, J = 8.4, 1.8 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.38, (s, 1H), 7.05 (m, 3H), 6.06 (s, 1H), 5.74 (s, 1H), 5.60 (s, 1H), 5.49 (s, 1H). Preparado por alquilación de (±)-8-cloro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo-[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona con trimetilsililetoximetil cloruro como se describe en el Ejemplo 19 seguido por formación de alqueno usando el reagente Tebbe y desalquilación usando 4N HCl/dioxano.	D

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273	(±)-5-(4-fluorofenil)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 501.2. ^{1}H NMR ($CDCl_3$) □ 8.65 (s, 1H), 7.93 (d, J = 6.5 Hz, 1H), 7.55 (s, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.10 (m, 6H), 6.87 (d, J = 7.4 Hz, 1H), 5.74 (s, 1H), 5.44 (d, J = 5.1 Hz, 1H), 3.60 (dd, J = 16.7, 4.7 Hz, 1H), 3.04 (d, J = 16.9 Hz, 1H). Preparado como se describe en Ejemplo 19 usando 5-cloro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol.	>100
274	(±)-5-ciclopropil-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol; MS 447.2 ^{1}H NMR ($CDCl_3$) □ 8.90 (d, J = 1.7 Hz, 1H), 8.02 (dd, J = 8.1, 1.7 Hz, 1H), 7.46 (d, J = 8.2 Hz, 1H), 6.89 (m, 2H), 6.43 (m, 1H), 6.07(s, 1H), 5.45 (d, J = 5.1 Hz, 1H), 3.60 (dd, J = 16.2, 5.6 Hz, 1H), 2.92 (d, J = 15.7 Hz, 1H), 1.67 (m, 1H), 0.98 (m, 2H), 0.51 (m, 2H). Preparado como se describe en Ejemplo 19 usando 5-cloro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol y ácido ciclopropilborónico.	D

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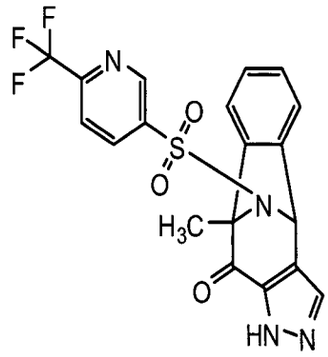
275	 (-)-9-metil-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona; MS 435.1. ^{1}H NMR ($CDCl_3$) □ 8.92 (d, 1H, J = 2.4 Hz), 8.16 (dd, J = 2.4, 8.4 Hz, 1H), 7.70 (d, 1H, J = 8.4 Hz), 7.67 (s, 1H), 7.30-7.21 (m, 4H), 6.30 (s, 1H), 1.96 (s, 3H). Preparado como se describe en Ejemplo 21 usando 6-(trifluorometil)piridina-3-sulfonil cloruro seguido por quiral cromatográfica separación de estereoisómeros.	D
276	(+)-9-metil-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona; MS 435.1 ^{1}H NMR ($CDCl_3$) □ 8.94 (d, 1H, J = 2.1 Hz), 8.16 (dd, J = 2.4, 8.4 Hz, 1H), 7.70 (d, 1H, J = 8.4 Hz), 7.66 (s, 1H), 7.32-7.18 (m, 4H), 6.30 (s, 1H), 1.96 (s, 3H). Preparado como se describe arriba para el (-)-estereoisómero.	>30
277	(-)-9-metil-11-{[4-(trifluorometil)fenil]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona; MS 434.0 ^{1}H NMR ($CDCl_3$) □ 7.83 (d, 2H, J = 8.4 Hz), 7.67 (s, 1H), 7.63 (d, 2H, J = 8.4 Hz), 7.29-7.17 (m, 4H), 6.28 (s, 1H), 1.92 (s, 3H). Preparado como se describe en Ejemplo 21 seguido por quiral cromatográfica separación de estereoisómeros.	D

278	(+)-9-metil-11-{[4-(trifluorometil)fenil]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona; MS 434.0 ^{1}H NMR ($CDCl_3$) □ 7.83 (d, 2H, J = 8.4 Hz), 7.67 (s, 1H), 7.63 (d, 2H, J = 8.4 Hz), 7.29-7.17 (m, 4H), 6.28 (s, 1H), 1.92 (s, 3H). Preparado como se describe arriba para el (-)-estereoisómero.	>30

En la tabla de arriba , "A" respresenta IC_{50} valores de >1 μM; "B" representa IC_{50} valores de 500 nM a 999 nM; "C" representa IC_{50} valores de 100 nM a 499 nM; y "D" representa IC_{50} valores de <100 nM. IC_{50} valores fueron generadas usando el ensayo descrito en el Ejemplo A.

Ejemplo A

Ensayo Gamma-Secretasa APP

El ensayo APP enzima gamma-secretasa fue diseñado para medir la específica partición proteolítica de un sustrato APP (proteína de fusión MBP-C125 Swe) en el sitio Aβ40. El ensayo usó un extracto parcialmente purificado de membranas celulares IMR-32 como la preparación de enzima gamma secretasa y un aproteína de fusión recombinante conteniendo amino ácidos C-terminales de la variante sueca de la APP (MBP-C125 Swe) como sustrato. Este ensayo involucró dos pasos comenzando con la reacción enzimática generando un producto de partición que fue capturado con un anticuerpo específico inmovilizado para el neo – epítope sitio Aβ40. El producto de partición capturado fue entonces detectado en un ensayo sándwich ELISA con un anticuerpo reportero biotinilado que es específico a Aβ (17-28). Alcalino fosfatasa streptavidin-unida fue entonces añadida para generar una señal fluorescente proporcional a la cantidad de producto de partición. Este ensayo fue usado para descubrir inhibidores de pequeña molécula de la gamma-secretasa.

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Resumidamente, una solución de detergente BIGCHAP de 149 mg/ml fue hecha con agua a 42° C y rotada por 30 minutos a la misma temperatura. Esta solución calentada de detergente BIGCHAP (N,N-Bis(3-D-gluconamidopropil) colamida) fue usada para disolver Extracto Cerebral Tipo V (lípido conteniendo un mínimo de 40% de fosfatidil etanol amina) de Sigma (St. Louis, Mo.) a una concentración de 8 mg/ml. Esta solución conteniendo BIGCHAP y lípido a 8 mg/ml es entonces diluida a 0.53 mg/ml de lípido con una solución precalentada de Hepes y cloruro de sodio. Esta solución final conteniendo el amortiguador Hepes, cloruro de sodio, detergente BIGCHAP y lípido es usada para crear soluciones de trabajode ambas, gamma secretasa (25 unidades) y el sustrao C125 (0.05 mg/ml).

Gamma-secretasa fue entonces añadida a una placa de 96 pozos de micro titulación e incubada con varias concentraciones de inhibidor por 30 minutos a 37°C. Sustrato MBPC125 fue entonces añadido para iniciar la reacción que correría por dos horas a 37°C y entonces 100µl de la mezcla de reacción fue transferida a un plato de captura ELISA e incubada durante la noche a 40°C.La detección del producto de partición fue realizada usando un ensayo sándwich estándar ELISA y cuantificado usando una curva estándar de seis puntos. Compuestos de la invención tiene valores IC50 de menos de 10 µM.

Ejemplo B

Ensayo *in vitro* Gamma-Notch

Este ensayo emplea la misma preparación de enzimas que es usada en el ensayo enzimático in vitro gamma-APP (descrito en el Ejemplo C de abajo), excepto a una concentración dos veces mayor, y los mismos amortiguadores de reacción y materiales para diluir la enzima. El sustrato de proteína de fusión APP fue reemplazado por un análogo sustrato de proteína de fusión Notch expresado en bacterias y purificado por cromatografía de afinidad antes de la incubación con enzima. El ensayo Gamma Notch fue diseñado para medir la específica partición proteolítica de un sustrato Notch (Notch ΔE) en la posición correspondiente a Val 1744 de longitud-completa, también conocido como el sitio de partición épsilon sobre el sustrato Notch. El producto específico fue medido por un sándwich ELISA

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utilizando un anticuerpo específico de captura neo-epitope 9F3 específico para el N-terminal del producto NICD particionado y un anticuerpo reportero biotinilado anti-HA-biotina (Roche) dirigido contra la HA-etiqueta en el terminal-C del sustrato.

Expresión Bacterial y Purificación de Afinidad de Sustrato de Proteína de Fusión Notch

Una proteína de fusión Notch recombinante conteniendo secuencial HA y etiquetas epítope His-6 en el C-terminal, fue expresada en *E.coli* y afinidad purificada de lisados usando una columna Níquel-sefarosa e imidazol usando procedimientos estándar. Esta proteína de fusión Notch purificada fue empleada como sustrato para partición in vitro por la enzima gamma secretasa (preparada de células IMR32). La proteína de fusión Notch fue construida para ser análoga al fragmento APP C99. Así, la proteína de fusión Notch estaba compuesta de 99 amino ácidos flanqueando el dominio transmembrana de Notch 1 de ratón, comenzando con los 17 residuos amino – terminal al dominio trans-membrana, también comprendiendo los 17 residuos dominio trans-membrana y extendiendo 66 residuos en el dominio citoplásmico. El amino-terminal de la proteína de fusión comienza en el residuo #1711 de Notch de ratón, y se extiende C-terminalmente al residuo #1809, seguido por un epítope en-marco etiqueta de fusión de la etiqueta HA, y seis residuos de histidina. Las etiquetas epítope fueron incorporadas para facilitar la detección ELISA del producto de partición NICD usando un anticuerpo anti-HA, y para más fácil purificación del sustrato de proteína de fusión de lisados de *E.coli* usando cromatografía de afinidad de columna de Níquel, respectivamente.

Siguiendo a la expresión durante la noche de la proteína de fusión en *E.coli*, el sustrato fue purificado en una columna níquel-sefarosa de lisados. La pureza del sustrato de proteína de fusión 16 kDa Notch eluido de la columna níquel-afinidad fue confirmada por SDS-PAGE. Fracciones conteniendo la proteína deseada fueron entonces reunidas, ajustadas a unaconcentración final de 0.5-0.6 mg/ml en 3M Guanidine-HCl, 0.1% Triton X-100 con 20mM DTT, y almacenadas a-80°C en

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alícuotas hasta ser usadas en la reacción enzimática. Esta proteína no era estable en largos períodos, y podría agregarse aún en el almacenamiento amortiguador a 80°C. Por tanto, era necesario preparar una nueva preparación cada tres meses para mantener un inventario activo para soportar actividades internas de clasificación.

Expresión bacterial y purificación de dominio intracelular Notch recombinante (NICD) estándar para ELISA.

El estándar NICD fue producido como una proteína de fusión a partir de un constructo conteniendo una metionina iniciadora y un sitio de partición enteroquinasa antes del producto gamma- secretasa NICD (Met-EK-NICD),con una etiqueta péptido de fusión de unión a calmodulin carboxi-terminal, y una etiqueta epítope HA. La proteína de fusión fue producida en *E.coli,* afinidad purificad usando una resina de afinidad calmodulin y probada su concentración de proteínas. La proteína fue entonces particionada con enteroquinasa a objeto de producir el N-terminal libre del producto NICD. La proteína particionada con enteroquinasa fue separada por SDS-PAGE en un gel al 12% de Tris-glicina. Productos de partición por enteroquinasa fueron detectados medianre transferencia Western usando un anticuerpo contra la etiqueta-HA. Densitometría fue usada para medir la eficiencia de la partición EK. La concentración estimada de NICD estándar particionado con EK fue calculada (% de NICD / proteína reactiva HA total). El estándar fue almacenado a -40°C. En el día de cada ensayo, una alícuota del estándar NICD fue diluida serialmente 1 :1. En Diluente Caseína (Facilidad Media) para generar un curva estándar con 0 - 200 ng/ml NICD.

Reacción in vitro de sustrato Notch con enzima

Sustrato purificado (arriba) fue desalado inmediatamente antes de su uso en una columna NAP-25 y su concentración fue determinada usando el ensayo de proteínas Biorad DC. Sustrato fue diluido 1:20 en la reacción final con una dilución 1:20 de enzima gamma – secretasa (0.4mg/ml final en Tipo V fosfolípido solubilizado en BigCHAP, 50mM MES pH6.0, 4mM DTT, 0.02% TX-100) y se incubó en presencia de inhibidores de proteasa (1mM 1,10-fenantrolina, 5□g/ml

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E64, and 5□g/ml leupeptina), más o menos un rango de concentraciones de inhibidores de la gamma – secretasa. Todas las reacciones fueron incubadas a 37°C en placas de 96 pozos durante 3 horas y luego extinguidas con 0.1% SDS durante 10 minutos a temperatura ambiental. Las reacciones extinguidas fueron entonces diluidas 1:1 en Diluente Caseína con 500mM NaCl, 0.02% TritonX-100 y transferidas a un plato de captura ELISA durante la noche a 4°C. Estándares NICD (sección 4.2 arriba, serialmente diluido 2X en un rango de concentración que va desde una concentración inicial de 50 ng/ml) fueron usados para establecer una curva estándar. El producto de reacción NICD y los estándares de concentración capturados en la placafueron cuantificados usando un esquema de detección ELISA. Un anticuerpo biotinilado –HA (1 μg/ml final conc., Roche Cat#. 1666851), seguido de estreptavidina alcalinofosfatasa-conjugada (diluída 1000X de stock, Roche Cat# 1089161) fue incubado en la placa de captura ELISA con pasos de lavado (Tris amortiguada solución salina, 0.1% Tween20) entre cada paso de incubación. La reacción alcalino fosfatasa fue desarrollada por incubación con 100 μl/pozo Sustrato I Fluorescente A por 15 min en RT, y la extensión de la fluorescencia, proporciona a la cantidad de Notch particionada, usando un lector de placa Cytofluor puesto @ 360nm Excitación, 460nm Emisión.

Ejemplo C

Ensayo de Señalización Notch

El ensayo de señalización Notch es una lectura de salida con base en un gen reportero luciferasa de lisados celulares generados del ensayo celular dual SNC. Siguiendo la transferencia de media condicionada (para medir A □ de células SNC incubadas durante la noche con inhibidores) las células fueron enjuagadas en PBS, lisadas y probadas para su actividad de gen reportero Luciferasa usando un protocolo y reagentes proporcionados por el fabricante (Promega).Las muestras fueron guardadas a la sombra hasta ser leídas en un luminómetro (lector de placas Safire, Tecan).

Cultivos celulares y tratamiento inhibidor

Células CHO establemente transfectadas con los constructos SweAPP y Notch□E

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fueron colocadas en placas de 96 pozos para cultivo de tejidos a 15.000 células por pozo en 130 µl media/pozo el anterior al tratamiento del compuesto. Células fueron cultivadas en DMEM conteniendo 2 mM glutamina, 10% FBS, 0.5 mg/ml G418, 1 mg/ml higromicina, y2.8 mg/ml puromicina.Los compuestos fueron diluidos primero 4 veces y luego 10 veces para seis diluciones sucesivas en DMSO como reserva de concentración final 250X. Los compuestos fueron entonces añadidos a células usando media precalentada a 37° C a una concentración final DMDO de 0.4%. Luego de 18 h, 100 µl de medios condicionados fueron removidos de cada pozo para ser usados en el ensayo ELISA. Los pozos fueron lavados con 200 µl/ pozo de PBS frío con $MgCl_2$ y $CaCl_2$. El amortiguador de lavado fue aspirado y las células fueron lisadas en 40 µl de reagente de lisis (20 mM Tris, pH 7.5, 0.2% TX100, 100 mM NaCl, 2 mM EDTA, 2X inhibidores de proteasa completos) por pozo durante 30 minutos para completar la lisis. 100 µl de reagente luciferasa fue entonces añadido a todos los pozos (Promega, en catálogo, N° #E1501) y la luminiscencia medida usando un lector de placas Safire II (Tecan).

Este ensayo se realizó de una forma completamente automatizada usando la plataforma Stacatto (Caliper Life Sciences).

Aβ 40 y Aβ42 específicos ELISA

La media condicionada (CM) de células CHO establemente transfectadas con los constructos SweAPP y Notch□E fue directamente tomada del pozo sin diluir para los ensayos ELISA A□(X-40) y A□ (X-42) después de incubación durante la noche con el compuesto de prueba. El anticuerpo de captura para ELISA A□(X-40) y A□ (X-42) fue 266 y el anticuerpo reportero (indicador) fue el biotinilado-2G3 (dirigido hacia A□40). El anticuerpo de captura para el ensayo A□(X-42) ELISA fue también 266 donde el anticuerpo reportero fue el biotinilado-21F12 (dirigido hacia Aβ 42). Unas curvas estándar Aβ (1-40) y Aβ (1-42) de péptidos sintéticos fueron usadas para calcular las concentraciones CM Aβ. IC_{50} determinaciones de los compuestos se calcularon usando el programa GraphPad Prism escogiendo la ecuación de curva variable respuesta dosis sigmoidal.

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Ejemplo D

Ensayo dual de células SNC para ensayo simultáneo de reducción A-beta y señalización Notch subsiguiente a la inhibición de la gamma secretasa en células

Producción de Células CHO Establemente Transfectadas Sobreexpresando APP (SWE), Notch-Δe, y un Gen indicador Luciferasa Sensible Dominio Intracelular Notch y Desarrollo de Ensayo Dual de Células SNC. Con el objeto de facilitar la prueba de la potencia de inhibidores gamma-secretasa sobre dos sustratos (APP y Notch) simultáneamente, un ensayo dual usando una línea de células establemente expresando APPSwe, un sustrato Notch careciendo de ecto-dominio, y un gen indicador Luciferasa Notch-sensible fue desarrollado. Células CHOSwe sobre-expresan establemente la isoforma FAD sueca de APP y secretan grandes cantidades de péptido Aβ en media condicionada de actividadenzimática de endógenas β- and γ-secretasa. Un gen indicador sensible al dominio intracelular Notch (NICD) y el constituyente sustrato Notch gamma secretasa, Notch-Δe, fueron establemente introducidos en células CHOSwe en un proceso de dos pasos. Células CHOwe fueron primero establemente transfectadas para expresar un constructo gen indicador Luciferasa sensible NCID (pGL2-CBF-Luc). Numerosos clones estables (clones SCH) fueron identificados desplegando señalización señalización Notch sensible-inhibidor gamma luego de una transitoria expresión con Notch-Δe. Los mejores tres clones, SCH-32, SCH-33 y SCH-54 fueron seleccionados como células huésped para subsiguientes expresión estable de Notch-Δe, como el paso final de la generación de la línea de ensayo dual. Líneas de células estables expresando Notch-Δe de ratas fueron entonces identificadas en el segundo paso incluyendo un inhibidoe de gamma secretasa en el proceso de selección (para suprimir la toxicidad Notch/NICD) subsiguiente a la transfección del constructo Notch-Δe de ratas.

Los clones SCH-32, SCH-33 y SCH-54 fueron transfectados con el vector de expresión Notch-Δe (pIRES-ZEDN), respectivamente. Este vector maneja la expresión de un constructo truncado Notch de ratas correspondiente al producto c-

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terminal subsiguiente a derrame ecto-dominio de proteína Notch de longitud completa. El producto c-terminal es un sustrato constituyente para partición gamma-secretasa, resultante en liberación del producto dominio intracelular Notch citoplásmico (NICD) el cual reubica al núcleo y libera los genes represados por CBF. Subsiguientemente, células transfectadas pIRES-ZEDN fueron re-colocadas en placas a baja densidad en presencia del compuesto de la prueba, y seleccionadas con tres antibióticos (G418 (0.5 mg/ml)/Hygro (1 mg/ml)/Puro (2.5 mg/ml)). Las colonias antibiótico-resistentes (llamadas clones SNC por los componentes de ensayo – dual: APP**S**we/**N**otchΔE/**C**BF) fueron aisladas y expandidas para caracterización de secreción Aβ y actividad del gen indicador Luciferasa sensible NCID (i.e., señal luciferasa en presencia vs. ausencia del compuesto de la prueba). Con base en la óptima secreción Aβ y la mejor señal/entorno de actividad de gen indicador, seleccionamos al clon designado como SNC-204B8 como la línea estable de ensayo dual para nuestros subsiguientes perfiles de más inhibidores gamma secretasa.

Un típico experimental ensayo – dual fue realizado en la siguiente forma:

Día 1, las células SNC fueron plateadas en placas de ensayo de 96 pozos en media libre de inhibidores.

Día 2, las células fueron alimentadas con media fresca (libre de inhibidores) y tratadas con los compuestos de prueba en un rango de concentración de 0 nM a 40.000 nM (en diluciones incrementales 10X) una hora después del cambio de media. Las células fueron tratadas con los compuestos durante la noche a 37°C.

Día 3, señalización Notch y la parte I de Aβ-ELISA fue realizada: para el ensayo de producción Aβ, media condicionada fue recolectada y añadida a las placas recubiertas con anticuerpo 266 para la captura Aβ durante la noche. Para el ensayo de señalización Notch, las células fueron lisadas y la actividad luciferasa del lisado fue medida usando el kit Promega (ver más adelante).

Día 4, Aβ-ELISA parte II fue conducido usando anticuerpos 3D6-biotina/AP-estreptavidina.

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Ejemplo E

Ensayos Alternativos de Señalización Notch

Los sistemas de ensayo descritos en las siguientes referencias pueden también ser usados para medir la modulación (e.g., inhibición) de señalización Notch por los compuestos de la invención. Un ensayo ejemplar de gen indicador para señalización Notch fue descrito en 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*" y por Lu, F. M. y S. E. Lux, *Mol. Cell Biol.* 1996, 16(3): 952-9: *"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. Otro ensayo de señalización Notch con base en gen indicador usa un constitutivamente activo constructo Notch 1 de rata (ZEDN1) como se describe en 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, en combinación con el gen indicador luciferasa reprimible 4xwtCBF1Luc como se decsribe en 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). Cada una de las referencias anteriores está incorporada aquí en su totalidad a modo referencial.

Cuando la 4xwtCBF1 Luciferasa es co-transfectada con NotchδE (ZEDN1), gamma-secretasa partición de NotchδE libera al dominio intracelular Notch (NICD), el cual reubica al núcleo y elimina la represión transcripcional mediada por CBF1, conduciendo a la transcripción del gen indicador Luciferasa. La actividad Luciferasa es fácilmente ensayada en en extractos celulares usando kits comercialmente disponibles. La actividad del gen indicador está directamente

correlacionada con la partición por gamma secretasa de NotchδE, y como tal, una reducción en la actividad Luciferasa proporciona una conveniente medida de la inhibición de la partición por gamma secretasa de NotchδE. Una comparación de los valores IC_{50} de compuestos para inhibir la señalización Notch vs. inhibición de producción de beta amiloides en células 293sw es empleada como guía en la selección de compuestos que tengan la propiedad deseada de potente inhibidor de la síntesis beta amiloide con mínima inhibición de la señalización Notch.

Data de Selectividad Notch

La evidencia indica que el complejo gamma secretasa, compuesto por las sub-unidades presenilina, es mediador en la partición intra-membrana de la proteína precursora de amiloide (APP) así como también en la familia de proteínas Notch. Inesperadamente, los inventores han descubierto que ciertos compuestos de la invención son potentes inhibidores de la partición secretasa-mediada de APP (inhibición de la síntesis beta-amiloide, e.g., como se describe en el Ejemplo A) pero exhiben una reducida partición proteolítica de un sustrato Notch (*e.g.*, Notch-ΔE, como se describe en el Ejemplo B) o inhibición de señalización Notch (e.g., como se describe en los Ejemplos C y D).E.g, los compuestos aquí presentados exhiben mayor selectividad para la inhibición de partición APP (i.e., producción de beta amiloides mediada por la gamma secretasa) vs. inhibición de partición Notch o inhibición de señalización Notch en comparación con conocidos inhibidores de la gamma secretasa. En lo sucesivo, compuestos que puedan inhibir la partición enzimática de Notch (e.g., inhibiendo la correspondiente actividad gamma secretasa) (e.g., como se describe en el Ejemplo B) o la señalización Notch (e.g., como se describe en el Ejemplo C) serán referidos como teniendo "actividad Notch *in vitro*" o "actividad Notch". Ensayos, que pueden ser usados para determinar actividades Notch, son conocidos por las personas con habilidades en el arte. Ensayos ejemplares son descritos aquí en los Ejemplos B, C, D y E.

Ciertos compuestos aquí declarados se caracterizan por una deseable baja actividad Notch. En un ejemplo, los compuestos de la invención están caracterizados por una actividad Notch in vitro (e.g., como es medida usando el

ensayo descrito en el Ejemplo B) equivalente a un valor IC_{50} mayor que alrededor de 20nM, alrededor de 30nM, alrededor de 40nM, o alrededor de 50nM. En otro ejemplo, los compuestos de la invención se caracterizan por una actividad Notch in vitro equivalente a un valor IC_{50} mayor que alrededor de 100 nM, mayor que alrededor de 200 nM, mayor que alrededor de 300 nM, mayor que alrededor de 400 nM, mayor que alrededor de 500 nM, mayor que alrededor de 600 nM, mayor que alrededor de 700 nM, mayor que alrededor de 800 nM, mayor que alrededor de 900 nM, o mayor que alrededor de 1 μM. En otro ejemplo más, los compuestos de la invención se caracterizan por una actividad Notch in vitro equivalente a un valor IC_{50} mayor que alrededor de 2 μM, mayor que alrededor de 3 μM, mayor que alrededor de 4 μM, mayor que alrededor de 5 μM, mayor que alrededor de 6 μM, mayor que alrededor de 7 μM, mayor que alrededor de 8 μM, mayor que alrededor de 9 μM, o mayor que alrededor de 10 μM.

En otro ejemplo más, los compuestos de la invención se caracterizan por una relación de actividad Notch (i.e., Notch IC_{50}) a actividad APP (*i.e.*, Aβ IC_{50}) (como se mide en los ensayos in vitro descritos en los Ejemplos A y B, respectivamente, o en un ensayo dual como se describe en el Ejemplo D) (*e.g.*, relación de selectividad Notch IC_{50}/Aβ ED_{50}) de más de alrededor de 500, más de alrededor de 400 o más de alrededor de 300. En ejemplo ulterior, la relación de selectividad Notch / APP es mayor que alrededor de 200, mayor que alrededor de 150, o mayor que alrededor de 100. En otro ejemplo ulterior, la relación de selectividad Notch / APP es mayor que alrededor de 90, mayor que alrededor de 80, mayor que alrededor de 70, mayor que alrededor de 60, mayor que alrededor de 50 mayor que alrededor de 40, mayor que alrededor de 30, mayor que alrededor de 20, o mayor que alrededor de 10. En otro ejemplo ulterior más, la relación de selectividad Notch / APP es mayor que alrededor de 9, mayor que alrededor de 8, mayor que alrededor de 7, mayor que alrededor de 6, mayor que alrededor de 5, mayor que alrededor de 4, mayor que alrededor de 3, mayor que alrededor de 2, o mayor que alrededor de 1. En una incorporación particular, los compuestos de la invención se

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caracterizan por una relación de selectividad (i.e., Notch IC_{50}/Aβ ED_{50}) de más de alrededor de 50.

Compuestos ejemplares y su relación de selectividad Notch / APP están sumariados en la Tabla 2 de abajo.

Tabla 2

Selectividad de compuestos para partición del péptido Aβ sobre Notch

Nombre del compuesto	**Relación deSelectividad** (Notch IC_{50} / Aβ ED_{50})
(±)-10-[(4-clorofenil)sulfonil]-6-(3-metilisoxazol-5-il)-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol	(++++)
(-)-5-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona	(++++)
(-)-8-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona	(++++)
(±)-10-[(4-clorofenil)sulfonil]-6-(3-metil-1,2,4-oxadiazol-5-il)-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol	(++++)
(±)-10-[(5-clorotiofen-2-il)sulfonil]-6-fenil-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol	(++++)
(±)-exo-6-(4-fluorofenil)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol	(+++)

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(+)-endo-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10-ol	(+++)
(±)-10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-carbonitrilo	(+++)
(±)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-6-[4-(trifluorometil)-1,3-tiazol-2-il]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol	(+++)
(+)-6-(3-fluorofenil)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol	(+++)
(+)-5,10-difluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol	(++)
(±)-6-(1,2,3-tiadiazol-4-il)-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol	(++)
(±)-endo-6-(4-fluorofenil)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol	(++)
5-fenil-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol	(++)
(±)-7-[3-(trifluorometil)fenil]-12-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,11-tetrahidro-3H-5,11-epiminobenzo[4,5]cicloocta[1,2-c]pirazol	(++)
(±)-7-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminopirazol[3',4':5,6]ciclohepta[1,2-b]piridina	(+)

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(±)-6-[3-(1H-pirazol-1-il)fenil]-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol	(+)
(±)-6-(3-bromofenil)-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol	(+)
(±)-6-(1,3-benzodioxol-5-il)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol	(+)
(-)-6-bromo-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol	(+)

En la Tabla de arriba, (++++) significa una relación de Notch IC_{50}/ Aβ EC_{50} (determinada como se describe en el Ejemplo D) de >200; (+++) significa una relación de desde alrededor de 150 hasta alrededor de 199; (++)significa una relación de desde alrededor de 100 hasta alrededor de 149; y (+)significa una relación de desde alrededor de 50 hasta alrededor de 99.

La invención, y la manera y el proceso de hacerla y usarla, están ahora descritos en términos tan completos, claros, concisos y exactos que permiten a cualquier persona calificada en el arte al cual estos se refieren, hacer y usar la misma. Debe entenderse que lo anterior describe aspectos preferenciales de la invención y que pueden hacerse modificaciones en los mismos sin apartarse del espíritu o el ámbitp de la invención como se establece en las reivindicaciones. Para particularmente señalar y claramente reivindicar la materia considerada como invención, las siguientes reivindicaciones concluyen esta especificación.

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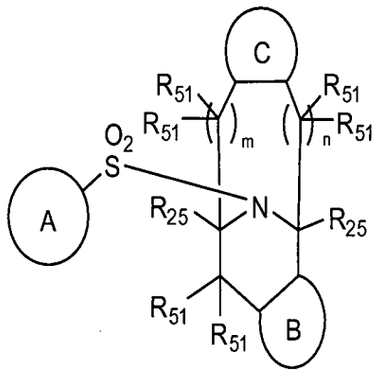
Lo reivindicado es:

1. Compuestos de la fórmula:



O una farmacéuticamente aceptable sal o solvato de este, en donde,

m y n son independientemente 0 ó 1, provisto que m + n es 0 ó 1;

el Anillo-A es aril, cicloalquil, heteroaril o heterocicloalquil, donde cada anillo es opcionalmente sustituido en una sustituible posición con halógeno, C_1-C_6 alquil, C_2-C_6 alquenil, C_2-C_6 alquinil, C_1-C_6 alcoxi, haloalquil, haloalcoxi, hidroxil, hidroxialquil, CN, ariloxi, -$S(O)_{0-2}$-(C_1-C_6 alquil), -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, NO_2, CN, C_2-C_6 alcanoil, C_0-C_3alquilCO_2R_{11}, heteroaril, heterocicloalquil, aril, arilalquil, -OCH_2O-, -OCH_2CH_2O- o -$SO_2NR_{11}R_{11}$;

el anillo-B es pirazolil, dihidropirazolil, pirazolonil o pirazolidinonil, cada uno opcionalmente sustituido con C_1-C_6 alquil, C_3-C_6 cicloalquil, C_2-C_4 alquenil, C_2-C_4 alquinil, C_1-C_4 alcoxi, amino, C_1-C_4 alquilamino, C_1-C_4 dialquilamino, hidroxi, hidroxialquil, halo, C_1-C_4 haloalquil, C_1-C_4 haloalcoxi, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$ o CN;

en donde el anillo-C es aril sustituido con R_{30}, R_{35}, R_{40}, y R_{45} o heteroaril, opcionalmente sustituido con halógeno, C_1-C_6 alquil, C_1-C_6 haloalquil, C_1-C_6 haloalcoxi, CN, hidroxil, C_1-C_6 alcoxi, -C_1-C_3 alquil-OH, -C_1-C_3 alquil-alcoxi, feniloxi, -$S(O_2)R_{10}$, -$SO_2NR_{11}R_{11}$, -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil, thienil, fenil o fenil C_1-C_4 alquil, en donde las porciones

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fenil de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_4 haloalqui o halógeno;

R_{30}, R_{35}, R_{40}, y R_{45} son independientemente H, halógeno, C_1-C_6 alquil, C_2-C_6 alquenil, C_2-C_6 alquinil, C_2-C_8 haloalquenil, C_2-C_8 haloalquinil, $-SO_2NR_{11}R_{11}$, arilalquil, cicloalquil, C_1-C_6 haloalquil, C_1-C_6 haloalcoxi, CN, NO_2, hidroxil, C_1-C_6 alcoxi, -C_1-C_6 alquil-OH, -C_1-C_6 alquil-C_1-C_6 alcoxi, ariloxi, $-S(O_2)R_{10}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, heteroarilalquil, heteroaril, en donde cada grupo heteroaril es opcionalmente sustituido con un grupo C_1-C_6 alquilo, heterocicloalquilalquil, heterocicloalquil, en donde cada grupo heterocicloalquil es opcionalmente sustituido con uno o dos grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi o halógeno, aril, ariloxi o arilalquil, donde las porciones aril de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi, hidroxilo, C_1-C_4 haloalqui o halógeno; y

Donde dos sustitutos adyacentes en el anillo-C junto con los carbonos a los que están unidos opcionalmente forman un anillo heterocicloalquil o heteroaril, cada uno opcionalmente sustituido con uno o más grupos que son independientemente alquil, alcoxi, halógeno o C_2-C_4 alcanoil en donde el grupo alcanoil es opcionalmente sustituido ulteriomente con hasta 3 átomos halógeno; o dos carbonos adyacentes al Anillo-C opcionalmente forman un anillo benzo el cual es opcionalmente sustituido con 1 a 4 grupos que son independientemente halógeno, hidroxil, alquil, alcoxi, haloalquil, haloalcoxi, CN o NO_2;

Cada R_{25} es independientemente H, C_1-C_6 alquil, C_1-C_6 haloalquil, $-C(O)O_{11}$, -(C_1-C_6 alquil)-$C(O)O_{11}$, C_1-C_6 alcoxi C_1-C_6 alquil, $-C(O)O_{11}$, $-CONR_{11}R_{11}$, CN, C_1-C_6 alquil-CN o hidroxi C_1-C_6 alquil;

Cada R_{51} está independientemente ausente, o es H, C_1-C_4 alquil, halógeno, CN, amino, mono alquilamino o dialquilamino, OH o C_1-C_4 haloalquil; ulteriomente cuando hay dos grupos R_{51} en un átomo de carbono, los dos grupos R_{51} y el carbono al cual están unidos pueden formar un anillo cicloalquil de 3 a 6

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miembros; o cuando hay dos grupos R_{51} en un carbono, los dos grupos R_{51} pueden formar un grupo oxo;

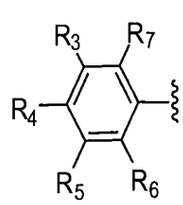
R_{10} y R_{11} en cada ocurrencia son independientemente C_1-C_6 alquil, heteroaril que es seleccionado de pirazolil, tiadiazolil, triazolil, isoxazolil, isotiazolil, imidazolil, tiazolil, oxadiazolil, y piridil o aril que es seleccionado de fenil y naftil, donde los grupos heteroaril y aril son opcionalmente sustituidos con 1 a 3 grupos que son independientemente halógeno, hidroxil, alquil, alcoxi, haloalquil, haloalcoxi, CN o NO_2; y adicionalmente R_{11} puede ser H; o si dos grupos R_{11} están en un nitrógeno, entonces los dos grupos R_{11} junto con el nitrógeno al cual están unidos, pueden formar un anillo de 3-8 miembros opcionalmente incluyendo un hetero átomo adicional tal como NH, NR_{12}, NR_{13}, O o S;

R_{12} es H, C_1-C_6 alquil, aril o $-SO_2$-aril, donde cada aril es opcionalmente sustituido con 1 a 5 grupos que son independientemente halógeno, hidroxil, alquil, alcoxi, haloalquil, haloalcoxi, CN o NO_2; y

R_{13} es H, aril o C_1-C_6 alquil opcionalmente sustituido con aril, hidroxil o halógeno, donde cada aril es opcionalmente sustituido con 1 a 5 grupos que son independientemente halógeno, hidroxil, alquil, alcoxi, haloalquil, haloalcoxi, CN o NO_2.

2. Compuestos o sales de acuerdo a la reivindicación 1, donde

El anillo-A es fenil, y tiene la siguiente fórmula:



donde

R_3, R_4, R_5, R_6, R_7 son independientemente uno de otro H, halógeno, C_1-C_6 alquil, C_1-C_6 haloalquil, C_1-C_6 haloalcoxi, CN, hidroxil, C_1-C_6 alcoxi, -C_1-C_3 alquil-OH, -C_1-C_3 alquil-alcoxi, feniloxi, -$S(O_2)R_{10}$, -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil, tienil, fenil o fenil C_1-C_4 alquil, donde las porciones fenil de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_4 haloalqui o halógeno; o

R_4 and R_5 o R_5 y R_6 y los carbonos a que están unidos forman un heterocicloalquil o un anillo heteroaril que es opcionalmente sustituido con 1, 2, 3 o 4 grupos que son independientemente C_1-C_4 alquil, C_1-C_4 alcoxi, halógeno o C_1-C_4 alcanoil donde el grupo alcanoil es opcionalmente sustituido con hasta 3 átomos halógeno; o

R_4 y R_5 o R_5 y R_6 y los carbonos a los que están unidos forman un anillo benzo que es opcionalmente sustituido con 1 a 5 grupos que son independientemente halógeno, hidroxil, alquil, alcoxi, haloalquil, haloalcoxi, CN o NO_2; o

El anillo-A es C_3-C_8 cicloalquil, que es opcionalmente sustituido en una posición sustituible con halógeno, C_1-C_6 alquil, C_2-C_6 alquenil, C_2-C_6 alquinil, C_1-C_6 alcoxi, haloalquil, haloalcoxi, hidroxil, hidroxialquil, CN, feniloxi, -$S(O)_{0-2}$-(C_1-C_6 alquil), -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, C_0-C_3alquilCO_2R_{10}, piridil, tienil, furanil, pirrolil, pirrolidinil, piperidinil, piperazinil, fenil, fenil C_1-C_4 alquil o -$SO_2NR_{11}R_{11}$, donde las porciones fenil de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_4 haloalquil o halógeno; o

el anillo-A es heteroaril que es piridil, pirimidil, piridazinil, pirazinil, tienil, furanil, pirrolil, pirazolil o imidazolil, cada uno opcionalmente sustituido en una o más posiciones sustituibles con halógeno, C_1-C_6 alquil, C_2-C_6 alquenil, C_2-C_6 alquinil, C_1-C_6 alcoxi, haloalquil, haloalcoxi, hidroxil, hidroxialquil, CN, feniloxi, -$S(O)_{0-2}$-(C_1-

C_6 alquil), $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, C_0-C_3alquilCO_2R_{10}, piridil, tienil, furanil, pirrolil, pirrolidinil, piperidinil, piperazinil, fenil, fenil C_1-C_4 alquil o $-SO_2NR_{11}R_{11}$, donde las porciones fenil de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_4 haloalqui o halógeno;

el anillo-A es heterocicloalquil que es pirrolidinil, piperidinil, piperazinil, morfolinil, tiomorfolinil o tiomorfolinil-S,S-dióxido, donde cada uno de los anillos de arriba es opcionalmente sustituido en una posición sustituible con halógeno, C_1-C_6 alquil, C_2-C_6 alquenil, C_2-C_6 alquinil, C_1-C_6 alcoxi, haloalquil, haloalcoxi, hidroxil, hidroxialquil, CN, feniloxi, $-S(O)_{0-2}$-(C_1-C_6 alquil), $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, C_0-C_3alquilCO_2R_{10}, piridil, tienil, furanil, pirrolil, pirrolidinil, piperidinil, piperazinil, fenil, fenil C_1-C_4 alquil o $-SO_2NR_{11}R_{11}$, donde las porciones fenil de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_4 haloalqui o halógeno.

3. Compuestos o sales de acuerdo a la reivindicación 2, donde el anillo-A es fenil o piridil, cada uno de los cuales es opcionalmente sustituido con halógeno o C_1-C_4 haloalquil.

4. Compuestos o sales de acuerdo a la reivindicación 2, donde

El anillo-C es fenil sustituido con R_{30}, R_{35}, R_{40}, and R_{45}; o heteroaril, donde el grupo heteroaril es opcionalmente sustituido con H, halógeno, C_1-C_6 alquil, C_1-C_6 haloalquil, C_1-C_6 haloalcoxi, CN, hidroxil, C_1-C_6 alcoxi, -C_1-C_3 alquil-OH, -C_1-C_3 alquil-alcoxi, feniloxi, $-S(O_2)R_{10}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil, tienil, fenil o fenil C_1-C_4 alquil, donde las porciones fenil de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_4 haloalquil o halógeno;

R_{30}, R_{35}, R_{40}, y R_{45} son independientemente H, halógeno, C_1-C_6 alquil, C_2-C_6 alquenil, C_2-C_6 alquinil, C_2-C_8 haloalquenil, C_2-C_8 haloalquinil, $-SO_2NR_{11}R_{11}$,

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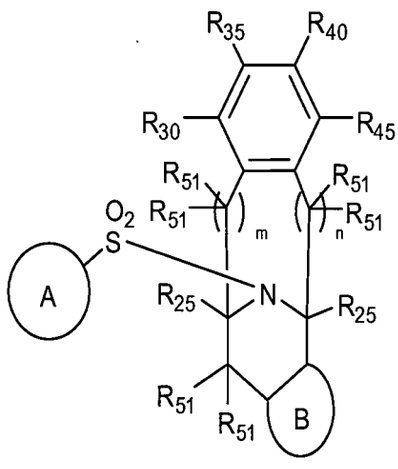
arilalquil, cicloalquil, C_1-C_6 haloalquil, C_1-C_6 haloalcoxi, CN, NO_2, hidroxil, C_1-C_6 alcoxi, -C_1-C_6 alquil-OH, -C_1-C_6 alquil-C_1-C_6 alcoxi, ariloxi, -$S(O_2)R_{10}$, -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, heteroarilalquil, heteroaril, donde cada grupo heteroaril es opcionalmente sustituido con un grupo alquil, heterocicloalquilalquil, heterocicloalquil, donde cada grupo heterocicloalquil es opcionalmente sustituido con uno o dos grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi o halógeno, aril, ariloxi o arilalquil, donde las porciones aril de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi, hidroxil, C_1-C_4 haloalqui o halógeno; y

Donde cuando el Anillo-C es aril o heteroaril, dos carbonos adyacentes del Anillo-C forman opcionalmente un anillo heterocicloalquil o un anillo heteroaril, cada uno opcionalmente sustituido con uno o más grupos que son independientemente alquil, alcoxi, halógeno o C_2-C_4 alcanoil donde el grupo alcanoil es opcionalmente sustituido ulteriormente con hasta 3 átomos de halógeno; o dos adyacentes carbonos del Anillo-C opcionalmente forman un anillo benzo ring el cual es opcionalmente sustituido con 1 a 4 grupos que son independientemente halógeno, hidroxil, alquil, alcoxi, haloalquil, haloalcoxi, CN o NO_2.

5. Compuestos o sales de acuerdo a la revindicación 4, de la fórmula:



O farmacéuticamente aceptables solvatos, sales o mezclas de estos, donde

cada R_{25} es independientemente H, C_1-C_4 alquil, C_1-C_4 haloalquil, hidroxi C_1-C_4 alquil, C_1-C_4 alcoxialquil, -$C(O)OR_{11}$ o -$C(O)NR_{11}R_{11}$; y

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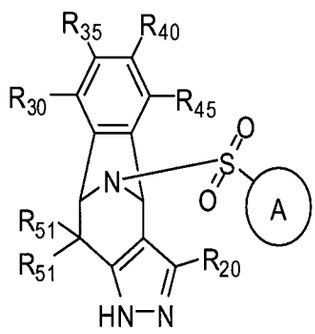
cada R_{51} es independientemente ausente, H, C_1-C_4 alquil, F, Cl, Br, CN, amino, mono alquilamino o dialquilamino, OH o CF_3; además, cuando hay dos grupos R_{51} en un átomo de carbono, los dos grupos R_{51} y el carbono al cual están unidos pueden formar un anillo cicloalquil o heterocicloalquil de 3 a 6 miembros; o cuando hay dos grupos R_{51} en un carbono, los dos grupos R_{51} pueden formar un grupo oxo;

6. Compuestos o sales de acuerdo a la revindicación 5, donde el anillo-B es pirazolil, el cual es opcionalmente sustituido con $-NR_{11}$-C_2-C_6 alcanoil, C_1-C_4 alquil, C_3-C_6 cicloalquil, C_2-C_4 alquenil, C_2-C_4 alquinil, C_1-C_4 alcoxi, amino, C_1-C_4 alquilamino, C_1-C_4 dialquilamino, hidroxi C_1-C_4 alquil, halo, CF_3, OCF_3 o CN.

7. Compuestos o sales de acuerdo a la revindicación 6, de la fórmula:



O farmacéuticamente aceptables solvatos, sales o mezclas de estos, donde

R_{20} es H, C_1-C_4 alquil, C_1-C_4 alcoxi, $-NR_{11}C(O)CH_3$, amino, C_1-C_4 alquilamino, C_1-C_4 dialquilamino, halo, CF_3 o CN; donde R_{11} es H o C_1-C_6 alquil; y

R_{30}, R_{35}, R_{40}, y R_{45} son independientemente H, halógeno, C_1-C_6 alquil, C_1-C_6 haloalquil, C_1-C_6 haloalcoxi, CN, hidroxil, C_1-C_6 alcoxi, $-C_1$-C_3 alquil-OH, $-C_1$-C_3 alquil-alcoxi, feniloxi, $-S(O_2)R_{10}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil, tienil, fenil o fenil C_1-C_4 alquil, donde las porciones fenil de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi o halógeno.

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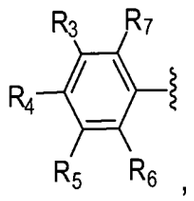
8. Compuestos o sales de acuerdo a la revindicación 7, donde el Anillo-A es:



donde,

R_3, R_4, R_5, R_6, R_7 son independientemente uno de otro H, halógeno, C_1-C_4 alquil, C_1-C_4 haloalquil, C_1-C_4 haloalcoxi, CN, hidroxil, C_1-C_4 alcoxi, -C_1-C_3 alquil-OH, -C_1-C_3 alquil-C_1-C_4 alcoxi, feniloxi, -$S(O_2)R_{10}$, -$SO_2NR_{11}R_{11}$, -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$ o C_2-C_4 alcanoil; o

el anillo-A es piridil, el cual es opcionalmente sustituido en una o más posiciones sustituibles con grupos que son independientemente halógeno, C_1-C_6 alquil, C_1-C_6 alcoxi, CF_3, OCF_3, hidroxil, CN, feniloxi, -SO_2-(C_1-C_6 alquil), -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, piridil, fenil o -$SO_2NR_{11}R_{11}$, donde

cada R_{10} y R_{11} es independientemente C_1-C_6 alquil o fenil; y adicionalmente R_{11} puede ser H.

9. Compuestos o sales de acuerdo con la reivindicación 8, donde

el Anillo-A es fenil, R_4 es halógeno, C_1-C_4 alquil, C_1-C_4 alcoxi, CF_3, OCF_3 o CN; y R_3, R_5 R_6, y R_7 son hidrógeno.

10. Compuestos o sales de acuerdo con la reivindicación 8, donde el Anillo-A es piridil, opcionalmente sustituido con un halógeno o CF_3.

11. Compuestos o sales de acuerdo con la reivindicación 8, donde al menos un grupo R_{51} es halógeno.

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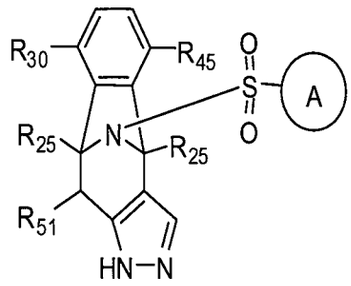
12. Compuestos o sales de acuerdo con la reivindicación 8, donde los dos grupos R_{51} son ambos H, ambos halógeno o forman un grupo oxo.

13. Compuestos o sales de acuerdo a la revindicación 8, de la fórmula:



incluyendo estéreo isómeros, tautómeros y mezclas de estéreo isómeros y/o tautómeros, y/o sales farmacéuticasde éstos, donde

cada R_{25} es independientemente H o CH_3;

R_{30} y R_{45} son independientemente H, halógeno, C_1-C_6 alquil, C_1-C_6 haloalquil, C_1-C_6 haloalcoxi, CN, hidroxil, C_1-C_6 alcoxi, -C_1-C_3 alquil-OH, -C_1-C_3 alquil-alcoxi, feniloxi, C_2-C_6 alquenil, C_2-C_6 alquinil, C_2-C_6 haloalquenil, C_2-C_6 haloalquinil, -C(O)OR_{11}, -S(O_2)R_{10}, -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alcanoil, oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil, tienil, fenil o fenil C_1-C_4 alquil, donde las porciones fenil de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_4 haloalquil o halógeno; y

R_{51} es H, C_1-C_4 alquil, F, Cl, Br, CN, amino, mono alquilamino o dialquilamino, OH o CF_3.

14. Compuestos o sales de acuerdo a la revindicación 13, donde al menos uno de R_{30} y R_{45} es F; y R_{51} es H, F o OH.

15. Compuestos o sales de acuerdo a la revindicación 8, de la fórmula:

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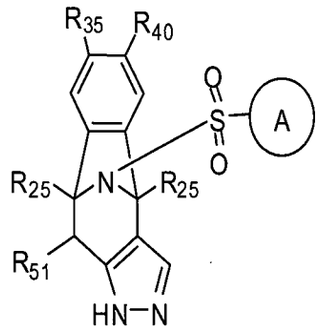

incluyendo estéreo isómeros, tautómeros y mezclas de estéreo isómers y/o tautómeros, y/o sales farmacéuticasde éstos, donde

cada R_{25} es independientemente H o CH_3;

R_{35} y R_{40} son independientemente H, halógeno, C_1-C_6 alquil, C_1-C_6 haloalquil, C_1-C_6 haloalcoxi, CN, hidroxil, C_1-C_6 alcoxi, -C_1-C_3 alquil-OH, -C_1-C_3 alquil-alcoxi, feniloxi, C_2-C_6 alquenil, C_2-C_6 alquinil, C_2-C_6 haloalquenil, C_2-C_6 haloalquinil, -C(O)OR_{11}, -S(O_2)R_{10}, -$SO_2NR_{11}R_{11}$, -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 al canoil, oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil, tienil, fenil o fenil C_1-C_4 alquil, donde las porciones fenil de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_4 haloalqui o halógeno; y

R_{51} es H, C_1-C_4 alquil, F, Cl, Br, CN, amino, mono alquilamino o dialquilamino, OH o CF_3.

16. Compuestos o sales de acuerdo a la revindicación 15, donde al menos uno de R_{35} y R_{40} es F; y R_{51} es H, F o OH.

17. Compuestos o sales de acuerdo a la revindicación 2, donde el

Anillo-C es un anillo heteroaril o heterocicloalquil que es opcionalmente sustituido con uno o más grupos que son independientemente halógeno, C_1-C_6 alquil, C_1-C_6 haloalquil, C_1-C_6 haloalcoxi, C_2-C_8 alquenil, C_2-C_8 alquinil, C_2-C_8

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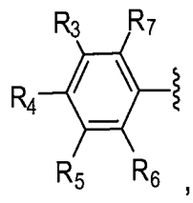
haloalquenil, C_2-C_8 haloalquinil, -C(O)OR_{11}, CN, hidroxil, C_1-C_6 alcoxi, -C_1-C_3 alquil-OH, -C_1-C_3 alquil-alcoxi, feniloxi, -S(O_2)R_{10}, -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alcanoil, oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil, tienil, fenil o fenil C_1-C_4 alquil, donde las porciones fenil de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_4 haloalqui o halógeno; cada R_{10} y R_{11} es independientemente C_1-C_6 alquil o fenil; y adicionalmente R_{11} puede ser H; y

el anillo-B es pirazoli, el cual es opcionalmente sustituido con C_1-C_4 alquil, C_3-C_6 cicloalquil, C_2-C_4 alquenil, C_2-C_4 alquinil, C_1-C_4 alcoxi, amino, C_1-C_4 alquilamino, C_1-C_4 dialquilamino, hidroxi C_1-C_4 alquil, halo, CF_3, OCF_3 o CN.

18. Compuestos o sales de acuerdo a la revindicación 17, donde el Anillo-A es fenil, y tiene la siguiente fórmula:



donde,

R_3, R_4, R_5, R_6, R_7 son independientemente uno de otro H, halógeno, C_1-C_4 alquil, C_1-C_4 haloalquil, C_1-C_4 haloalcoxi, CN, hidroxil, C_1-C_4 alcoxi, -C_1-C_3 alquil-OH, -C_1-C_3 alquil-C_1-C_4 alcoxi, feniloxi, -S(O_2)R_{10}, -$SO_2NR_{11}R_{11}$, -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$ o C_2-C_4 alcanoil; o

el Anillo-A es piridil, el cual es opcionalmente sustituido en una o más posiciones sustituibles con grupos que son independientemente halógeno, C_1-C_6 alquil, C_1-C_6 alcoxi, CF_3, OCF_3, hidroxil, CN, feniloxi, -SO_2-(C_1-C_6 alquil), -$NR_{11}R_{11}$, -C(O)$NR_{11}R_{11}$, -NR_{11}C(O)R_{10}, -$NR_{11}SO_2R_{10}$, -O-C(O)$NR_{11}R_{11}$, C_2-C_6 alcanoil, piridil, fenil o -$SO_2NR_{11}R_{11}$, donde

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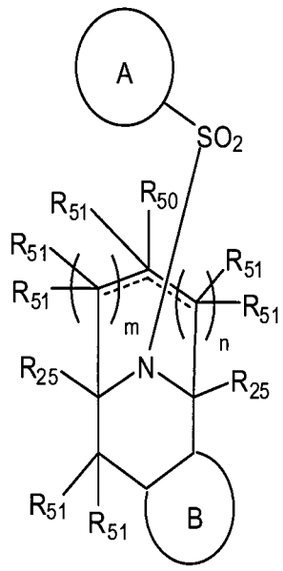
cada R_{10} y R_{11} es independientemente C_1-C_6 alquil o fenil; y adicionalmente R_{11} puede ser H; y

cada R_{25} es independientemente H o CH_3.

19. Compuestos o sales de acuerdo a la revindicación 17, donde el Anillo-A es fenil o piridil, y cada uno es opcionalmente sustituido con halógeno o C_1-C_4 haloalquil.

20. Compuestos teniendo las fórmulas:



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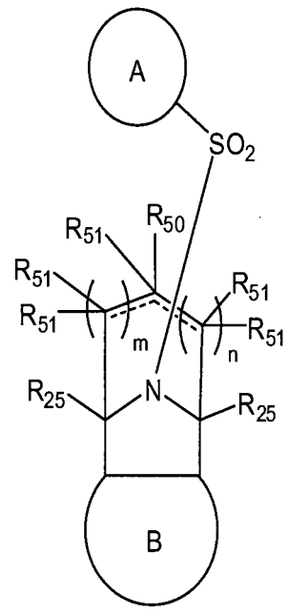

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Fòrmula 1 Fórmula 2

O farmacéuticamente aceptables solvatos o sales de estos, donde

m y n son independientemente seleccionados de 0, 1 y 2, siempre y cuando (m + n) sea 1 ó 2;

el Anillo-A es aril, cicloalquil, heteroaril o heterocicloalquil, donde cada anillo es opcionalmente sustituido en una o más posiciones sustituibles con halógeno, C_1-C_6 alquil, C_2-C_6 alquenil, C_2-C_6 alquinil, C_1-C_6 alcoxi, haloalquil, haloalcoxi, hidroxil, hidroxialquil, CN, ariloxi, $-S(O)_{0-2}-(C_1-C_6$ alquil), $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, NO_2, CN, C_2-C_6 al canoil, C_0-

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C_3alquilCO_2R_{11}, heteroaril, heterocicloalquil, aril, arilalquil, $-OCH_2O-$, $-OCH_2CH_2O-$ o $-SO_2NR_{11}R_{11}$;

el anillo-B es pirazolil, dihidropirazolil, pirazolonil o pirazolidinonil, cada uno opcionalmente sustituido con $-NR_{11}$-C_2-C_6 alcanoil, C_1-C_6 alquil, C_3-C_6 cicloalquil, C_2-C_4 alquenil, C_2-C_4 alquinil, C_1-C_4 alcoxi, amino, C_1-C_4 alquilamino, C_1-C_4 dialquilamino, hidroxi, hidroxialquil, halo, C_1-C_4 haloalquil, C_1-C_4 haloalcoxilo, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$ o CN;

R_{50} es C_2-C_6 alquenil, C_2-C_6 alquinil, halo C_2-C_6 alquenil, halo C_2-C_6 alquinil, C_2-C_6 alcanoil, $OS(O)_2R_{10}$, $-S(O)_2R_{10}$, $-NR_{11}R_{11}$, $C(O)OR_{11}$, $-SO_2NR_{11}R_{11}$, heteroaril, heterocicloalquil, C_3 –C_6 cicloalquil, aril; donde los antes nombrados grupos heteroaril, heterocicloalquil, cicloalquil y aril son opcionalmente sustituidos con 1 o más grupos que son independientemente halógeno, C_1-C_6 alquil, C_2-C_6 alquenil, C_2-C_6 alquinil, hidroxi, hidroxiC_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_6 haloalcoxi, C_1-C_6 haloalquil, halo C_2-C_6 alquenil, halo C_2-C_6 alquinil, $-C(O)OR_{11}$, -(C_1-C_4 alquil)-$C(O)OR_{11}$, $-CONR_{11}R_{11}$, $-OC(O)NR_{11}R_{11}$, $-NR_{11}C(O)OR_{10}$, $-NR_{11}S(O)_2R_{10}$, $-OS(O)_2R_{10}$, $-S(O)_2R_{10}$, $-NR_{11}C(O)R_{10}$, CN, $=N-NHR_{12}$, $-NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, heteroaril, heterocicloalquil, C_3 –C_6 cicloalquil, aril; donde los antes mencionados sustitutos heteroaril, heterocicloalquil, cicloalquil y aril son opcionalmente sustituidos con 1 o más grupos que son independientemente halógeno, C_1-C_6 alquil, C_1-C_6 alcoxi, hidroxi, C_1-C_6 hidroxialquil, C_1-C_6 haloalcoxi o C_1-C_6 haloalquil;

Cada R_{25} es independientemente H, C_1-C_6 alquil, C_1-C_6 haloalquil, $-C(O)OR_{11}$, -(C_1-C_6 alquil)-$C(O)OR_{11}$, C_1-C_6 alcoxi C_1-C_6 alquil, $-C(O)OR_{11}$, $-CONR_{11}R_{11}$, CN, C_1-C_6 alquil-CN o hidroxi C_1-C_6 alquil;

cada R_{51} es independientemente ausente, H, C_1-C_4 alquil, halógeno, CN, amino, mono alquilamino, dialquilamino, OH o C_1-C_4 haloalquil; además cuando hay dos grupos R_{51} en un átomo de carbono, los dos grupos R_{51} y el carbono al cual están unidos pueden formar un anillo cicloalquil o heterocicloalquil de 3 a 6 miembros; o cuando hay dos grupos R_{51} en un carbono, los dos grupos R_{51} pueden formar un grupo oxo;

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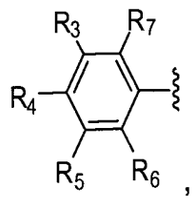
R_{10} y R_{11} a cada occurrencia son independientemente C_1-C_6 alquil, heteroaril que es seleccionado de pirazolil, tiadiazolil, triazolil, isoxazolil, isotiazolil, imidazolil, tiazolil, oxadiazolil, y piridil o aril que es seleccionado de fenil y naftil, donde los grupos heteroaril y aril son opcionalmente sustituidos con 1 to 3 grupos que son independientemente halógeno, hidroxil, alquil, alcoxi, haloalquil, haloalcoxi, CN o NO_2; y adicionalmente R_{11} puede ser H; o si dos grupos R_{11} están en un nitrógeno, entonces los dos grupos R_{11} y el carbono al cual están unidos pueden formar un anillo de 3 a 8 miembros opcionalmente incluyendo un heterátomo adicional tal como NH, NR_{12}, NR_{13}, O o S;

R_{12} es H, C_1-C_6 alquil, aril o $-SO_2$-aril, donde cada aril es opcionalmente sustituido con 1 a 5 grupos que son independientemente halógeno, hidroxil, alquil, alcoxi, haloalquil, haloalcoxi, CN o NO_2.

21. Compuestos o sales de acuerdo a la revindicación 20, donde el anillo-A es fenil y tiene la siguiente fórmula:



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En donde,

R_3, R_4, R_5, R_6, R_7 son independientemente uno de otro H, halógeno, C_1-C_6 alquil, C_1-C_6 halo alquil, C_1-C_6 haloalcoxi, CN, hidroxilo, C_1-C_6 alcoxi, -C_1-C_3 alquil-OH, -C_1-C_3 alquil- alcoxi, feniloxi, $-S(O_2)R_{10}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil, tienil, fenil o fenil C_1-C_4 alquil, donde las porciones fenil de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_4 haloalquil o halógeno; o

R_4 y R_5 o R_5 y R_6 y los carbonos a los cuales están unidos pueden formar un anillo heterociclo alquil o heteroaril que es opcionalmente sustituido con 1, 2, 3 o 4 grupos que son independientemente C_1-C_4 alquil, C_1-C_4 alcoxi, halógeno o C_1-

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C_4 alcanoil donde el grupo alcanoil es opcionalmente sustiuido con hasta 3 átomos halógeno; o

R_4 y R_5 o R_5 y R_6 y los carbonos a los cuales están unidos forman un anillo benzo que es opcionalmente sustituido con 1 a 5 grupos que son independientemente halógeno, hidroxilo, alquil, alcoxi, halo alquil, haloalcoxi, CN o NO_2; o

El anillo-A es C_3-C_8 ciclo alquil, el cual es opcionalmente sustituido en una o más posiciones sustituibles con halógeno, C_1-C_6 alquil, C_2-C_6 alquenil, C_2-C_6 alquiinil, C_1-C_6 alcoxi, halo alquil, haloalcoxi, hidroxilo, hidroxi alquil, CN, feniloxi, -$S(O)_{0-2}$-(C_1-C_6 alquil), -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alquianoil, C_0-C_3 alquilCO_2R_{10}, piridil, tienil, furanil, pirrolil, pirrolidinil, piperidinil, piperazinil, fenil, fenil C_1-C_4 alquil or -$SO_2NR_{11}R_{11}$, donde las porciones fenil de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_4 haloalquil o halógeno; o

El anillo-A es heteroaril que es piridil, pirimidil, piridazinil, pirazinil, tienil, furanil, pirrolil, pirazolil or imidazolil, cada uno de los cuales es opcionalmente sustituido en una o más posiciones sustituibles con halógeno, C_1-C_6 alquil, C_2-C_6 alquenil, C_2-C_6 alquinil, C_1-C_6 alcoxi, haloalquil, haloalcoxi, hidroxilo, hidroxialquil, CN, feniloxi, -$S(O)_{0-2}$-(C_1-C_6alquil), -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, C_0-C_3 alquilCO_2R_{10}, piridil, tienil, furanil, pirrolil, pirrolidinil, piperidinil, piperazinil, fenil, fenil C_1-C_4 alquil o -$SO_2NR_{11}R_{11}$, donde las porciones fenil de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_4 haloalqui o halógeno; o

El anillo-A es heterocicloalquil que es pirrolidinil, piperidinil, piperazinil, morfolinil, tiomorfolinil o tiomorfolinil-S,S-dióxido, donde cada uno de los anillos de arriba es opcionalmente sustituido en una posición sustituible con halógeno, C_1-C_6 alquil, C_2-C_6 alkenil, C_2-C_6 alquinil, C_1-C_6 alcoxi, halo alquil, haloalcoxi, hidroxilo, hidroxi alquil, CN, feniloxi, -$S(O)_{0-2}$-(C_1-C_6 alquil), -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, C_0-C_3 alquilCO_2R_{10}, piridil, tienil,

furanil, pirrolil, pirrolidinil, piperidinil, piperazinil, fenil, fenil C_1-C_4 alquil o -$SO_2NR_{11}R_{11}$, donde las porciones fenil de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_4 haloalquil o halógeno.

22. Compuestos o sales de acuerdo a la revindicación 20, donde el anillo-A es fenil o piridill, cada uno de los cuales es opcionalmente sustituido con halógeno o C_1-C_4 halo alquil.

23. Compuestos o sales de acuerdo a la revindicación 20, donde R_{50} es C_2-C_6 alquenil, C_2-C_6 alquinil, halo C_2-C_6 alquenil, halo C_2-C_6 alquinil, C_2-C_6 alcanoil, $OS(O)_2R_{10}$, -$S(O)_2R_{10}$, -$NR_{11}R_{11}$, $C(O)OR_{11}$ -$SO_2NR_{11}R_{11}$, heteroaril que es seleccionado de pirazolil, tiadiazolil, triazolil, isoxazolil, isotiazolil, imidazolil, tiazolil, oxadiazolil, oxazolil, tetrazolil, y piridil, heterocicloalquil que es seleccionado de tetrahidrofuranil, pirrolidinil, piperidinil, morfolinil, e imidazolidinil, C_3 –C_6 ciclo alquil aril que es seleccionado de fenil, benzo[d][1,3]dioxolil, y naftil; donde los antes nombrados grupos heteroaril, heterociclo alquil, ciclo alquil y aril son opcionalmente sustituidos con uno o más grupos que son independientemente halógeno, C_1-C_6 alquil, C_2-C_6 alquenil, C_2-C_6 alquinil, hidroxi, hidroxiC_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_6 haloalcoxi, C_1-C_6 halo alquil, halo C_2-C_6 alquenil, halo C_2-C_6 alquinil, -$C(O)OR_{11}$, -(C_1-C_4 alquil)-$C(O)OR_{11}$, -$CONR_{11}R_{11}$, -$OC(O)NR_{11}R_{11}$, -$NR_{11}C(O)OR_{10}$, -$NR_{11}S(O)_2R_{10}$, -$OS(O)_2R_{10}$, -$S(O)_2R_{10}$, -$NR_{11}C(O)R_{10}$, CN, =N-NHR_{12}, -$NR_{11}R_{11}$, -$SO_2NR_{11}R_{11}$, heteroaril que es seleccionado de pirazolil, tiadiazolil, triazolil isoxazolil, isotiazolil, imidazolil, tiazolil, oxadiazolil, oxazolil, tetrazolil, y piridil, heterociclo alquil que es seleccionado de tetrahidrofuranil, pirrolidinil, piperidinil, morfolinil, y imidazolidinil, C_3 –C_6 ciclo alquil, aril que es seleccionado de fenil, benzo[d][1,3]dioxolil, y naftil; donde los antes nombrados sustitutos heteroaril, heterociclo alquil, ciclo alquil y aril son opcionalmente sustituidos con 1 o más grupos que son independientemente halógeno, C_1-C_6

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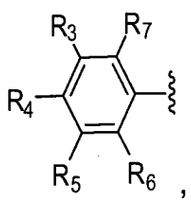
alquil, C_1-C_6 alcoxi, hidroxi, C_1-C_6 hidroxi alquil, C_1-C_6 haloalcoxi o C_1-C_6 halo alquil.

24. Compuestos o sales de acuerdo a la revindicación 23, donde el Anillo-B es pirazolil, el cual es opcionalmente sustituido con $-NR_{11}$-C_2-C_6 alcanoil, C_1-C_4 alquil, C_1-C_4 halo alquil, C_3-C_6 ciclo alquil, C_2-C_4 alquenil, C_2-C_4 alquinil, C_1-C_4 alcoxi, amino, C_1-C_4 alquilamino, C_1-C_4 di alquilamino, hidroxi C_1-C_4 alquil, halo, CF_3, OCF_3 or CN.

25. Compuestos o sales de acuerdo a la revindicación 24, donde el anillo-A es:



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Donde

R_3, R_4, R_5, R_6, R_7 son independientemente uno de otro halógeno, C_1-C_4 alquil, C_1-C_4 halo alquil, C_1-C_4 haloalcoxi, CN, hidroxilo, C_1-C_4 alcoxi, -C_1-C_3 alquil-OH, -C_1-C_3 alquil-C_1-C_4 alcoxi, feniloxi, $-S(O_2)R_{10}$, $-SO_2NR_{11}R_{11}$, $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$ or C_2-C_4 alcanoil; o

El anillo-A es piridil, el cual es opcionalmente sustituido en una o más posiciones sustituibles con grupos que son independientemente halógeno, C_1-C_6 alquil, C_1-C_6 alcoxi, CF_3, OCF_3, hidroxilo, CN, feniloxi, $-SO_2$-(C_1-C_6 alquil), $-NR_{11}R_{11}$, $-C(O)NR_{11}R_{11}$, $-NR_{11}C(O)R_{10}$, $-NR_{11}SO_2R_{10}$, $-O-C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, piridil, fenil o $-SO_2NR_{11}R_{11}$, donde

Cada R_{10} y R_{11} es independientemente C_1-C_6 alquil o fenil; y adicionalmente R_{11} puede ser H.

26. Compuestos o sales de acuerdo a la revindicación 25, donde

El anillo-A es fenil, R_4 es halógeno, C_1-C_4 alquil, C_1-C_4 alcoxi, C_1-C_4 halo alquil, C_1-C_4 haloalcoxi, o CN; y R_3, R_5 R_6, y R_7 son hidrógeno.

27. Compuestos o sales de acuerdo a la revindicación 25, donde el anillo-A es piridil, el cual es opcionalmente sustituido con un halógeno o CF_3.

28. Compuestos o sales de acuerdo a la revindicación 25, donde al menos un grupo R_{51} es halógeno.

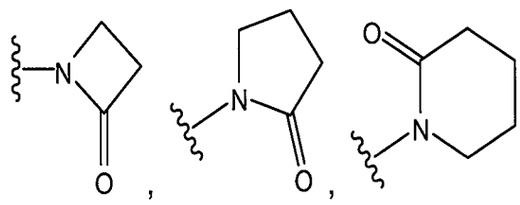
29. Compuestos o sales de acuerdo a la revindicación 25, donde los dos grupos pares R_{51} que son alfa al Anillo-B son ambos H, ambos halógeno o forman un grupo oxo.

30. Compuestos o sales de acuerdo a la reivindicación 25, donde

R_{50} es $NR_{11}R_{11}$ or $-SO_2NR_{11}R_{11}$ o $-S(O)_2R_{10}$ o

oxadiazolil opcionalmente sustituido con C_1-C_4 alquil; o

C_3-C_6 ciclo alquil el cual es opcionalmente sustituido con C_1-C_4 alquil o C_1-C_4 alcoxi; o

fenil el cual es opcionalmente sustituido con uno o más grupos que son independientemente C_1-C_4 alquil, C_1-C_4 alcoxi, halógeno, $-OCH_2O-$, $-OCH_2CH_2O-$, oxazolidinona, imidazolil, tiazolil, $-NR_{11}$-ciclohexil, donde el ciclohexil es opcionalmente sustituido con $NR_{11}R_{11}$, C_1-C_4 alquil o C_1-C_4 alcoxi; pirazolil, tetrazolil, pirrolidinonil, $-NR_{11}R_{11}$, morfolinil, 
o C_2-C_6 alcanoil; o

pirazolil opcionalmente sustituido con C_1-C_4 alquil; o

tiazolil opcionalmente sustituido con C_1-C_4 alquil, C_1-C_4 halo alquil; o

oxazolil opcionalmente sustituido con C_1-C_4 alquil; o

benzimidazolil opcionalmente sustituido con C_1-C_4 alquil, C_1-C_4 alcoxi o halógeno; o

C_2-C_6 alquenil opcionalmente sustituido con halógeno o C_1-C_4 halo alquil; o

triazolil opcionalmente sustituido con uno o dos grupos que son independientemente C_1-C_4 alquil; o

C_2-C_6 alquinil opcionalmente sustituido con halógeno o C_1-C_4 alcoxi; o

tiadiazolil opcionalmente sustituido con C_1-C_4 alquil, C_1-C_4 halo alquil; o

piridil opcionalmente sustituido con uno o más grupos que son independientemente C_1-C_4 alquil, halógeno o C_1-C_4 alcoxi;

donde R_{11} es H, C_1-C_6 alquil o C_2-C_6 alcanoil, donde las porciones alquil de R_{11} son opcionalmente sustituidos con uno o dos grupos que son independientemente -CO_2-(C_1-C_6 alquil), C_1-C_6 alquil-O-(C_1-C_6 alquil), C_1-C_6 alquil-O-(C_1-C_4 alquil)-CO_2-(C_1-C_6 alquil), C_1-C_6 alquil-O-(C_1-C_4 alquil)-CO_2H.

31. Una composición farmacéutica comprendiendo un compuesto de la reivindicación 1 y al menos un portador farmacéuticamente aceptable.

32. Un método para tratar una enfermedad neurodegenerativa comprendiendo administrar una cantidad terapéuticamente efectiva de un compuesto o sal de la reivindicación 1 a un sujeto mamífero en necesidad de tal tratamiento.

33. El método de la reivindicación 32, donde dicha enfermedad neurodegenerativa es seleccionada de Enfermedad de Alzheimer, tipo difuso corporal Lewy de la Enfermedad de Alzheimer, Enfermedad de Parkinson, síndrome de Down, demencia, discapacidad cognitiva leve (MCI), esclerosis lateral amiotróficA (ALS), lesiones traumáticas cerebrales, daño cerebral isquémico, ataque isquémico o hemorrágico, Hemorragia cerebral Hereditaria con amiloidosis de tipo holandés y angiopatía cerebral amiloide.

34. El método de la reivindicación 33, donde dicha enfermedad neurodegenerativa es la Enfermedad de Alzheimer o el tipo difuso corporal Lewy de la Enfermedad de Alzheimer, y el sujeto mamífero es un humano.

35. Un método para tratar una enfermedad seleccionada de esclerosis múltiple, cáncer, degeneración macular asociada con la edad, retinopatía diabética, y neurodegeneración retiniana relacionada con glaucoma o traumatismo ocular, comprendiendo la administración de una cantidad terapéuticamente efectiva de un compuesto o sal de la reivindicación 20 a un sujeto mamífero en necesidad de tal tratamiento.

36. Un método para el tratamiento de la Enfermedad de Alzheimer, tipo difuso corporal Lewy de la Enfermedad de Alzheimer, Enfermedad de Parkinson, síndrome de Down, demencia, discapacidad cognitiva leve (MCI), esclerosis lateral amiotróficA (ALS), lesiones traumáticas cerebrales, daño cerebral isquémico, ataque isquémico o hemorrágico, Hemorragia cerebral Hereditaria con amiloidosis de tipo holandés, angiopatía cerebral amiloide, esclerosis múltiple, cáncer, degeneración macular asociada con la edad, retinopatía diabética, y neurodegeneración retiniana relacionada con glaucoma o traumatismo ocular, comprendiendo la administración de una cantidad terapéuticamente efectiva de una composición farmacéutica de la reivindicación 31 a un humano en necesidad de dicho tratamiento.

37. Una composición farmacéutica comprendiendo un compuesto de la reivindicación 20 y al menos un portador farmacéuticamente aceptable.

38. Un método para el tratamiento de una enfermedad neurodegenerativa comprendiendo administrar una cantidad terapéuticamente efectiva de un compuesto o sal de la reivindicación 20 a un sujeto mamífero en necesidad de tal tratamiento.

39. El método de la reivindicación 38, donde dicha enfermedad neurodegenerativa es seleccionada de Enfermedad de Alzheimer, tipo difuso corporal Lewy de la Enfermedad de Alzheimer, Enfermedad de Parkinson, síndrome de Down, demencia, discapacidad cognitiva leve (MCI), esclerosis lateral amiotróficA (ALS),

lesiones traumáticas cerebrales, daño cerebral isquémico, ataque isquémico o hemorrágico, Hemorragia cerebral Hereditaria con amiloidosis de tipo holandés y angiopatía cerebral amiloide.

40. El método de la reivindicación 39, donde dicha enfermedad neurodegenerativa es Enfermedad de Alzheimer o tipo difuso corporal Lewy de la Enfermedad de Alzheimer, y el sujeto mamífero es un humano.

41. Un método para tratar una enfermedad seleccionada de esclerosis múltiple, cáncer, degeneración macular asociada con la edad, retinopatía diabética, y neurodegeneración retiniana relacionada con glaucoma o traumatismo ocular, comprendiendo la administración de una cantidad terapéuticamente efectiva de un compuesto o sal de la reivindicación 20 a un sujeto mamífero en necesidad de tal tratamiento.

42. Un método para el tratamiento de la Enfermedad de Alzheimer, tipo difuso corporal Lewy de la Enfermedad de Alzheimer, Enfermedad de Parkinson, síndrome de Down, demencia, discapacidad cognitiva leve (MCI), esclerosis lateral amiotróficA (ALS), lesiones traumáticas cerebrales, daño cerebral isquémico, ataque isquémico o hemorrágico, Hemorragia cerebral Hereditaria con amiloidosis de tipo holandés, angiopatía cerebral amiloide, esclerosis múltiple, degeneración macular asociada con la edad, retinopatía diabética, y neurodegeneración retiniana relacionada con glaucoma o traumatismo ocular,o cáncer, comprendiendo la administración de una cantidad terapéuticamente efectiva de una composición farmacéutica de la reivindicación 37 a un humano en necesidad de dicho tratamiento.

43. Un compuesto que es

(±)-10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-carbonitrilo;

(±)-10-[(4-clorofenil)sulfonil]-6-(3-metil-1,2,4-oxadiazol-5-il)-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

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(-)-10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-carbonitrilo;

(+)-10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-carbonitrilo;

(±)-10-[(4-clorofenil)sulfonil]-6-(1-metoxiciclopropil)-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

5-ciclopropil-9-{[4-(trifluorometil)fenil]sulfonil}-1,4,7,8-tetrahidro-4,7-epiminociclohepta[c]pirazol;

5-ciclopropil-9-{[4-(trifluorometil)fenil]sulfonil}-1,4,5,6,7,8-hexahidro-4,7-epiminociclohepta[c]pirazol;

(±)-6-(4-metoxifenil)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

5,5-dimetil-9-{[4-(trifluorometil)fenil]sulfonil}-5,6,7,8-tetrahidro-1H-4,7-epiminopirazol[4,3-b]azepina;

6,6-dimetil-9-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,8-tetrahidro-1H-4,7-epiminopirazol[3,4-c]azepina;

(±)-6-fenil-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

(±)-6-fenil-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

(±)-10-[(5-clorotiofen-2-il)sulfonil]-6-fenil-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

6-(1-metil-1H-pirazol-3-il)-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

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6-(1-metil-1H-pirazol-5-il)-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

(±)-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(±)-exo-6-(4-fluorofenil)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

(±)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-6-[4-(trifluorometil)-1,3-tiazol-2-il]-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

(±)-6-(5-metil-1,3-oxazol-2-il)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

(±)-endo-6-(4-fluorofenil)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

(±)-6-(5-metil-1,3-tiazol-2-il)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

(±)-6-(1*H*-benzimidazol-2-il)-10-[(4-clorofenil)sulfonil]-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol;

(±)-5-(4-fluorofenil)-9-{[4-(trifluorometil)fenil]sulfonil}-1,4,7,8-tetrahidro-4,7-epiminociclohepta[*c*]pirazol;

6-(4-fluorofenil)-9-{[4-(trifluorometil)fenil]sulfonil}-1,4,7,8-tetrahidro-4,7-epiminociclohepta[*c*]pirazol;

5-(4-fluorofenil)-9-{[4-(trifluorometil)fenil]sulfonil}-1,4,5,6,7,8-hexahidro-4,7-epiminociclohepta[*c*]pirazol;

(±)-6,7-difluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol;

6-(4-fluorofenil)-9-{[4-(trifluorometil)fenil]sulfonil}-1,4,5,6,7,8-hexahidro-4,7-epiminociclohepta[*c*]pirazol;

(±)-6,7-difluoro-11-{[4-(trifluorometil)fenil]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol-10(1*H*)-ona;

(±)-6-(3-fluorofenil)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooocta[*c*]pirazol;

(±)-11-{[4-(trifluorometil)fenil]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol-10(1*H*)-ona;

(-)-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol;

(+)-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol;

(±)-10,10-difluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol;

(±)-7-fenil-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooocta[*c*]pirazol;

(±)-10-[(4-clorofenil)sulfonil]-6-(3-metilisoxazol-5-il)-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooocta[*c*]pirazol;

(±)-6,7,10,10-tetrafluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-*c*]pirazol;

(+)-6-(3-fluorofenil)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooocta[*c*]pirazol;

(-)-6-(3-fluorofenil)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooocta[*c*]pirazol;

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(±)-6-(1,3-dimetil-1*H*-1,2,4-triazol-5-il)-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1*H*-4,8-epiminociclooctа[*c*]pirazol;

(±)-9-{[4-(trifluorometil)fenil]sulfonil}-1,4,7,8-tetrahidro-4,7-epiminociclohepta[*c*]pirazol;

(±)-6-(1H-1,2,4-triazol-3-il)-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

(-)-7-fenil-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

(+)-7-fenil-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

(±)-6-(5-metil-1H-1,2,4-triazol-3-il)-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

(±)-6-(1,2,3-tiadiazol-4-il)-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

(±)-12-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,10,11-tetrahidro-1H-4,10-epiminobenzo[5,6]ciclooctа[1,2-c]pirazol;

5-fenil-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

6-(piridin-3-il)-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

(±)-12-{[4-(trifluorometil)fenil]sulfonil}-1,4,10,11-tetrahidro-4,10-epimino[1,3]benzodioxolo[5',6':4,5]ciclohepta[1,2-c]pirazol;

(±)-10-[(4-clorofenil)sulfonil]-6-(5-metil-1,3,4-tiadiazol-2-il)-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

(±)-10-[(4-clorofenil)sulfonil]-6-(1H-1,2,3-triazol-4-il)-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

(-)-6,7-difluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(+)-6,7-difluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(±)-5-fluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(±)-8-fluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(±)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(-)-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminopirazol[4',3':4,5]ciclohepta[1,2-b]piridina;

(+)-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminopirazol[4',3':4,5]ciclohepta[1,2-b]piridina;

(+)-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminopirazol[3',4':5,6]ciclohepta[1,2-b]piridina;

(-)-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminopirazol[3',4':5,6]ciclohepta[1,2-b]piridina;

(±)-5-fluoro-11-{[4-(trifluorometil)fenil]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona;

(±)-8-fluoro-11-{[4-(trifluorometil)fenil]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona;

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(±)-6,7-difluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(±)-6-(4-bromofenil)-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

(±)-10-[(4-clorofenil)sulfonil]-6-(piridin-4-il)-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

(±)-6-(1,3-benzodioxol-5-il)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

(±)-12-{[4-(trifluorometil)fenil]sulfonil}-1,4,10,11-tetrahidro-4,10-epimino[1,3]benzodioxolo[5',6':4,5]ciclohepta[1,2-c]pirazol-7-ona;

(-)-6,7-difluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(+)-6,7-difluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(±)-3-[4-(10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-il)fenil]-1,3-oxazolidin-2-ona;

(±)-6-[4-(1H-imidazol-1-il)fenil]-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

(-)-5-fluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(+)-5-fluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(±)-6-[4-(1,3-tiazol-4-il)fenil]-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

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N-[4-(10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-il)fenil]ciclohexano-1,2-diamina;

(+)-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminopirazol[4',3':4,5]ciclohepta[1,2-c]piridina;

(+)-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminopirazol[3',4':5,6]ciclohepta[1,2-c]piridina;

(-)-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminopirazol[3',4':5,6]ciclohepta[1,2-c]piridina;

(±)-8,10,10-trifluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(±)-5-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(±)-5,10,10-trifluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(±)-6-[4-(1*H*-pirazol-1-il)fenil]-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

(±)-6-(3-bromofenil)-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

(±)-6-(1*H*-tetrazol-5-il)-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

(-)-5,10,10-trifluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(+)-5,10,10-trifluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

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(-)-5-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(+)-5-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(±)-5,8-difluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(±)-6-[3-(1H-imidazol-1-il)fenil]-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

(±)-6-[3-(1H-pirazol-1-il)fenil]-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

(±)-7-ciclopropil-12-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,6,11-tetrahidro-3H-5,11-epiminobenzo[4,5]ciclooctа[1,2-c]pirazol;

(±)-6-ciclopropil-12-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,10,11-tetrahidro-1H-4,10-epiminobenzo[5,6]ciclooctа[1,2-c]pirazol;

(±)-10-[(4-clorofenil)sulfonil]-6-(1-metil-1H-1,2,3-triazol-5-il)-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

10-[(4-clorofenil)sulfonil]-6-(1-metil-1H-1,2,3-triazol-4-il)-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

10-[(4-clorofenil)sulfonil]-6-(1-metil-1H-1,2,3-triazol-4-il)-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

(-)-10-[(4-clorofenil)sulfonil]-6-(2-metil-2H-1,2,3-triazol-4-il)-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

(+)-10-[(4-clorofenil)sulfonil]-6-(2-metil-2H-1,2,3-triazol-4-il)-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

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(±)-1-[4-(10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-il)fenil]pirrolidin-2-ona;

(±)-metil 4-{[4-(10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-il)fenil]amino}butanoato;

(±)-4-[4-(10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-il)fenil]morfolin-3-ona;

(±)-metil (2-{[4-(10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-il)fenil]amino}etoxi)acetato;

(±)-(2-{[4-(10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-il)fenil]amino}etoxi)ácido acético;

(±)-metil N-[4-(10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-il)fenil]-b-alaninato;

(±)-6-[4-(1H-1,2,4-triazol-1-il)fenil]-10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol;

(±)-6,7-difluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona;

(-)-5,8-difluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(+)-5,8-difluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(±)-7-fluoro-5-metil-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(±)-N-[4-(10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-il)fenil]acetamida;

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(±)-1-[4-(10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-il)fenil]azetidin-2-ona;

(±)-1-[4-(10-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,7,8,9-hexahidro-1H-4,8-epiminociclooctа[c]pirazol-6-il)fenil]etanona;

(±)-6-(trifluorometil)-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(±)-7-(trifluorometil)-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(±)-6,7,10,10-tetrafluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(-)-7-fluoro-5-metil-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(+)-7-fluoro-5-metil-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

13-{[4-(trifluorometil)fenil]sulfonil}-7,10,11,12-tetrahidro-7,12-epiminonafto[2',1':4,5]ciclohepta[1,2-c]pirazol;

(-)-5-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona;

(±)-7-(4-fluorofenil)-12-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,11-tetrahidro-3H-5,11-epiminobenzo[4,5]cicloocta[1,2-c]pirazol;

(±)-12-{[4-(trifluorometil)fenil]sulfonil}-4,5,10,11-tetrahidro-1H-4,10-epiminobenzo[5,6]cicloocta[1,2-c]pirazol;

(±)-12-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,11-tetrahidro-3H-5,11-epiminobenzo[4,5]cicloocta[1,2-c]pirazol;

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(±)-6-(4-fluorofenil)-12-{[4-(trifluorometil)fenil]sulfonil}-4,5,10,11-tetrahidro-1H-4,10-epiminobenzo[5,6]cicloocta[1,2-c]pirazol;

5,10,10-trifluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(±)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-7-carbonitrilo;

(+)-13-{[4-(trifluorometil)fenil]sulfonil}-7,10,11,12-tetrahidro-7,12-epiminonafto[2',1':4,5]ciclohepta[1,2-c]pirazol;

(-)-13-{[4-(trifluorometil)fenil]sulfonil}-7,10,11,12-tetrahidro-7,12-epiminonafto[2',1':4,5]ciclohepta[1,2-c]pirazol;

(+)-13-{[4-(trifluorometil)fenil]sulfonil}-7,8,9,12-tetrahidro-7,12-epiminonafto[1',2':4,5]ciclohepta[1,2-c]pirazol;

(-)-13-{[4-(trifluorometil)fenil]sulfonil}-7,8,9,12-tetrahidro-7,12-epiminonafto[1',2':4,5]ciclohepta[1,2-c]pirazol;

(-)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-7-carbonitrilo;

(-)-11-{[4-(trifluorometil)fenil]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona;

(+)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-7-carbonitrilo;

(+)-endo-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10-ol;

(±)-6-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

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(±)-6-[3-(trifluorometil)fenil]-12-{[4-(trifluorometil)fenil]sulfonil}-4,5,10,11-tetrahidro-1H-4,10-epiminobenzo[5,6]cicloocta[1,2-c]pirazol;

(±)-7-[3-(trifluorometil)fenil]-12-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,11-tetrahidro-3H-5,11-epiminobenzo[4,5]cicloocta[1,2-c]pirazol;

(-)-6-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(+)-6-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(±)-9-fluoro-12-{[4-(trifluorometil)fenil]sulfonil}-4,5,10,11-tetrahidro-1H-4,10-epiminobenzo[5,6]cicloocta[1,2-c]pirazol;

(±)-10-fluoro-12-{[4-(trifluorometil)fenil]sulfonil}-4,5,6,11-tetrahidro-3H-5,11-epiminobenzo[4,5]cicloocta[1,2-c]pirazol;

(±)-8-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(-)-8-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(+)-8-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(+)-exo-10-fluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(±)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,8,9-tetrahidro-4,8-epiminopirazol[3',4':5,6]ciclohepta[1,2-d][1,3]tiazol;

(-)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,8,9-tetrahidro-4,8-epiminopirazol[3',4':5,6]ciclohepta[1,2-d][1,3]tiazol;

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(+)-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,8,9-tetrahidro-4,8-epiminopirazol[3',4':5,6]ciclohepta[1,2-d][1,3]tiazol;

(-)-9-fluoro-12-{[4-(trifluorometil)fenil]sulfonil}-4,5,10,11-tetrahidro-1H-4,10-epiminobenzo[5,6]cicloocta[1,2-c]pirazol;

(+)-9-fluoro-12-{[4-(trifluorometil)fenil]sulfonil}-4,5,10,11-tetrahidro-1H-4,10-epiminobenzo[5,6]cicloocta[1,2-c]pirazol;

(-)-8-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona;

(+)-8-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona;

(±)-metil 11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-6-carboxilato;

(±)-exo-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10-ol;

(-)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(+)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(±)-exo-10-fluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

endo-5-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10-ol;

(-)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona;

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(+)-6-(3-metil-1,2,4-oxadiazol-5-il)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(-)-6-(3-metil-1,2,4-oxadiazol-5-il)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(-)-metil 11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-6-carboxilato;

(±)-7-metil-10-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,7,8,9-tetrahidro-1H-4,8-epiminociclohepta[1,2-c:5,4-c']dipirazol;

(+)-metil 11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-6-carboxilato;

exo-10-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(+)-exo-5,10-difluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

endo-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10-ol;

(±)-11-[(4-clorofenil)sulfonil]-5-fluoro-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(±)-5-fluoro-11-[(4-fluorofenil)sulfonil]-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(±)-5-fluoro-11-{[5-(trifluorometil)piridin-2-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(+)-9-bromo-12-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,10,11-tetrahidro-1H-4,10-epiminobenzo[5,6]cicloocta[1,2-c]pirazol;

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(-)-9-bromo-12-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,10,11-tetrahidro-1H-4,10-epiminobenzo[5,6]cicloocta[1,2-c]pirazol;

exo-8,10-difluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(+)-8,10,10-trifluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

endo-8-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10-ol;

(-)-10-bromo-12-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,6,11-tetrahidro-3H-5,11-epiminobenzo[4,5]cicloocta[1,2-c]pirazol;

(+)-10-bromo-12-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,5,6,11-tetrahidro-3H-5,11-epiminobenzo[4,5]cicloocta[1,2-c]pirazol;

(±)-6-cloro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(±)-metil 11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-8-carboxilato;

(-)-6-cloro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(+)-6-cloro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(-)-7-cloro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(+)-7-cloro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

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(±)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-6-ol;

(+)-metil 11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-8-carboxilato;

(-)-metil 11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-8-carboxilato;

(+)-8-cloro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(-)-8-cloro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(-)-11-[(4-clorofenil)sulfonil]-5-fluoro-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(+)-11-[(4-clorofenil)sulfonil]-5-fluoro-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(-)-5-cloro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(+)-5-cloro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(+)-8-(3-metil-1,2,4-oxadiazol-5-il)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(-)-8-(3-metil-1,2,4-oxadiazol-5-il)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(±)-11-[(4-clorofenil)sulfonil]-5-fluoro-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona;

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(-)-(10*S*)-5-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10-ol;

(+)-(10*S*)-5-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10-ol;

(-)-(10*S*)-8-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10-ol;

(+)-(10S)-8-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10-ol;

(±)-6-(4-fluorofenil)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(-)-11-[(4-clorofenil)sulfonil]-5-fluoro-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona;

(+)-11-[(4-clorofenil)sulfonil]-5-fluoro-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona;

(-)-6-(4-fluorofenil)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(+)-6-(4-fluorofenil)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(-)-6-ciclopropil-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(+)-6-ciclopropil-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(+)-6-bromo-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminopirazol[3',4':5,6]ciclohepta[1,2-b]piridina;

(+)-6-bromo-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminopirazol[3',4':5,6]ciclohepta[1,2-b]piridina;

(+)-6-bromo-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(-)-6-bromo-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(±)-(11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-8-il)metanol;

metil (±)-11-{[6-(trifluorometil)-1,2-dihidropiridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-8-carboxilato;

(+)-6-(4-fluorofenil)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminopirazol[3',4':5,6]ciclohepta[1,2-b]piridina;

(+)-6-ciclopropil-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminopirazol[3',4':5,6]ciclohepta[1,2-b]piridina;

(-)-6-ciclopropil-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminopirazol[3',4':5,6]ciclohepta[1,2-b]piridina;

(±)-8-(fluorometil)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(±)-7-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminopirazol[3',4':5,6]ciclohepta[1,2-b]piridina;

(-)-7-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-2,4,9,10-tetrahidro-4,9-epiminopirazol[3',4':5,6]ciclohepta[1,2-b]piridina;

(+)-7-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-2,4,9,10-tetrahidro-4,9-epiminopirazol[3',4':5,6]ciclohepta[1,2-b]piridina;;

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(4R,9S)-6-(prop-1-in-1-il)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(-)-exo-5,10-difluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(+)-5,10-difluoro-11-{[4-(trifluorometil)fenil]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(±)-8-cloro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona;

(±)-8-cloro-N-hidroxi-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-imina;

(±)-8-(4-fluorofenil)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(4S,9S,10R)-5,10-difluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(4R,9R,10R)-5,10-difluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(±)-8-cloro-N-metoxi-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-imina;

(±)-8-ciclopropil-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

exo-10-fluoro-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-2,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(±)-8-cloro-10-metilidene-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

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(±)-5-(4-fluorofenil)-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(±)-5-ciclopropil-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-1,4,9,10-tetrahidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol;

(-)-9-metil-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona;

(+)-9-metil-11-{[6-(trifluorometil)piridin-3-il]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona;

(-)-9-metil-11-{[4-(trifluorometil)fenil]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona;

(+)-9-metil-11-{[4-(trifluorometil)fenil]sulfonil}-4,9-dihidro-4,9-epiminobenzo[4,5]ciclohepta[1,2-c]pirazol-10(1H)-ona,

O una farmacéuticamente aceptable sal o solvato de éstos.

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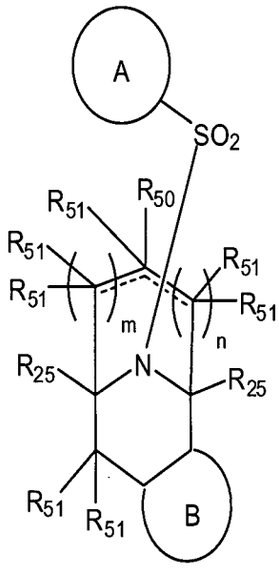
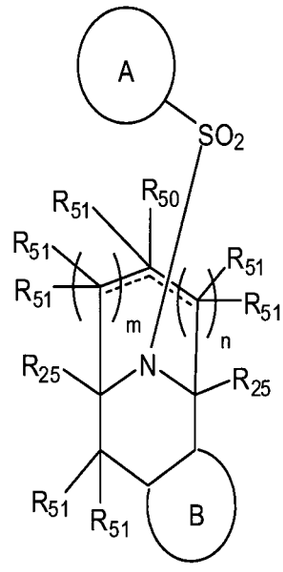
RESUMEN

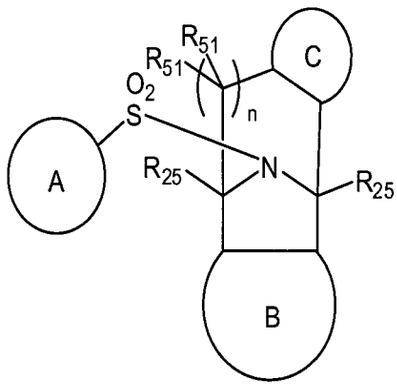
La presente invención proporciona compuestos teniendo una estructura de acuerdo a las Fórmulas 1, 2, 3 y 4:



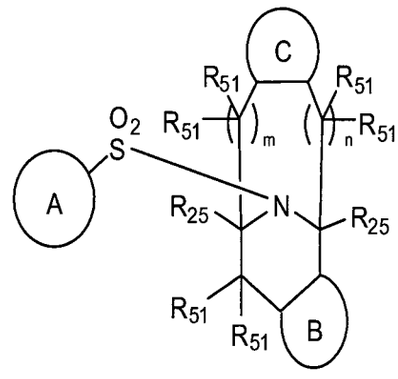
Fórmula 1



Fórmula 2



Fórmula 3



Fórmula 4

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Donde el anillo-A, el anillo-B, el anillo-C, m, n, R_{25}, R_{50}, y R_{51} son como se describe en la especificación. La invención también proporciona composiciones farmacéuticas comprendiendo compuestos de las Fórmulas 1, 2, 3 y 4, así como también métodos para el tratamiento de desórdenes cognitivos, tales como la Enfermedad de Alzheimer. La invención además proporciona sustancias intermedias útiles en la preparación de los compuestos de las Fórmulas 1, 2, 3 y 4.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/055987

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D451/00 A61K31/438 A61K31/46 A61P25/28

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

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, CHEM ABS 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	WO 2007/022502 A (ELAN PHARM INC [US]; BOWERS SIMEON [US]; GAROFALO ALBERT W [US]; HOM R) 22 February 2007 (2007-02-22) page 1, line 12 - line 17; examples 8,11,14,19, 20,35,36,54, 56.4, 57, 75, 80-82, 91	20-26, 29,31-43
A	WO 2005/113542 A (ELAN PHARM INC [US]; NEITZEL MARTIN L [US]; MARUGG JENNIFER L [US]) 1 December 2005 (2005-12-01) example 9	1-19, 31-36,43
A	WO 2007/143523 A (ELAN PHARM INC [US]; NEITZEL MARTIN L [US]; AUBELE DANNIELLE L [US]; H) 13 December 2007 (2007-12-13) claims 1,24	1-19, 31-36,43

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[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
25 March 2010	08/04/2010
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax (+31-70) 340-3016	Authorized officer Bakboord, Joan

Form PCT/ISA/210 (second sheet) (April 2005)

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/055987

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 2008/147800 A (ELAN PHARM INC [US]; DRESSEN DARREN [US]; BOWERS SIMEON [US]; GAROFALO) 4 December 2008 (2008-12-04) claims 1,19	1-19, 31-36,43
X	MITSUHASHI K. ET AL: "Reactions of 7-oxa- and -aza-norobrnenes and -dienes with 1,3-dipolar compounds" SEIKEI DAIGAKU KOGAKUBU KOGAKU HOKOKU, vol. 44, 1 January 1987 (1987-01-01), pages 2983-2992, XP002575111 Scheme 1	20-22

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

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International application No.
PCT/US2009/055987

INTERNATIONAL SEARCH REPORT

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. [ ] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

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:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional 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 report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest 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.

[X] No protest accompanied the payment of additional search fees.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-19, 31-36(completely); 43(partially)

   compounds of claim 1

   ---

2. claims: 20-30, 37-43(all partially)

   compounds of formula 1

   ---

3. claims: 20-30, 37-43(all partially)

   compounds of formula 2

6+1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/055987

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007022502 A	22-02-2007	AR 056470 A1	10-10-2007
		AU 2006279312 A1	22-02-2007
		AU 2006283567 A1	01-03-2007
		CA 2618087 A1	01-03-2007
		CA 2632670 A1	22-02-2007
		CN 101426860 A	06-05-2009
		CN 101304997 A	12-11-2008
		EC SP088293 A	28-04-2008
		EP 1915371 A2	30-04-2008
		EP 1916985 A2	07-05-2008
		JP 2009504773 T	05-02-2009
		JP 2009506988 T	19-02-2009
		KR 20080042135 A	14-05-2008
		WO 2007024651 A2	01-03-2007
		ZA 200803521 A	30-12-2009
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
WO 2007143523 A	13-12-2007	AR 061161 A1	06-08-2008
		AU 2007256860 A1	13-12-2007
		CA 2651550 A1	13-12-2007
		EA 200870577 A1	30-06-2009
		EC SP089019 A	27-02-2009
		EP 2038280 A2	25-03-2009
		JP 2009539773 T	19-11-2009
		KR 20090015159 A	11-02-2009
		US 2008021056 A1	24-01-2008
		UY 30377 A1	02-01-2008
WO 2008147800 A	04-12-2008	AR 066712 A1	09-09-2009
		AU 2008256940 A1	04-12-2008
		CA 2687765 A1	04-12-2008
		CL 15162008 A1	10-10-2008
		EP 2152713 A1	17-02-2010
		US 2009099235 A1	16-04-2009

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Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

(21) N° de solicitud:

22) Fecha de solicitud:

(30) Prioridad

(31) *Prioridad*	(32) *Fecha*	(33) *País*
61/094,799	**05/09/2008**	**US**
61/099,241	**23/09/2008**	**US**
61/173,278	**28/04/2009**	**US**
61/226,532	**17/07/2009**	**US**

(51) Int Cl: **C07D 451/000**

(71)Solicitante(s) **ELAN PHARMACEUTICALS, INC.**

(72) Inventor(es) **ANDREI W. KONRADI Y OTROS**

(74) Apoderado: **LUZ CLEMENCIA DE PAEZ**

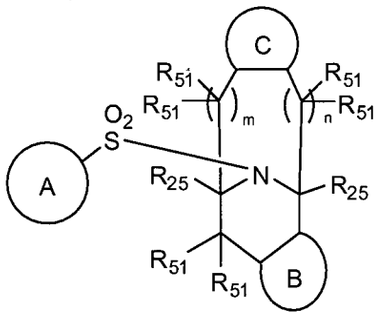
(85) Fecha limite inicio fase nacional: 05/04/2011
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 04/09/2009
No. de solicitud PCT/US2009/055987

(87) Publicación internacional
Fecha: 11/03/2010
N° publicación: ***WO 2010/028213 A3***

(54) Titulo: **COMPUESTOS N- SULFONAMIDO PIRAZOLIL POLICÍCLICOS**

Reivindicación(es):

1. Compuestos de la fórmula:



O una farmacéuticamente aceptable sal o solvato de este, en donde,

m y n son independientemente 0 ó 1, provisto que m + n es 0 ó 1;

el Anillo-A es aril, cicloalquil, heteroaril o heterocicloalquil, donde cada anillo es opcionalmente sustituido en una sustituible posición con halógeno, C_1-C_6 alquil, C_2-C_6 alquenil, C_2-C_6 alquinil, C_1-C_6 alcoxi, haloalquil, haloalcoxi, hidroxil, hidroxialquil, CN, ariloxi, -$S(O)_{0-2}$-(C_1-C_6 alquil), -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, NO_2, CN, C_2-C_6 alcanoil, C_0-C_3alquilCO_2R_{11}, heteroaril, heterocicloalquil, aril, arilalquil, -OCH_2O-, -OCH_2CH_2O- o -$SO_2NR_{11}R_{11}$;

el anillo-B es pirazolil, dihidropirazolil, pirazolonil o pirazolidinonil, cada uno opcionalmente sustituido con C_1-C_6 alquil, C_3-C_6 cicloalquil, C_2-C_4 alquenil, C_2-C_4 alquinil, C_1-C_4 alcoxi, amino, C_1-C_4 alquilamino, C_1-C_4 dialquilamino, hidroxi, hidroxialquil, halo, C_1-C_4 haloalquil, C_1-C_4 haloalcoxi, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$ o CN;

en donde el anillo-C es aril sustituido con R_{30}, R_{35}, R_{40}, y R_{45} o heteroaril, opcionalmente sustituido con halógeno, C_1-C_6 alquil, C_1-C_6 haloalquil, C_1-C_6 haloalcoxi, CN, hidroxil, C_1-C_6 alcoxi, -C_1-C_3 alquil-OH, -C_1-C_3 alquil-alcoxi, feniloxi, -$S(O_2)R_{10}$, -$SO_2NR_{11}R_{11}$, -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, oxazolil, pirazolil, tiazolil, piridil, pirimidinil, imidazolil, indolil, furanil, thienil, fenil o fenil C_1-C_4 alquil, en donde las porciones fenil de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi, C_1-C_4 haloalqui o halógeno;

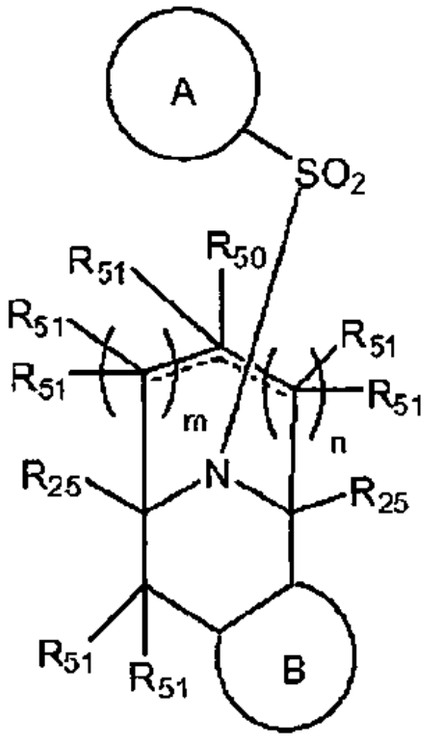
R_{30}, R_{35}, R_{40}, y R_{45} son independientemente H, halógeno, C_1-C_6 alquil, C_2-C_6 alquenil, C_2-C_6 alquinil, C_2-C_8 haloalquenil, C_2-C_8 haloalquinil, -$SO_2NR_{11}R_{11}$, arilalquil, cicloalquil, C_1-C_6 haloalquil, C_1-C_6 haloalcoxi, CN, NO_2, hidroxil, C_1-C_6 alcoxi, -C_1-C_6 alquil-OH, -C_1-C_6 alquil-C_1-C_6 alcoxi, ariloxi, -$S(O_2)R_{10}$, -$NR_{11}R_{11}$, -$C(O)NR_{11}R_{11}$, -$NR_{11}C(O)R_{10}$, -$NR_{11}SO_2R_{10}$, -O-$C(O)NR_{11}R_{11}$, C_2-C_6 alcanoil, heteroarilalquil, heteroaril, en donde cada grupo heteroaril es opcionalmente sustituido con un grupo C_1-C_6 alquilo, heterocicloalquilalquil, heterocicloalquil, en donde cada grupo heterocicloalquil es opcionalmente sustituido con uno o dos grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi o halógeno, aril, ariloxi o arilalquil, donde las porciones aril de arriba son opcionalmente sustituidas con uno o más grupos que son independientemente C_1-C_6 alquil, C_1-C_6 alcoxi, hidroxilo, C_1-C_4 haloalqui o halógeno; y

Donde dos sustitutos adyacentes en el anillo-C junto con los carbonos a los que están unidos opcionalmente forman un anillo heterocicloalquil o heteroaril, cada uno opcionalmente sustituido con uno o más grupos que son independientemente alquil, alcoxi, halógeno o C_2-C_4 alcanoil en donde el grupo alcanoil es opcionalmente sustituido ulteriomente con hasta 3 átomos halógeno; o dos carbonos adyacentes al Anillo-C opcionalmente forman un anillo benzo el cual es opcionalmente sustituido con 1 a 4 grupos que son independientemente halógeno, hidroxil, alquil, alcoxi, haloalquil, haloalcoxi, CN o NO_2;

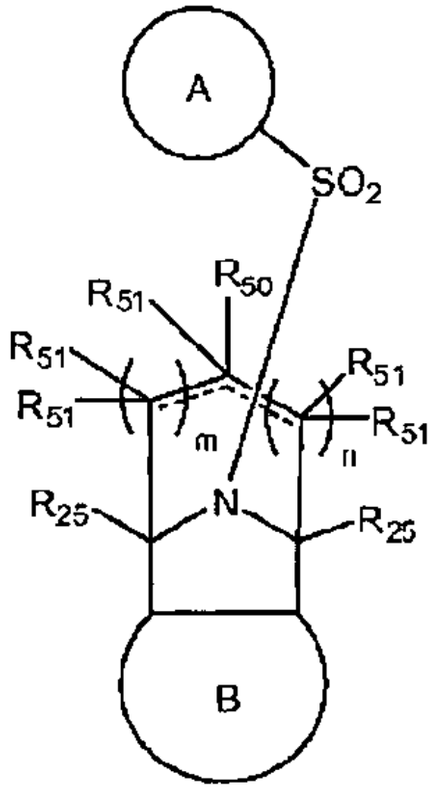
Cada R_{25} es independientemente H, C_1-C_6 alquil, C_1-C_6 haloalquil, -$C(O)O_{11}$, -(C_1-C_6 alquil)-$C(O)O_{11}$, C_1-C_6 alcoxi C_1-C_6 alquil, -$C(O)O_{11}$, -$CONR_{11}R_{11}$, CN, C_1-C_6 alquil-CN o hidroxi C_1-C_6 alquil;

Cada R_{51} está independientemente ausente, o es H, C_1-C_4 alquil, halógeno, CN, amino, mono alquilamino o dialquilamino, OH o C_1-C_4 haloalquil; ulteriomente cuando hay dos grupos R_{51} en un átomo de carbono, los dos grupos R_{51} y el carbono al cual están unidos pueden formar un anillo cicloalquil de 3 a 6 miembros; o cuando hay dos grupos R_{51} en un carbono, los dos grupos R_{51} pueden formar un grupo oxo;

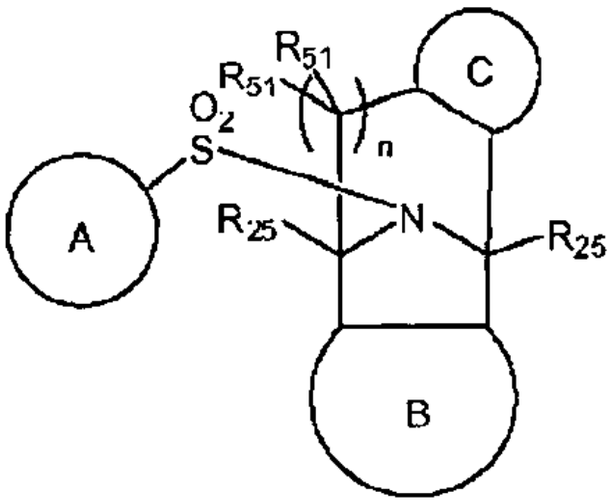
R_{10} y R_{11} en cada ocurrencia son independientemente C_1-C_6 alquil, heteroaril que es seleccionado de pirazolil, tiadiazolil, triazolil, isoxazolil, isotiazolil, imidazolil, tiazolil, oxadiazolil, y piridil o aril que es seleccionado de fenil y naftil, donde los grupos heteroaril y aril son opcionalmente sustituidos con 1 a 3 grupos que son independientemente halógeno, hidroxil, alquil, alcoxi, haloalquil, haloalcoxi, CN o NO_2; y


A
SO2
R50
R51
R51
R51
R51
R51
m
n
R25
N
R25
R51
R51
B

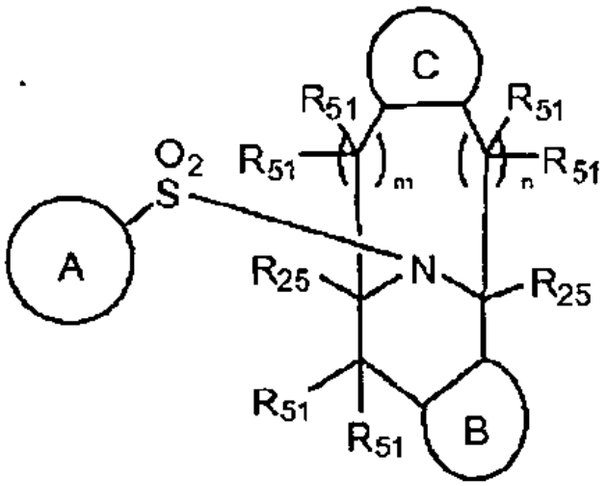
(1)


A
SO2
R50
R51
R51
R51
R51
R51
m
n
R25
N
R25
B

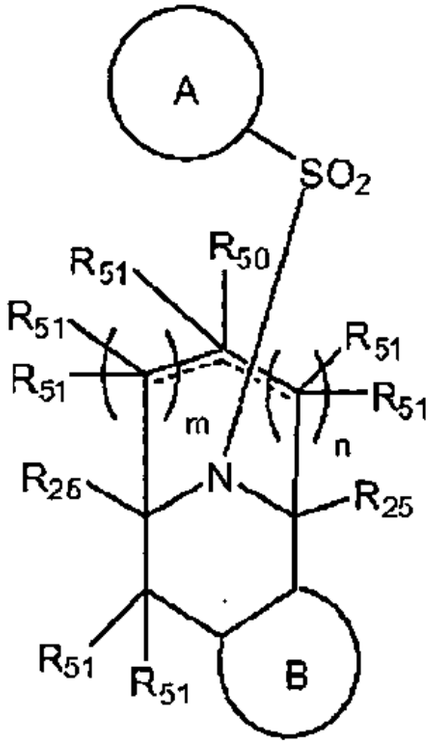
(2)


R51
R51
C
O2
S
n
A
R25
N
R25
B

(3)


C
R51
R51
O2
R51
m
n
R51
S
A
R25
N
R25
R51
R51
B

(4)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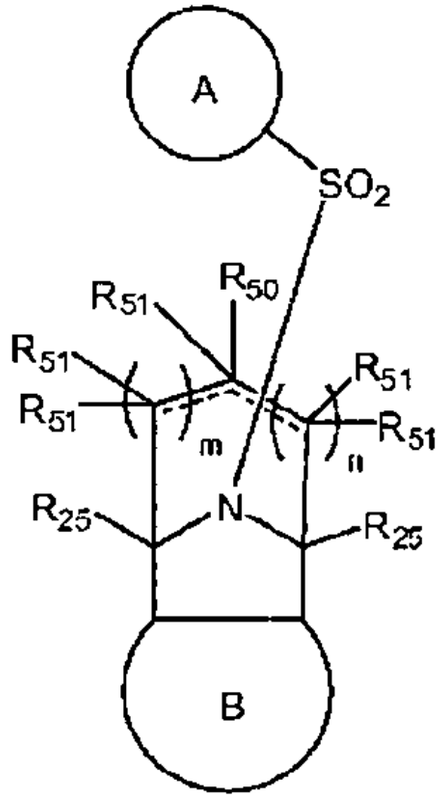
(1)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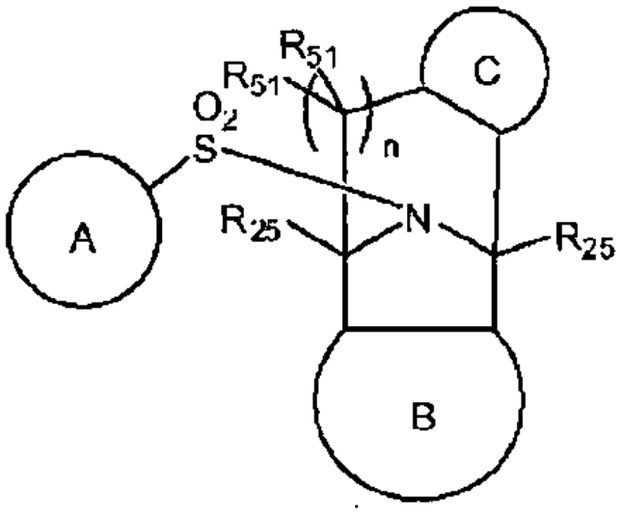
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R25
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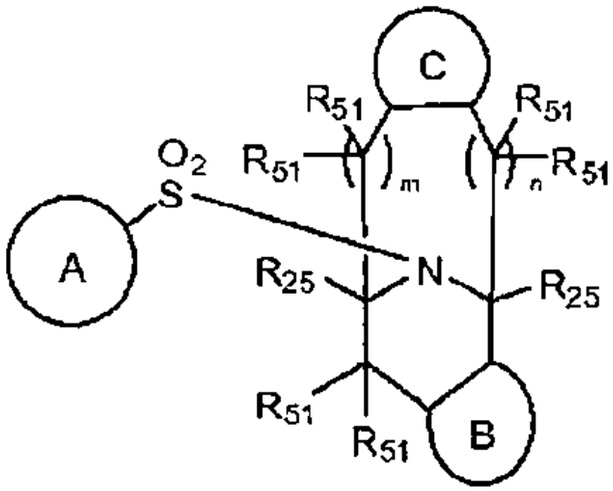
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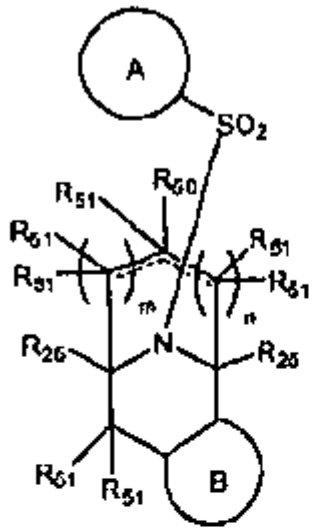
(4)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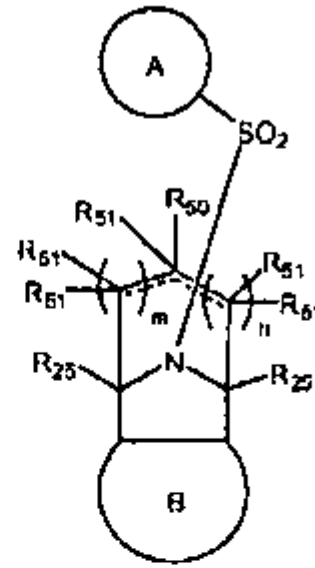
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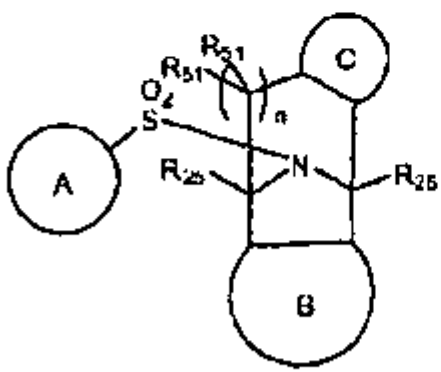
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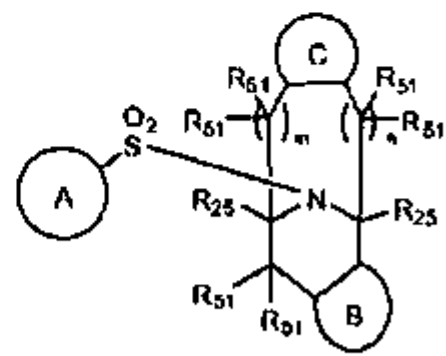
(3)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(4)

674

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176099-2

RECIBO OFICIAL DE CAJA : 10 - 96,485
FECHA : NOVIEMBRE 12 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-039494- -00000-0000

Fecha: 2011-03-31 10:49:34 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 679

***** 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	062754397	146320731	12/10/2010	12,390,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	*** S.DISTINTIVO INSCRIPCION AFECTACI	280,000.00
		TOTAL : $	290,000.00

SON: DOSCIENTOS OCHENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

~~Colo: 15986-719-009-6.~~

Colo 13170-841-010-8

675

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0023111

Bogotá D.C., Marzo 14 de 2011 - 16:53:20

RECIBIDO DE : CAVELIER ABOGADOS NI 860.041.367

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	157700664	14/03/2011	51.804.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-03 CAMBIO DE MODALIDAD Y MODIFICACIONES	ED N.CREACION CORRECCION A SOLICITUD EN TRAMITE / MODOFICA	118.000.00	118.000.00
				$118.000.00

SON: **CIENTO DIECIOCHO MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-********-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-039494- -00000-0000
Fecha: 2011-03-31 10:49:34 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 679

Colo: 13170-841-010-8

676

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0027996

Bogotá D.C., Marzo 29 de 2011 - 07:07:02

RECIBIDO DE : CAVELIER ABOGADOS NI 860.041.367

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	157700675	28/03/2011	65.222.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	114 PTC CAP-II EXAMEN DE PATENTIBILIDAD DE INVENSION	485.000.00	485.000.00
				$485.000.00

SON: **CUATROCIENTOS OCHENTA Y CINCO MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-039494- -00000-0000

Fecha: 2011-03-31 10:49:34 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 679

Colo: 13170-841-010-8

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

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Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0028009

Bogotá D.C., Marzo 29 de 2011 - 07:07:02

RECIBIDO DE : CAVELIER ABOGADOS NI 860.041.367

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	157700675	28/03/2011	65.222.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	571.000.00	571.000.00
				$571.000.00

SON: **QUINIENTOS SETENTA Y UN MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-*********-
Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-039494- -00000-0000
Fecha: 2011-03-31 10:49:34 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 679

CODO: 13170-891-010-8

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0028095

Bogotá D.C., Marzo 29 de 2011 - 07:07:02

RECIBIDO DE : CAVELIER ABOGADOS NI 860.041.367

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	157700675	28/03/2011	65.222.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD INDUSTRIAL	99 OTROS SERVCIOS ADMINISTRATIVOS	5.000.00	5.000.00
				$5.000.00

SON: **CINCO MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-****-
Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-039494- -00000-0000
Fecha: 2011-03-31 10:49:34 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 679

Colo: 13170-841-010-8

679

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0028096

Bogotá D.C., Marzo 29 de 2011 - 07:07:02

RECIBIDO DE : CAVELIER ABOGADOS NI 860.041.367

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	157700675	28/03/2011	65.222.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD INDUSTRIAL	99 OTROS SERVCIOS ADMINISTRATIVOS	5.000.00	5.000.00
				$5.000.00

SON: **CINCO MIL PESOS MONEDA CORRIENTE***

Responsable: _____
*****
Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-039494- -00000-0000
Fecha: 2011-03-31 10:49:34 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 679

Colo: 13170-841-010-8

680

Industria y Comercio
SUPERINTENDENCIA

ADM

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-039494- -00000-0000
Fecha: 2011-03-31 10:49:34 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 679

PATENTE DE INVENCIÓN ☐ MODELO DE UTILIDAD ☐

- ☐ Indicación que se solicita 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 (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☑ MODELO DE UTILIDAD PCT ☐ **Art.33 Decisión 486/00, Circular Única**

- ☑ Indicación que se solicita una PCT
- ☑ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☐ Dibujos de ser estos pertinentes
- ☑ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☐ Incompleta ☐

DISEÑO INDUSTRIAL ☐ **(Art. 119 Decisión 486/00)**

- ☐ Indicación que se solicita 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 ☐ **(Art. 92 Decisión 486/00)**

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

Industria y Comercio
SUPERINTENDENCIA

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Bogotá D.C.,
2020

Doctor(a)
SUAREZ DE PAEZ LUZ CLEMENCIA
Apoderado(a) y/o Representante de
ELAN PHARMACEUTICALS, INC.

REFERENCIA	Radicación No.	11 039494
	Solicitud internacional	PCT/US2009/55987
	Fecha inicio fase nacional	05/04/2011
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	№ 08228

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 consideraró 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.

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 20 MAYO 2011.
adpa11

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Sede CAN: Av. Cra 50 No. 26-55 int. 2 Tel: 5880070
Call Center 6513240. Línea 01800-910165
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Bogotá D.C. - Colombia