OLARTERAISBECK
OLARTE RAISBECK MOURE

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-009526- -00000-0000
Fecha: 2010-01-29 17:28:10 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 909

**PETITORIO - FORMULARIO ÚNICO DE SOLICITUD**
**PATENTE PCT**
**ENTRADA EN FASE NACIONAL** **P2010/000008**

**SOLICITUD DE:**

(1) [X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

**Nombre:** ARDEA BIOSCIENCES, INC.
**Dirección:** 3300 Hyland Avenue, Costa Mesa, California 92626 E.U.A.
**Nacionalidad o Domicilio:** Estadounidense
**Lugar de Constitución:** Estados Unidos de America
**Teléfono:** _____ **Fax:** _____
**E-mail:** _____

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

**REPRESENTANTE O APODERADO**

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

**IDENTIFICACIÓN**
**C.C.** [x] **NIT** [ ]
**C.E.** [ ] **Otro** [ ]
**Cual** _____
**Número** 79.376.996 Btá
**TP** 135.799

**INVENTOR (ES) (72)**

**Nombre:** **1)** Jean-Michel VERNIER, **2)** Colin Edward ROWLINGS, **3)** Jean-Iuc GIRARDET, **4)** Stuart DIMOCK, **5)** Barry QUART, **6)** Jeffrey N. Miner
**Dirección:** **1)** 24831 Cutter, Laguna Niguel, California 92677 EUA; **2)** 198 Paxton Way, Encinitas, CA 92024 EUA; **3)** 24144 Graystone Drive, Lake Forest, CA 92630 EUA; **4)** 24 Blue Summit Irvine, California 92656, E.U.A. **5)** 3273 Violet Ridge, Encinitas, CA 92024 EUA, **6)** 4572 Pauling Ave., San Diego, CA 92122 E.U.A.
**Nacionalidad o Domicilio:** **1)** Francesa **2)** Estadounidense **3)** Francesa **4)** Estadounidense **5y 6)** Estadounidenses

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2008/071392 Fecha Julio 28, 2008

Publicación Internacional No. WO 2009/018233 Fecha Febrero 5, 2009

(6) **Título (54)** **DERIVADOS DE N-(ARILAMINO) SULFONAMIDAS QUE INCLUYEN POLIMORFOS COMO INHIBIDORES DE MEK ASI COMO COMPOSICIONES, MÉTODOS DE USO Y DE PREPARACIÓN DE LOS MISMOS**

**Clasificación Internacional (51)** A01N 41/06, A61K 31/18

**Prioridad** **SI** [X] **NO** [ ]

| (33) País de Origen | (32) Fecha | (31) Número de Solicitud |
|---|---|---|
| US | Julio 30, 2007 | 11/830,733 |
| US | Marzo 6, 2008 | 61/034,466 |
| US | Marzo 6, 2008 | 61/034,464 |
| US | Abril 14, 2008 | 61/044,886 |

(9) **Comprobante de pago No.** 10-4530 **Fecha** Enero 27, 2010

(10) **ANEXOS**

[X] Comprobante de pago de la tasa de presentación de la solicitud.

[ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.

[X] Poderes, si fuere el caso. Adjunto copia simple. Ver Expediente No. 09-074.929.

[ ] Documento de cesión del inventor al solicitante o a su causante.

[ ] Declaraciones.

[X] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).

[X] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).

[ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).

[ ] Traducción del examen preliminar internacional efectuado por la IPEA.

[ ] De ser el caso, copia del contrato de acceso.

[ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.

[ ] De ser el caso, certificado de depósito del material biológico.

[ ] Arte final 12 x 12.

[ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.

[ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.

[X] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: J. IAN RAISBECK FIRMA: _____

C.C. 79.376.996 Btá T.P. 135.799

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

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 4,530
FECHA : ENERO 20 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-009526- -00000-0000

Fecha: 2010-01-29 17:28:10 Dep. 2020 DIR NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 909

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

| DEPOSITANTE | TIPO PAGO | BANCO | CUENTA | No. PAGO | FECHA PAG | Vr. PAGO |
|---|---|---|---|---|---|---|
| CLARTE RAISBEY | CONSIGNACION | BANCO DE BOGOTA | 062754397 | 170522324 | 20/01/2010 | 6.769.000.00 |

***** C O N C E P T O *****

| CANT. | RENTISTICO | CONCEPTO | TOTAL CONCEPTO |
|---|---|---|---|
| 1 | 50006-01-01 SOLICITUDES | 1 TRAMITES DE SOL. DE PATENTE DE IN | 554.000.00 |
| | | TOTAL : $ | 554.000.00 |

SON: QUINIENTOS CINCUENTA Y CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

COLEGIO DE ESCRIBANOS · CIUDAD DE BUENOS AIRES · CAPITAL FEDERAL - REPUBLICA ARGENTINA

ACTUACION NOTARIAL

ISABEL MARTINEZ DIEGO
MATRICULA 4462
ESCRIBANA

N 011263616

0/7587

FOLIO 561. PRIMERA COPIA. SUSTITUCION DE MANDATO.- DAGMAR MESSERER POR "ARDEA BIOSCIENCES, INC." A CARLOS REINALDO OLARTE Y OTRO.- ESCRITURA NUMERO DOSCIENTOS ONCE. En la Ciudad de Buenos Aires, Capital de la República Argentina, a veinticuatro de septiembre del año dos mil nueve, ante mi, escribana autorizante, comparece doña Dagmar MESSERER, soltera, mayor de edad, con documento nacional de identidad nº 20.383.892, vecina de esta Ciudad y de mi conocimiento, doy fe, así como que dice: Que SUSTITUYE a favor de los señores CARLOS REINALDO OLARTE y/o JAMES IAN RAISBECK, para que lo ejerzan conjunta, separada e indistintamente, el mandato otorgado por "ARDEA BIOSCIENCES, INC." domiciliada en 4939 Directors Place, San Diego, California 92121, Estados Unidos de América, transcripto por escritura nº 210 de fecha 24 de septiembre de 2009, ante mi, al folio 558 de este mismo Registro, que en primera copia tengo a la vista, doy fe, y copiada dice: "Folio 558. Primera Copia. Transcripcion de mandato.- "Ardea Biosciences, Inc." a Dagmar Messerer. Escritura doscientos diez. En la Ciudad de Buenos Aires, Capital de la República Argentina, a veinticuatro de septiembre del año dos mil nueve, ante mi, escribana autorizante, comparece doña Dagmar MESSERER, soltera, mayor de edad, con documento nacional de identidad nº 20.383.892, vecina de esta Ciudad y de mi conocimiento, doy fe, así como que dice: Que para su TRANSCRIPCION en el protocolo de este Registro, me entrega un poder otorgado por ARDEA BIOSCIENCES, INC,

LEGALIZACION 090928 439312 28/09/2009 12:53:34

APOSTILLA 090928 088701 28/09/2009 12:53:46 $39.00

N 011263616

domiciliada en 4939 Directors Place, San Diego, California 92121, Estados Unidos de América, el que en su original con su correspondiente traducción y legalización, tengo a la vista, doy fe, y copiado dice: "PODER. Los abajo firmante/s Ardea Biosciences, Inc, domiciliados en 4939 Directors Place, San Diego, California 92121, EEUU declaran por el presente otorgar a Dagmar MESSERER poder general amplio y suficiente para recabar de las autoridades argentinas, sud y centroamericanas así como mexicanas que correspondan, la obtención de patentes de invención, el registro y la renovación de marcas y modelos y/o derechos de propiedad intelectual y/o nombres de dominio, a cuyo efecto los faculta/n para llevar a cabo ante dichas autoridades todas las gestiones necesarias al objeto indicado, presentar solicitudes, formular descripciones, oposiciones, protestos, declaraciones, apelaciones y reclamos, oblar impuestos, justificar explotaciones, solicitar testimonios, aceptar transferencias, recibir documentos y valores, percibir y hacer cuanto fuere necesario ante las autoridades administrativas de cualquier orden. Por otra parte, les confieren mandato para que en su nombre y representación puedan iniciar y proseguir cualquier juicio que actualmente los que suscriben tengan o en el futuro tuvieran en la República Argentina, en Sudamerica, Centroamérica y México, con motivo de su nombre, marcas de fábrica o de comercio, patentes de invención y modelos y/o de sus derechos de propiedad intelectual que actual-

COLEGIO DE ESCRIBANOS · CAPITAL FEDERAL · REPUBLICA ARGENTINA · CIUDAD DE BUENOS AIRES

ACTUACION NOTARIAL

LEY 404

ISABEL MARTINEZ DIEGO
MATRICULA 4452
ESCRIBANA

N 011263617

mente posean o adquieran en lo sucesivo, promover juicios de cualquier jurisdicción, criminales, correccionales, civiles o comerciales contra los falsificadores, usurpadores o imitadores y contra los tenedores de artículos que infrinjan su nombre, marcas o patentes de invención, seguir los juicios por oposición u otros en que fueran parte como actores o demandados, defender el nombre, las marcas, patentes y modelos y/o derechos de propiedad intelectual y/o nombres de dominio, haciendo las protestas del caso o diciendo de nulidad. Al efecto, podrán presentarse con escritos, querellas, pedidos, y lo que fuere necesario ante cualquier autoridad judicial, presentar testigos, documentos y demás justificativos, rendir pruebas de cualquier especie, pedir nombramientos de peritos, pedir y absolver posiciones, asistir a juicios verbales, declinar y prorrogar de jurisdicción, tachar, recusar, apelar, transar, someter a arbitraje o mediación, hacer renuncias, exigir y dar cauciones, pedir embargos preventivos, definitivos o inhibiciones y su levantamiento, pedir la venta de los bienes de los deudores, solicitar y obtener el cumplimiento de sentencias, prestar juramentos, decir de nulidad, desistir, percibir, otorgar recibos y en general practicar todos los actos y diligencias que sean precisos al desempeño de este mandato. Podrán asimismo sustituir el presente poder en todo o en parte. En relación a Brasil, este poder incluye recibir citaciones, intimaciones, notificaciones en dicho país conforme el

N 011263617

articulo 217 de la Ley Brasilera 9279/96 y/o hacer substituciones a otros abogados / agentes brasileros con facultad para recibir dichas citaciones, intimaciones, notificaciones. Dado y firmado en San Diego CA 09/02/09. Sigue una firma ilegible." "TRADUCCIÓN PUBLICA. (A continuación de un PODER otorgado en idioma nacional, por la sociedad "Ardea Biosciences, Inc", con sede en San Diego, California, EE.UU., aparecen las siguientes certificaciones, que traducidas dicen:) La versión en inglés es para su información únicamente.- Dado y firmado en (ilegible) San Diego, CA, - 02-09-09.- CERTIFICACIÓN DE CALIFORNIA PARA TODO USO (ilegible) Estado de California, Condado de San Diego - El 2 de setiembre de 2009 compareció personalmente ante mí Jackie Hannah, Escribana, Barry Quast quien demostró en base a prueba suficiente, que es la persona cuya firma en el instrumento adjunto es auténtica y que procede de su persona, y me comprobó que su firma en el instrumento es auténtica. Certifico bajo pena de perjurio, según las leyes de California, que lo que consta arriba es fiel y exacto. En fe de lo cual firmo y estampo el sello oficial - Firma: (firmado) Jackie Hannah - (Sello:) Jackie Hannah, Mandato N°1800633; Escribana Pública de California, Condado de San Diego, Mi mandato vence el 8 de junio de 2012. OPCIONAL - Descripción del documento adjunto: PODER. Cantidad de páginas: 1 (una).- Carácter del firmante: Nombre Barry Quast - Cargo: Director-Gerente - (Impresión digital). CONDADO DE SAN DIEGO - ASESOR EN JEFE

COLEGIO DE ESCRIBANOS · CIUDAD DE BUENOS AIRES · CAPITAL FEDERAL · REPUBLICA ARGENTINA

ACTUACION NOTARIAL

ISABEL MARTINEZ DIEGO
MATRICULA
ESCRIBANA

N 011263618

DE REGISTRO-SECRETARIO DEL CONDADO - Oficina del Registrador del Condado: 1600 Pacific Highway, Oficina 260. Yo, David Butler, Asesor/Registrador/Funcionario del Condado, del Condado de San Diego, Estado de California, que por la ley tiene su sello, CERTIFICO POR EL PRESENTE que JACKIE HANNAH, cuya firma figura al pie del Certificado de Prueba o Reconocimiento en el instrumento anexo y que figura allí, era en la fecha de dicho juramento o Prueba de Reconocimiento, Escribana Pública en y para dicho Condado, debidamente comisionada y juramentada, y debidamente autorizada por la ley de dicho Estado para administrar juramentos y tomar reconocimientos y Pruebas de Instrumentos Públicos y otros documentos escritos a ser registrados en dicho Estado. Conozco la letra de dicha Escribana Pública y creo que la firma en dicha declaración jurada o Certificado de Prueba de Reconocimiento es auténtica. Certifico además que según las leyes del Estado de California dicho juramento o Certificado de Prueba o reconocimiento son requeridos provistos de sello, pero la impresión de dicho sello no está obligada por las leyes del Estado de California de registrarse en mi despacho o en ningún otro lugar. Fechado el 2 de setiembre de 2009 - Doy fe - (Firma ilegible, aclarada:) DAVID BUTLER, Asesor del Condado/Jefe de Registro/-Funcionario- (Sello:) Asesor/Jefe de Registro/Funcionario del Condado de San Diego. Sucursales con oficinas disponibles que están bajo su servicio. ESTADO DE CALIFORNIA - SECRETARIO DE ESTADO. Solici-

N 011263618

tado para ser usado en Argentina - No podrá usarse en los Estados Unidos de América. APOSTILLA - (Convención de La Haya del 5 de octubre de 1961) - País: Estado Unidos de América. Este documento público fue firmado por David Butler, que procedió en su carácter de Asesor/Registrador/Secretario del Condado de San Diego, Estado de California, y lleva el sello del Condado de San Diego, Estado de California.- Certificado en San Diego, el 2 de setiembre de 2009, por el Secretario de Estado del Estado de California - Número 723539- (Sello:) Hay un sello aplicado: Gran sello del Estado de California - Firma Devra Bowen- Secretaria de Estado - (Hay otro firma ilegible) ES TRADUCCIÓN FIEL del documento de referencia, que en idioma inglés tengo a la vista y he vertido al idioma nacional, en Buenos Aires, a 21 de setiembre de 2009.- Sigue una firma ilegible. Hay un sello que dice: Laura Thieberger Matrícula de Traductores Aleman - Frances Tomo II Folio 254 (Cap.) Tomo III - 93 (La Plata) Ingles Tomo III Folio 14 (Cap.) Tomo III Folio 329 (La Plata) Colegio Traductores Públicos nº 173. Sigue la legalización de la firma de la Traductora Laura Thieberger realizada por el Colegio de Traductores Públicos de la Ciudad de Buenos Aires. ES COPIA FIEL, doy fe. LEIDA que le es, así la otorga y firma ante mi, doy fe. Dagmar Messerer.- Hay un sello. Ante mí: I.Martinez Diego. Concuerda con su escritura matriz que pasó ante mi al folio 558 del Registro 2011 a mi cargo, doy fe. Para la apoderada expido la presente primera

COLEGIO DE ESCRIBANOS · CIUDAD DE BUENOS AIRES · CAPITAL FEDERAL - REPUBLICA ARGENTINA

ACTUACION NOTARIAL

N 011263619

copia en tres sellos de actuación notarial números N 011263613 correlativos al presente, los que firmo y sello en el lugar y fecha de su otorgamiento. Hay un sello I. Martínez Diego", ES COPIA FIEL, doy fe, LEIDA que le es, así la otorga y firma ante mi, doy fe. DAGMAR MESSERER.- Hay un sello. Ante mí: I.MARTINEZ DIEGO. CONCUERDA con su escritura matriz que pasó ante mi al folio 561 del Registro 2011 a mi cargo, doy fe. PARA LOS APODERADOS expido la presente PRIMERA COPIA en cuatro sellos de actuación notarial números N 011263616 correlativos al presente, los que firmo y sello en el lugar y fecha de su otorgamiento.

ISABEL MARTINEZ DIEGO
MATRICULA 4452
ESCRIBANA

COLEGIO DE ESCRIBANOS
CIUDAD DE BUENOS AIRES
CAPITAL FEDERAL - REPUBLICA ARGENTINA

N 011263619

CONSEJO FEDERAL DEL NOTARIADO ARGENTINO
Serie B 01951418
CERONUNOUEVECINCO
UNOCUATROUNOOCHO

# APOSTILLE

REPUBLICA ARGENTINA

(Convention de La Haye du 5 octobre 1961)

A 00240257

1. PAÍS: REPUBLICA ARGENTINA

El presente documento público

2. Ha sido firmado por HORACIO FRANCISCO BALLESTRIN----------

3. Quien actúa en calidac de LEGALIZADOR----------

4. Lleva el sello / timbre ce COLEGIO DE ESCRIBANOS DE LA CIUDAD DE BUENOS AIRES----------

5. En LA CIUDAD DE BUENOS AIRES 6. El día 28/09/2009

7. Por EL COLEGIO DE ESCRIBANOS DE LA CIUDAD DE BUENOS AIRES

MINISTERIO DE RELACIONES EXTERIORES, COMERCIO INTERNACIONAL Y CULTO

(Convenio 02/09/2003)

8. Bajo el número: 090928088701

9. Sello / Timbre

COLEGIO DE ESCRIBANOS · APOSTILLA ·

10. Firma

GRAFICA LATINA S.R.L.

COLEGIO DE ESCRIBANOS • CIUDAD DE BUENOS AIRES • CAPITAL FEDERAL - REPUBLICA ARGENTINA

LEGALIZACION

Serie B 01951418
CERO UNO NUEVE CINCO UNO CUATRO UNO OCHO

L 009076161

EL COLEGIO DE ESCRIBANOS de la Ciudad de Buenos Aires, Capital Federal de la República Argentina, en virtud de las facultades que le confiere la ley orgánica vigente, LEGALIZA la firma y sello del escribano ISABEL MARTINEZ DIEGO obrantes en el documento anexo, presentado en el día de la fecha bajo el Nº 090928439312/7 La presente legalización no juzga sobre el contenido y forma del documento.

Buenos Aires, Lunes 28 de Septiembre de 2009

COLEGIO DE ESCRIBANOS • LEGALIZACION • CIUDAD DE BUENOS AIRES • CAPITAL FEDERAL - REPUBLICA ARGENTINA

ESC. HORACIO FRANCISCO BALLESTRIN
COLEGIO DE ESCRIBANOS
LEGALIZADOR


Serie B 01951418
CERO UNO NUEVE CINCO
UNO CUATRO UNO OCHO

**APOSTILLA**

(Convención de la Haya, Octubre 5, 1961)

1. PAIS: ESTADOS UNIDOS DE AMERICA
   ESTE DOCUMENTO PÚBLICO
2. HA SIDO FIRMADO POR: JEFFREY W. BULLOCK
3. ACTUANDO EN SU CALIDAD DE NOTARIO PUBLICO DELAWARE
4. LLEVA EL SELLO /ESTAMPILLA DE SECRETARIO DE ESTADO

CERTIFICADO

5. EN DOVER, DELAWARE
6. EL DIA 3 DE NOVIEMBRE DE 2009
7. POR SECRETARIO DE ESTADO, DELAWARE DEPARTAMENTO DE ESTADO
8. No. 0399391
9. SELLO/ESTAMPILLA
10. FIRMADO

(HAY FIRMA)

**DELAWARE**
**El Primer Estado**

Yo, Jeffrey W. BULLOCK, Secretario de Estado del Estado de Delaware, certifico el documento adjunto es una copia fiel y exacta del certificado de propiedad, que fusiona:

"APOTHOGEN, INC"., una compañía de Delaware,
con y en "INTRABIOTICS PHARMACEUTICALS, INC." bajo el nombre de "ARDEA BIOSCIENCES, INC", una compañía organizada y existente bajo las leyes del Estado de Delaware, recibidas y presentadas en esta oficina el día 21 de diciembre A.D. de 2006, a las 7:45 pm en punto.

(firma ilegible ) Bullock W. Jeffrey
Secretario de Estado
Autenticacion: 7619215
Fecha: marzo 11 de 2009

Sello
2370807
090986639
Usted puede verificar esto en at corp. delaware.gov/authver.st

*Estado de Delaware*
*Secretario de Estado*
*División de Sociedades*
*Entregados 07:50 PM 12/21/2006*
*Presentada 04:45 PM 12/21/2006*
*SRV 080178223 - 2370807 ARCHIVO*

**CERTIFICADO DE PROPIEDAD Y FUSIÓN**
**FUSIÓN**

**APOTHOGEN, INC**
**(Una compañía de Delaware)**
**EN**
**INTRABIOTICS PHARMACEUTICALS INC**
**(a compañía de Delaware)**

**(virtud de las disposiciones de la Sección 253 de la Delaware**
**Ley General de Sociedades)**

IntraBiotics Pharmaceuticlas, Inc, una compañía de Delaware (la "Compañía"), sociedad constituida y existente en virtud y bajo de la Ley General de Sociedades de Delaware (la "DGCL"), se certifica que:

PRIMERO: El nombre y estado de la incorporación de cada una de las compañías constituidas de la fusión es de la siguiente manera:

| **Nombre** | **Estado de Incorporación** |
|---|---|
| IntraBiotics Pharmaceticals, Inc | Delaware |
| Apothogen, Inc. | Delaware |

SEGUNDO: La Compañía es propietaria del cien por ciento (100%) de las acciones en circulación de cada clase de acciones del capital de Apothogen, Inc., una compañía de Delaware (la "subsidiario").

TERCERO: La Compañía, por las siguientes resoluciones de su Junta Directiva (la "Junta"), debidamente aprobados por la Junta el 21 de diciembre de 2006, determinó la fusión en sí misma el Subsidiario de las condiciones establecidas en las resoluciones de este tipo:

CONSIDERANDO QUE, la compañía es el dueño legal y beneficioso de todas las acciones en circulación del capital social de capitales de Apothogen Inc., una compañía de Delaware ("subsidiario").

CONSIDERANDO QUE, la Junta considera estar en los mejores intereses de la compañía de fusionar con una compañía subsidiaria conforme a la sección 253 de la Ley General de Sociedades de Delaware ("DGCL") (la "Fusión"), y

CONSIDERANDO QUE, en relación con la fusión, la Junta cree que es en el mejor interés de la compañía para cambiar el nombre de la compañía por ARDEA BIOSCIENCES, INC.

RESUELVE, que la Junta aprueba la fusión con arreglo a los siguientes términos:

1. Sobre la efectividad de la fusión, cada acción en circulación del capital social de la filial dejará de ser excepcional, sin que se efectúe en las mismas,

2. La compañía será la supervivencia de la corporación en la fusión y asumirá la totalidad de las responsabilidades y obligaciones de la subsidiaria, y

3. A efectos de la fusión, el nombre de la empresa será ARDEA BIOSCIENCES, INC, y,

**RESUELVE ADEMÁS**, que la fusión se hará efectiva mediante la presentación de un Certificado de Propiedad y de Fusión ante el Secretario de Estado de Delaware.

**CUARTO**: la Compañía será la entidad superviviente. De la eficacia de la presentación de este certificado de propiedad y de fusión, la Compañía va a cambiar su nombre a ARDEA BIOSCIENCES, INC. Y

**QUINTO**: El Certificado de incorporación de la compañía será el acta de constitución de la entidad superviviente.

**SEXTO**: El presente certificado de propiedad y de la fusión será efectivo tras la presentación.

**EN FE DE LO CUAL,** este Certificado de propiedad y fusión se ejecuta en nombre de las empresas por un funcionario debidamente autorizado, el 21 de diciembre 2006

INTRABIOTICS PHARMACEUTICALS, INC.,
Una compañía de Delaware

Por /s/ Barry D. Quart
Barry Quart,
Oficial Ejecutivo

# 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 third day of November, A.D. 2009*

7. *by Secretary of State, Delaware Department of State*

8. *No. 0399391*

9. *Seal/Stamp:*




10. *Signature:*

Secretary of State

# Delaware

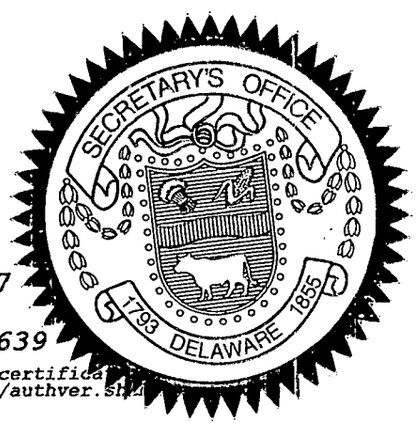


## The First State

I, JEFFREY W. BULLOCK, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF OWNERSHIP, WHICH MERGES:

"APOTHOGEN, INC.", A DELAWARE CORPORATION,

WITH AND INTO "INTRABIOTICS PHARMACEUTICALS, INC." UNDER THE NAME OF "ARDEA BIOSCIENCES, INC.", A CORPORATION ORGANIZED AND EXISTING UNDER THE LAWS OF THE STATE OF DELAWARE, AS RECEIVED AND FILED IN THIS OFFICE THE TWENTY-FIRST DAY OF DECEMBER, A.D. 2006, AT 7:45 O'CLOCK P.M.




Jeffrey W. Bullock, Secretary of State

2370807

090986639

AUTHENTICATION: 7619215

DATE: 11-03-09

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

State of Delaware
Secretary of State
Division of Corporations
Delivered 07:50 PM 12/21/2006
FILED 07:45 PM 12/21/2006
SRV 061178223 - 2370807 FILE

# CERTIFICATE OF OWNERSHIP AND MERGER MERGING

**APOTHOGEN, INC.**
**(a Delaware corporation)**

**INTO**
**INTRABIOTICS PHARMACEUTICALS, INC.**
**(a Delaware corporation)**

**(Pursuant to Section 253 of the Delaware General Corporation Law)**

IntraBiotics Pharmaceuticals, Inc., a Delaware corporation (the ***"Corporation"***), a corporation organized and existing under and by virtue of the Delaware General Corporation Law (the ***"DGCL"***), does hereby certify that:

**FIRST:** The name and state of incorporation of each of the constituent corporations of the merger is as follows:

| Name | State of Incorporation |
|---|---|
| IntraBiotics Pharmaceuticals, Inc. | Delaware |
| Apothogen, Inc. | Delaware |

**SECOND:** The Corporation owns one hundred percent (100%) of the outstanding shares of each class of the capital stock of Apothogen, Inc., a Delaware corporation (the ***"Subsidiary"***).

**THIRD:** The Corporation, by the following resolutions of its Board of Directors (the ***"Board"***) duly adopted by the Board on December 21, 2006, determined to merge into itself the Subsidiary on the conditions set forth in such resolutions:

**WHEREAS,** the Company is the legal and beneficial owner of all of the outstanding shares of capital stock of Apothogen, Inc., a Delaware corporation (***"Subsidiary"***);

**WHEREAS,** the Board considers it to be in the best interests of the Corporation to merge Subsidiary with and into the Company pursuant to Section 253 of the Delaware General Corporation Law (***"DGCL"***) (the ***"Merger"***); and

**WHEREAS,** in connection with the Merger, the Board believes it is in the best interests of the Company to change the name of the Company to **ARDEA BIOSCIENCES, INC.**

**RESOLVED,** that the Board approves the Merger pursuant to the following terms:

1. upon the effectiveness of the Merger, each outstanding share of capital stock of Subsidiary shall cease to be outstanding, without any payment being made in respect thereof;

2. the Company shall be the surviving corporation in the Merger and shall assume all of the liabilities and obligations of Subsidiary; and

3. upon effectiveness of the Merger, the name of the Company shall be **ARDEA BIOSCIENCES, INC.**; and

**RESOLVED FURTHER**, that the Merger shall become effective upon the filing of a Certificate of Ownership and Merger with the Delaware Secretary of State.

**FOURTH:** The Corporation shall be the surviving corporation. Upon the effectiveness of the filing of this Certificate of Ownership and Merger, the Corporation will change its name to **ARDEA BIOSCIENCES, INC.**

**FIFTH:** The Certificate of Incorporation of the Corporation shall be the Certificate of Incorporation of the surviving corporation.

**SIXTH:** This Certificate of Ownership and Merger shall be effective upon filing.

**IN WITNESS WHEREOF**, this Certificate of Ownership and Merger is hereby executed on behalf of the Corporation by an officer thereunto duly authorized as of December 21, 2006.

**INTRABIOTICS PHARMACEUTICALS, INC.,**
a Delaware corporation

By: /s/ Barry Quart
Barry Quart
Chief Executive Officer

**APOSTILLA**
(Convención de la Haya, Octubre 5, 1961)

1. PAIS: ESTADOS UNIDOS DE AMERICA
   ESTE DOCUMENTO PÚBLICO
2. HA SIDO FIRMADO POR: JEFFREY W. BULLOCK
3. ACTUANDO EN SU CALIDAD DE NOTARIO PUBLICO DE DELAWARE
4. LLEVA EL SELLO /ESTAMPILLA DE SECRETARIO DE ESTADO.

CERTIFICADO

5. EN DOVER, DELAWARE
6. EL DIA 3 DE NOVIEMBRE DE 2009
7. POR SECRETARIO DE ESTADO, DELAWARE DEPARTAMENTO DE ESTADO
8. No. 0399392
9. SELLO/ESTAMPILLA
10. FIRMADO

(HAY FIRMA)

**DELAWARE**
**El Primer Estado**

Yo **JEFFREY W. BULLOCK**, secretario de Estado de Estado de Delaware, por la presente certifico el documento adjunto es una copia fiel y correcta del certificado de denominación de "**ARDEA BIOSCIENCES, INC.**", presentó en esta oficina el 27 de julio de 2007 a las 1:55 pm en punto.

(firma ilegible ) Bullock W. Jeffrey
Secretario de Estado
Autenticación: 7619216
Fecha: marzo 11 de 2009

Sello
2370807
090986639
Usted puede verificar esto en at corp. delaware. gov./authver.st

*Estado de Delaware*
*Secretario de Estado*
*Division de Sociedades*
*Entregados 02:09 PM 07/27/2007*
*Presentada 01:55 PM 07/27 2007*
*SRV 0862248 - 2370807 ARCHIVO*

# CERTIFICADO DE MODIFICACIÓN DE LA MODIFICACION Y REFORMULACION DE UN CERTICADO DE INCORPORACION DE ARDEA BIOSCIENCES, INC

**ARDEA BIOSCIENCES, Inc.**, una compañía organizada y existente en virtud y bajo la Ley General de Sociedades del Estado de Delaware (la **DGCL**), se certifica:

PRIMERO: El nombre de la compañía es ARDEA BIOSCIENCES, INC.

SEGUNDO: El nombre original de la compañía es **IntraBiotics Pharmaceuticals, Inc**. La fecha en que el Certificado de Constitución original de la compañia se presentó ante el Secretario de Estado del Estado de Delaware fue el 19 de enero de 1994.

TERCERO: El Consejo de Directores de la Compañía, actuando de conformidad con las disposiciones de las Secciones 141 y 242 de la DGCL, resoluciones adoptadas que modifican su Certificado de incorporación modificado y expuesto en forma modificada como sigue:

1. Artículo V. Sección A1. el certificado de incorporación enmendado y expuesto en forma modificada será enmendado y expuesto en forma modificada para leer dentro de su totalidad como sigue:

"1. La gestión de la Empresa y la dirección de los asuntos de la Sociedad será ejercida por la Junta Directiva. El número de directores que constituirán la Junta Directiva no será menos de 5 y no mayor que 11 directores y se fija exclusivamente por resolución adoptada por una mayoría del número autorizado de directores que constituyan la Junta Directiva".

2. Artículo V. Sección A.2 el certificado de incorporación enmendado y expuesto en forma modificada será enmendado y expuesto en forma modificada para leer dentro de su totalidad como sigue:

"2. ELECCION DE DIRECTORES. Conforme a los derechos de los titulares de cualquier serie de acción preferida para elegir a los directores adicionales bajo circunstancias especificas, elegirán a los directores en cada reunión anual de accionistas para mantener la oficina hasta la reunión anual siguiente. Cada director servirá hasta que elijan y se califiquen o hasta su sucesor debido a su muerte, dimisión o retiro. Ninguna disminución del número de directores que constituyen a las juntas directivas acortará el término de cualquier director apoyado.

3. Artículo V, Sección A.3 (a) y (b) certificado de incorporacion modificado y expuesto en forma modificada por este medio se elimina y se sustituye por el siguiente nuevo Artículo V, Sección A.3:

"3. RETIRO DE DIRECTORES. La Junta Directiva o cualquier director individual puede ser destituido en cualquier momento con o sin causa por el voto afirmativo de los titulares de al menos, la mayoría de los votos de todas las partes entonces-excepcionales del capital social de la compañía, con derecho a voto en una elección de tales directores.

4. Artículo V, sección B.1 el certificado de incorporación enmendado y expuesto en forma modificada será enmendado y expuesto en forma modificada para leer dentro de su totalidad como sigue:

"1. La Junta Directiva está expresamente facultada para proteger, modificar o derogar el reglamento de la compañía. Los accionistas tendrán competencia para adoptar, modificar o derogar los Estatutos de la compañía; con tal que, sin embargo, eso, además de cualquier voto de los titulares de cualquier clase o series de acción de la compañía requerida por la ley o por esta certificación de la incorporación o cualquier certificado de designación archivado con respecto a una serie de acción preferida, con el voto afirmativo de los titulares por lo menos de una mayoria de la votación de todas las partes entonces-excepcionales de las acciones del capital social de la compañía con derecho a votar generalmente en la elección de directores, votando junto como una sola clase, estarán obligados a adoptar, modificar o derogar cualquier disposición de los Estatutos de la compañía ".

5. Artículo VII. el certificado de incorporación enmendado y expuesto en forma modificada será enmendado y expuesto en forma modificada para leer dentro de su totalidad como sigue:

"La compañía se reserva el derecho de modificar, alterar, modificar o derogar cualquier disposición contenida en este Certificado incorporación en la forma de ahora o de aquí en adelante prescritos por el estatuto, y todos los derechos conferidos a los accionistas en este documento estarán sujetas a la reserva".

**CUARTO:** La modificación anterior se presentó a los accionistas de la compañía para su aprobación, y fue debidamente aprobado de conformidad con lo dispuesto en la Sección 242 de la Ley General de Sociedades del Estado de Delaware.

**EN FE DE LO CUAL.** Ardea Biosciences, Inc. ha causado este certificado de modificación para ser firmado por su Director Ejecutivo en este día 27 de julio de 2007.

ARDEA BIOSCIENCES, INC.

Por /s/ Barry D. Quart
Barry D. Quart. Pharm D.

# 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 third day of November, A.D. 2009*

7. *by Secretary of State, Delaware Department of State*

8. *No. 0399392*

9. *Seal/Stamp:*




10. *Signature:*

Secretary of State

# Delaware



*The First State*

I, JEFFREY W. BULLOCK, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF AMENDMENT OF "ARDEA BIOSCIENCES, INC.", FILED IN THIS OFFICE ON THE TWENTY-SEVENTH DAY OF JULY, A.D. 2007, AT 1:55 O'CLOCK P.M.




Jeffrey W. Bullock, Secretary of State

2370807

090986639

AUTHENTICATION: 7619216

DATE: 11-03-09

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

State of Delaware
Secretary of State
Division of Corporations
Delivered 02:09 PM 07/27/2007
FILED 01:55 PM 07/27/2007
SRV 070862248 - 2370807 FILE

# CERTIFICATE OF AMENDMENT OF AMENDED AND RESTATED CERTIFICATE OF INCORPORATION OF ARDEA BIOSCIENCES, INC.

**ARDEA BIOSCIENCES, INC.** (the ***"Corporation"***), a corporation organized and existing under and by virtue of the General Corporation Law of the State of Delaware (the ***"DGCL"***), does hereby certify that:

**FIRST:** The name of the Corporation is Ardea Biosciences, Inc.

**SECOND:** The original name of the Corporation is IntraBiotics Pharmaceuticals, Inc. The date on which the Corporation's original Certificate of Incorporation was originally filed with the Secretary of State of the State of Delaware was January 19, 1994.

**THIRD:** The Board of Directors of the Corporation, acting in accordance with the provisions of Sections 141 and 242 of the DGCL, adopted resolutions amending its Amended and Restated Certificate of Incorporation as follows:

1. Article V, Section A.1 of the Amended and Restated Certificate of Incorporation shall be amended and restated to read in its entirety as follows:

> "1. The management of the business and the conduct of the affairs of the Corporation shall be vested in its Board of Directors. The number of directors which shall constitute the Board of Directors shall be no less than 5 and no greater than 11 directors and shall be fixed exclusively by resolutions adopted by a majority of the authorized number of directors constituting the Board of Directors."

2. Article V, Section A.2 of the Amended and Restated Certificate of Incorporation shall be amended and restated to read in its entirety as follows:

> "2. ELECTION OF DIRECTORS. Subject to the rights of the holders of any series of Preferred Stock to elect additional directors under specified circumstances, directors shall be elected at each annual meeting of stockholders to hold office until the next annual meeting. Each director shall serve until his or her successor is duly elected and qualified or until his or her death, resignation or removal. No decrease in the number of directors constituting the Board of Directors shall shorten the term of any incumbent director."

3. Article V, Section A.3(a) and (b) of the Amended and Restated Certificate of Incorporation is hereby deleted and replaced with the following new Article V, Section A.3:

> "3. REMOVAL OF DIRECTORS. The Board of Directors or any individual director may be removed from office at any time with or without cause by the affirmative vote of the holders of at least a majority of the voting power of

all the then-outstanding shares of capital stock of the Corporation, entitled to vote at an election of such directors."

4. Article V, Section B.1 of the Amended and Restated Certificate of Incorporation shall be amended and restated to read in its entirety as follows:

"1. The Board of Directors is expressly empowered to adopt, amend or repeal the Bylaws of the corporation. The stockholders shall have power to adopt, amend or repeal the Bylaws of the Corporation; provided, however, that, in addition to any vote of the holders of any class or series of stock of the Corporation required by law or by this Certificate of Incorporation or any certificate of designation filed with respect to a series of Preferred Stock, the affirmative vote of the holders of at least a majority of the voting power of all of the then-outstanding shares of the capital stock of the Corporation entitled to vote generally in the election of directors, voting together as a single class, shall be required to adopt, amend or repeal any provision of the Bylaws of the Corporation."

5. Article VII of the Amended and Restated Certificate of Incorporation shall be amended and restated to read in its entirety as follows:

"The corporation reserves the right to amend, alter, change or repeal any provision contained in this Certificate of Incorporation, in the manner now or hereafter prescribed by statute, and all rights conferred upon the stockholders herein are granted subject to this reservation."

**FOURTH:** The foregoing amendment was submitted to the stockholders of the Corporation for their approval, and was duly adopted in accordance with the provisions of Section 242 of the General Corporation Law of the State of Delaware.

**IN WITNESS WHEREOF**, Ardea Biosciences, Inc. has caused this Certificate of Amendment to be signed by its Chief Executive Officer this 27th day of July, 2007.

**ARDEA BIOSCIENCES, INC.**

By: /s/ Barry D. Quart
Barry D. Quart, Pharm.D

**APOSTILLA**
(Convención de la Haya, Octubre 5, 1961)

1. PAIS: ESTADOS UNIDOS DE AMERICA
   ESTE DOCUMENTO PÚBLICO
2. HA SIDO FIRMADO POR: JEFFREY W. BULLOCK
3. ACTUANDO EN SU CALIDAD DE NOTARIO PUBLICO DE DELAWARE
4. LLEVA EL SELLO ESTAMPILLA DE SECRETARIO DE ESTADO.

CERTIFICADO

5. EN DOVER, DELAWARE
6. EL DIA 3 DE NOVIEMBRE DE 2009
7. POR SECRETARIO DE ESTADO, DELAWARE DEPARTAMENTO DE ESTADO
8. No. 0399394
9. SELLO/ESTAMPILLA
10. FIRMADO

(HAY FIRMA)

**DELAWARE**
**El Primer Estado**

Yo **JEFFREY W. BULLOCK**, secretario de Estado de Estado de Delaware, por la presente certifico el documento adjunto es una copia fiel y correcta del certificado de denominación de "**ARDEA BIOSCIENCES, INC.**", presentó en esta oficina en el décimo dia de septiembre de 2008 a las 8:19 pm en punto.

(firma ilegible ) Bullock W. Jeffrey
Secretario de Estado
Autenticación: 7619218
Fecha: 11 de marzo de 2009

Sello
2370807
090986639
Usted puede verificar esto en at corp.delaware.gov/authver.st

*Estado de Delaware*
*Secretario de Estado*
*Division de Sociedades*
*Entregados 09:13 PM 09/10/2008*
*Presentada 09:13 PM 09/10/2008*
*SRV 080944108 - 2370807 ARCHIVO*

# REINSTAURACION DE CERTIFICADO DE INCORPORACION DE ARDEA BIOSCIENCES, INC

El abajo firmante, Barry D. Quart, Pharm Dm certifica que:

UNO: Él está debidamente elegido y consejero delegado en funciones de Ardea Biosciences, Inc. (la "compañía").

DOS: La Compañía fue constituida en Delaware el 19 de enero de 1994, y el nombre original de la compañía era IntraBiotics Pharmaceuticals, Inc.

TERCERA: El certificado enmendado y expuesto en forma modificada de la incorporación, según la enmienda prevista de la compañía se expone en forma modificada por este medio para leer por completo como sigue

I.

El nombre de esta compañía es ARDEA BIOSCIENCES, INC.

II.

La dirección del domicilio social de la compañía en el Estado de Delaware es Corporación Trust Compañía, 1209 Orange Street, Ciudad de Wilmington, Condado de New Castle, y el nombre del agente registrado de la Corporación en el Estado de Delaware en esa dirección es la compañía de confianza de la corporación.

III.

El propósito de esta corporación es enganchar a cualquier acto o actividad legal para los cuales una corporación se pueda organizar bajo Ley General de Sociedades del Estado de Delaware.

IV.

A. Esta corporación esta autorizada a emitir dos clases de acciones que serán designados, respectivamente, "Acciones Comunes" y "Acciones Preferidas" El número total de acciones que la sociedad os está autorizada a emitir es de setenta y cinco años de Millón (75.000.000) acciones, (70.000.000) Setenta millones) las acciones de las acciones ordinarias, cada una con un valor nominal de un décimo del uno por el cien ($ 001). Cinco millones (5.000.000) acciones se Acciones Preferidas, cada una con un valor nominal de un décimo del uno por centavo ($ 001).

B. La acción preferida se puede publicar de vez en cuando en una o más series. La Junta Directiva por medio de la presente autoriza, mediante la presentación de un certificado (un "Designación de las acciones preferidas") de conformidad a la Ley General

de Sociedades de Delaware ( "DGCL"), para fijar o modificar de vez en cuando la designación, facultades, las preferencias y los derechos de las acciones de cada serie y las calificaciones, las limitaciones o las restricciones de cualquier serie enteramente sin publicar de las acciones preferidas, y para establecer de vez en cuando el número de acciones que constituyen cualesquiera series o cualesquiera de ellos; y para aumentar o disminuir el número de acciones de cualesquiera series subsecuentes a la emisión de acciones de esa serie, pero no por debajo del número de acciones de dichas series entonces excepcionales. En caso de que el número de acciones de cualquier serie sea disminuido de acuerdo con la frase anterior, las acciones que constituyen tal disminución reasumirán el estado que tenían antes de la adopción de la resolución original que fijaba el número de acciones de tales series.

V.

La gestión de la Empresa y la dirección de los asuntos de la Sociedad y en la definición, la limitación y la reglamentación adicional de las competencias de la compañía, de sus directores y de sus accionistas o cualquier otra clase y de acuerdo con las circunstancias, es más futuro a condición de que:

A. JUNTA DIRECTIVA

1. La gestión de la Empresa y la dirección de los asuntos de la Sociedad será ejercida por la Junta Directiva. El número de directores que constituirán la Junta Directiva no será menos de 5 y no mayor que 11 directores y se fija exclusivamente por resolución adoptada por una mayoría del numero autorizado de directores que constituyan la Junta Directiva".

2. ELECCION DE DIRECTORES. Conforme a los derechos de los titulares de cualquier serie de acción preferida para elegir a los directores adicionales bajo circunstancias especificas, elegirán a los directores en cada reunión anual de accionistas para mantener la oficina hasta la reunión anual siguiente. Cada director servirá hasta que elijan y se califiquen o hasta su sucesor debido a su muerte, dimisión o retiro. Ninguna disminución del número de directores que constituyen a las juntas directivas acortará el término de cualquier director apoyado.

3. RETIRO DE DIRECTORES. La Junta Directiva o cualquier director individual puede ser destituido en cualquier momento con o sin causa por el voto afirmativo de los titulares de al menos, la mayoría de los votos de todas las partes entonces-excepcionales del capital social de la compañía, con derecho a voto en una elección de tales directores.

1. VACANTES

a. Sin perjuicio de los derechos de los titulares de cualquier serie de acciones preferentes, cualesquiera de las vacantes en la Junta Directiva resultado de muerte, renuncia, descalificación, retiro u otras causas y cualesquiera de los cargos directivos creado recientemente resultado de cualquier aumento en el numero de directores, será, a menos de que la Junta Directiva determine por resolución que cualesquiera de esas vacantes o direcciones creadas recientemente serán llenadas por los accionistas, a menos

que según lo proporcionado de otra manera por las establecidas por la ley, sea llenado solamente por el voto afirmativo de la mayoría de los directores en funciones, aunque menos de un quórum de la Junta de Directiva, y no por los accionistas. Cualquier director elegido de acuerdo con la frase anterior, ocupará el cargo por el resto del período total del director de la vacante que se creó o se produjo hasta que su sucesor y el director de dicha hayan sido elegidos y calificados.

b. Si en el momento de llenar cualquier vacante o cualquier otra dirección creada recientemente, los directores entonces en funciones constituirán menos de la mayoría de la junta general (tal como estaba constituida antes de cualquier aumento de este tipo), el Tribunal de Justicia de Delaware, a petición de cualquier accionista o accionistas que reúnan al menos el diez por ciento (10%) del total de las acciones pendientes en el momento en que tenga derecho a votar para tales directores, sumariamente para una elección para ser tenido en cuenta para llenar cualesquiera de las vacantes o puestos directivos creados recientemente, o para sustituir a los directores elegidos por los directores de entonces en las oficinas como se ha dicho, que la elección se regirá por la Sección 211 del DGCL.

B.

1. La Junta Directiva está expresamente facultada para proteger, modificar o derogar el reglamento de la compañía. Los accionistas tendrán competencia para adoptar, modificar o derogar los Estatutos de la compañía; con tal que, sin embargo, eso, además de cualquier voto de los titulares de cualquier clase o series de acción de la compañía requerida por la ley o por esta certificación de la incorporación o cualquier certificado de designación archivado con respecto a una serie de acción preferida, con el voto afirmativo de los titulares por lo menos de una mayoría de la votación de todas las partes entonces-excepcionales de las acciones del capital social de la compañía con derecho a votar generalmente en la elección de directores, votando junto como una sola clase, estarán obligados a adoptar, modificar o derogar cualquier disposición de los Estatutos de la compañía ".

2. Los directores de la corporación no necesitan ser elegidos por votación escrita a menos que así lo prevean los Estatutos Sociales.

3. Ninguna acción será tomada por los accionistas de la sociedad, salvo en una asamblea anual o extraordinaria de accionistas convocada con arreglo a los Estatutos y no se tomarán medidas por los accionistas por consentimiento por escrito.

4. Comunicación previa de los nombramientos de los accionistas para la elección de directores y del negocio de ser traído por los accionistas antes de que cualquier reunión de los accionistas de la corporación sea dada de la manera prevista en los Estatutos de la compañía.

VI.

A. La responsabilidad de los directores para los daños monetarios será eliminada en la mayor medida en virtud de la legislación aplicable.

B. Cualquier derogación o modificación de este Artículo VI será anticipada y

no afectará a los derechos previstos en este Artículo VI de afecto en el momento de la supuesta ocurrencia de cualquier acto u omisión de actuar dará lugar a la responsabilidad o de indemnización.

VII.

Las reservas de derecho de enmendar, alterar, modificar o derogar cualquier disposición ahora contenida en este certificado de incorporación, de la manera o de aquí en adelante prescrita por el estatuto y de todos los derechos conferidos a los accionistas en este documento estarán sujetas a la reserva.

CUATRO: El certificado de incorporación modificado fue debidamente aprobado de conformidad con lo dispuesto en el artículo 245 de la Ley General de Sociedades del Estado de Delaware, y fue aprobado por la Junta Directiva de la Corporación de conformidad y con arreglo a la Sección 141 de la Ley General de Sociedades del Estado de Delaware.

CINCO: El certificado de incorporación modificado sólo reafirma y se integra más y no modifica las disposiciones del Certificado de incorporación modificado y expuesto en forma modificada, y no hay discrepancia entre las disposiciones y las disposiciones de este Certificado de incorporación modificado.

EN FE DE LO CUAL, este certificado de incorporación modificado ha sido suscrito el día 10 de septiembre de 2008 por el abajo firmante, que afirma que la declaración hecha en este documento son verdaderos y correctos

ARDEA BIOSCIENCES, INC

Por /s/ Barry D. Quart
Barry D. Quart.
Director Ejecutivo encargado.

# 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 third day of November, A.D. 2009*

7. *by Secretary of State, Delaware Department of State*

8. *No. 0399394*

9. *Seal/Stamp:*

SECRETARY'S OFFICE
1793 DELAWARE 1855

10. *Signature:*

Secretary of State

# Delaware



*The First State*

I, JEFFREY W. BULLOCK, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE RESTATED CERTIFICATE OF "ARDEA BIOSCIENCES, INC.", FILED IN THIS OFFICE ON THE TENTH DAY OF SEPTEMBER, A.D. 2008, AT 9:13 O'CLOCK P.M.




Jeffrey W. Bullock, Secretary of State

2370807

090986639

AUTHENTICATION: 7619218

DATE: 11-03-09

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

State of Delaware
Secretary of State
Division of Corporations
Delivered 09:13 PM 09/10/2008
FILED 09:13 PM 09/10/2008
SRV 080944108 - 2370807 FILE

RESTATED
CERTIFICATE OF INCORPORATION OF
ARDEA BIOSCIENCES, INC.

The undersigned, Barry D. Quart, Pharm. D., hereby certifies that:

ONE: He is the duly elected and acting Chief Executive Officer of Ardea Biosciences, Inc. (the "corporation").

TWO: The corporation was originally incorporated in Delaware on January 19, 1994 and the original name of the corporation was IntraBiotics Pharmaceuticals, Inc.

THREE: The Amended and Restated Certificate of Incorporation, as amended, of the corporation is hereby restated to read in full as follows:

"

**I.**

The name of this corporation is **ARDEA BIOSCIENCES, INC.**

**II.**

The address of the registered office of the corporation in the State of Delaware is Corporation Trust Company, 1209 Orange Street, City of Wilmington, County of New Castle, and the name of the registered agent of the corporation in the State of Delaware at such address is the Corporation Trust Company.

**III.**

The purpose of this corporation is to engage in any lawful act or activity for which a corporation may be organized under the General Corporation Law of the State of Delaware.

**IV.**

**A.** This corporation is authorized to issue two classes of stock to be designated, respectively, "Common Stock" and "Preferred Stock." The total number of shares which the corporation is authorized to issue is Seventy-Five Million (75,000,000) shares. Seventy Million (70,000,000) shares shall be Common Stock, each having a par value of one-tenth of one cent ($.001). Five Million (5,000,000) shares shall be Preferred Stock, each having a par value of one-tenth of one cent ($.001).

**B.** The Preferred Stock may be issued from time to time in one or more series. The Board of Directors is hereby authorized, by filing a certificate (a "Preferred Stock Designation") pursuant to the Delaware General Corporation Law ("DGCL"), to fix or alter from time to time the designation, powers, preferences and rights of the shares of each such series and the qualifications, limitations or restrictions of any wholly unissued series of Preferred Stock, and to establish from time to time the number of shares constituting any such series or any of them; and to increase or decrease the number of shares of any series subsequent to the issuance of shares of

that series, but not below the number of shares of such series then outstanding. In case the number of shares of any series shall be decreased in accordance with the foregoing sentence, the shares constituting such decrease shall resume the status that they had prior to the adoption of the resolution originally fixing the number of shares of such series.

V.

For the management of the business and for the conduct of the affairs of the corporation, and in further definition, limitation and regulation of the powers of the corporation, of its directors and of its stockholders or any class thereof, as the case may be, it is further provided that:

A. BOARD OF DIRECTORS.

1. The management of the business and the conduct of the affairs of the corporation shall be vested in its Board of Directors. The number of directors which shall constitute the Board of Directors shall be no less than 5 and no greater than 11 directors and shall be fixed exclusively by resolutions adopted by a majority of the authorized number of directors constituting the Board of Directors.

2. ELECTION OF DIRECTORS. Subject to the rights of the holders of any series of Preferred Stock to elect additional directors under specified circumstances, directors shall be elected at each annual meeting of stockholders to hold office until the next annual meeting. Each director shall serve until his or her successor is duly elected and qualified or until his or her death, resignation or removal. No decrease in the number of directors constituting the Board of Directors shall shorten the term of any incumbent director.

3. REMOVAL OF DIRECTORS. The Board of Directors or any individual director may be removed from office at any time with or without cause by the affirmative vote of the holders of at least a majority of the voting power of all the then-outstanding shares of capital stock of the corporation, entitled to vote at an election of such directors.

4. VACANCIES

a. Subject to the rights of the holders of any series of Preferred Stock, any vacancies on the Board of Directors resulting from death, resignation, disqualification, removal or other causes and any newly created directorships resulting from any increase in the number of directors, shall, unless the Board of Directors determines by resolution that any such vacancies or newly created directorships shall be filled by the stockholders, except as otherwise provided by law, be filled only by the affirmative vote of a majority of the directors then in office, even though less than a quorum of the Board of Directors, and not by the stockholders. Any director elected in accordance with the preceding sentence shall hold office for the remainder of the full term of the director for which the vacancy was created or occurred and until such director's successor shall have been elected and qualified.

b. If at the time of filling any vacancy or any newly created directorship, the directors then in office shall constitute less than a majority of the whole board (as constituted immediately prior to any such increase), the Delaware Court of Chancery may,

upon application of any stockholder or stockholders holding at least ten percent (10%) of the total number of the shares at the time outstanding having the right to vote for such directors, summarily order an election to be held to fill any such vacancies or newly created directorships, or to replace the directors chosen by the directors then in offices as aforesaid, which election shall be governed by Section 211 of the DGCL.

**B.**

**1.** The Board of Directors is expressly empowered to adopt, amend or repeal the Bylaws of the corporation. The stockholders shall have power to adopt, amend or repeal the Bylaws of the corporation; provided, however, that, in addition to any vote of the holders of any class or series of stock of the corporation required by law or by this Certificate of Incorporation or any certificate of designation filed with respect to a series of Preferred Stock, the affirmative vote of the holders of at least a majority of the voting power of all of the then-outstanding shares of the capital stock of the corporation entitled to vote generally in the election of directors, voting together as a single class, shall be required to adopt, amend or repeal any provision of the Bylaws of the corporation.

**2.** The directors of the corporation need not be elected by written ballot unless the Bylaws so provide.

**3.** No action shall be taken by the stockholders of the corporation except at an annual or special meeting of stockholders called in accordance with the Bylaws and no action shall be taken by the stockholders by written consent.

**4.** Advance notice of stockholder nominations for the election of directors and of business to be brought by stockholders before any meeting of the stockholders of the corporation shall be given in the manner provided in the Bylaws of the corporation.

**VI.**

**A.** The liability of the directors for monetary damages shall be eliminated to the fullest extent under applicable law.

**B.** Any repeal or modification of this Article VI shall be prospective and shall not affect the rights under this Article VI in effect at the time of the alleged occurrence of any act or omission to act giving rise to liability or indemnification.

**VII.**

The corporation reserves the right to amend, alter, change or repeal any provision contained in this Certificate of Incorporation, in the manner now or hereafter prescribed by statute, and all rights conferred upon the stockholders herein are granted subject to this reservation."

* * *

FOUR: This Restated Certificate of Incorporation was duly adopted in accordance with the provisions of Section 245 of the General Corporation Law of the State of Delaware, and was approved by the Board of Directors of the corporation in accordance with and pursuant to Section 141 of the General Corporation Law of the State of Delaware.

FIVE: This Restated Certificate of Incorporation only restates and integrates and does not further amend the provisions of the corporation's Amended and Restated Certificate of Incorporation, as amended, and there is no discrepancy between those provisions and the provisions of this Restated Certificate of Incorporation.

IN WITNESS WHEREOF, this Restated Certificate of Incorporation has been subscribed this 10th day of September, 2008 by the undersigned who affirms that the statements made herein are true and correct.

ARDEA BIOSCIENCES, INC.

By: /s/ Barry D. Quart
Barry D. Quart, Pharm. D.
Chief Executive Officer

01 '30

36

## APOSTILLA

(Convención de la Haya, Octubre 5, 1961)

1. PAIS: ESTADOS UNIDOS DE AMERICA
ESTE DOCUMENTO PÚBLICO
2. HA SIDO FIRMADO POR: JEFFREY W. BULLOCK
3. ACTUANDO EN SU CALIDAD DE NOTARIO PUBLICO DE DELAWARE
4. LLEVA EL SELLO /ESTAMPILLA DE SECRETARIO DE ESTADO.

CERTIFICADO

5. EN DOVER, DELAWARE
6. EL DIA 3 DE NOVIEMBRE DE 2009
7. POR SECRETARIO DE ESTADO, DELAWARE DEPARTAMENTO DE ESTADO
8. No. 0399393
9. SELLO/ESTAMPILLA
10. FIRMADO
(HAY FIRMA)

MINISTERIO DE RELACIONES EXTERIORES
2009 DIC -9 P 2:43
JEFE DE LEGALIZACIONES
BOGOTA D.C.

**DELAWARE**
**El Primer Estado**

Yo **JEFFREY W. BULLOCK**, secretario de Estado de Estado de Delaware, por la presente certifico el documento adjunto es una copia fiel y correcta del certificado de denominación de "**ARDEA BIOSCIENCES, INC.**", presentado en esta oficina en el décimo día de septiembre de 2008 a las 8:19 pm en punto.

NO SE ASUME RESPONSABILIDAD DEL TEXTO
0030590
CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

(firma ilegible ) Bullock W. Jeffrey
Secretario de Estado
Autenticación: 7619217
Fecha: marzo 11 de 2009

Sello
2370807
090986639
Usted puede verificar esto en: at corp. delaware.gov/authver.st

MAURICIO URRUTIA V.
TRADUCTOR OFICIAL
INGLES - ESPAÑOL
RES. MINJUSTICIA 1/0

*Estado de Delaware*
*Secretario de Estado*
*División de Sociedades*
*Entregados 09:13 PM 09/10/2008*
*Presentada 08:19 PM 09/10/2008*
*SRV 080944107-2370807 ARCHIVO*

# CERTIFICADO DE ELIMINACIÓN DEL CERTIFICADO DE DESIGNACIÓN DE UNA SERIE DE ACCIONES PREFERENTES CONVERTIBLES DE ARDEA BIOSCIENCES, INC.

(de conformidad con el Sección 151 de la ley General de Sociedades del Estado de Delaware)

**ARDEA BIOSCIENCES, Inc.,** una compañía organizada y existente en virtud bajo la Ley General de Sociedades del Estado de Delaware (**"DGCL"**), por medio de la presente certifica:

PRIMERO: El nombre de la compañía es ARDEA BIOSCIENCES, INC.

SEGUNDO: El nombre original de la compañía es **IntraBiotics Pharmaceuticals, Inc.** La fecha en que el Certificado de Constitución original de la compañía se presentó ante el Secretario de Estado del Estado de Delaware fue el 19 de enero de 1994.

TERCERO: La compañía presentó el 1 de mayo de 2003 con el Secretario de Estado del Estado de Delaware, un certificado de designación de la Serie A, Acción Preferida Convertible que señalabas los derechos, preferencias y privilegios de la compañía de la Series A, Acción Preferida Convertible.

CUARTO: El Junta Directiva de la compañía, actuando de conformidad con las disposiciones de la DGCL, aprobó las siguientes resoluciones:

RESUELVE, que ninguna de las acciones autorizadas de la Serie A de la empresa Acciones Preferidas Convertibles están pendientes, y que ninguno se expedirán previo certificado de denominación de la Serie A Acciones Preferidas Convertibles presentada anteriormente en relación con dichas acciones, y

RESUELVE ADEMÁS, que los propios oficiales de las Sociedades quedan autorizados y obligados a tomar todas las medidas que estimen necesarias o convenientes a fin de presentar un certificado con el Secretario de Estado del Estado de Delaware para eliminar todas las disposiciones establecidas figuren en el certificado de las Denominaciones de la Serie A Acciones Preferidas Convertibles de conformidad con la Sección 151 (g) de la DGCL.

QUINTO: Que todas las disposiciones establecidas en el certificado de denominación de la Serie A Acciones Preferidas Convertibles quedan eliminados.

EN FE DE LO CUAL, Ardea Biosciences, Inc. ha producido este Certificado de Eliminación para ser firmado por su Director Ejecutivo a partir de 10 de septiembre de 2008.

ARDEA BIOSCIENCES, INC

Por /s/ Barry D. Quart
Oficina Director Ejecutivo

09/130

# 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 third day of November, A.D. 2009*

7. *by Secretary of State, Delaware Department of State*

8. *No. 0399393*

9. *Seal/Stamp:*




10. *Signature:*

Secretary of State

# Delaware



*The First State*

I, JEFFREY W. BULLOCK, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF DESIGNATION OF "ARDEA BIOSCIENCES, INC.", FILED IN THIS OFFICE ON THE TENTH DAY OF SEPTEMBER, A.D. 2008, AT 8:19 O'CLOCK P.M.




Jeffrey W. Bullock, Secretary of State

2370807

090986639

AUTHENTICATION: 7619217

DATE: 11-03-09

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

State of Delaware
Secretary of State
Division of Corporations
Delivered 09:13 PM 09/10/2008
FILED 08:19 PM 09/10/2008
SRV 080944107 - 2370807 FILE

# CERTIFICATE OF ELIMINATION
# OF THE
# CERTIFICATE OF DESIGNATION OF
# SERIES A CONVERTIBLE PREFERRED STOCK
# OF ARDEA BIOSCIENCES, INC.

(Pursuant to Section 151 of the General Corporation Law
of the State of Delaware)

**ARDEA BIOSCIENCES, INC.**, a corporation organized and existing under and by virtue of the General Corporation Law of the State of Delaware (the "***DGCL***"), does hereby certify:

**FIRST:** The name of the corporation is ARDEA BIOSCIENCES, INC.

**SECOND:** The original name of the corporation is IntraBiotics Pharmaceuticals, Inc. The date on which the corporation's original Certificate of Incorporation was filed with the Secretary of State of the State of Delaware was January 19, 1994.

**THIRD:** The corporation filed on May 1, 2003 with the Secretary of State of the State of Delaware a Certificate of Designation of Series A Convertible Preferred Stock designating the rights, preferences and privileges of the corporation's Series A Convertible Preferred Stock.

**FOURTH:** The Board of Directors of the corporation, acting in accordance with the provisions of the DGCL, adopted the following resolutions:

> **RESOLVED**, that none of the authorized shares of the corporation's Series A Convertible Preferred Stock are outstanding, and that none will be issued subject to the Certificate of Designation of Series A Convertible Preferred Stock previously filed with respect to such shares; and
>
> **RESOLVED FURTHER**, that the proper officers of the corporation are hereby authorized and directed to take all such actions as they may deem to be necessary or advisable in order to file a certificate with the Secretary of State of the State of Delaware to eliminate all provisions set forth in the Certificate of Designation of Series A Convertible Preferred Stock pursuant to Section 151(g) of the DGCL.

**FIFTH:** That all provisions set forth in the Certificate of Designation of Series A Convertible Preferred Stock are hereby eliminated.

**IN WITNESS WHEREOF**, Ardea Biosciences, Inc. has caused this Certificate of Elimination to be signed by its Chief Executive Officer as of September 10, 2008.

**ARDEA BIOSCIENCES, INC.**

By: /s/ Barry D. Quart
Barry D. Quart, Pharm.D.
Chief Executive Officer

600616 v1/SD

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 February 2009 (05.02.2009)

PCT

(10) International Publication Number
WO 2009/018233 A1

(51) International Patent Classification:
*A01N 41/06* (2006.01) *A61K 31/18* (2006.01)

(21) International Application Number:
PCT/US2008/071392

(22) International Filing Date: 28 July 2008 (28.07.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

| | | |
|---|---|---|
| 11/830,733 | 30 July 2007 (30.07.2007) | US |
| 61/034,466 | 6 March 2008 (06.03.2008) | US |
| 61/034,464 | 6 March 2008 (06.03.2008) | US |
| 61/044,886 | 14 April 2008 (14.04.2008) | US |

(71) Applicant *(for all designated States except US)*: **ARDEA BIOSCIENCES, INC.** [US/US]; 4939 Directors Place, San Diego, CA 92121 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **VERNIER, Jean-michel** [FR/US]; 24831 Cutter, Laguna Niguel, CA 92677 (US). **ROWLINGS, Colin, Edward** [US/US]; 1908 Paxton Way, Encinitas, CA 92024 (US). **GIRARDET, Jean-luc** [FR/US]; 17 Open View Lane, Aliso Viejo, CA 92656 (US). **DIMOCK, Stuart** [US/US]; 24144 Graystone Drive, Lake Forest, CA 92630 (US). **QUART, Barry** [US/US]; 3273 Violet Ridge, Encinitas, CA 92024 (US). **MINER, Jeffrey, N.** [US/US]; 4572 Pauling Ave., San Diego, CA 92122 (US).

(74) Agents: **HADDACH, Aubrey, A.** et al.; Wilson Sonsini Goodrich & Rosati, 650 Page Mill Road, Palo Alto, CA 94304-1050 (US).

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**
— *with international search report*

(54) Title: DERIVATIVES OF N-(ARYLAMINO) SULFONAMIDES INCLUDING POLYMORPHS AS INHIBITORS OF MEK AS WELL AS COMPOSITIONS, METHODS OF USE AND METHODS FOR PREPARING THE SAME

(57) Abstract: This invention concerns N-(2-arylamino) aryl sulfonamide compounds which are inhibitors of MEK including crystalline polymorphic forms which exhibit a specific powder x-ray diffraction profile and/or a specific differential scanning calorimetry profile. This invention also concerns pharmaceutical compositions comprising the compounds described herein and methods of use of the compounds and compositions described herein, including the use in the treatment and/or prevention of cancer, hyperproliferative diseases and inflammatory conditions. The invention also concerns methods of making the compunds and compositions described herein.

WO 2009/018233 A1

# DERIVATIVES OF N-(ARYLAMINO) SULFONAMIDES INCLUDING POLYMORPHS AS INHIBITORS OF MEK AS WELL AS COMPOSITIONS, METHODS OF USE AND METHODS FOR PREPARING THE SAME

## CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application Ser. Nos. 61/044,886, filed April 14, 2008, 61/034,466 filed March 6, 2008, and 61/034,464 filed March 6, 2008, each of which is hereby incorporated by reference in the entirety. This application also claims priority to US Application Serial No. 11/830,733, filed July 30, 2007, which claims the benefit of U.S. Provisional Application Ser. No. 60/833,886 filed July 28, 2006 and of International Application Ser. No PCT/US2006/028326 filed July 21, 2006 as a continuation-in-part application, each of which is hereby incorporated by reference in the entirety. International Application Serial No PCT/US2006/028326 also claims priority to U.S. Provisional Application Ser. Nos. 60/701,814 filed July 21, 2005; 60/706,719 filed August 8, 2005, and to 60/731,633 filed October 28, 2005, each of which is hereby incorporated by reference in the entirety.

## FIELD OF THE INVENTION

This invention concerns N-(2-arylamino) aryl sulfonamide compounds which are inhibitors of MEK including crystalline polymorphic forms which exhibit a specific powder x-ray diffraction profile and/or a specific differential scanning calorimetry profile. This invention also concerns pharmaceutical compositions comprising the compounds described herein and methods of use of the compounds and compositions described herein, including the use in the treatment and/or prevention of cancer, hyperproliferative diseases and inflammatory conditions. The invention also concerns methods of making the compunds and compositions described herein.

## BACKGROUND OF THE INVENTION

Oncogenes -- genes that contribute to the production of cancers -- are generally mutated forms of certain normal cellular genes ("proto-oncogenes"). Oncogenes often encode abnormal versions of signal pathway components, such as receptor tyrosine kinases, serine-threonine kinases, or downstream signaling molecules. The central downstream signaling molecules are the Ras proteins, which are anchored on the inner surfaces of cytoplasmic membranes, and which hydrolyze bound guanosine triphosphate (GTP) to guanosine diphosphate (GDP). When activated by a growth factor, growth factor receptors initiate a chain of reactions that leads to the activation of guanine nucleotide exchange activity on Ras. Ras alternates between an active "on" state with a bound GTP (hereafter "Ras.GTP") and an inactive "off state with a bound GDP. The active "on" state, Ras.GTP, binds to and activates proteins that control the growth and differentiation of cells.

For example, in the "*m*itogen-*a*ctivated *p*rotein kinase (MAP kinase) cascade," Ras.GTP leads to the activation of a cascade of serine/threonine kinases. One of several groups of kinases known to require a Ras.GTP for their own activation is the Raf family. The Raf proteins activate "MEK1" and "MEK2," abbreviations for *m*itogen-activated *E*RK-activating *k*inases (where ERK is extracellular signal-regulated protein kinase, another designation for MAPK). MEK1 and MEK2 are dual-function serine/threonine and tyrosine protein kinases and are also known as MAP kinase kinases. Thus, Ras.GTP activates Raf, which activates MEK1 and MEK2, which activate MAP kinase (MAPK). Activation of MAP kinase by mitogens appears to be essential for proliferation, and constitutive activation of this kinase is sufficient to induce cellular transformation. Blockade of downstream Ras signaling, as by use of a dominant negative Raf-1 protein, can completely inhibit mitogenesis, whether induced from cell surface receptors or from oncogenic Ras mutants.

The interaction of Raf and Ras is a key regulatory step in the control of cell proliferation. To date, no substrates of MEK other than MAPK have been identified; however, recent reports indicate that MEK may also be activated by other upstream signal proteins such as MEK kinase or MEKK1 and PKC. Activated MAPK translocates and accumulates in the nucleus, where it can phosphorylate and activate transcription factors such as Elk-1 and Sapla, leading to the enhanced expression of genes such as that for c-fos.

Once activated, Raf and other kinases phosphorylate MEK on two neighboring serine residues, $S^{218}$ and $S^{222}$ in the case of MEK1. These phosphorylations are required for activation of MEK as a kinase. In turn, MEK phosphorylates MAP kinase on two residues separated by a single amino acid: a tyrosine, $Y^{185}$ and a threonine, $T^{183}$. MEK appears to associate strongly with MAP kinase prior to phosphorylating it, suggesting that phosphorylation of MAP kinase by MEK may require a prior strong interaction between the two proteins. Two factors — MEK's unusual specificity and its requirement for a strong interaction with MAP kinase prior to phosphorylation – suggest that MEK's mechanism of action may differ sufficiently from the mechanisms of other protein kinases as to allow for selective inhibitors of MEK. Possibly, such inhibitors would operate through allosteric mechanisms rather than through the more usual mechanism involving blockage of an ATP binding site.

Thus, MEK1 and MEK2 are validated and accepted targets for anti-proliferative therapies, even when the oncogenic mutation does not affect MEK structure or expression. See, *e.g.*, U.S. Patent Publications 2003/0149015 by Barrett *et al.* and 2004/0029898 by Boyle *et al.*

Several examples of 1-substituted-2(*p*-substituted-phenylamino)-aryl inhibitors of MEK have been reported. U.S. Patent Nos. 6,440,966 and 6,750,217 and corresponding publication WO 00/42003 described carboxylic and hydroxamic acid esters and N-substituted amide derivatives of sulfonamide-substituted-2(4-iodophenylamino)-benzoic acid esters and N-substituted benzamides as functioning as MEK inhibitors. The sulfonamide may also be N-substituted.

U.S. Patent 6,545,030 and corresponding publication WO 00/42029 describe MEK inhibitors that are 1-heterocyclyl-2(4-iodophenylamino)-benzene, where the heterocycle is a five-membered nitrogen-containing ring such as pyrazole, triazole, oxazole, isoxazole, and isoxazolinone. The more recent U.S. Patent Publication 2005/004186 describes related compounds in which the 4-iodo substituent of the '030 patent is replaced by a very broad genus of moieties including alkyl, alkoxy, acyloxy, alkenyl, carbamoyl, carbamoylalkyl, carboxyl, carboxylalkyl, N-acylsulfonamido, and others.

U.S. Patent 6,469,004 and corresponding publication WO 00/42022 describe carboxylic and hydroxamic acid esters of a group of heterocyclo-condensed phenylene compounds, *i.e.*, benzimidazoles, benzooxazoles, benzothiazoles, benzothiadiazoles, quinazolines, *etc.* The heterocycles are 7-F-6-(4-iodo-phenylamino)-5-carboxylic acid esters, carboxylic acid amides or hydroxamic acid esters. More recent publication U.S. 2005/0026970 described similar compounds in which the 4-iodo substituent was replaced by a very broad genus of structures. Related compounds are described in patent publications WO 03/077855, WO 03/77914 and US 2005/0554701. Further examples of 2-(4-iodophenylamino)-phenylhydroxamic acid esters which are reported to be useful as MEK inhibitors can be found in WO 2005/028426.

Patent Publication WO 02/06213 and corresponding U.S. Application Ser. No. 10/333,399 (U.S. 2004/0054172) describe hydroxy-substituted acid esters of 1-oxamic acid- 2(4-halophenylamino)-3,4-difluorobenzene. U.S. Patent No. 6,891,066 and corresponding publication WO 03/62191 describe similar compounds wherein the 4-halo substituent is replaced by a very broad genus of structures. Among the substituents in the 4-position were methyl, ethyl, ethynyl, and 2-hydroxyethyl. Specific related compounds are described in U.S. Patent No. 6,770,778.

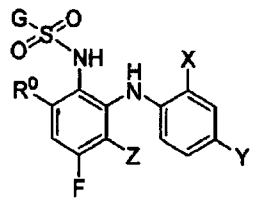
Patent Publication WO 04/083167, published September 30, 2004, (in Japanese) discloses more than two thousand – but provides NMR data for only 400 – l-(N-substituted sulfonyl urea)-2(2,4-dihalophenylamino)-3,4-difluorobenzenes and asserts that they useful as MEK inhibitors. Data indicating inhibition of MEK were presented for a subgroup of just twelve. In addition to a secondary or tertiary amine, these twelve compounds all contained one of the following groups: an N, N-disubstituted sulfonyl urea, N-piperazinesulfonamide, N-piperidinesulfonamide or N-pyrrolidinesulfonamide.

The MEK cascade has also been implicated in inflammatory diseases and disorders. U.S. Application Publication No. 2006/0030610 to Koch *et al.*, U.S. Application Publication No. 2006/0140872 to Furue *et al.* This includes both acute and chronic inflammation disorders. Examples of such disorders are allergic contact dermatitis, rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, chronic obstructive pulmonary disorder, psoriasis, multiple sclerosis, asthma, diseases and disorders related to diabetic complications, and inflammatory complications of the cardiovascular system such as acute coronary syndrome. Among inflammatory bowel diseases are Crohn's disease and ulcerative colitis.

MEKl and MEK2 are validated and accepted targets for anti-proliferative therapies, even when the oncogenic mutation does not affect MEK structure or expression. See, *e.g.*, U.S. Patent Publications 2003/0149015 by Barrett *et al.* and 2004/0029898 by Boyle *et al.*

## SUMMARY OF THE INVENTION

Provided herein are compounds of formula I, or pharmaceutically acceptable salts, solvates, polymorphs, esters, tautomers or prodrugs thereof:



formula I

wherein

Z is H or F;

X is F, Cl, $CH_3$, $CH_2OH$, $CH_2F$, $CHF_2$, or $CF_3$;

Y is I, Br, Cl, $CF_3$, $C_1$-$C_3$ alkyl, $C_2$-$C_3$ alkenyl, $C_2$-$C_3$ alkynyl, cyclopropyl, OMe, OEt, SMe, phenyl or Het, where Het is a 5- to 10- membered mono- or bicyclic heterocyclic group, which group is saturated, olefinic, or aromatic, containing 1-5 ring heteroatoms selected independently from N, 0, and S; where

all said phenyl or Het groups are optionally substituted with F, Cl, Br, I, acetyl, methyl, CN, $NO_2$, $CO_2H$, $C_1$-$C_3$ alkyl, $C_1$-$C_3$ alkoxy, $C_1$-$C_3$ alkyl-C(=O)-, $C_1$-$C_3$ alkyl-C(=S)-, $C_1$-$C_3$ alkoxy-C(=S)-, $C_1$-$C_3$ alkyl-C(=O)O-, $C_1$-$C_3$ alkyl-0-(C=O)-, $C_1$-$C_3$ alkyl-C(=O)NH-, $C_1$-$C_3$ alkyl-C(=NH)NH-, $C_1$-$C_3$ alkyl-NH-(C=O)-, di-$C_1$-$C_3$ alkyl-N-(C=O)-, $C_1$-$C_3$ alkyl-C(=O)N($C_1$-$C_3$ alkyl)-, $C_1$-$C_3$ alkyl-S(=O)$_2$NH- or trifluoromethyl;

all said methyl, ethyl, $C_1$-$C_3$ alkyl, and cyclopropyl groups are optionally substituted with OH;

all said methyl groups are optionally substituted with one, two, or three F atoms;

$R^0$ is H, F, Cl, Br, I, $CH_3NH$-, $(CH_3)_2N$-, $C_1$-$C_6$ alkyl, $C_1$-$C_4$ alkoxy, $C_3$-$C_6$ cycloalkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, phenyl, monosubstituted phenyl, O($C_1$-$C_4$ alkyl), O-C(=O)($C_1$-$C_4$ alkyl) or C(=O)O($C_1$-$C_4$ alkyl); where

said alkyl, alkoxy, cycloalkyl, alkenyl, alkynyl and phenyl groups are optionally substituted with 1-3 substituents selected independently from F, Cl, Br, I, OH, CN, cyanomethyl, nitro, phenyl and trifluoromethyl;

said $C_1$-$C_6$ alkyl and $C_1$-$C_4$ alkoxy groups also optionally substituted with $OCH_3$or $OCH_2CH_3$;

G is $G_1$, $G_2$, $R_{1a}$, $R_{1b}$, $R_{1c}$, $R_{1d}$, $R_{1e}$, $Ar_1$, $Ar_2$ or $Ar_3$; where

$G_1$ is $C_1$-$C_6$ alkyl optionally substituted with one amino, $C_1$-$C_3$ alkylamino, or dialkylamino group, said dialkylamino group comprising two $C_1$-$C_4$ alkyl groups which may be identical or non-identical; or

$G_1$ is a $C_3$-$C_8$ diamino alkyl group;

$G_2$ is a 5- or 6- membered ring, which is saturated, unsaturated, or aromatic, containing 1-3 ring heteroatoms selected independently from N, 0, and S, optionally substituted with 1-3 substituents selected independently from F, Cl, OH, O($C_1$-$C_3$ alkyl), $OCH_3$, $OCH_2CH_3$, $CH_3C(=O)NH$, $CH_3C(=O)O$, CN, $CF_3$, and a 5-membered aromatic heterocyclic group containing 1-4 ring heteroatoms selected independently from N, O , and S;

$R_{1a}$ is methyl, optionally substituted with 1-3 fluorine atoms or 1-3 chlorine atoms, or with OH, cyclopropoxy, or $C_1$- $C_3$ alkoxy, where said cyclopropoxy group or the $C_1$- $C_3$ alkyl moieties of said $C_1$- $C_3$ alkoxy groups are optionally substituted with one hydroxy or methoxy group, and where all $C_3$- alkyl groups within said $C_1$- $C_4$ alkoxy are optionally further substituted with a second OH group;

$R_{1b}$ is $CH(CH_3)$-$C_{1-3}$ alkyl or $C_3$-$C_6$ cycloalkyl, said alkyl and cycloalkyl groups optionally substituted with 1-3 substituents selected independently from F, Cl, Br, I, OH, $OCH_3$, and CN;

$R_{1c}$ is $(CH_2)_nO_mR'$; where

m is 0 or 1; and where

when m is 0, n is 1 or 2;

when m is 1, n is 2 or 3;

R' is $C_1$-$C_6$ alkyl, optionally substituted with 1-3 substituents selected independently from F, Cl, OH, $OCH_3$, $OCH_2CH_3$, and $C_3$-$C_6$ cycloalkyl;

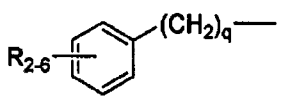
$R_{1d}$ is C(A)(A')(B)-; where

B is H or $C_{1-4}$ alkyl, optionally substituted with one or two OH groups;

A and A' are independently H or $C_{1-4}$ alkyl, optionally substituted with one or two OH groups; or

A and A', together with the carbon atom to which they are attached, form a 3- to 6- member saturated ring;

$R_{1e}$ is




$R_{1e}$

where

q is 1 or 2;

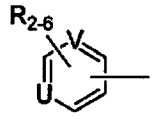
$R_2$ and $R_3$ are each independently, H, F, Cl, Br, $CH_3$, $CH_2F$, $CHF_2$, $CF_3$ $OCH_3$, $OCH_2F$, $OCHF_2$, $OCF_3$, ethyl, *n*-propyl, isopropyl, cyclopropyl, isobutyl, *sec*-butyl, *tert*-butyl or methylsulfonyl;

$R_4$ is H, F, Cl, Br, $CH_3$, $CH_2F$, $CHF_2$, $CF_3$ $OCH_3$, $OCH_2F$, $OCHF_2$, $OCF_3$, ethyl, *n*-propyl, isopropyl, cyclopropyl, isobutyl, *sec*-butyl, *tert*-butyl, methylsulfonyl, nitro, acetamido, amidinyl, cyano, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, l,3,4-oxadiazol-2-yl, 5-methyl-l,3,4- oxadiazol, 1,3,4-thiadiazol, 5-methyl-l,3,4-thiadiazol lH-tetrazolyl, N-morpholyl carbonyl amino, N-morpholylsulfonyl and N-pyrrolidinylcarbonylamino;

$R_5$ is H, F, Cl or methyl;

$R_6$ is H, F, Cl or methyl;

$Ar_1$ is



$Ar_1$

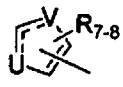
where

U and V are, independently, N, $CR_2$ or $CR_3$;

$R_2$, $R_3$ and $R_4$ are, independently, H, F, Cl, Br, $CH_3$, $CH_2F$, $CHF_2$, $CF_3$ $OCH_3$, $OCH_2F$, $OCHF_2$, $OCF_3$, ethyl, *n*-propyl, isopropyl, cyclopropyl, isobutyl, *sec*-butyl, *tert*-butyl, acetamido, amidinyl, cyano, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, 1,3,4-oxadiazol-2-yl, 5-methyl-1,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, 5-methyl-1,3,4-thiadiazolyl, 1H-tetrazolyl, N-morpholylcarbonylamino, N-morpholylsulfonyl, N-pyrrolidinylcarbonylamino, and methylsulfonyl;

$R_5$ and $R_6$ are, independently, H, F, Cl or methyl;

$Ar_2$ is



$Ar_2$

where

the dashed line represents alternative formal locations for the second ring double bond;

U is -S-, -O- or -N =, and where

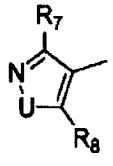
when U is -O- or -S-, V is -CH=, -CCl= or -N =;

when U is -N =, V is -CH=, -CCl=, or -N=;

$R_7$ is H or methyl;

$R_8$ is H, acetamido, methyl, F or Cl;

$Ar_3$ is



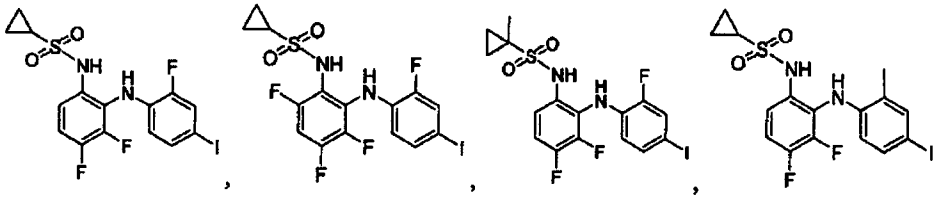
$Ar_3$

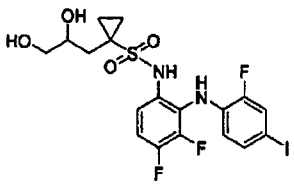
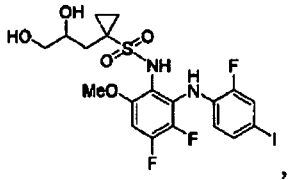
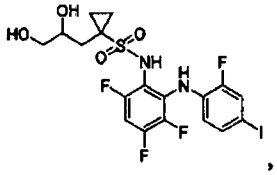
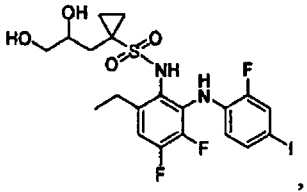
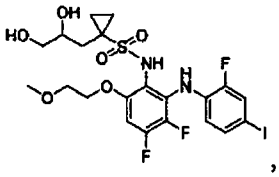
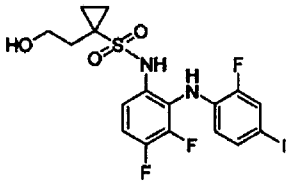
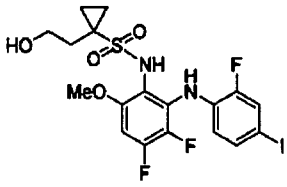
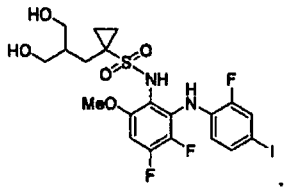
where

U is -NH-, $-NCH_3$- or -O-;

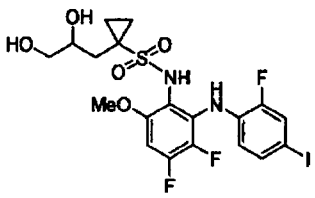
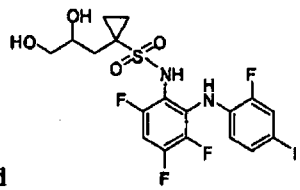
$R_7$ and $R_8$ are, independently, H, F, Cl, or methyl.

In some embodiments, the invention provides a compound of formula I, selected from the compounds below:

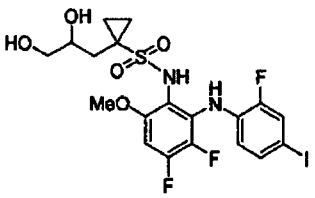
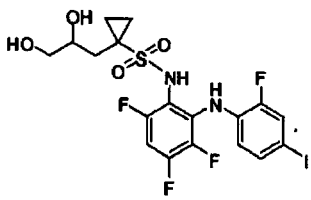



,

,

,

,

,

,

and

.

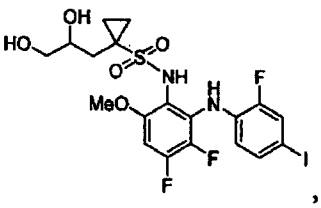
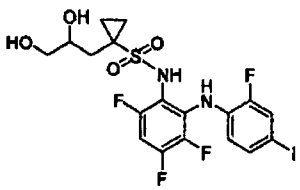
In some embodiments, the invention provides a compound of formula I, selected from:


and

, where the 2-OH carbon is in the R configuration.

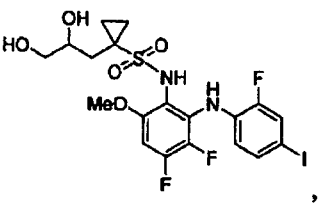
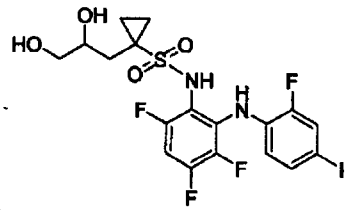
In some embodiments, the invention provides a compound of formula I, selected from:


and

, where the 2-OH carbon is in the S configuration.

In some embodiments, the invention provides a composition comprising a compound of formula I, selected from those shown below, where the 2-OH carbon is in the R configuration, substantially free of the S- isomer.


,

.

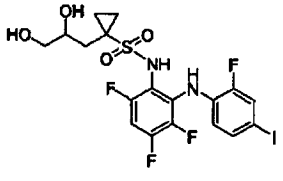
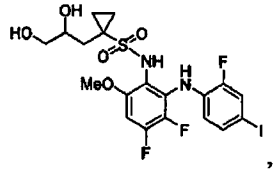
In some embodiments, the invention provides a composition comprising a compound of formula I, selected from those shown below, where the 2-OH carbon is in the S configuration, substantially free of the R- isomer.

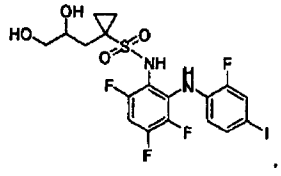

,

.

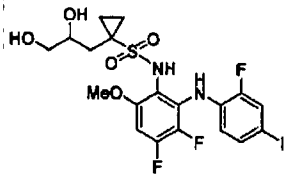
In some embodiments, this invention provides a compound of formula I, where Y is phenyl, pyridyl, or pyrazolyl. In another subgeneric embodiment, this invention provides a compound of formula I, where Y is substituted phenyl, pyridyl, or pyrazolyl. In yet another subgeneric embodiment, this invention provides a compound of formula I, where Y is Br or I. In one subgeneric embodiment, this invention provides a compound of formula I, where G is 1-piperidyl, 2-

piperidyl, 3-piperidyl, or 4-piperidyl. In another subgeneric embodiment, this invention provides a compound of formula I, where G is 1-piperazyl or 2-piperazyl. In another subgeneric embodiment, this invention provides a compound of formula I, where G is morpholyl. In another subgeneric embodiment, this invention provides a compound of formula I, where G is N-methyl-2-aminoethyl. In one subgeneric embodiment, this invention provides a compound of formula I, where G is N-methyl-3-amino-n-propyl. In another subgeneric embodiment, this invention provides a compound of formula I, where G is $(CH_3)_2N\text{-}CH_2CH_2\text{-}NH\text{-}(CH_2)_n\text{-}$, where n is 1, 2, or 3. In another subgeneric embodiment, this invention provides a compound of formula I, where G is $(CH_3CH_2)_2N\text{-}CH_2CH_2\text{-}NH\text{-}(CH_2)_n\text{-}$, where n is 1 or 2. In a more specific subgeneric embodiment, this invention provides a compound of formula I, where G is 1-piperidyl, 2-piperidyl, 3-piperidyl, or 4-piperidyl; $R^o$ is H, halo, or methoxy; X is F; and Y is I. In another more specific subgeneric embodiment, this invention provides a compound of formula I, where G is 1-piperazyl or 2-piperazyl; $R^o$ is H, halo, or methoxy; X is F; and Y is I In another more specific subgeneric embodiment, this invention provides a compound of formula I, where G is morpholyl; $R^o$ is H, halo, or methoxy; X is F; and Y is I. In another more specific subgeneric embodiment, this invention provides a compound of formula I, where G is N-methyl-2-aminoethyl; $R^o$ is H, halo, or methoxy; X is F; and Y is I In another more specific subgeneric embodiment, this invention provides a compound of formula I, where G is N-methyl-3-amino-n-propyl; $R^o$ is H, halo, or methoxy; X is F; and Y is I. In another more specific subgeneric embodiment, this invention provides a compound of formula I, where G is $(CH_3)_2N\text{-}CH_2CH_2\text{-}NH\text{-}(CH_2)_n\text{-}$, where n is 1, 2, or 3; $R^o$ is H, halo, or methoxy; X is F; and Y is I. In another more specific subgeneric embodiment, this invention provides a compound of formula I, where G is $(CH_3CH_2)_2N\text{-}CH_2CH_2\text{-}NH\text{-}(CH_2)_n\text{-}$, where n is 1 or 2; $R^o$ is H, halo, or methoxy; X is F; and Y is I.

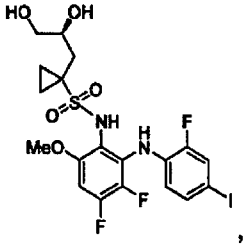
In some embodiments, the invention provides a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof. In some embodiments the pharmaceutical composition further comprises at least one pharmaceutically acceptable carrier.

In some embodiments, the invention provides a pharmaceutical composition comprising a compound selected from:  and  , or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof. In some embodiments, the pharmaceutical composition further comprises at least one pharmaceutically acceptable carrier. In some embodiments, the compound is in the R configuration. In some embodiments, the compound is in the R configuration, substantially free of the S- isomer. In some embodiments, the compound is in the S configuration.

In some embodiments, the compound is in the S configuration, substantially free of the R- isomer. In some embodiments, the compound is:  . In some embodiments, the compound is:

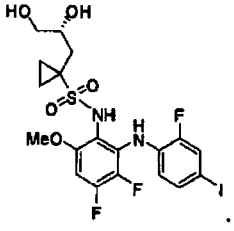


The invention also relates to a crystalline polymorph form A of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-l-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide (also referred to herein as "Compound A" and "N-(-)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-l-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide"):



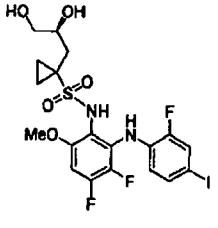
, that exhibits a specific powder x-ray diffraction pattern. In some embodiments, the powder x-ray diffraction pattern contains at least 50% of the peaks shown in **FIG. 5**. In some embodiments, the powder x-ray diffraction pattern contains at least 70% of the peaks shown in **FIG. 5**. In some embodiments, the powder x-ray diffraction pattern contains at least 90% of the peaks shown in **FIG. 5**. In some embodiments, the powder x-ray diffraction pattern is substantially the same as the powder x-ray diffraction pattern shown in **FIG. 5**. Compound A has been characterized as the "S" isomer by making the R and S-MTPA esters at the secondary alcohol and comparing the proton chemical shift difference. *See, e.g.,* Dale, J.A.; Mosher, H.S., *J. Am. Chem. Soc.*, 1973, 95, 512 and Ohtani *et al., J. Am. Chem. Soc.*, 1991, 113, 4092.

The invention also relates to N-(R)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-l-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide (also referred to herein as "Compound B" and "N-(+)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-l-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide"):



. Compound B has been characterized as the "R" isomer by making the R and S-MTPA esters at the secondary alcohol and comparing the proton chemical shift difference. *See, e.g.,* Dale, J.A.; Mosher, H.S., *J. Am. Chem. Soc.*, 1973, 95, 512 and Ohtani *et al., J. Am. Chem. Soc.*, 1991, 113, 4092.

The invention also relates to a crystalline polymorph form A of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-l-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide:



that exhibits a specific differential scanning calorimetry pattern. In some embodiments, the differential scannine calorimetry pattern is substantially the same as the differential scanning calorimetry pattern shown in **FIG. 6**.

The invention also relates to pharmaceutical compositions comprising an effective amount of crystalline polymorph form A of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-l-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide and a pharmaceutically acceptable carrier or vehicle.

In some embodiments, the crystalline polymorph form A of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-l-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide is useful for treating or preventing cancer or an inflammatory disease. The invention further relates to methods for treating or preventing cancer or an inflammatory disease, comprising administering an effective amount of a crystalline polymorph form A of N-(S)-(3,4-difluoro-2-(2-

fluoro-4-iodophenylamino)-6-methoxyphenyl)-l-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide to a subject in need thereof.

In other aspects, the present invention is directed to pharmaceutical compositions comprising effective amounts of a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof. In some embodiments, the pharmaceutical compositions further comprise a pharmaceutically acceptable carrier. Such compositions may contain adjuvants, excipients, and preservatives, agents for delaying absorption, fillers, binders, adsorbents, buffers, disintegrating agents, solubilizing agents, other carriers, and other inert ingredients. Methods of formulation of such compositions are well-known in the art.

In other aspects, the present invention is directed to a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof. In some embodiments, the pharmaceutical composition is in a form suitable for oral administration. In further or additional embodiments, the pharmaceutical composition is in the form of a tablet, capsule, pill, powder, sustained release formulation, solution, suspension, for parenteral injection as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. In further or additional embodiments, the pharmaceutical composition is in unit dosage forms suitable for single administration of precise dosages. In further or additional embodiments the amount of compound of formula I is in the range of about 0.001 to about 1000 mg/kg body weight/day. In further or additional embodiments the amount of compound of formula I is in the range of about 0.5 to about 50 mg/kg/day. In further or additional embodiments the amount of compound of formula I is about 0.001 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.002 to about 6 g/day. In further or additional embodiments the amount of compound of formula I is about 0.005 to about 5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.01 to about 5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.02 to about 5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.05 to about 2.5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.1 to about 1 g/day.

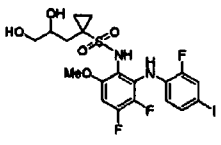
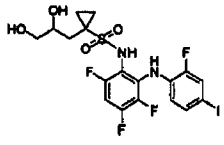
In further or additional embodiments, dosage levels below the lower limit of the aforesaid range may be more than adequate. In further or additional embodiments, dosage levels above the upper limit of the aforesaid range may be required. In further or additional embodiments the compound of formula I is administered in a single dose, once daily. In further or additional embodiments the compound of formula I is administered in multiple doses, more than once per day. In further or additional embodiments the compound of formula I is administered twice daily. In further or additional embodiments the compound of formula I is administered three times per day. In further or additional embodiments the compound of formula I is administered four times per day. In further or additional embodiments the compound of formula I is administered more than four times per day.

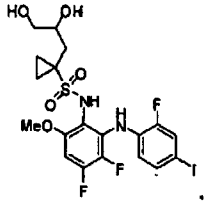
In some embodiments, the pharmaceutical composition is for administration to a mammal. In further or additional embodiments, the mammal is human.

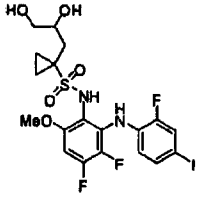
In further or additional embodiments, the pharmaceutical composition further comprises a pharmaceutical carrier, excipient and/or adjuvant. In further or additional embodiments, the pharmaceutical composition further comprises at least one therapeutic agent In further or additional embodiments, the therapeutic agent is selected from the group of cytotoxic agents, anti-angiogenesis agents and anti-neoplastic agents. In further or additional embodiments, the anti-neoplastic agent is selected from the group of consisting of alkylating agents, anti-metabolites, epidophyllotoxins; antineoplastic enzymes, topoisomerase inhibitors, procarbazines, mitoxantrones, platinum coordination complexes, biological response modifiers and growth inhibitors, hormonal/anti-hormonal therapeutic agents, and haematopoietic

growth factors. In further or additional embodiments, the therapeutic agent is taxol, bortezomib or both. In further or additional embodiments, the pharmaceutical composition is administered in combination with an additional therapy. In further or additional embodiments, the additional therapy is radiation therapy, chemotherapy, surgery or any combination thereof. In further or additional embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable salt of a compound of formula I.

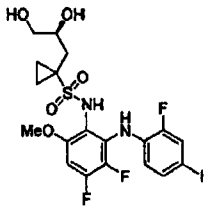
Provided herein are compositions and methods for using a composition comprising a compound selected from:


and

. In some embodiments, the 2-OH carbon on the compound is in the R configuration. In some embodiments, the 2-OH carbon on the compound is in the S configuration. In some embodiments, composition is substantially free of the S- isomer of the compound. In some embodiments, the composition is substantially free of the R- isomer of the compound. In some embodiments, the compound contains less than 10% of the S- isomer of the compound. In some embodiments, the compound contains less than 10% of the R- isomer of the compound. In some embodiments, the compound contains less than 5% of the S- isomer of the compound. In some embodiments, the compound contains less than 5% of the R- isomer of the compound. In some embodiments, the compound contains less than 1% of the S- isomer of the compound. In some embodiments, the compound contains less than 1% of the R- isomer of the compound.

Also provided herein are compositions and methods of treating cancer or inflammation with compositions comprising about 1-100 mg of a compound having the following structure:

. In some embodiments, the composition allows for modified release of the compound. In some embodiments, the composition allows for sustained release of the compound. In some embodiments, the composition allows for delayed release of the compound. In some embodiments, the compound is present in an amount of about 1-50 mgs. In some embodiments, the compound is present in an amount of about 1-10 mgs. In some embodiments, the compound is present in an amount of about 10-20 mgs. In some embodiments, the compound is present in an amount of about 20-40 mgs. In some embodiments, the compound is present in an amount of about 40-50 mgs.

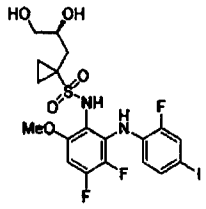
Also provided herein are compositions and methods of treating cancer or inflammation with compositions comprising: about 1-50 mg of a compound having the following structure

, wherein the composition allows for modified release of the drug. In some embodiments, the composition further comprises microcrystalline cellulose. In some embodiments, the composition further comprises croscarmellose sodium. In some embodiments, the composition further comprises sodium lauryl sulfate. In some embodiments, the composition further comprises magnesium stearate.

Also provided here in are compositions comprising about 1mg of a compound having the following structure:



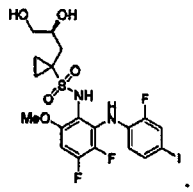
. In some embodiments, the composition further comprises about 222.2mg of microcrystalline cellulose. In some embodiments, the composition further comprises about 12.0mg of croscarmellose sodium. In some embodiments, the composition further comprises about 2.4mg of sodium lauryl sulfate. In some embodiments, the composition further comprises about 2.4mg of magnesium stearate.

Also provided herein are compositions and methods of treating cancer or inflammation with compositions comprising about 10mg of a compound having the following structure



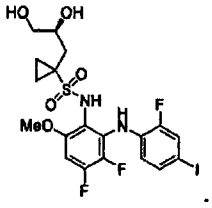
. In some embodiments, the composition further comprises about 213.2mg of microcrystalline cellulose. In some embodiments, the composition further comprises about 12.0mg of croscarmellose sodium. In some embodiments, the composition further comprises about 2.4mg of sodium lauryl sulfate. In some embodiments, the composition further comprises about 2.4mg of magnesium stearate.

Also provided herein are compositions and methods of treating cancer or inflammation with compositions comprising about 20mg of a compound having the following structure:

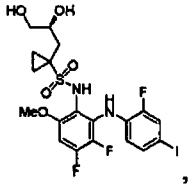


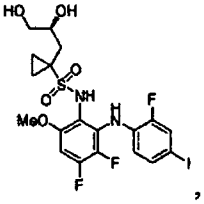
. In some embodiments, the composition further comprises about 203.2mg of microcrystalline cellulose. In some embodiments, the composition further comprises about 12.0mg of croscarmellose sodium. In some embodiments, the composition further comprises about 2.4mg of sodium lauryl sulfate. In some embodiments, the composition further comprises about 2.4mg of magnesium stearate.

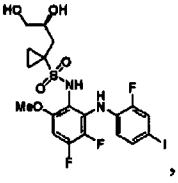
Also provided herein are compositions and methods of treating cancer or inflammation with compositions comprising about 40mg of a compound having the following structure

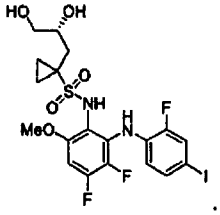


. In some embodiments, the composition further comprises about 183.2mg of microcrystalline cellulose. In some embodiments, the composition further comprises about 12.0mg of croscarmellose sodium. In some embodiments, the composition further comprises about 2.4mg of sodium lauryl sulfate. In some embodiments, the composition further comprises about 2.4mg of magnesium stearate.

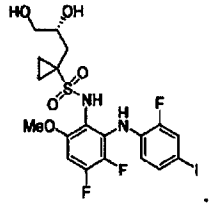
Also provided herein are compositions and methods of treating cancer or inflammation with compositions comprising: about 0.4% by weight of a compound having the following structure  , and about 99.6% by weight of a pharmaceutically acceptable carrier or vehicle. In some embodiments, the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose. In some embodiments, the microcrystalline cellulose is about 92.6% by weight of the composition. In some embodiments, the composition further comprises about 5% by weight croscarmellose sodium. In some embodiments, the composition further comprises about 1% by weight sodium lauryl sulfate. In some embodiments, the composition further comprises about 1% by weight magnesium stearate.

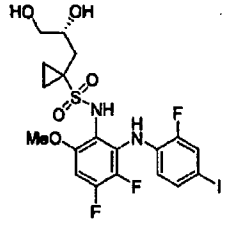
Also provided herein are compositions and methods of treating cancer or inflammation with compositions comprising about 4.2% by weight of a compound having the following structure  , and about 95.8 % by weight of a pharmaceutically acceptable carrier or vehicle. In some embodiments, the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose. In some embodiments, the microcrystalline cellulose is about 88.8% by weight of the composition. In some embodiments, the composition further comprises about 5% by weight croscarmellose sodium. In some embodiments, the composition further comprises about 1% by weight sodium lauryl sulfate. In some embodiments, the composition further comprises about 1% by weight magnesium stearate.

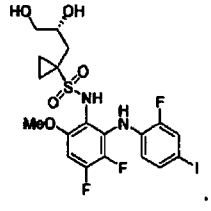
Also provided herein are compositions and methods of treating cancer or inflammation with compositions comprising from about 2% to about 10% by weight of a compound having the following structure  , and from about 98% to about 90% by weight of a pharmaceutically acceptable carrier or vehicle. In some embodiments, the pharmaceutically acceptable carrier or vehicle further comprises microcrystalline cellulose. In some embodiments, the microcrystalline cellulose is from about 85% to about 95% by weight of the composition. In some embodiments, the composition further comprises from about 1% to about 6% by weight croscarmellose sodium. In some embodiments, the composition further comprises from about 0.1% to about 2% by weight sodium lauryl sulfate. In some embodiments, the composition further comprises from about 0.25% to about 1.5% by weight magnesium stearate.

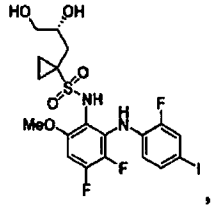
Also provided herein are compositions and methods of treating cancer or inflammation with compositions comprising about 1mg of a compound having the following structure  . In some embodiments, the composition further comprises about 222.2mg of microcrystalline cellulose. In some embodiments, the composition further comprises about 12.0mg of croscarmellose sodium. In some embodiments, the composition further comprises

about 2.4mg of sodium lauryl sulfate. In some embodiments, the composition further comprises about 2.4mg of magnesium stearate.

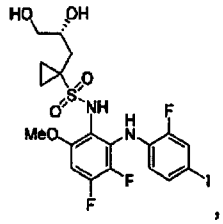
Also provided herein are compositions and methods of treating cancer or inflammation with compositions comprising about 10mg of a compound having the following structure:  . In some embodiments, the composition further comprises about 213.2mg of microcrystalline cellulose. In some embodiments, the composition further comprises about 12.0mg of croscarmellose sodium. In some embodiments, the composition further comprises about 2.4mg of sodium lauryl sulfate. In some embodiments, the composition further comprises about 2.4mg of magnesium stearate.

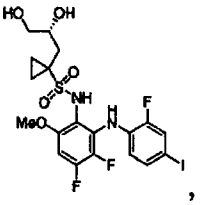
Also provided herein are compositions and methods of treating cancer or inflammation with compositions comprising about 20mg of a compound having the following structure:  . In some embodiments, the composition further comprises about 203.2mg of microcrystalline cellulose. In some embodiments, the composition further comprises about 12.0mg of croscarmellose sodium. In some embodiments, the composition further comprises about 2.4mg of sodium lauryl sulfate. In some embodiments, the composition further comprises about 2.4mg of magnesium stearate.

Also provided herein are compositions and methods of treating cancer or inflammation with compositions comprising about 40mg of a compound having the following structure:  . In some embodiments, the composition further comprises about 183.2mg of microcrystalline cellulose. In some embodiments, the composition further comprises about 12.0mg of croscarmellose sodium. In some embodiments, the composition further comprises about 2.4mg of sodium lauryl sulfate. In some embodiments, the composition further comprises about 2.4mg of magnesium stearate.

Also provided herein are compositions and methods of treating cancer or inflammation with compositions comprising about 0.4% by weight of a compound having the following structure  , and about 99.6% by weight of a pharmaceutically acceptable carrier or vehicle. In some embodiments, the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose. In some embodiments, the microcrystalline cellulose is about 92.6% by weight of the composition. In some embodiments, the composition further comprises about 5% by weight

croscarmellose sodium. In some embodiments, the composition further comprises about 1% by weight sodium lauryl sulfate. In some embodiments, the composition further comprises about 1% by weight magnesium stearate.

Also provided herein are compositions and methods of treating cancer or inflammation with compositions comprising about 4.2% by weight of a compound having the following structure  , and about 95.8 % by weight of a pharmaceutically acceptable carrier or vehicle. In some embodiments, the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose. In some embodiments, the microcrystalline cellulose is about 88.8% by weight of the composition. In some embodiments, the composition further comprises about 5% by weight croscarmellose sodium. In some embodiments, the composition further comprises about 1% by weight sodium lauryl sulfate. In some embodiments, the composition further comprises about 1% by weight magnesium stearate.

Also provided herein are compositions and methods of treating cancer or inflammation with compositions comprising from about 2% to about 10% by weight of a compound having the following structure  , and from about 98% to about 90% by weight of a pharmaceutically acceptable carrier or vehicle. In some embodiments, the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose. In some embodiments, the microcrystalline cellulose is from about 85% to about 95% by weight of the composition. In some embodiments, the composition further comprises from about 1% to about 6% by weight croscarmellose sodium. In some embodiments, the composition further comprises from about 0.1% to about 2% by weight sodium lauryl sulfate. In some embodiments, the composition further comprises from about 0.25% to about 1.5% by weight magnesium stearate.

Also provided herein is a crystalline polymorph Form A of N-(-)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-l-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide that exhibits a powder x-ray diffraction pattern comprising at least 50% of the peaks identified in the powder x-ray diffraction pattern shown in FIG. 5 and compositions comprising this compound.. In some embodiments, the crystalline polymorph Form A, wherein the powder x-ray diffraction pattern comprises at least 70% of the peaks identified in the powder x-ray diffraction pattern shown in FIG. 5. In some embodiments, the powder x-ray diffraction pattern comprises at least 90% of the peaks identified in the powder x-ray diffraction pattern shown in FIG. 5. In some embodiments, the powder x-ray diffraction pattern substantially the same as the powder x-ray diffraction pattern shown in FIG. 5. In some embodiments, the crystalline polymorph has a melting point onset as determined by differential scanning calorimetry at about 143°C. In some embodiments, the crystalline polymorph is substantially free of water. In some embodiments, the crystalline polymorph is substantially free of solvent.

Also provided herein is a crystalline polymorph Form A of N-(-)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-l-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide that exhibits a differential scanning calorimetry pattern substantially the same as the differential scanning calorimetry pattern shown in FIG. 6 and compositions comprising this compound. In some embodiments, the crystalline polymorph has a melting point onset as determined by differential scanning calorimetry at about 143°C. In some embodiments, the crystalline polymorph of claim 67 or 68,

wherein the crystalline polymorph is substantially free of water. In some embodiments, the crystalline polymorph of any of claims 67-69, wherein the crystalline polymorph is substantially free of solvent.

Also provided herein is a polymorphic form of N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide made by a method comprising the step of crystallizing amorphous N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide and compositions comprising this compound. In some embodiments, the crystallization step comprises crystallizing from a mixture of ethyl acetate and heptane. In some embodiments, the mixture of ethyl acetate and heptane is in a ratio of from about 1-4 parts ethyl acetate to about 2-10 parts heptane. In some embodiments, the mixture of ethyl acetate and heptane is in a ratio of from about 2 parts ethyl acetate to about 5 parts heptane.

Also provided herein are methods for inhibiting MEK enzymes comprising contacting said MEK enzyme with a compound or composition described herein, wherein the compound is present in an amount sufficient to inhibit said enzyme by at least 25%. In some embodiments, the MEK enzyme is MEK kinase. In some embodiments, said contacting occurs within a cell.

Also provided herein are methods for treating a MEK mediated disorder in an individual suffering from said disorder, comprising administering to said individual an effective amount of a compound or composition described herein. In some embodiments, the MEK inhibitor is administered in combination with an additional therapy. In some embodiments, the additional therapy is radiation therapy, non-MEK kinase inhibitor therapy, chemotherapy, surgery, Glucocorticoid, methotrexate, biological response modifiers, or any combination thereof. In some embodiments, the MEK mediated disorder is selected from the group consisting of inflammatory diseases, infections, autoimmune disorders, stroke, ischemia, cardiac disorder, neurological disorders, fibrogenetic disorders, proliferative disorders, hyperproliferative disorders, tumors, leukemias, neoplasms, cancers, carcinomas, metabolic diseases and malignant diseases. In some embodiments, the MEK mediated disorder is a hyperproliferative disease. In some embodiments, the MEK mediated disorder is cancer, tumors, leukemias, neoplasms, or carcinomas. In some embodiments, the MEK mediated disorder is an inflammatory disease. In some embodiments, said inflammatory disease is rheumatoid arthritis or multiple sclerosis.

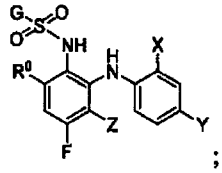
Also provided herein are methods for the treatment or prophylaxis of a proliferative disease in an individual comprising administering to said individual an effective amount of a compound or composition described herein. In some embodiments, the proliferative disease is cancer, psoriasis, restenosis, disease, or atherosclerosis. In some embodiments, the proliferative disease is cancer. In some embodiments, the cancer is brain cancer, breast cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, colorectal cancer, leukemia, myeloid leukemia, glioblastoma, follicular lymphona, pre-B acute leukemia, chronic lymphocytic B-leukemia, stomach cancer, mesothelioma or small cell lung cancer. In some embodiments, the method further comprises administering at least one therapeutic agent. In some embodiments, this step comprises the administration of at least one additional cancer therapy. In some embodiments, the additional therapy is radiation therapy, non-MEK kinase inhibitor therapy, chemotherapy, surgery, Glucocorticoid, methotrexate, biological response modifiers, or any combination thereof.

Also provided herein are methods for the treatment or prophylaxis of an inflammatory disease in an individual comprising administering to said individual an effective amount of a composition comprising a compound described herein. In some embodiments, the inflammatory disease is rheumatoid arthritis or multiple sclerosis.

Also provided herein are methods for degrading, inhibiting the growth of or killing cancer cells comprising contacting the cells with an amount of the compound or composition described herein effective to degrade, inhibit the

growth of or kill cancer cells. In some embodiments, the cancer cells comprise brain, breast, lung, ovarian, pancreatic, prostate, renal, stomach or colorectal cancer cells.

Also provided herein are methods of inhibiting tumor size increase, reducing the size of a tumor, reducing tumor proliferation or preventing tumor proliferation in an individual comprising administering to said individual an effective amount of the compound or composition described herein to inhibit tumor size increase, reduce the size of a tumor, reduce tumor proliferation or prevent tumor proliferation. In some embodiments, the tumor occurs in the brain, breast, lung, ovaries, pancreas, prostate, kidney, stomach, colon or rectum.

Also provided herein are methods for treating or preventing ankylosing spondylitis, gout, tendonitis, bursitis or sciatica, comprising administering to a subject in need thereof an effective amount of a compound of formula (I) or a pharmaceutical salt thereof:  ; wherein:

Z is H or F;

X is F, Cl, $CH_3$, $CH_2OH$, $CH_2F$, $CHF_2$, or $CF_3$;

Y is I, Br, Cl, $CF_3$, $C_1$-$C_3$ alkyl, $C_2$-$C_3$ alkenyl, $C_2$-$C_3$ alkynyl, cyclopropyl, OMe, OEt, SMe, phenyl or Het, where Het is a 5- to 10- membered mono- or bicyclic heterocyclic group, which group is saturated, olefinic, or aromatic, containing 1-5 ring heteroatoms selected independently from N, 0, and S; where

all said phenyl or Het groups are optionally substituted with F, Cl, Br, I, acetyl, methyl, CN, $NO_2$, $CO_2H$, $C_1$-$C_3$ alkyl, $C_1$-$C_3$ alkoxy, $C_1$-$C_3$ alkyl-C(=O)-, $C_1$-$C_3$ alkyl-C(=S)-, $C_1$-$C_3$ alkoxy-C(=S)-, $C_1$-$C_3$ alkyl-C(=O)O-, $C_1$-$C_3$ alkyl-0-(C=O)-, $C_1$-$C_3$ alkyl-C(=O)NH-, $C_1$-$C_3$ alkyl-C(=NH)NH-, $C_1$-$C_3$ alkyl-NH-(C=O)-, di-$C_1$-$C_3$ alkyl-N-(C=O)-, $C_1$-$C_3$ alkyl-C(=O)N($C_1$-$C_3$ alkyl)-, $C_1$-$C_3$ alkyl-S(=O)$_2$NH- or trifluoromethyl;

all said methyl, ethyl, $C_1$-$C_3$ alkyl, and cyclopropyl groups are optionally substituted with OH;

all said methyl groups are optionally substituted with one, two, or three F atoms;

$R^0$ is H, F, Cl, Br, I, $CH_3NH$-, $(CH_3)_2N$-, $C_1$-$C_6$ alkyl, $C_1$-$C_4$ alkoxy, $C_3$-$C_6$ cycloalkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, phenyl, monosubstituted phenyl, O($C_1$-$C_4$ alkyl), O-C(=O)($C_1$-$C_4$ alkyl) or C(=O)O($C_1$-$C_4$ alkyl); where

said alkyl, alkoxy, cycloalkyl, alkenyl, alkynyl and phenyl groups are optionally substituted with 1-3 substituents selected independently from F, Cl, Br, I, OH, CN, cyanomethyl, nitro, phenyl and trifluoromethyl;

said $C_1$-$C_6$ alkyl and $C_1$-$C_4$ alkoxy groups also optionally substituted with $OCH_3$or $OCH_2CH_3$;

G is $G_1$, $G_2$, $R_{1a}$, $R_{1b}$, $R_{1c}$, $R_{1d}$, $R_{1e}$, $Ar_1$, $Ar_2$ or $Ar_3$; where

$G_1$ is $C_1$-$C_6$ alkyl optionally substituted with one amino, $C_1$-$C_3$ alkylamino, or dialkylamino group, said dialkylamino group comprising two $C_1$-$C_4$ alkyl groups which may be identical or non-identical; or

$G_1$ is a $C_3$-$C_8$ diamino alkyl group;

$G_2$ is a 5- or 6- membered ring, which is saturated, unsaturated, or aromatic, containing 1-3 ring heteroatoms selected independently from N, 0, and S, optionally substituted with 1-3 substituents selected independently from F, Cl, OH, O($C_1$-$C_3$ alkyl), $OCH_3$, $OCH_2CH_3$, $CH_3C(=O)NH$, $CH_3C(=O)O$, CN, $CF_3$, and a 5-membered aromatic heterocyclic group containing 1-4 ring heteroatoms selected independently from N, O , and S;

$R_{1a}$ is methyl, optionally substituted with 1-3 fluorine atoms or 1-3 chlorine atoms, or with OH, cyclopropoxy, or $C_1$- $C_3$ alkoxy, where said cyclopropoxy group or the $C_1$- $C_3$ alkyl moieties of said $C_1$- $C_3$

alkoxy groups are optionally substituted with one hydroxy or methoxy group, and where all $C_3$- alkyl groups within said $C_1$- $C_4$ alkoxy are optionally further substituted with a second OH group;

$R_{1b}$ is $CH(CH_3)$-$C_{1-3}$ alkyl or $C_3$-$C_6$ cycloalkyl, said alkyl and cycloalkyl groups optionally substituted with 1-3 substituents selected independently from F, Cl, Br, I, OH, $OCH_3$, and CN;

$R_{1c}$ is $(CH_2)_nO_mR'$; where

m is 0 or 1; and where

when m is 0, n is 1 or 2;

when m is 1, n is 2 or 3;

R' is $C_1$-$C_6$ alkyl, optionally substituted with 1-3 substituents selected independently from F, Cl, OH, $OCH_3$, $OCH_2CH_3$, and $C_3$-$C_6$ cycloalkyl;

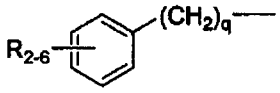
$R_{1d}$ is C(A)(A')(B)-; where

B is H or $C_{1-4}$ alkyl, optionally substituted with one or two OH groups;

A and A' are independently H or $C_{1-4}$ alkyl, optionally substituted with one or two OH groups; or

A and A', together with the carbon atom to which they are attached, form a 3- to 6- member saturated ring;

$R_{1e}$ is




$R_{1e}$

where

q is 1 or 2;

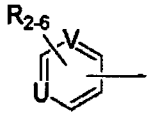
$R_2$ and $R_3$ are each independently, H, F, Cl, Br, $CH_3$, $CH_2F$, $CHF_2$, $CF_3$ $OCH_3$, $OCH_2F$, $OCHF_2$, $OCF_3$, ethyl, *n*-propyl, isopropyl, cyclopropyl, isobutyl, *sec*-butyl, *tert*-butyl or methylsulfonyl;

$R_4$ is H, F, Cl, Br, $CH_3$, $CH_2F$, $CHF_2$, $CF_3$ $OCH_3$, $OCH_2F$, $OCHF_2$, $OCF_3$, ethyl, *n*-propyl, isopropyl, cyclopropyl, isobutyl, *sec*-butyl, *tert*-butyl, methylsulfonyl, nitro, acetamido, amidinyl, cyano, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, 1,3,4-oxadiazol-2-yl, 5-methyl-1,3,4- oxadiazol, 1,3,4-thiadiazol, 5-methyl-1,3,4-thiadiazol lH-tetrazolyl, N-morpholyl carbonyl amino, N-morpholylsulfonyl and N-pyrrolidinylcarbonylamino;

$R_5$ is H, F, Cl or methyl;

$R_6$ is H, F, Cl or methyl;

$Ar_1$ is




$Ar_1$

where

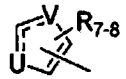
U and V are, independently, N, $CR_2$ or $CR_3$;

$R_2$, $R_3$ and $R_4$ are, independently, H, F, Cl, Br, $CH_3$, $CH_2F$, $CHF_2$, $CF_3$ $OCH_3$, $OCH_2F$, $OCHF_2$, $OCF_3$, ethyl, *n*-propyl, isopropyl, cyclopropyl, isobutyl, *sec*-butyl, *tert*-butyl, acetamido, amidinyl, cyano, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, 1,3,4-oxadiazol-2-yl, 5-methyl-1,3,4-oxadiazolyl, 1,3,4-

thiadiazolyl, 5-methyl-l,3,4-thiadiazolyl, lH-tetrazolyl, N-morpholylcarbonylamino, N-morpholylsulfonyl, N-pyrrolidinylcarbonylamino, and methylsulfonyl;

$R_5$ and $R_6$ are, independently, H, F, Cl or methyl;

$Ar_2$ is



$Ar_2$

where

the dashed line represents alternative formal locations for the second ring double bond;

U is -S-, -O- or -N =, and where

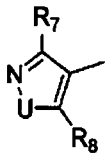
when U is -O- or -S-, V is -CH=, -CCl= or -N =;

when U is -N =, V is -CH=, -CCl=, or -N=;

$R_7$ is H or methyl;

$R_8$ is H, acetamido, methyl, F or Cl;

$Ar_3$ is

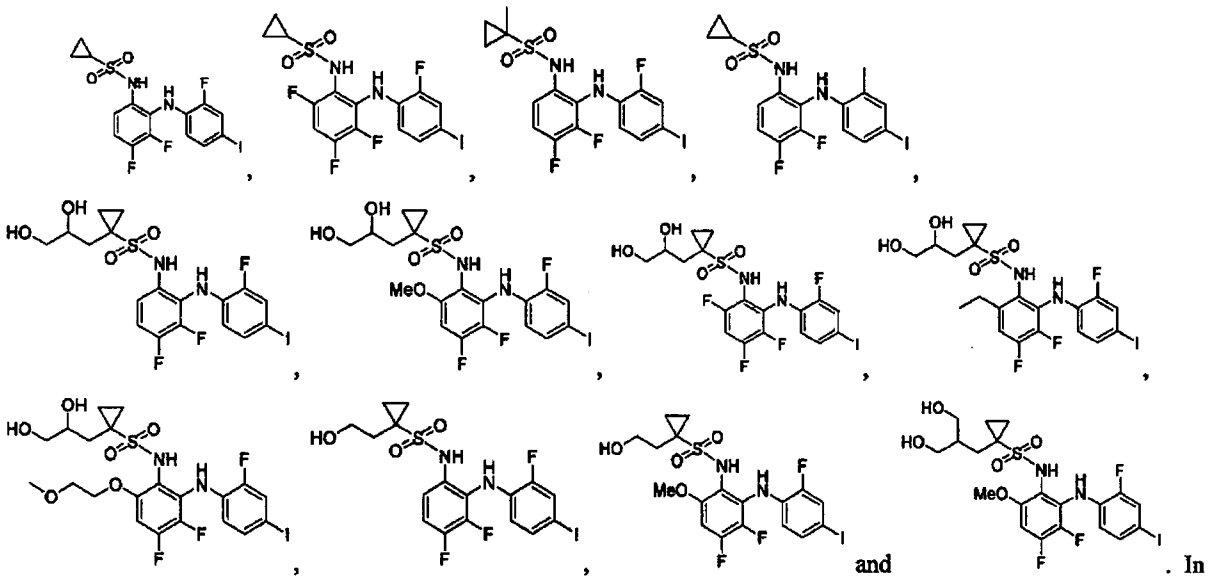


$Ar_3$

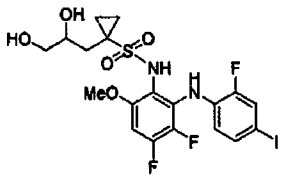
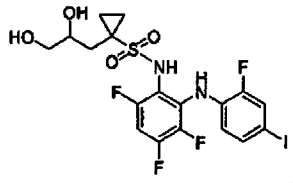
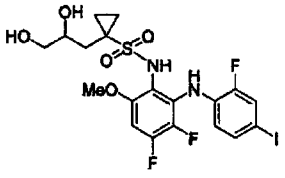
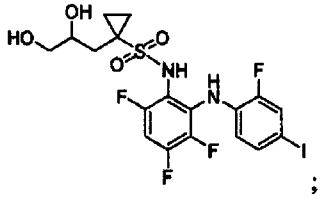
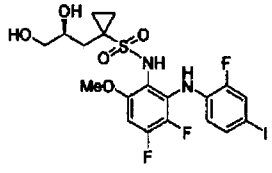
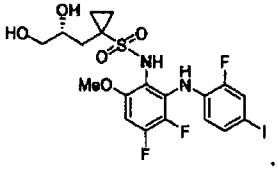
where

U is -NH-, -$NCH_3$- or -O-;

$R_7$ and $R_8$ are, independently, H, F, Cl, or methyl. In some embodiments, the compound is selected from:



and . In

some embodiments, the compound is selected from  and  ; where the 2-OH carbon is in the R configuration. In some embodiments, the compound of formula (I), or a pharmaceutical salt thereof, is selected from  and  ; where the 2-OH carbon is in the S configuration. In some embodiments, the compound is  . In some embodiments, the compound is  .

Provided herein are also methods for treating stomach cancer by administering a therapeutically effective amount of a compound or composition described herein. Provided herein are also methods for treating leukemiam melanoma, or hepatoma by administering a therapeutically effective amount of a compound or composition described herein.

Provided herein are also methods for treating non-small cell lung cancer by administering a therapeutically effective amount of a compound or composition described herein. Provided herein are also methods for treating colon cancer by administering a therapeutically effective amount of a compound or composition described herein. Provided herein are also methods for treating CNS cancer by administering a therapeutically effective amount of a compound or composition described herein. Provided herein are also methods for treating ovarian cancer by administering a therapeutically effective amount of a compound or composition described herein. Provided herein are also methods for treating renal cancer by administering a therapeutically effective amount of a compound or composition described herein. Provided herein are also methods for treating prostate cancer by administering a therapeutically effective amount of a compound or composition described herein. Provided herein are also methods for treating breast cancer by administering a therapeutically effective amount of a compound or composition described herein. In various embodiments, these methods further comprise administering at least one additional therapeutic agent. In some embodiments, at least one additional cancer therapy is performed. In some embodiments, the additional cancer therapy is radiation therapy, chemotherapy, surgery, or any combination thereof.

Also provided herein are methods for treating or preventing psoriasis by administering a therapeutically effective amount of a compound or composition described herein in a topical dosage form.

In various embodiments, the compositions are administered orally. In some embodiments, the composition is administered once a day or twice a day. In some embodiments, the composition is administered once a day for at least one week.

In some embodiments, upon oral administration of the composition, $T_{max}$ of the compound is achieved between 1 hour and 3 hours after administration of the composition to a fasted subject. In some embodiments, upon administration

to a subject, the compound reaches a $C_{max}$ between about 0.01 μg/ml to about 1.0 μg/ml on day 1. In some embodiments, upon administration to a subject, the compound reaches a $C_{max}$ between about 0.01 μg/ml to about 0.8 μg/ml on day 1. In some embodiments, upon administration to a subject, the compound reaches a $C_{max}$ between about 0.03 μg/ml to about 0.5 μg/ml on day 1. In some embodiments, the compound has an AUC between about 0.1 μg hr/mL to about 5.0 μg hr/mL from 0-12 hours. In some embodiments, the compound has an AUC between about 0.1 μg hr/mL to about 4.0 μg hr/mL. In some embodiments, the compound has an AUC between about 0.5 μg hr/mL to about 3.0 μg hr/mL. In some embodiments, the compound has a $T_{max}$ between 0.5 and 5.0 hours. In some embodiments, the compound has a $T_{max}$ between 1.0 and 3.0 hours. In some embodiments, the compound has a $T_{max}$ between 1.0 and 2.5 hours. In some embodiments, the compound has a plasma concentration greater than about 0.01 mg/mL after 5 hours after a single dose. In some embodiments, the compound has a plasma concentration greater than about 0.01 mg/mL after 10 hours after a single dose. In some embodiments, the compound has a plasma concentration greater than about 0.01 mg/mL after 15 hours after a single dose.

In some embodiments, upon administration to a group of 10 subjects, the compound reaches a mean $C_{max}$ between about 0.01 μg/ml to about 1.0 μg/ml on day 1. In some embodiments, upon administration to a group of 10 subjects, the compound reaches a mean $C_{max}$ between about 0.01 μg/ml to about 0.8 μg/ml on day 1. In some embodiments, upon administration to a group of 10 subjects, the compound reaches a mean $C_{max}$ between about 0.03 μg/ml to about 0.5 μg/ml on day 1. In some embodiments, the compound has a mean AUC between about 0.1 μg hr/mL to about 5.0 μg hr/mL. In some embodiments, the compound has a mean AUC between about 0.1 μg hr/mL to about 4.0 μg hr/mL. In some embodiments, the compound has a mean AUC between about 0.5 μg hr/mL to about 3.0 μg hr/mL. In some embodiments, the compound has a mean $T_{max}$ between 0.5 and 5.0 hours. In some embodiments, the compound has a mean $T_{max}$ between 1.0 and 3.0 hours. In some embodiments, the compound has a mean $T_{max}$ between 1.0 and 2.5 hours.

Also provided herein are methods for decreasing tumor volume by administering the compounds and compositions described herein. In some embodiments, after daily administration of the drug for 5 days, the tumor decreases in volume by at least about 25%. In some embodiments, after daily administration of the drug for 5 days, the tumor decreases in volume by at least about 50%. In some embodiments, after daily administration of the drug for 5 days, the tumor decreases in volume by at least about 20-70%. In some embodiments, after daily administration of the drug for 15 days, the tumor decreases in volume by at least about 25%. In some embodiments, after daily administration of the drug for 15 days, the tumor decreases in volume by at least about 50%. In some embodiments, after daily administration of the drug for 15 days, the tumor decreases in volume by at least about 20-70%. In some embodiments, after daily administration of the drug for 30 days, the tumor decreases in volume by at least about 25%. In some embodiments, after daily administration of the drug for 30 days, the tumor decreases in volume by at least about 50%. In some embodiments, after daily administration of the drug for 30 days, the tumor decreases in volume by at least about 20-70%.

Also provided herein are methods for inhibiting tumor growth by administering the compounds and compounds described herein. In some embodiments, after administration of the drug, the tumor growth is inhibited by at least about 20%. In some embodiments, after administration of the drug, the tumor growth is inhibited by at least about 40%. In some embodiments, after administration of the drug, the tumor growth is inhibited by at least about 60%. In some embodiments, after administration of the drug, the tumor growth is inhibited by at least about 80%. In some embodiments, after administration of the drug, the tumor growth is inhibited by between about 20% to about 100%. In some embodiments, after administration of the drug, the tumor growth is substantially inhibited.

In some embodiments, the composition is administered twice a day. In some embodiments, the composition is administered once a day.

In some embodiments, the MEK inhibitor does not interfere with the coadministration of a second tumor suprressing agent.

In some embodiments, the composition is in the form of a tablet, a capsule, a gel cap, a caplet, a pellet, or a bead. In some embodiments, the composition is in the form of a capsule or tablet dosage form has a total weight of about 50 mg to about 1000 mg. In some embodiments, the composition is in the form of a capsule or tablet has a total weight selected from the group consisting of 50 mg, 75mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, and 500 mg. In some embodiments, the composition is in the form of a capsule or tablet has a total weight of about 240 mg.

In some embodiments, the composition further comprises at least one filler selected from microcrystalline cellulose, silicified microcrystalline cellulose, lactose, a compressible sugar, xylitol, sorbitol, mannitol, pregelatinized starch, maltodextrin, calcium phosphate, calcium carbonate, starch and a calcium silicate.

In some embodiments, the composition further comprises at least one disintegrant selected from croscarmellose sodium, sodium starch glycolate, crospovidone, methylcellulose, alginic acid, sodium alginate, starch derivatives, betonite and veegum.

In some embodiments, the composition further comprises at least one lubricant selected from magnesium stearate, metallic stearates, talc, sodium stearyl fumarate and stearic acid.

In some embodiments, the composition further comprises at least one wetting agent or surfactant selected from sodium lauryl sulfate, glycerol, sorbitan oleates, sorbitan stearates, polyoxyethylenated sorbitan laurate, palmitate, stearate, oleate or hexaolate, polyoxyethylene stearyl alcohol and sorbitan monolaurate.

Provided herein are compositions in the form of a capsule or tablet and the capsule or tablet releases at least 60 percent of the drug within 30 minutes using *U.S. Pharmacopeia* (USP) Apparatus II at 50 rpm with 1% sodium lauryl sulfate in water as the dissolution medium. In some embodiments, the composition is in the form of a capsule or tablet and the capsule or tablet releases about 60-100 percent of the drug within 30 minutes using *U.S. Pharmacopeia* (USP) Apparatus II at 50 rpm with 1% sodium lauryl sulfate in water as the dissolution medium. In some embodiments, the composition is in the form of a capsule or tablet and the capsule or tablet releases about 60-90 percent of the drug within 30 minutes using *U.S. Pharmacopeia* (USP) Apparatus II at 50 rpm with 1% sodium lauryl sulfate in water as the dissolution medium. In some embodiments, the composition is in the form of a capsule or tablet and the capsule or tablet releases about 60-80 percent of the drug within 30 minutes using *U.S. Pharmacopeia* (USP) Apparatus II at 50 rpm with 1% sodium lauryl sulfate in water as the dissolution medium.

Provided herein are also batches of capsules or tablets, each comprising from about 1 to about 50 mg of a compound described herein and having a USP acceptance value for content uniformity of less than about 15.

***Methods of Treatment***

The invention relates to methods for treating or preventing cancer, comprising administering to a subject in need an effective amount of a pharmaceutical composition comprising a compound of formula (I), as described herein. In various embodiments, the compounds and compositions useful in these methods are as described by the genus of formula (I) or any sub-genus or species exemplified throughout the present application falling within formula (I).

The invention relates to methods for treating or preventing an inflammation disease, comprising administering to a subject in need an effective amount of a pharmaceutical composition comprising a compound of formula (I), as described herein. In various embodiments, the compounds and compositions useful in these methods are as described by the genus of formula (I) or any sub-genus or species exemplified throughout the present application falling within formula (I).

In some embodiments, the invention relates to methods for treating or preventing ankylosing spondylitis, gout, tendonitis, bursitis or sciatica, comprising administering to a subject in need thereof an effective amount of a

pharmaceutical composition comprising a compound of formula (I), as described herein. In various embodiments, the compounds and compositions useful in these methods are as described by the genus of formula (I) or any sub-genus or species exemplified throughout the present application falling within formula (I).

In some aspects, the present invention is also directed to a method of treating a disease in an individual suffering from said disease comprising administering to said individual an effective amount of a composition comprising a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof.

In other aspects, the present invention is directed to a method of treating a disorder in a mammal, comprising administering to said mammal a therapeutically effective amount of the compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof

In other aspects, the present invention is directed to a method of treating a disorder in a human, comprising administering to said mammal a therapeutically effective amount of the compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof

In other aspects, the present invention is directed to a method of treating a hyperproliferative disorder in a mammal, including a human, comprising administering to said mammal a therapeutically effective amount of the compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof

In other aspects, the present invention is directed to a method of treating an inflammatory disease, condition, or disorder in a mammal, including a human, comprising administering to said mammal a therapeutically effective amount of the compound of formula I, or a pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof.

In other aspects, the present invention is directed to a method of treating a disorder or condition which is modulated by the MEK cascade in a mammal, including a human, comprising administering to said mammal an amount of the compound of formula I, or a pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof, effective to modulate said cascade. The appropriate dosage for a particular patient can be determined, according to known methods, by those skilled in the art.

Inhibition of MEK Enzyme

In other aspects, the present invention is directed to a method for inhibiting a MEK enzyme. In some embodiments, the method comprises contacting said MEK enzyme with an amount of a composition comprising a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof, sufficient to inhibit said enzyme, wherein said enzyme is inhibited. In further or additional embodiments the enzyme is at least about 1% inhibited. In further or additional embodiments the enzyme is at least about 2% inhibited. In further or additional embodiments the enzyme is at least about 3% inhibited. In further or additional embodiments the enzyme is at least about 4% inhibited. In further or additional embodiments the enzyme is at least about 5% inhibited. In further or additional embodiments the enzyme is at least about 10% inhibited. In further or additional embodiments the enzyme is at least about 20% inhibited. In further or additional embodiments the enzyme is at least about 25% inhibited. In further or additional embodiments the enzyme is at least about 30% inhibited. In further or additional embodiments the enzyme is at least about 40% inhibited. In further or additional embodiments the enzyme is at least about 50% inhibited. In further or additional embodiments the enzyme is at least about 60% inhibited. In further or additional embodiments the enzyme is at least about 70% inhibited. In further or additional embodiments the enzyme is at least about 75% inhibited. In further or additional embodiments the enzyme is at least about 80% inhibited. In further or additional embodiments the enzyme is at least about 90% inhibited. In further or additional embodiments the enzyme is essentially completely inhibited. In further or additional embodiments the MEK enzyme is MEK kinase. In further or additional embodiments the MEK enzyme is MEK1. In further or additional embodiments the MEK enzyme is MEK2. In further or additional

embodiments the contacting occurs within a cell. In further or additional embodiments the cell is a mammalian cell. In further or additional embodiments the mammalian cell is a human cell. In further or additional embodiments, the MEK enzyme is inhibited with a composition comprising a pharmaceutically acceptable salt of a compound of formula I.

MEK Mediated Disorder

In other aspects, the present invention is directed to a method of treatment of a MEK mediated disorder in an individual suffering from said disorder comprising administering to said individual an effective amount of a composition comprising a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof. In some embodiments, the composition comprising a compound of formula I is administered orally, intraduodenally, parenterally (including intravenous, subcutaneous, intramuscular, intravascular or by infusion), topically or rectally. In some embodiments, the pharmaceutical composition is in a form suitable for oral administration. In further or additional embodiments, the pharmaceutical composition is in the form of a tablet, capsule, pill, powder, sustained release formulations, solution, suspension, for parenteral injection as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. In further or additional embodiments, the pharmaceutical composition is in unit dosage forms suitable for single administration of precise dosages. In further or additional embodiments, the pharmaceutical composition further comprises a pharmaceutical carrier, excipient and/or adjuvant.

In further or additional embodiments the amount of compound of formula I is in the range of about 0.001 to about 1000 mg/kg body weight/day. In further or additional embodiments the amount of compound of formula I is in the range of about 0.5 to about 50 mg/kg/day. In further or additional embodiments the amount of compound of formula I is about 0.001 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.01 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.02 to about 5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.05 to about 2.5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.1 to about 1 g/day. In further or additional embodiments, dosage levels below the lower limit of the aforesaid range may be more than adequate. In further or additional embodiments, dosage levels above the upper limit of the aforesaid range may be required.

In further or additional embodiments the compound of formula I is administered in a single dose, once daily. In further or additional embodiments the compound of formula I is administered in multiple doses, more than once per day. In further or additional embodiments the compound of formula I is administered twice daily. In further or additional embodiments the compound of formula I is administered three times per day. In further or additional embodiments the compound of formula I is administered four times per day. In further or additional embodiments the compound of formula I is administered more than four times per day. In some embodiments, the individual suffering from the MEK mediated disorder is a mammal. In further or additional embodiments, the individual is a human.

In some embodiments, the composition comprising a compound of formula I is administered in combination with an additional therapy. In further or additional embodiments, the additional therapy is radiation therapy, chemotherapy, surgery or any combination thereof. In further or additional embodiments, the composition comprising a compound of formula I is administered in combination with at least one therapeutic agent. In further or additional embodiments, the therapeutic agent is selected from the group of cytotoxic agents, anti-angiogenesis agents and anti-neoplastic agents. In further or additional embodiments, the anti-neoplastic agent is selected from the group of consisting of alkylating agents, anti-metabolites, epidophyllotoxins; antineoplastic enzymes, topoisomerase inhibitors, procarbazines, mitoxantrones, platinum coordination complexes, biological response modifiers and growth inhibitors, hormonal/anti-hormonal

therapeutic agents, and haematopoietic growth factors. In further or additional embodiments, the therapeutic agent is selected from taxol, bortezomib or both.

In some embodiments, the MEK mediated disorder is selected from the group consisting of inflammatory diseases, infections, autoimmune disorders, stroke, ischemia, cardiac disorder, neurological disorders, fibrogenetic disorders, proliferative disorders, hyperproliferative disorders, non-cancer hyperproliferative disorders, tumors, leukemias, neoplasms, cancers, carcinomas, metabolic diseases, malignant disease, vascular restenosis, psoriasis, atherosclerosis, rheumatoid arthritis, osteoarthritis, heart failure, chronic pain, neuropathic pain, dry eye, closed angle glaucoma and wide angle glaucoma. In further or additional embodiments, the MEK mediated disorder is an inflammatory disease. In further or additional embodiments, the MEK mediated disorder is a hyperproliferative disease. In further or additional embodiments, the MEK mediated disorder is selected from the group consisting of tumors, leukemias, neoplasms, cancers, carcinomas and malignant disease. In further or additional embodiments, the cancer is brain cancer, breast cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, stomach cancer, renal cancer, colorectal cancer or leukemia. In further or additional embodiments, the fibrogenetic disorder is scleroderma, polymyositis, systemic lupus, rheumatoid arthritis, liver cirrhosis, keloid formation, interstitial nephritis or pulmonary fibrosis. In further or additional embodiments, an effective amount of a composition comprising a pharmaceutically acceptable salt of a compound of formula I is administered.

Achieving Effects

In other aspects, the present invention is directed to a method for achieving an effect in a patient comprising the administration of an effective amount of a composition comprising a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof, to a patient, wherein the effect is selected from the group consisting of inhibition of various cancers, immunological diseases, and inflammatory diseases. In some embodiments, the effect is inhibition of various cancers. In further or additional embodiments, the effect is inhibition of immunological diseases. In further or additional embodiments, the effect is inhibition inflammatory diseases.

In some embodiments, the composition comprising a compound of formula I is administered in combination with an additional therapy. In further or additional embodiments, the additional therapy is radiation therapy, chemotherapy, surgery or any combination thereof. In further or additional embodiments, the composition comprising a compound of formula I is administered in combination with at least one therapeutic agent.

In some embodiments, the composition is administered orally, intraduodenally, parenterally (including intravenous, subcutaneous, intramuscular, intravascular or by infusion), topically or rectally. In further or additional embodiments the amount of compound of formula I is in the range of about 0.001 to about 1000 mg/kg body weight/day. In further or additional embodiments the amount of compound of formula I is in the range of about 0.5 to about 50 mg/kg/day. In further or additional embodiments the amount of compound of formula I is about 0.001 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.01 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.02 to about 5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.05 to about 2.5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.1 to about 1 g/day. In further or additional embodiments, dosage levels below the lower limit of the aforesaid range may be more than adequate. In further or additional embodiments, dosage levels above the upper limit of the aforesaid range may be required.

In further or additional embodiments the compound of formula I is administered in a single dose, once daily. In further or additional embodiments the compound of formula I is administered in multiple doses, more than once per day. In further or additional embodiments the compound of formula I is administered twice daily. In further or additional

embodiments the compound of formula I is administered three times per day. In further or additional embodiments the compound of formula I is administered four times per day. In further or additional embodiments the compound of formula I is administered more than four times per day. In some embodiments, the individual suffering from cancer is a mammal. In further or additional embodiments, the individual is a human. In further or additional embodiments, an effective amount of a composition comprising a pharmaceutically acceptable salt of a compound of formula I is administered.

In other aspects, the present invention is directed to a method for degrading, inhibiting the growth of or killing a cancer cell comprising contacting said cell with an amount of a composition effective to degrade, inhibit the growth of or to kill said cell, the composition comprising a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof. In some embodiments, the cancer cells comprise brain, breast, lung, ovarian, pancreatic, prostate, renal, or colorectal cancer cells. In further or additional embodiments, the composition is administered with at least one therapeutic agent. In further or additional embodiments, the therapeutic agent is taxol, bortezomib or both. In further or additional embodiments, the therapeutic agent is selected from the group consisting of cytotoxic agents, anti-angiogenesis agents and anti-neoplastic agents. In further or additional embodiments, the anti-neoplastic agents selected from the group of consisting of alkylating agents, anti-metabolites, epidophyllotoxins; antineoplastic enzymes, topoisomerase inhibitors, procarbazines, mitoxantrones, platinum coordination complexes, biological response modifiers and growth inhibitors, hormonal/anti-hormonal therapeutic agents, and haematopoietic growth factors. In some embodiments, the cancer cells are degraded. In further or additional embodiments, 1% of the cancer cells are degraded. In further or additional embodiments, 2% of the cancer cells are degraded. In further or additional embodiments, 3% of the cancer cells are degraded. In further or additional embodiments, 4% of the cancer cells are degraded. In further or additional embodiments, 5% of the cancer cells are degraded. In further or additional embodiments, 10% of the cancer cells are degraded. In further or additional embodiments, 20% of the cancer cells are degraded. In further or additional embodiments, 25% of the cancer cells are degraded. In further or additional embodiments, 30% of the cancer cells are degraded. In further or additional embodiments, 40% of the cancer cells are degraded. In further or additional embodiments, 50% of the cancer cells are degraded. In further or additional embodiments, 60% of the cancer cells are degraded. In further or additional embodiments, 70% of the cancer cells are degraded. In further or additional embodiments, 75% of the cancer cells are degraded. In further or additional embodiments, 80% of the cancer cells are degraded. In further or additional embodiments, 90% of the cancer cells are degraded. In further or additional embodiments, 100% of the cancer cells are degraded. In further or additional embodiments, essentially all of the cancer cells are degraded. In various embodiments, the aforementioned degradation occurs in one day, five days, ten days, one month, two months, six months or one year.

In some embodiments, the cancer cells are killed. In further or additional embodiments, 1% of the cancer cells are killed. In further or additional embodiments, 2% of the cancer cells are killed. In further or additional embodiments, 3% of the cancer cells are killed. In further or additional embodiments, 4% of the cancer cells are killed. In further or additional embodiments, 5% of the cancer cells are killed. In further or additional embodiments, 10% of the cancer cells are killed. In further or additional embodiments, 20% of the cancer cells are killed. In further or additional embodiments, 25% of the cancer cells are killed. In further or additional embodiments, 30% of the cancer cells are killed. In further or additional embodiments, 40% of the cancer cells are killed. In further or additional embodiments, 50% of the cancer cells are killed. In further or additional embodiments, 60% of the cancer cells are killed. In further or additional embodiments, 70% of the cancer cells are killed. In further or additional embodiments, 75% of the cancer cells are killed. In further or additional embodiments, 80% of the cancer cells are killed. In further or additional embodiments, 90% of the cancer cells

are killed. In further or additional embodiments, 100% of the cancer cells are killed. In further or additional embodiments, essentially all of the cancer cells are killed. In various embodiments, the aforementioned cancer cell killing occurs in one day, five days, ten days, one month, two months, six months or one year.

In further or additional embodiments, the growth of the cancer cells is inhibited. In further or additional embodiments, the growth of the cancer cells is about 1% inhibited. In further or additional embodiments, the growth of the cancer cells is about 2% inhibited. In further or additional embodiments, the growth of the cancer cells is about 3% inhibited. In further or additional embodiments, the growth of the cancer cells is about 4% inhibited. In further or additional embodiments, the growth of the cancer cells is about 5% inhibited. In further or additional embodiments, the growth of the cancer cells is about 10% inhibited. In further or additional embodiments, the growth of the cancer cells is about 20% inhibited. In further or additional embodiments, the growth of the cancer cells is about 25% inhibited. In further or additional embodiments, the growth of the cancer cells is about 30% inhibited. In further or additional embodiments, the growth of the cancer cells is about 40% inhibited. In further or additional embodiments, the growth of the cancer cells is about 50% inhibited. In further or additional embodiments, the growth of the cancer cells is about 60% inhibited. In further or additional embodiments, the growth of the cancer cells is about 70% inhibited. In further or additional embodiments, the growth of the cancer cells is about 75% inhibited. In further or additional embodiments, the growth of the cancer cells is about 80% inhibited. In further or additional embodiments, the growth of the cancer cells is about 90% inhibited. In further or additional embodiments, the growth of the cancer cells is about 100% inhibited. In various embodiments, the aforementioned inhibition occurs in one day, five days, ten days, one month, two months, six months or one year.

In other aspects, the present invention is directed to a method of reducing the size of a tumor, inhibiting tumor size increase, reducing tumor proliferation or preventing tumor proliferation in an individual, comprising administering to said individual an effective amount of a composition comprising a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof. In some embodiments, the size of a tumor is reduced. In further or additional embodiments, the size of a tumor is reduced by at least 1%. In further or additional embodiments, the size of a tumor is reduced by at least 2%. In further or additional embodiments, the size of a tumor is reduced by at least 3%. In further or additional embodiments, the size of a tumor is reduced by at least 4%. In further or additional embodiments, the size of a tumor is reduced by at least 5%. In further or additional embodiments, the size of a tumor is reduced by at least 10%. In further or additional embodiments, the size of a tumor is reduced by at least 20%. In further or additional embodiments, the size of a tumor is reduced by at least 25%. In further or additional embodiments, the size of a tumor is reduced by at least 30%. In further or additional embodiments, the size of a tumor is reduced by at least 40%. In further or additional embodiments, the size of a tumor is reduced by at least 50%. In further or additional embodiments, the size of a tumor is reduced by at least 60%. In further or additional embodiments, the size of a tumor is reduced by at least 70%. In further or additional embodiments, the size of a tumor is reduced by at least 75%. In further or additional embodiments, the size of a tumor is reduced by at least 80%. In further or additional embodiments, the size of a tumor is reduced by at least 85%. In further or additional embodiments, the size of a tumor is reduced by at least 90%. In further or additional embodiments, the size of a tumor is reduced by at least 95%. In further or additional embodiments, the tumor is eradicated. In some embodiments, the size of a tumor does not increase. In various embodiments, the aforementioned effects on tumor size occurs in one day, five days, ten days, one month, two months, six months or one year.

In some embodiments, tumor proliferation is reduced. In some embodiments, tumor proliferation is reduced by at least 1 %. In some embodiments, tumor proliferation is reduced by at least 2 %. In some embodiments, tumor

proliferation is reduced by at least 3 %. In some embodiments, tumor proliferation is reduced by at least 4 %. In some embodiments, tumor proliferation is reduced by at least 5 %. In some embodiments, tumor proliferation is reduced by at least 10 %. In some embodiments, tumor proliferation is reduced by at least 20 %. In some embodiments, tumor proliferation is reduced by at least 25 %. In some embodiments, tumor proliferation is reduced by at least 30 %. In some embodiments, tumor proliferation is reduced by at least 40 %. In some embodiments, tumor proliferation is reduced by at least 50 %. In some embodiments, tumor proliferation is reduced by at least 60 %. In some embodiments, tumor proliferation is reduced by at least 70 %. In some embodiments, tumor proliferation is reduced by at least 75 %. In some embodiments, tumor proliferation is reduced by at least 75 %. In some embodiments, tumor proliferation is reduced by at least 80 %. In some embodiments, tumor proliferation is reduced by at least 90 %. In some embodiments, tumor proliferation is reduced by at least 95 %. In some embodiments, tumor proliferation is prevented. In various embodiments, the aforementioned effects on cell proliferation occurs in one day, five days, ten days, one month, two months, six months or one year.

In some embodiments, the composition comprising a compound of formula I is administered in combination with an additional therapy. In further or additional embodiments, the additional therapy is radiation therapy, chemotherapy, surgery or any combination thereo. In further or additional embodiments, the composition comprising a compound of formula I is administered in combination with at least one therapeutic agent. In further or additional embodiments, the therapeutic agent is selected from the group of cytotoxic agents, anti-angiogenesis agents and anti-neoplastic agents. In further or additional embodiments, the anti-neoplastic agent is selected from the group of consisting of alkylating agents, anti-metabolites, epidophyllotoxins; antineoplastic enzymes, topoisomerase inhibitors, procarbazines, mitoxantrones, platinum coordination complexes, biological response modifiers and growth inhibitors, hormonal/anti-hormonal therapeutic agents, and haematopoietic growth factors. In further or additional embodiments, the therapeutic agent is selected from taxol, bortezomib or both.

In some embodiments, the composition is administered orally, intraduodenally, parenterally (including intravenous, subcutaneous, intramuscular, intravascular or by infusion), topically or rectally. In further or additional embodiments the amount of compound of formula I is in the range of about 0.001 to about 1000 mg/kg body weight/day. In further or additional embodiments the amount of compound of formula I is in the range of about 0.5 to about 50 mg/kg/day. In further or additional embodiments the amount of compound of formula I is about 0.001 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.01 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.02 to about 5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.05 to about 2.5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.1 to about 1 g/day. In further or additional embodiments, dosage levels below the lower limit of the aforesaid range may be more than adequate. In further or additional embodiments, dosage levels above the upper limit of the aforesaid range may be required.

In further or additional embodiments the compound of formula I is administered in a single dose, once daily. In further or additional embodiments the compound of formula I is administered in multiple doses, more than once per day. In further or additional embodiments the compound of formula I is administered twice daily. In further or additional embodiments the compound of formula I is administered three times per day. In further or additional embodiments the compound of formula I is administered four times per day. In further or additional embodiments the compound of formula I is administered more than four times per day. In some embodiments, the individual suffering from cancer is a mammal. In further or additional embodiments, the individual is a human. In further or additional embodiments, an

effective amount of a composition comprising a pharmaceutically acceptable salt of a compound of formula I is administered.

Proliferative Diseases

In other aspects, the present invention is directed to a method for the treatment or prophylaxis of a proliferative disease in an individual comprising administering to said individual an effective amount of a composition comprising a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof. In some embodiments, the proliferative disease is cancer, psoriasis, restenosis, autoimmune disease, or atherosclerosis. In further or additional embodiments, the proliferative disease is a hyperproliferative disease. In further or additional embodiments, the proliferative disease is selected from the group consisting of tumors, leukemias, neoplasms, cancers, carcinomas and malignant disease. In further or additional embodiments, the cancer is brain cancer, breast cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, colorectal cancer, stomach cancer, head and neck cancer or leukemia. In further or additional embodiments, the fibrogenetic disorder is scleroderma, polymyositis, systemic lupus, rheumatoid arthritis, liver cirrhosis, keloid formation, interstitial nephritis or pulmonary fibrosis. In further or additional embodiments, stomach cancer, brain cancer, breast cancer, lung cancer, non small cell lung cancer, ovarian cancer, pancreatic cancer, liver cancer, prostate cancer, renal cancer, colorectal cancer or leukemia. In further or additional embodiments, the cancer is brain cancer or adrenocortical carcinoma. In further or additional embodiments, the cancer is breast cancer. In further or additional embodiments, the cancer is ovarian cancer. In further or additional embodiments, the cancer is pancreatic cancer. In further or additional embodiments, the cancer is prostate cancer. In further or additional embodiments, the cancer is renal cancer. In further or additional embodiments, the cancer is colorectal cancer. In further or additional embodiments, the cancer is myeloid leukemia. In further or additional embodiments, the cancer is glioblastoma. In further or additional embodiments, the cancer is follicular lymphona. In further or additional embodiments, the cancer is pre-B acute leukemia. In further or additional embodiments, the cancer is chronic lymphocytic B-leukemia. In further or additional embodiments, the cancer is mesothelioma. In further or additional embodiments, the cancer is small cell lung cancer. In further embodiments, the cancer is stomach cancer.

In some embodiments, the composition comprising a compound of formula I is administered in combination with an additional therapy. In further or additional embodiments, the additional therapy is radiation therapy, chemotherapy, surgery, or any combination thereof. In further or additional embodiments, the composition comprising a compound of formula I is administered in combination with at least one therapeutic agent. In further or additional embodiments, the therapeutic agent is selected from the group of cytotoxic agents, anti-angiogenesis agents and anti-neoplastic agents. In further or additional embodiments, the anti-neoplastic agent is selected from the group of consisting of alkylating agents, anti-metabolites, epidophyllotoxins; antineoplastic enzymes, topoisomerase inhibitors, procarbazines, mitoxantrones, platinum coordination complexes, biological response modifiers and growth inhibitors, hormonal/anti-hormonal therapeutic agents, and haematopoietic growth factors.

In further or additional embodiments, the therapeutic agent is selected from taxol, bortezomib or both. In some embodiments, the composition is administered orally, intraduodenally, parenterally (including intravenous, subcutaneous, intramuscular, intravascular or by infusion), topically or rectally.

In further or additional embodiments the amount of compound of formula I is in the range of about 0.001 to about 1000 mg/kg body weight/day. In further or additional embodiments the amount of compound of formula I is in the range of about 0.5 to about 50 mg/kg/day. In further or additional embodiments the amount of compound of formula I is about 0.001 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.01 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.02 to about 5 g/day. In

further or additional embodiments the amount of compound of formula I is about 0.05 to about 2.5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.1 to about 1 g/day. In further or additional embodiments, dosage levels below the lower limit of the aforesaid range may be more than adequate. In further or additional embodiments, dosage levels above the upper limit of the aforesaid range may be required.

In further or additional embodiments the compound of formula I is administered in a single dose, once daily. In further or additional embodiments the compound of formula I is administered in multiple doses, more than once per day. In further or additional embodiments the compound of formula I is administered twice daily. In further or additional embodiments the compound of formula I is administered three times per day. In further or additional embodiments the compound of formula I is administered four times per day. In further or additional embodiments the compound of formula I is administered more than four times per day. In some embodiments, the individual suffering from the proliferative disease is a mammal. In further or additional embodiments, the individual is a human. In further or additional embodiments, an effective amount of a composition comprising a pharmaceutically acceptable salt of a compound of formula I is administered.

Inflammatory Diseases

In other aspects, the present invention is directed to a method for the treatment or prophylaxis of an inflammatory disease in an individual comprising administering to said individual an effective amount of a composition comprising a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof. In further or additional embodiments, the inflammatory disease is selected from chronic inflammatory diseases, rheumatoid arthritis, rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, juvenile arthritis, acute rheumatic arthritis, enteropathic arthritis, neuropathic arthritis, psoriatic arthritis, pyogenic arthritis, atherosclerosis, systemic lupus erythematosus, inflammatory bowel disease, irritable bowel syndrome, ulcerative colitis, reflux esophagitis, Crohn's disease, gastritis, asthma, allergies, respiratory distress syndrome, pancreatitis, chronic obstructive pulmonary disease, pulmonary fibrosis, psoriasis, eczema or scleroderma.

In some embodiments, the composition comprising a compound of formula I is administered in combination with an additional therapy. In further or additional embodiments, the composition comprising a compound of formula I is administered in combination with at least one therapeutic agent.

In some embodiments, the composition is administered orally, intraduodenally, parenterally (including intravenous, subcutaneous, intramuscular, intravascular or by infusion), topically or rectally. In further or additional embodiments the amount of compound of formula I is in the range of about 0.001 to about 1000 mg/kg body weight/day. In further or additional embodiments the amount of compound of formula I is in the range of about 0.5 to about 50 mg/kg/day. In further or additional embodiments the amount of compound of formula I is about 0.001 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.01 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.02 to about 5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.05 to about 2.5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.1 to about 1 g/day. In further or additional embodiments, dosage levels below the lower limit of the aforesaid range may be more than adequate. In further or additional embodiments, dosage levels above the upper limit of the aforesaid range may be required.

In further or additional embodiments the compound of formula I is administered in a single dose, once daily. In further or additional embodiments the compound of formula I is administered in multiple doses, more than once per day. In further or additional embodiments the compound of formula I is administered twice daily. In further or additional embodiments the compound of formula I is administered three times per day. In further or additional embodiments the

compound of formula I is administered four times per day. In further or additional embodiments the compound of formula I is administered more than four times per day. In some embodiments, the individual suffering from the inflammatory disease is a mammal. In further or additional embodiments, the individual is a human. In further or additional embodiments, an effective amount of a composition comprising a pharmaceutically acceptable salt of a compound of formula I is administered.

Cancer

In other aspects, the present invention is directed to a method for the treatment or prophylaxis of cancer in an individual comprising administering to said individual an effective amount of a composition comprising a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof. In further or additional embodiments, the cancer is brain cancer, breast cancer, stomach cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, colorectal cancer or leukemia. In further or additional embodiments, the fibrogenetic disorder is scleroderma, polymyositis, systemic lupus, rheumatoid arthritis, liver cirrhosis, keloid formation, interstitial nephritis or pulmonary fibrosis. In further or additional embodiments, the cancer is brain cancer, breast cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, stomach cancer, colorectal cancer or leukemia. In further or additional embodiments, the cancer is brain cancer or adrenocortical carcinoma. In further or additional embodiments, the cancer is breast cancer. In further or additional embodiments, the cancer is ovarian cancer. In further or additional embodiments, the cancer is pancreatic cancer. In further or additional embodiments, the cancer is prostate cancer. In further or additional embodiments, the cancer is renal cancer. In further or additional embodiments, the cancer is colorectal cancer. In further or additional embodiments, the cancer is myeloid leukemia. In further or additional embodiments, the cancer is glioblastoma. In further or additional embodiments, the cancer is follicular lymphona. In further or additional embodiments, the cancer is pre-B acute leukemia. In further or additional embodiments, the cancer is chronic lymphocytic B-leukemia. In further or additional embodiments, the cancer is mesothelioma. In further or additional embodiments, the cancer is small cell lung cancer. In some embodiments, the cancer is stomach cancer.

In some embodiments, the composition comprising a compound of formula I is administered in combination with an additional therapy. In further or additional embodiments, the additional therapy is radiation therapy, chemotherapy, surgery, or any combination thereof. In further or additional embodiments, the composition comprising a compound of formula I is administered in combination with at least one therapeutic agent. In further or additional embodiments, the therapeutic agent is selected from the group of cytotoxic agents, anti-angiogenesis agents and anti-neoplastic agents. In further or additional embodiments, the anti-neoplastic agent is selected from the group of consisting of alkylating agents, anti-metabolites, epidophyllotoxins; antineoplastic enzymes, topoisomerase inhibitors, procarbazines, mitoxantrones, platinum coordination complexes, biological response modifiers and growth inhibitors, hormonal/anti-hormonal therapeutic agents, and haematopoietic growth factors. In further or additional embodiments, the therapeutic agent is selected from taxol, bortezomib or both.

In some embodiments, the composition is administered orally, intraduodenally, parenterally (including intravenous, subcutaneous, intramuscular, intravascular or by infusion), topically or rectally. In further or additional embodiments the amount of compound of formula I is in the range of about 0.001 to about 1000 mg/kg body weight/day. In further or additional embodiments the amount of compound of formula I is in the range of about 0.5 to about 50 mg/kg/day. In further or additional embodiments the amount of compound of formula I is about 0.001 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.01 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.02 to about 5 g/day. In further or additional

embodiments the amount of compound of formula I is about 0.05 to about 2.5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.1 to about 1 g/day. In further or additional embodiments, dosage levels below the lower limit of the aforesaid range may be more than adequate.

In further or additional embodiments, dosage levels above the upper limit of the aforesaid range may be required. In further or additional embodiments the compound of formula I is administered in a single dose, once daily. In further or additional embodiments the compound of formula I is administered in multiple doses, more than once per day. In further or additional embodiments the compound of formula I is administered twice daily. In further or additional embodiments the compound of formula I is administered three times per day. In further or additional embodiments the compound of formula I is administered four times per day. In further or additional embodiments the compound of formula I is administered more than four times per day. In some embodiments, the individual suffering from cancer is a mammal. In further or additional embodiments, the individual is a human. In further or additional embodiments, an effective amount of a composition comprising a pharmaceutically acceptable salt of a compound of formula I is administered.

## INCORPORATION BY REFERENCE

All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

## BRIEF DESCRIPTION OF THE DRAWINGS

The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

**Figure 1** shows graphs of average tumor volume against time (days) in mice implanted with A375 Melanoma, Colo205 Colon Tumor, A431 Epidermoid Tumor or HT-29 Colon Tumor cells. Mice were dosed orally (25mg/kg, 50mg/kg or 100mg/kg), once a day, for 14 days.

**Figure 2** shows a graph of % Tumor growth inhibition (%TGI) in A375 Xenograft mice dosed 50mg/kg QD, 25mg/kg BID, 50mg/kg QD and 12.5mg/kg BID.

**Figure 3** shows a graph of plasma concentration (log nM) against pERK % inhibition in female nu/nu mice implanted with Colo205 tumor cells. Mice were given a single dose of 2.5, 5, 10, or 25 mg/kg.

**Figure 4** shows a graph of plasma concentration (ng/mL) against time (hours) in humans after administration of a single dose 2mg (2 x 1mg capsules), 4mg (4 x 1mg capsules) or 6mg (6 x 1mg capsules).

**Figure 5** is a graph of a powder x-ray diffraction (PXRD) pattern of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide Form A, generated using a Inel XRG-3000 diffractometer. The graph plots the intensity of the peaks as defined by counts per second versus the diffraction angle 2θ in degrees.

**Figure 6** is a graph of a modulated Differential Scanning Calorimetry (DSC) thermogram of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide Form A generated using a TA Instruments differential scanning calorimeter Q1000. The graph plots the normalized heat flow in units of Watts/gram (W/g) versus the measured sample temperature in °C.

**Figure 7** is a graph of the PXRD patterns of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide Form A (top) and N-(S)-(3,4-difluoro-2-(2-fluoro-

4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide amorphous (bottom), generated using a Inel XRG-3000 diffractometer. The graph plots the intensity of the peaks as defined by counts per second versus the diffraction angle 2θ in degrees.

**Figure 8** shows a Dynamic Vapor Sorption/Desorption (DVS) isotherm of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide Form A generated using a VTI SGA-100 Vapor Sorption Analyzer.

**Figure 9** shows a Thermogravimetry (TG) thermogram of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide Form A) generated using a TA Instrument 2950 thermogravimetric analyzer.

**Figure 10(a)** and **Figure 10(b)** show growth arrest of Log phase dividing A375 cells exposed to increasing concentrations of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide. Cells were analyzed for ATP content. 100% growth arrest was determined using 1μM N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide.

**Figure 11** shows a 48 hr AK assay in A375 cells. Log phase dividing A375 cells were exposed to N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide and PD-325901 for 48 hr and analyzed for AK release.

**Figures 12A-12C** show N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide growth inhibition of (A) human colorectal carcinoma Colo205 cells ($GI_{50}$ = 11 nM); (B) A375 cells ($GI_{50}$ = 22 nM) and (C) inhibition of MDA-MB231 cells which do not show N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide - induced growth arrest in 2-dimensional anchorage dependent assays.

**Figure 13A** shows inhibition of growth of human colorectal carcinoma Colo205 cells, with $GI_{50}$ values at 6 nM and 11 nM respectively.

**Figure 13B** shows inhibition of growth of A375 cells with $GI_{50}$ values at 5 nM and 22 nM.

**Figures14A** and **Figure 14B** show the effect of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide on cell cycle progression, demonstrating that exposure of A375 cells to N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide causes arrest in the G1 phase of the cell cycle, indicated by the depletion of cells in both the G2 and S phases.

**Figure 15A** and **Figure 15B** show the effect of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide on the stomach cancer (gastric adenocarcinoma) cell line AGS after 3 days (Figure 15A) and 6 days (Figure 15B). The y axis is the cell number relative to vehicle and the x axis is uM of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide.

**Figure 16** shows the mean liver weights in tumor bearing mice after treatment with N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide (2mg/kg, once daily, po; 10mg/kg, once daily, po and 50mg/kg, once daily, po).

**Figure 17** shows liver tumor weights in tumor bearing mice after treaement with N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide (2mg/kg, once daily, po; 10mg/kg, once daily, po and 50mg/kg, once daily, po).

**Figure 18** shows the average tumor weights in after treaement with N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide (2mg/kg; 10mg/kg; and 50mg/kg).

**Figure 19** shows the inhibition of Hs746t Cell proliferation in a graph of cell number (relative to vehicle) vs concentration of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide.

**Figure 20A** depicts a graph comparing the respective apoptosis levels at increasing concentrations of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide at day 5 of treatment of non-small cell lung cancer (NSCLC) MV522 cells.

**Figure 20B** is a graph demonstrating the respective apoptosis levels at increasing concentrations N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide at day 5 of treatment of non-small cell lung cancer (NSCLC) H358 cells.

**Figure 20C** is a graph demonstrating the respective apoptosis levels at increasing concentrations of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide at day 6 of treatment of non-small cell lung cancer (NSCLC) A549 cells.

**Figure 20D** is a graph demonstrating the respective apoptosis levels at increasing concentrations of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide at day 5 of treatment of non-small cell lung cancer (NSCLC) H727 cells.

**Figure 20E** is a graph demonstrating the respective apoptosis levels at increasing concentrations of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide at day 5 of treatment of colon HT29 cells.

**Figure 20F** is a graph demonstrating the respective apoptosis levels at increasing concentrations of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide at day 6 of treatment of colon HCT116 cells.

**Figure 20G** is a graph demonstrating the respective apoptosis levels at increasing concentrations of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide at day 5 of treatment of colon HUH7 Hepatoma cells.

**Figure 20H** is a graph depicting the respective apoptosis levels at increasing concentrations of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide at day 5 of treatment of Sarcoma U2-OS cells.

**Figure 20I** is a graph demonstrating the respective apoptosis levels at increasing concentrations of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide at day 5 of treatment of Glioma D37 cells.

**Figure 21** shows the selectivity of Compound A towards MEK1 and MEK2 against a pane of 205 enzymes at 10 μM. Cell lines were Colo205, A375, A431 and HT-29.

**Figure 22** is a graph showing the increases in paw volume in each of the treatment groups and the reduction in edema relative to vehicle control, after dosing the rats with 6, 20, 60, and 200 mg/kg of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide in Rat Carrageenan Paw Edema Model.

**Figure 23A** shows inhibition of swelling in adjuvant induced arthritis model, in the acute phase for rats treated with 2, 6 and 20mg/kg of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide.

**Figure 23B** shows inhibition of swelling in adjuvant induced arthritis model, in the delayed phase for rats treated with 2, 6 and 20mg/kg of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide.

**Figure 24** shows mean arthritic scores in Collagen-Antibody Induced-Arthritis (CAIA) Mice treated with 1, 3 & 10 mg/kg QD N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide.

## DETAILED DESCRIPTION OF THE INVENTION

The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in the application including, without limitation, patents, patent applications, articles, books, manuals, and treatises are hereby expressly incorporated by reference in their entirety for any purpose.

***Certain Chemical Terminology***

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the claimed subject matter belongs. All patents, patent applications, published materials referred to throughout the entire disclosure herein, unless noted otherwise, are incorporated by reference in their entirety. In the event that there is a plurality of definitions for terms herein, those in this section prevail. Where reference is made to a URL or other such identifier or address, it is understood that such identifiers can change and particular information on the internet can come and go, but equivalent information can be found by searching the internet or other appropriate reference source. Reference thereto evidences the availability and public dissemination of such information.

It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of any subject matter claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise. It must be noted that, as used in the specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the context clearly dictates otherwise. It should also be noted that use of "or" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "include", "includes", and "included" is not limiting.

Definition of standard chemistry terms may be found in reference works, including Carey and Sundberg "ADVANCED ORGANIC CHEMISTRY 4TH ED." Vols. A (2000) and B (2001), Plenum Press, New York. Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, IR and UV/Vis spectroscopy and pharmacology, within the skill of the art are employed. Unless specific definitions are provided, the nomenclature employed in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those known in the art. Standard techniques can be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients. Reactions and purification techniques can be performed e.g., using kits of manufacturer's specifications or as commonly accomplished in the art or as described herein. The foregoing techniques and procedures can be generally performed of conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. Throughout the specification, groups and substituents thereof can be chosen by one skilled in the field to provide stable moieties and compounds.

Where substituent groups are specified by their conventional chemical formulas, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left. As a non-limiting example, $-CH_2O-$ is equivalent to $-OCH_2-$.

Unless otherwise noted, the use of general chemical terms, such as though not limited to "alkyl," "amine," "aryl," are equivalent to their optionally substituted forms. For example, "alkyl," as used herein, includes optionally substituted alkyl.

The compounds presented herein may possess one or more stereocenters and each center may exist in the R or S configuration, or combinations thereof. Likewise, the compounds presented herein may possess one or more double bonds and each may exist in the E (*trans*) or Z (*cis*) configuration, or combinations thereof. Presentation of one particular stereoisomer, regioisomer, diastereomer, enantiomer or epimer should be understood to include all possible stereoisomers, regioisomers, diastereomers, enantiomers or epimers and mixtures thereof. Thus, the compounds presented herein include all separate configurational stereoisomeric, regioisomeric, diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. Presentation of one particular chemical structure or chemical name for a compound which contains one or more chiral centers, but which does not designate a particular stereochemistry, should be understood to include all possible stereoisomers, including mixtures of all possible stereoisomers, pure forms or substantially pure forms of one particular stereoisomer and pure forms or substantially pure forms of the alternate stereoisomer. Techniques for inverting or leaving unchanged a particular stereocenter, and those for resolving mixtures of stereoisomers are well known in the art and it is well within the ability of one of skill in the art to choose an appropriate method for a particular situation. See, for example, Furniss *et al.* (eds.), VOGEL'S ENCYCLOPEDIA OF PRACTICAL ORGANIC CHEMISTRY 5.sup.TH ED., Longman Scientific and Technical Ltd., Essex, **1991**, 809-816; and Heller, *Acc. Chem. Res.* **1990**, *23*, 128.

The terms "moiety", "chemical moiety", "group" and "chemical group", as used herein refer to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

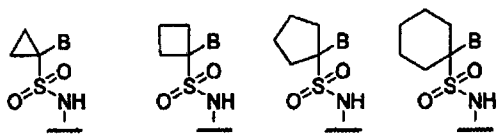
The term "bond" or "single bond" refers to a chemical bond between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure.

The term "optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted alkyl" means either "alkyl" or "substituted alkyl" as defined below. Further, an optionally substituted group may be un-substituted (e.g., $-CH_2CH_3$), fully substituted (e.g., $-CF_2CF_3$), mono-substituted (e.g., $-CH_2CH_2F$) or substituted at a level anywhere in-between fully substituted and mono-substituted (e.g., $-CH_2CHF_2$, $-CH_2CF_3$, $-CF_2CH_3$, $-CFHCHF_2$, etc). 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 (e.g., substituted alkyl includes optionally substituted cycloalkyl groups, which in turn are defined as including optionally substituted alkyl groups, potentially *ad infinitum*) that are sterically impractical and/or synthetically non-feasible. Thus, any substituents described should generally be understood as having a maximum molecular weight of about 1,000 daltons, and more typically, up to about 500 daltons (except in those instances where macromolecular substituents are clearly intended, e.g., polypeptides, polysaccharides, polyethylene glycols, DNA, RNA and the like).

Unless otherwise noted, the use of general chemical terms, such as though not limited to "alkyl," "amine," "aryl," are unsubstituted.

As used herein, $C_1$-$C_x$ includes $C_1$-$C_2$, $C_1$-$C_3$ . . . $C_1$-$C_x$. By way of example only, a group designated as "$C_1$-$C_4$" indicates that there are one to four carbon atoms in the moiety, i.e. groups containing 1 carbon atom, 2 carbon atoms, 3 carbon atoms or 4 carbon atoms, as well as the ranges $C_1$-$C_2$ and $C_1$-$C_3$. Thus, by way of example only, "$C_1$-$C_4$ alkyl" indicates that there are one to four carbon atoms in the alkyl group, *i.e.*, the alkyl group is selected from among methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, and *t*-butyl. Whenever it appears herein, a numerical range such as "1 to 10" refers to each integer in the given range; *e.g.*, "1 to 10 carbon atoms" means that the group may have 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, 6 carbon atoms, 7 carbon atoms, 8 carbon atoms, 9 carbon atoms, or 10 carbon atoms.

The term " A and A', together with the carbon atom to which they are attached, form a 3- to 6- member saturated ring ", as used herein, refers to the following structures for compounds of formula I:



The terms "heteroatom" or "hetero" as used herein, alone or in combination, refer to an atom other than carbon or hydrogen. Heteroatoms are may be independently selected from among oxygen, nitrogen, sulfur, phosphorous, silicon, selenium and tin but are not limited to these atoms. In embodiments in which two or more heteroatoms are present, the two or more heteroatoms can be the same as each another, or some or all of the two or more heteroatoms can each be different from the others.

The term "alkyl" as used herein, alone or in combination, refers to a straight-chain or branched-chain saturated hydrocarbon monoradical having from one to about ten carbon atoms, or one to six carbon atoms. Examples include, but are not limited to methyl, ethyl, n-propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, tert-amyl and hexyl, and longer alkyl groups, such as heptyl, octyl and the like. Whenever it appears herein, a numerical range such as "$C_1$-$C_6$ alkyl" or "$C_{1-6}$ alkyl", means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms. In one embodiment, the "alkyl" is substituted. Unless otherwise indicated, the "alkyl" is unsubstitituted.

The term "alkenyl" as used herein, alone or in combination, refers to a straight-chain or branched-chain hydrocarbon monoradical having one or more carbon-carbon double-bonds and having from two to about ten carbon atoms, or two to about six carbon atoms. The group may be in either the *cis* or *trans* conformation about the double bond(s), and should be understood to include both isomers. Examples include, but are not limited to ethenyl (-CH=$CH_2$), 1-propenyl (-$CH_2$CH=$CH_2$), isopropenyl [-C($CH_3$)=$CH_2$], butenyl, 1,3-butadienyl and the like. Whenever it appears herein, a numerical range such as "$C_2$-$C_6$ alkenyl" or "$C_{2-6}$ alkenyl", means that the alkenyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms. In one embodiment, the "alkenyl" is substituted. Unless otherwise indicated, the "alkenyl" is unsubstitituted.

The term "alkynyl" as used herein, alone or in combination, refers to a straight-chain or branched-chain hydrocarbon monoradical having one or more carbon-carbon triple-bonds and having from two to about ten carbon atoms, or from two to about six carbon atoms. Examples include, but are not limited to ethynyl, 2-propynyl, 2-butynyl, 1,3-butadiynyl and the like. Whenever it appears herein, a numerical range such as "$C_2$-$C_6$ alkynyl" or "$C_{2-6}$ alkynyl", means that the alkynyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms. In one embodiment, the "alkynyl" is substituted. Unless otherwise indicated, the "alkynyl" is unsubstitituted.

The terms "heteroalkyl", "heteroalkenyl" and "heteroalkynyl" as used herein, alone or in combination, refer to alkyl, alkenyl and alkynyl structures respectively, as described above, in which one or more of the skeletal chain carbon atoms (and any associated hydrogen atoms, as appropriate) are each independently replaced with a heteroatom (i.e. an atom other than carbon, such as though not limited to oxygen, nitrogen, sulfur, silicon, phosphorous, tin or combinations thereof), or heteroatomic group such as though not limited to -O-O-, -S-S-, -O-S-, -S-O-, =N-N=, -N=N-, -N=N-NH-, -$P(O)_2$-, -O-$P(O)_2$-, -$P(O)_2$-O-, -S(O)-, -$S(O)_2$-, -$SnH_2$- and the like.

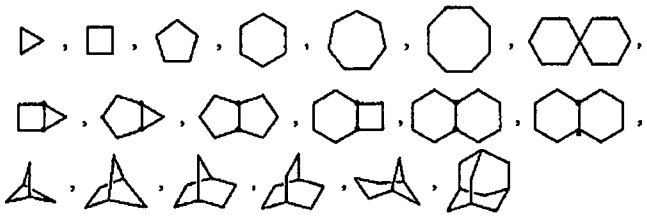
The terms "haloalkyl", "haloalkenyl" and "haloalkynyl" as used herein, alone or in combination, refer to alkyl, alkenyl and alkynyl groups respectively, as defined above, in which one or more hydrogen atoms is replaced by fluorine, chlorine, bromine or iodine atoms, or combinations thereof. In some embodiments two or more hydrogen atoms may be replaced with halogen atoms that are the same as each another (e.g. difluoromethyl); in other embodiments two or more hydrogen atoms may be replaced with halogen atoms that are not all the same as each other (e.g. 1-chloro-1-fluoro-1-iodoethyl). Non-limiting examples of haloalkyl groups are fluoromethyl, chloromethyl and bromoethyl. A non-limiting example of a haloalkenyl group is bromoethenyl. A non-limiting example of a haloalkynyl group is chloroethynyl.

The term "carbon chain" as used herein, alone or in combination, refers to any alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl or heteroalkynyl group, which is linear, cyclic, or any combination thereof. If the chain is part of a linker and that linker comprises one or more rings as part of the core backbone, for purposes of calculating chain length, the "chain" only includes those carbon atoms that compose the bottom or top of a given ring and not both, and where the top and bottom of the ring(s) are not equivalent in length, the shorter distance shall be used in determining the chain length. If the chain contains heteroatoms as part of the backbone, those atoms are not calculated as part of the carbon chain length.

The terms "cycle", "cyclic", "ring" and "membered ring" as used herein, alone or in combination, refer to any covalently closed structure, including alicyclic, heterocyclic, aromatic, heteroaromatic and polycyclic fused or non-fused ring systems as described herein. Rings can be optionally substituted. Rings can form part of a fused ring system. The term "membered" is meant to denote the number of skeletal atoms that constitute the ring. Thus, by way of example only, cyclohexane, pyridine, pyran and pyrimidine are six-membered rings and cyclopentane, pyrrole, tetrahydrofuran and thiophene are five-membered rings.

The term "fused" as used herein, alone or in combination, refers to cyclic structures in which two or more rings share one or more bonds.

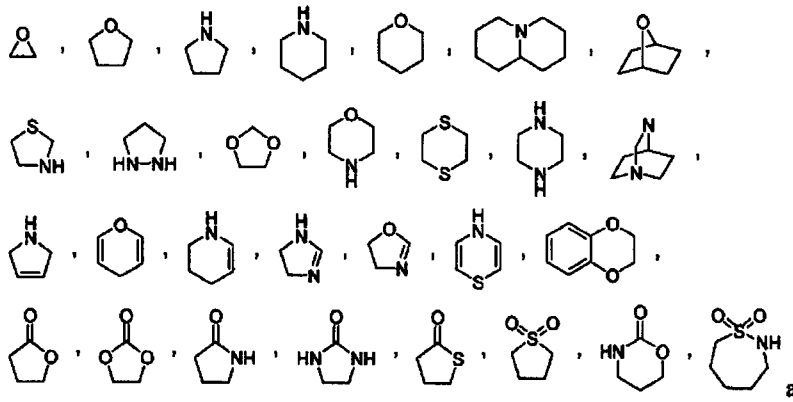
The term "cycloalkyl" as used herein, alone or in combination, refers to a saturated, hydrocarbon monoradical ring, containing from three to about fifteen ring carbon atoms or from three to about ten ring carbon atoms, though may include additional, non-ring carbon atoms as substituents (e.g. methylcyclopropyl). Whenever it appears herein, a numerical range such as "$C_3$-$C_6$ cycloalkyl " or "$C_{3-6}$ cycloalkyl ", means that the cycloalkyl group may consist of 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, i.e., is cyclopropyl, cyclobutyl, cyclopentyl or cyclohepty, although the present definition also covers the occurrence of the term " cycloalkyl " where no numerical range is designated. The term includes fused, non-fused, bridged and spiro radicals. A fused cycloalkyl may contain from two to four fused rings where the ring of attachment is a cycloalkyl ring, and the other individual rings may be alicyclic, heterocyclic, aromatic, heteroaromatic or any combination thereof. Examples include, but are not limited to cyclopropyl, cyclopentyl, cyclohexyl, decalinyl, and bicyclo [2.2.1] heptyl and adamantyl ring systems. Illustrative examples include, but are not limited to the following moieties:



and the like.

In one embodiment, the "cycloalkyl" is substituted. Unless otherwise indicated, the "cycloalkyl" is unsubstitituted.

The terms "non-aromatic heterocyclyl" and "heteroalicyclyl" as used herein, alone or in combination, refer to a saturated, partially unsaturated, or fully unsaturated nonaromatic ring monoradicals containing from three to about twenty ring atoms, where one or more of the ring atoms are an atom other than carbon, independently selected from among oxygen, nitrogen, sulfur, phosphorous, silicon, selenium and tin but are not limited to these atoms. In embodiments in which two or more heteroatoms are present in the ring, the two or more heteroatoms can be the same as each another, or some or all of the two or more heteroatoms can each be different from the others. The terms include fused, non-fused, bridged and spiro radicals. A fused non-aromatic heterocyclic radical may contain from two to four fused rings where the attaching ring is a non-aromatic heterocycle, and the other individual rings may be alicyclic, heterocyclic, aromatic, heteroaromatic or any combination thereof. Fused ring systems may be fused across a single bond or a double bond, as well as across bonds that are carbon-carbon, carbon-hetero atom or hetero atom-hetero atom. The terms also include radicals having from three to about twelve skeletal ring atoms, as well as those having from three to about ten skeletal ring atoms. Attachment of a non-aromatic heterocyclic subunit to its parent molecule can be via a heteroatom or a carbon atom. Likewise, additional substitution can be via a heteroatom or a carbon atom. As a non-limiting example, an imidazolidine non-aromatic heterocycle may be attached to a parent molecule via either of its N atoms (imidazolidin-1-yl or imidazolidin-3-yl) or any of its carbon atoms (imidazolidin-2-yl, imidazolidin-4-yl or imidazolidin-5-yl). In certain embodiments, non-aromatic heterocycles contain one or more carbonyl or thiocarbonyl groups such as, for example, oxo- and thio-containing groups. Examples include, but are not limited to pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinolizinyl. Illustrative examples of heterocycloalkyl groups, also referred to as non-aromatic heterocycles, include:

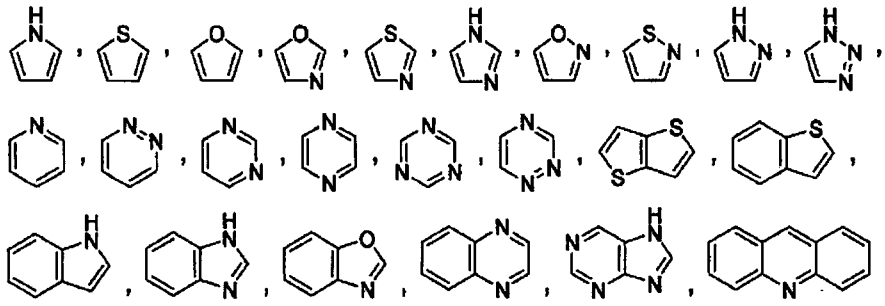


and the like.

The terms also include all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides. In one embodiment, the "non-aromatic heterocyclyl" or "heteroalicyclyl" is substituted. Unless otherwise indicated, the "non-aromatic heterocyclyl" or "heteroalicyclyl" is unsubstitituted.

The term "aryl" as used herein, alone or in combination, refers to an aromatic hydrocarbon radical of six to about twenty ring carbon atoms, and includes fused and non-fused aryl rings. A fused aryl ring radical contains from two to four fused rings where the ring of attachment is an aryl ring, and the other individual rings may be alicyclic, heterocyclic, aromatic, heteroaromatic or any combination thereof. Further, the term aryl includes fused and non-fused rings containing from six to about twelve ring carbon atoms, as well as those containing from six to about ten ring carbon atoms. A non-limiting example of a single ring aryl group includes phenyl; a fused ring aryl group includes naphthyl, phenanthrenyl, anthracenyl, azulenyl; and a non-fused bi-aryl group includes biphenyl. In one embodiment, the "aryl" is substituted. Unless otherwise indicated, the "aryl" is unsubstitituted.

The term "heteroaryl" as used herein, alone or in combination, refers to an aromatic monoradicals containing from about five to about twenty skeletal ring atoms, where one or more of the ring atoms is a heteroatom independently selected from among oxygen, nitrogen, sulfur, phosphorous, silicon, selenium and tin but not limited to these atoms and with the proviso that the ring of said group does not contain two adjacent O or S atoms. In embodiments in which two or more heteroatoms are present in the ring, the two or more heteroatoms can be the same as each another, or some or all of the two or more heteroatoms can each be different from the others. The term heteroaryl includes fused and non-fused heteroaryl radicals having at least one heteroatom. The term heteroaryl also includes fused and non-fused heteroaryls having from five to about twelve skeletal ring atoms, as well as those having from five to about ten skeletal ring atoms. Bonding to a heteroaryl group can be via a carbon atom or a heteroatom. Thus, as a non-limiting example, an imidazole group may be attached to a parent molecule via any of its carbon atoms (imidazol-2-yl, imidazol-4-yl or imidazol-5-yl), or its nitrogen atoms (imidazol-1-yl or imidazol-3-yl). Likewise, a heteroaryl group may be further substituted via any or all of its carbon atoms, and/or any or all of its heteroatoms. A fused heteroaryl radical may contain from two to four fused rings where the ring of attachment is a heteroaromatic ring and the other individual rings may be alicyclic, heterocyclic, aromatic, heteroaromatic or any combination thereof. A non-limiting example of a single ring heteroaryl group includes pyridyl; fused ring heteroaryl groups include benzimidazolyl, quinolinyl, acridinyl; and a non-fused bi-heteroaryl group includes bipyridinyl. Further examples of heteroaryls include, without limitation, furanyl, thienyl, oxazolyl, acridinyl, phenazinyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, benzothiophenyl, benzoxadiazolyl, benzotriazolyl, imidazolyl, indolyl, isoxazolyl, isoquinolinyl, indolizinyl, isothiazolyl, isoindolyloxadiazolyl, indazolyl, pyridyl, pyridazyl, pyrimidyl, pyrazinyl, pyrrolyl, pyrazinyl, pyrazolyl, purinyl, phthalazinyl, pteridinyl, quinolinyl, quinazolinyl, quinoxalinyl, triazolyl, tetrazolyl, thiazolyl, triazinyl, thiadiazolyl and the like, and their oxides, such as for example pyridyl-N-oxide. Illustrative examples of heteroaryl groups include the following moieties:



and the like.

In one embodiment, the "heteroaryl" is substituted. Unless otherwise indicated, the "heteroaryl" is unsubstitituted.

The term "heterocyclyl" as used herein, alone or in combination, refers collectively to heteroalicyclyl and heteroaryl groups. Herein, whenever the number of carbon atoms in a heterocycle is indicated (e.g., $C_1$-$C_6$ heterocycle), at least one non-carbon atom (the heteroatom) must be present in the ring. Designations such as "$C_1$-$C_6$ heterocycle" refer only to the number of carbon atoms in the ring and do not refer to the total number of atoms in the ring. Designations such as "4-6 membered heterocycle" refer to the total number of atoms that are contained in the ring (i.e., a four, five, or six membered ring, in which at least one atom is a carbon atom, at least one atom is a heteroatom and the remaining two to four atoms are either carbon atoms or heteroatoms). For heterocycles having two or more heteroatoms, those two or more heteroatoms can be the same or different from one another. Non-aromatic heterocyclic groups include groups having only three atoms in the ring, while aromatic heterocyclic groups must have at least five atoms in the ring. Bonding (i.e. attachment to a parent molecule or further substitution) to a heterocycle can be via a heteroatom or a carbon atom. In one embodiment, the "heterocyclyl" is substituted. Unless otherwise indicated, the "heterocycyl" is unsubstitituted.

The terms "halogen", "halo" or "halide" as used herein, alone or in combination refer to fluoro, chloro, bromo and/or iodo.

The term "amino" as used herein, alone or in combination, refers to the monoradical $-NH_2$.

The term "alkylamino" as used herein, alone or in combination, refers to the monoradical -NH(alkyl) where alkyl is as defined herein.

The term "dialkylamino" as used herein, alone or in combination, refers to the monoradical -N(alkyl)(alkyl) where each alkyl may be identical or non-identical and is as defined herein.

The term "diamino alkyl" as used herein, alone or in combination, refers to an alkyl group containing two amine groups, wherein said amine groups may be substituents on the alkyl group which may be amino, alkylamino, or dialkylamino groups, or wherein one or both of said amine groups may form part of an alkyl chain to form -alkylene-N(H or alkyl)-alkylene-N(H or alkyl or alkylene-)(H or alkyl or alkylene-).

The term "hydroxy" as used herein, alone or in combination, refers to the monoradical -OH.

The term "cyano" as used herein, alone or in combination, refers to the monoradical -CN.

The term "cyanomethyl" as used herein, alone or in combination, refers to the monoradical $-CH_2CN$.

The term "nitro" as used herein, alone or in combination, refers to the monoradical $-NO_2$.

The term "oxy" as used herein, alone or in combination, refers to the diradical -O-.

The term "oxo" as used herein, alone or in combination, refers to the diradical =O.

The term "carbonyl" as used herein, alone or in combination, refers to the diradical -C(=O)-, which may also be written as -C(O)-.

The terms "carboxy" or "carboxyl" as used herein, alone or in combination, refer to the moiety -C(O)OH, which may also be written as -COOH.

The term "alkoxy" as used herein, alone or in combination, refers to an alkyl ether radical, -O-alkyl, including the groups -O-aliphatic and -O-carbocyclyl, wherein the alkyl, aliphatic and carbocyclyl groups may be optionally substituted, and wherein the terms alkyl, aliphatic and carbocyclyl are as defined herein. Non-limiting examples of alkoxy radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy and the like.

The term "sulfinyl" as used herein, alone or in combination, refers to the diradical -S(=O)-.

The term "sulfonyl" as used herein, alone or in combination, refers to the diradical $-S(=O)_2-$.

The terms "sulfonamide", "sulfonamido" and "sulfonamidyl" as used herein, alone or in combination, refer to the diradical groups $-S(=O)_2-NH-$ and $-NH-S(=O)_2-$.

The terms "sulfamide", "sulfamido" and "sulfamidyl" as used herein, alone or in combination, refer to the diradical group -NH-S(=O)$_2$-NH-.

The term "reactant," as used herein, refers to a nucleophile or electrophile used to create covalent linkages.

It is to be understood that in instances where two or more radicals are used in succession to define a substituent attached to a structure, the first named radical is considered to be terminal and the last named radical is considered to be attached to the structure in question. Thus, for example, the radical arylalkyl is attached to the structure in question by the alkyl group.

***Certain Pharmaceutical Terminology***

The term "MEK inhibitor" as used herein refers to a compound that exhibits an $IC_{50}$ with respect to MEK activity, of no more than about 100μM or not more than about 50μM, as measured in the Mek1 kinase assay described generally herein. "$IC_{50}$" is that concentration of inhibitor which reduces the activity of an enzyme (e.g., MEK) to half-maximal level. Compounds described herein have been discovered to exhibit inhibition against MEK. Compounds of the present invention preferably exhibit an $IC_{50}$with respect to MEK of no more than about 10μM, more preferably, no more than about 5μM, even more preferably not more than about 1μM, and most preferably, not more than about 200nM, as measured in the Mek1 kinase assay described herein.

The term "subject", "patient" or "individual" as used herein in reference to individuals suffering from a disorder, and the like, encompasses mammals and non-mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. Examples of non-mammals include, but are not limited to, birds, fish and the like. In one embodiment of the methods and compositions provided herein, the mammal is a human.

The terms "treat," "treating" or "treatment," and other grammatical equivalents as used herein, include alleviating, abating or ameliorating a disease or condition symptoms, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition, and are intended to include prophylaxis. The terms further include achieving a therapeutic benefit and/or a prophylactic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient may still be afflicted with the underlying disorder. For prophylactic benefit, the compositions may be administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may not have been made.

The terms "effective amount", "therapeutically effective amount" or "pharmaceutically effective amount" as used herein, refer to an amount of at least one agent or compound being administered that is sufficient to treat or prevent the particular disease or condition. The result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in a disease. An appropriate "effective" amount in any individual case may be determined using techniques, such as a dose escalation study.

The terms "substantially free of water" and "substantially free of solvent" as used herein, refer to crystalline polymorph forms comprising less than 0.01, 0.1, 0.2, 0.3, 0.4, 0.5, 1 or 2% by weight of water or solvent respectively.

The term "substantially the same as" as used herein, refers to a powder x-ray diffraction pattern or differential scanning calorimetry pattern that may be non-identical to those depicted herein, but that falls within the limits of experimental error, when considered by one of ordinary skill in the art.

The terms "administer," "administering", "administration," and the like, as used herein, refer to the methods that may be used to enable delivery of compounds or compositions to the desired site of biological action. These methods include, but are not limited to oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intraperitoneal, intramuscular, intravascular or infusion), topical and rectal administration. Those of skill in the art are familiar with administration techniques that can be employed with the compounds and methods described herein, e.g., as discussed in Goodman and Gilman, The Pharmacological Basis of Therapeutics, current ed.; Pergamon; and Remington's, Pharmaceutical *Sciences* (current edition), Mack Publishing Co., Easton, Pa. In preferred embodiments, the compounds and compositions described herein are administered orally.

The term "acceptable" as used herein, with respect to a formulation, composition or ingredient, means having no persistent detrimental effect on the general health of the subject being treated.

The term "pharmaceutically acceptable" as used herein, refers to a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compounds described herein, and is relatively nontoxic, i.e., the material may be administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

The term "pharmaceutical composition," as used herein, refers to a biologically active compound, optionally mixed with at least one pharmaceutically acceptable chemical component, such as, though not limited to carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients.

The term "carrier" as used herein, refers to relatively nontoxic chemical compounds or agents that facilitate the incorporation of a compound into cells or tissues.

The term "agonist," as used herein, refers to a molecule such as a compound, a drug, an enzyme activator or a hormone modulator which enhances the activity of another molecule or the activity of a receptor site.

The term "antagonist," as used herein, refers to a molecule such as a compound, a drug, an enzyme inhibitor, or a hormone modulator, which diminishes, or prevents the action of another molecule or the activity of a receptor site.

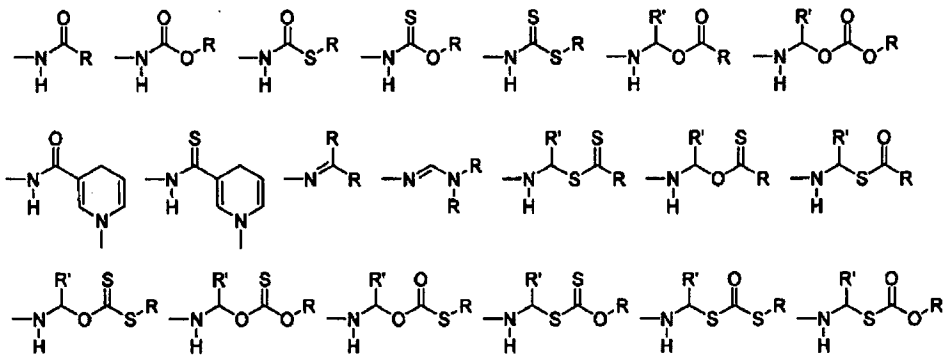
The term "modulate," as used herein, means to interact with a target either directly or indirectly so as to alter the activity of the target, including, by way of example only, to enhance the activity of the target, to inhibit the activity of the target, to limit the activity of the target, or to extend the activity of the target.

The term "modulator," as used herein, refers to a molecule that interacts with a target either directly or indirectly. The interactions include, but are not limited to, the interactions of an agonist and an antagonist.

The term "pharmaceutically acceptable derivative or prodrug" as used herein, refers to any pharmaceutically acceptable salt, ester, salt of an ester or other derivative of a compound of formula I, which, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or a pharmaceutically active metabolite or residue thereof. Particularly favored derivatives or prodrugs are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a patient (*e.g.*, by allowing orally administered compound to be more readily absorbed into blood) or which enhance delivery of the parent compound to a biological compartment (*e.g.*, the brain or lymphatic system).

As used herein, a "prodrug" is a compound that may be converted under physiological conditions or by solvolysis to the specified compound or to a pharmaceutically acceptable salt of such compound. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more amino acid residues, is covalently joined through an amide or ester bond to a free amino, hydroxy, or carboxylic acid group of compounds of Formulas I. The amino acid residues contemplated include but are not limited to the 20 naturally- occurring amino acids. Other suitable amino acids include 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methyl histidine, norvaline, β-alanine, γ-aminobutyric acid, cirtulline, homocysteine, homoserine, ornithine and methionine sulfone. Additional types of prodrugs are well known in the art.

Pharmaceutically acceptable prodrugs of the compounds described herein include, but are not limited to, esters, carbonates, thiocarbonates, N-acyl derivatives, N-acyloxyalkyl derivatives, quaternary derivatives of tertiary amines, N-Mannich bases, Schiff bases, amino acid conjugates, phosphate esters, metal salts and sulfonate esters. Various forms of prodrugs are well known in the art. See for example *Design of Prodrugs*, Bundgaard, A. Ed., Elseview, 1985 and *Method in Enzymology*, Widder, K. *et al.*, Ed.; Academic, 1985, vol. 42, p. 309-396; Bundgaard, H. "Design and Application of Prodrugs" in *A Textbook of Drug Design and Development*, Krosgaard-Larsen and H. Bundgaard, Ed., 1991, Chapter 5, p. 113-191; and Bundgaard, H., *Advanced Drug Delivery Review*, 1992, *8*, 1-38, each of which is incorporated herein by reference. The prodrugs described herein include, but are not limited to, the following groups and combinations of these groups; amine derived prodrugs:



Hydroxy prodrugs include, but are not limited to acyloxyalkyl esters, alkoxycarbonyloxyalkyl esters, alkyl esters, aryl esters and disulfide containing esters.

The term "pharmaceutically acceptable salt" as used herein, includes salts that retain the biological effectiveness of the free acids and bases of the specified compound and that are not biologically or otherwise undesirable. Compounds described may possess acidic or basic groups and therefore may react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. Examples of pharmaceutically acceptable salts include those salts prepared by reaction of the compounds described herein with a mineral or organic acid or an inorganic base, such salts including, acetate, acrylate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, bisulfite, bromide, butyrate, butyn-1,4-dioate, camphorate, camphorsulfonate, caproate, caprylate, chlorides, chlorobenzoate, chloride, citrate, cyclopentanepropionate, decanoate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hexyne-1,6-dioate, hydroxybenzoate, γ-hydroxybutyrate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isobutyrate, lactate, maleate, malonate, methanesulfonate, mandelate. metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, 1-napthalenesulfonate, 2-napthalenesulfonate, nicotinate, nitrate, oxalates, palmoate, pectinate, persulfate, phenylacetates, phenylpropionates, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, pyrosulfate, pyrophosphate, propiolate, propionates, phthalate,

, phenylbutyrate, propanesulfonate, pyrophosphates, salicylate, succinate, sulfate, sulfite, succinate, suberate, sebacate, sulfonate, tartrate, thiocyanate, tosylate undeconate and xylenesulfonate. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts. (See for example Berge *et al.*, *J. Pharm. Sci.* **1977**, *66*, 1-19.) Further, those compounds described herein which may comprise a free acid group may react with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts and the like. Illustrative examples of bases include sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate, $N^+(C_{1-4}$ alkyl$)_4$, and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. It should be understood that the compounds described herein also include the quaternization of any basic nitrogen-containing groups they may contain. Water or oil-soluble or dispersible products may be obtained by such quaternization. See, for example, Berge *et al.*, *supra*. These salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or by separately reacting a purified compound in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed.

The terms "enhance" or "enhancing," as used herein, means to increase or prolong either in potency or duration a desired effect. Thus, in regard to enhancing the effect of therapeutic agents, the term "enhancing" refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system. An "enhancing-effective amount," as used herein, refers to an amount adequate to enhance the effect of another therapeutic agent in a desired system.

The terms "pharmaceutical combination", "administering an additional therapy", "administering an additional therapeutic agent" and the like, as used herein, refer to a pharmaceutical therapy resulting from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that at least one of the compounds described herein, and at least one co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that at least one of the compounds described herein, and at least one co-agent, are administered to a patient as separate entities either simultaneously, concurrently or sequentially with variable intervening time limits, wherein such administration provides effective levels of the two or more compounds in the body of the patient. These also apply to cocktail therapies, e.g. the administration of three or more active ingredients.

The terms "co-administration", "administered in combination with" and their grammatical equivalents or the like, as used herein, are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different times. In some embodiments the compounds described herein will be co-administered with other agents. These terms encompass administration of two or more agents to an animal so that both agents and/or their metabolites are present in the animal at the same time. They include simultaneous administration in separate compositions, administration at different times in separate compositions, and/or administration in a composition in which both agents are present. Thus, in some embodiments, the compounds of the invention and the other agent(s) are administered in a single composition. In some embodiments, compounds of the invention and the other agent(s) are admixed in the composition.

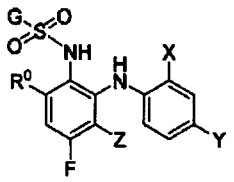
The term "metabolite," as used herein, refers to a derivative of a compound which is formed when the compound is metabolized.

The term "active metabolite," as used herein, refers to a biologically active derivative of a compound that is formed when the compound is metabolized.

The term "metabolized," as used herein, refers to the sum of the processes (including, but not limited to, hydrolysis reactions and reactions catalyzed by enzymes) by which a particular substance is changed by an organism. Thus, enzymes may produce specific structural alterations to a compound. For example, cytochrome P450 catalyzes a variety of oxidative and reductive reactions while uridine diphosphate glucuronyltransferases catalyze the transfer of an activated glucuronic-acid molecule to aromatic alcohols, aliphatic alcohols, carboxylic acids, amines and free sulphydryl groups. Further information on metabolism may be obtained from *The Pharmacological Basis of Therapeutics*, 9th Edition, McGraw-Hill (1996).

***Compounds***

Described herein are compounds of formula I, and pharmaceutically acceptable salts, solvates, polymorphs, esters, amides, tautomers or prodrugs thereof:



formula I

wherein

Z is H or F;

X is F, Cl, $CH_3$, $CH_2OH$, $CH_2F$, $CHF_2$, or $CF_3$;

Y is I, Br, Cl, $CF_3$, $C_1$-$C_3$ alkyl, $C_2$-$C_3$ alkenyl, $C_2$-$C_3$ alkynyl, cyclopropyl, OMe, OEt, SMe, phenyl or Het, where Het is a 5- to 10- membered mono- or bicyclic heterocyclic group, which group is saturated, olefinic, or aromatic, containing 1-5 ring heteroatoms selected independently from N, 0, and S; where

all said phenyl or Het groups are optionally substituted with F, Cl, Br, I, acetyl, methyl, CN, $NO_2$, $CO_2H$, $C_1$-$C_3$ alkyl, $C_1$-$C_3$ alkoxy, $C_1$-$C_3$ alkyl-C(=O)-, $C_1$-$C_3$ alkyl-C(=S)-, $C_1$-$C_3$ alkoxy-C(=S)-, $C_1$-$C_3$ alkyl-C(=O)O-, $C_1$-$C_3$ alkyl-0-(C=O)-, $C_1$-$C_3$ alkyl-C(=O)NH-, $C_1$-$C_3$ alkyl-C(=NH)NH-, $C_1$-$C_3$ alkyl-NH-(C=O)-, di-$C_1$-$C_3$ alkyl-N-(C=O)-, $C_1$-$C_3$ alkyl-C(=O)N($C_1$-$C_3$ alkyl)-, $C_1$-$C_3$ alkyl-S(=O)$_2$NH- or trifluoromethyl;

all said methyl, ethyl, $C_1$-$C_3$ alkyl, and cyclopropyl groups are optionally substituted with OH;

all said methyl groups are optionally substituted with one, two, or three F atoms;

$R^0$ is H, F, Cl, Br, I, $CH_3NH$-, $(CH_3)_2N$-, $C_1$-$C_6$ alkyl, $C_1$-$C_4$ alkoxy, $C_3$-$C_6$ cycloalkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, phenyl, monosubstituted phenyl, O($C_1$-$C_4$ alkyl), O-C(=O)($C_1$-$C_4$ alkyl) or C(=O)O($C_1$-$C_4$ alkyl); where

said alkyl, alkoxy, cycloalkyl, alkenyl, alkynyl and phenyl groups are optionally substituted with 1-3 substituents selected independently from F, Cl, Br, I, OH, CN, cyanomethyl, nitro, phenyl and trifluoromethyl;

said $C_1$-$C_6$ alkyl and $C_1$-$C_4$ alkoxy groups also optionally substituted with $OCH_3$or $OCH_2CH_3$;

G is $G_1$, $G_2$, $R_{1a}$, $R_{1b}$, $R_{1c}$, $R_{1d}$, $R_{1e}$, $Ar_1$, $Ar_2$ or $Ar_3$; where

$G_1$ is $C_1$-$C_6$ alkyl optionally substituted with one amino, $C_1$-$C_3$ alkylamino, or dialkylamino group, said dialkylamino group comprising two $C_1$-$C_4$ alkyl groups which may be identical or non-identical; or

$G_1$ is a $C_3$-$C_8$ diamino alkyl group;

$G_2$ is a 5- or 6- membered ring, which is saturated, unsaturated, or aromatic, containing 1-3 ring heteroatoms selected independently from N, 0, and S, optionally substituted with 1-3 substituents selected independently from F, Cl, OH, O($C_1$-$C_3$ alkyl), $OCH_3$, $OCH_2CH_3$, $CH_3C(=O)NH$, $CH_3C(=O)O$, CN, $CF_3$, and a 5-membered aromatic heterocyclic group containing 1-4 ring heteroatoms selected independently from N, O , and S;

$R_{1a}$ is methyl, optionally substituted with 1-3 fluorine atoms or 1-3 chlorine atoms, or with OH, cyclopropoxy, or $C_1$- $C_3$ alkoxy, where said cyclopropoxy group or the $C_1$- $C_3$ alkyl moieties of said $C_1$- $C_3$ alkoxy groups are optionally substituted with one hydroxy or methoxy group, and where all $C_3$- alkyl groups within said $C_1$- $C_4$ alkoxy are optionally further substituted with a second OH group;

$R_{1b}$ is $CH(CH_3)$-$C_{1-3}$ alkyl or $C_3$-$C_6$ cycloalkyl, said alkyl and cycloalkyl groups optionally substituted with 1-3 substituents selected independently from F, Cl, Br, I, OH, $OCH_3$, and CN;

$R_{1c}$ is $(CH_2)_nO_mR'$; where

m is 0 or 1; and where

when m is 0, n is 1 or 2;

when m is 1, n is 2 or 3;

R' is $C_1$-$C_6$ alkyl, optionally substituted with 1-3 substituents selected independently from F, Cl, OH, $OCH_3$, $OCH_2CH_3$, and $C_3$-$C_6$ cycloalkyl;

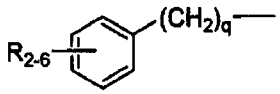
$R_{1d}$ is C(A)(A')(B)-; where

B is H or $C_{1-4}$ alkyl, optionally substituted with one or two OH groups;

A and A' are independently H or $C_{1-4}$ alkyl, optionally substituted with one or two OH groups; or

A and A', together with the carbon atom to which they are attached, form a 3- to 6- member saturated ring;

$R_{1e}$ is




$R_{1e}$

where

q is 1 or 2;

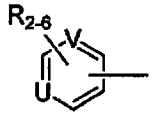
$R_2$ and $R_3$ are each independently, H, F, Cl, Br, $CH_3$, $CH_2F$, $CHF_2$, $CF_3$ $OCH_3$, $OCH_2F$, $OCHF_2$, $OCF_3$, ethyl, *n*-propyl, isopropyl, cyclopropyl, isobutyl, *sec*-butyl, *tert*-butyl or methylsulfonyl;

$R_4$ is H, F, Cl, Br, $CH_3$, $CH_2F$, $CHF_2$, $CF_3$ $OCH_3$, $OCH_2F$, $OCHF_2$, $OCF_3$, ethyl, *n*-propyl, isopropyl, cyclopropyl, isobutyl, *sec*-butyl, *tert*-butyl, methylsulfonyl, nitro, acetamido, amidinyl, cyano, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, 1,3,4-oxadiazol-2-yl, 5-methyl-1,3,4- oxadiazol, 1,3,4-thiadiazol, 5-methyl-1,3,4-thiadiazol lH-tetrazolyl, N-morpholyl carbonyl amino, N-morpholylsulfonyl and N-pyrrolidinylcarbonylamino;

$R_5$ is H, F, Cl or methyl;

$R_6$ is H, F, Cl or methyl;

$Ar_1$ is



$Ar_1$

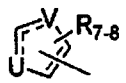
where

U and V are, independently, N, $CR_2$ or $CR_3$;

$R_2$, $R_3$ and $R_4$ are, independently, H, F, Cl, Br, $CH_3$, $CH_2F$, $CHF_2$, $CF_3$ $OCH_3$, $OCH_2F$, $OCHF_2$, $OCF_3$, ethyl, *n*-propyl, isopropyl, cyclopropyl, isobutyl, *sec*-butyl, *tert*-butyl, acetamido, amidinyl, cyano, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, l,3,4-oxadiazol-2-yl, 5-methyl-l,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, 5-methyl-l,3,4-thiadiazolyl, lH-tetrazolyl, N-morpholylcarbonylamino, N-morpholylsulfonyl, N-pyrrolidinylcarbonylamino, and methylsulfonyl;

$R_5$ and $R_6$ are, independently, H, F, Cl or methyl;

$Ar_2$ is




$Ar_2$

where

the dashed line represents alternative formal locations for the second ring double bond;

U is -S-, -O- or -N =, and where

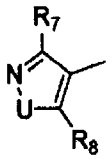
when U is -O- or -S-, V is -CH=, -CCl= or -N =;

when U is -N =, V is -CH=, -CCl=, or -N=;

$R_7$ is H or methyl;

$R_8$ is H, acetamido, methyl, F or Cl;

$Ar_3$ is




$Ar_3$

where

U is -NH-, -$NCH_3$- or -O-;

$R_7$ and $R_8$ are, independently, H, F, Cl, or methyl.

In addition to the definitions given herein for the groups G, $R^0$, X, Y and Z, additional substitutions which could be contemplated by those of skill in the chemical and pharmaceutical arts are included.

In some embodiments, the invention provides a compound of formula I, where G is $G_1$ or $G_2$. In other embodiments, G is $G_1$. In further or additional embodiments, G is $G_2$.

In some embodiments, the invention provides a compound of formula I, where G is $R_{1a}$, $R_{1b}$, $R_{1c}$, $R_{1d}$, $R_{1e}$, $Ar_1$, $Ar_2$ or $Ar_3$. In further or additional embodiments, G is $R_{1a}$, $R_{1b}$, $R_{1c}$, $R_{1d}$ or $R_{1e}$. In further or additional embodiments, G is $R_{1a}$. In further or additional embodiments, G is $R_{1b}$. In further or additional embodiments, G is $R_{1c}$. In further or additional embodiments, G is $R_{1d}$. In further or additional embodiments, G is $R_{1e}$. In further or additional embodiments, G is $Ar_1$, $Ar_2$ or $Ar_3$. In further or additional embodiments, G is $Ar_1$. In further or additional embodiments, G is $Ar_2$. In further or additional embodiments, G is $Ar_3$

In some embodiments provided are compounds of formula I, or their pharmaceutically acceptable salts. In further or additional embodiments, provided herein are compounds of formula I, or their solvates. In further or additional

embodiments, provided herein are compounds of formula I or their polymorphs. In further or additional embodiments, provided herein are compounds of formula I, or their esters. In further or additional embodiments, provided herein are compounds of formula I, or their amides. In further or additional embodiments, provided herein are compounds of formula I or their tautomers. In further or additional embodiments, provided herein are compounds of formula I or their prodrugs.

In some embodiments, Z is H. In some embodiments, Z is F. In some embodiments, X is F. In some embodiments, X is Cl. In some embodiments, X is $CH_3$. In some embodiments, X is $CH_2OH$. In some embodiments, X is $CH_2F$. In some embodiments, X is $CHF_2$. In some embodiments, X is $CF_3$. In some embodiments, X is F, Cl, or $CH_3$.

In some embodiments, G is $G_1$ or $G_2$, X is F, Cl, or $CH_3$; Y is I, Br, Cl, $CF_3$, $C_1$-$C_3$ alkyl, phenyl, pyridyl, pyrrolyl, pyrazolyl, said phenyl, pyridyl, pyrrolyl, and pyrazolyl groups optionally substituted with F, Cl, Br, I, acetyl, methyl, CN, $NO_2$, $CO_2H$, $C_1$-$C_3$ alkyl, $C_1$-$C_3$ alkoxy, $C_1$-$C_3$ alkyl-C(=O)-, $C_1$-$C_3$ alkyl-C(=S)-, $C_1$-$C_3$ alkoxy-C(=S)-, $C_1$-$C_3$ alkyl-C(=O)O-, $C_1$-$C_3$ alkyl-0-(C=O)-, $C_1$-$C_3$ alkyl-C(=O)NH-, $C_1$-$C_3$ alkyl-C(=NH)NH-, $C_1$-$C_3$ alkyl-NH-(C=O)-, di-$C_1$-$C_3$ alkyl-N-(C=O)-, $C_1$-$C_3$ alkyl-C(=O)N($C_1$-$C_3$ alkyl)-, $C_1$-$C_3$ alkyl-S(=O)$_2$NH- or trifluoromethyl; and Z is H or F. In further or additional embodiments, G is $G_1$ or $G_2$, and $R^0$ is F, Cl, $C_1$-$C_4$ alkyl or $C_1$-$C_4$ alkoxy, said $C_1$-$C_4$ alkyl group and the $C_1$-$C_4$ alkyl moiety of said $C_1$-$C_4$ alkoxy group optionally substituted with F, Cl, $OCH_3$, or $OCH_2CH_3$. In further or additional embodiments, G is $G_1$ or $G_2$, and $R^0$ is H, F, Cl, $C_1$-$C_4$ alkyl, methoxy, ethoxy, or 2-methoxy-ethoxy.

In some embodiments, $G_1$ is N-methyl-2-aminoethyl. In further or additional embodiments, $G_1$is $(CH_3)_2N$-$CH_2CH_2$-NH-$(CH_2)_n$-, where n is 1, 2, or 3. In further or additional embodiments, $G_1$is $(CH_3)_2N$-$CH_2CH_2$-NH-$(CH_2)_n$-, where n is 1, 2, or 3, and X is F. In further or additional embodiments, $G_1$is $(CH_3)_2N$-$CH_2CH_2$-NH-$(CH_2)_n$-, where n is 1, 2, or 3, X is F and Z is F.

In some embodiments, $G_2$ is 1-piperidyl, 2-piperidyl, 3-piperidyl, or 4-piperidyl. In further or additional embodiments, $G_2$ is morpholyl, 1-piperazyl, or 2-piperazyl.

In some embodiments, G is $R_{1a}$, $R_{1b}$, $R_{1c}$, $R_{1d}$, $R_{1e}$, $Ar_1$, $Ar_2$ or $Ar_3$ and X is F, Cl, or $CH_3$. In further or additional embodiments, G is $R_{1a}$, $R_{1b}$, $R_{1c}$, $R_{1d}$, $R_{1e}$, $Ar_1$, $Ar_2$ or $Ar_3$, X is F, Cl, or $CH_3$ and Y is I, Br, Cl, $CF_3$, or $C_1$-$C_3$ alkyl In further or additional embodiments, G is $R_{1a}$, $R_{1b}$, $R_{1c}$, $R_{1d}$, $R_{1e}$, $Ar_1$, $Ar_2$ or $Ar_3$, X is F, Cl, or $CH_3$, Y is I, Br, Cl, $CF_3$, or $C_1$-$C_3$ alkyl and Z is H or F

In further or additional embodiments, G is $R_{1a}$, $R_{1b}$, $R_{1c}$, $R_{1d}$, $R_{1e}$, $Ar_1$, $Ar_2$ or $Ar_3$ and $R^0$ is F, Cl, $C_1$-$C_4$ alkyl or $C_1$-$C_4$ alkoxy, said $C_1$-$C_4$ alkyl group and the $C_1$-$C_4$ alkyl moiety of said $C_1$-$C_4$ alkoxy group optionally substituted with F, Cl, $OCH_3$, or $OCH_2CH_3$. In further or additional embodiments, G is $R_{1a}$, $R_{1b}$, $R_{1c}$, $R_{1d}$, $R_{1e}$, $Ar_1$, $Ar_2$ or $Ar_3$ and $R^0$ is H, F, Cl, $C_1$-$C_4$ alkyl, methoxy, ethoxy, or 2- methoxy-ethoxy.

In some embodiments, G is $R_{1a}$; and Z is F. In further or additional embodiments, G is $R_{1a}$ where $R_{1a}$ is $CH_3$, $R^0$ is H; and Y is Br, I, $CF_3$, or $CH_3$.In some embodiments, G is $R_{1b}$ and Z is F. In further or additional embodiments, G is $R_{1b}$, Z is F, and $R^0$ is H, F, or $OCH_3$. In further or additional embodiments, G is $R_{1b}$, Z is F, $R^0$ is H, F, or $OCH_3$, and X is F or $CH_3$. In further or additional embodiments, G is $R_{1b}$, Z is F, $R^0$ is H, F, or $OCH_3$, X is F or $CH_3$ and Y is Br, I or $CH_3$. In further or additional embodiments, G is $R_{1b}$ where $R_{1b}$ is $C_3$-$C_6$ cycloalkyl. In further or additional embodiments, G is $R_{1b}$ where $R_{1b}$ is substituted $C_3$-$C_6$ cycloalkyl. In further or additional embodiments, G is $R_{1b}$ where $R_{1b}$ is unsubstituted $C_3$-$C_6$ cycloalkyl. In further or additional embodiments, G is $R_{1b}$ where $R_{1b}$ is unsubstituted $C_3$-$C_6$ cycloalkyl and $R^0$ is H. In further or additional embodiments, G is $R_{1b}$ where $R_{1b}$ is isopropyl or cyclopropyl.

In some embodiments, G is $R_{1c}$, and Y is I, Br, $CH_3$, or $CF_3$. In further or additional embodiments, G is $R_{1c}$, Y is I, Br, $CH_3$, or $CF_3$, and Z is F. In further or additional embodiments, G is $R_{1c}$, Y is I, Br, $CH_3$, or $CF_3$, Z is F and m is zero.

In some embodiments, G is $R_{1d}$ and $R^0$ is fluoro, chloro, methyl, ethyl, propyl, isopropyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, cyclopropyl, cyclobutyl, fluoromethyl, methoxy, fluoromethoxy, methylamino or dimethylamino. In further or additional embodiments, G is $R_{1d}$, $R^0$ is fluoro, chloro, methyl, ethyl, propyl, isopropyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, cyclopropyl, cyclobutyl, fluoromethyl, methoxy, fluoromethoxy, methylamino or dimethylamino and X is F, Cl, $CH_3$, or mono-, di- or tri- fluoromethyl. In further or additional embodiments, G is $R_{1d}$, $R^0$ is fluoro, chloro, methyl, ethyl, propyl, isopropyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, cyclopropyl, cyclobutyl, fluoromethyl, methoxy, fluoromethoxy, methylamino or dimethylamino, X is F, Cl, $CH_3$, or mono-, di- or tri- fluoromethyl and Y is I, Br, Cl, or mono-, di- or tri-fluoromethyl. In further or additional embodiments, G is $R_{1d}$, $R^0$ is fluoro, chloro, methyl, ethyl, propyl, isopropyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, cyclopropyl, cyclobutyl, fluoromethyl, methoxy, fluoromethoxy, methylamino or dimethylamino, X is F, Cl, $CH_3$, or mono-, di- or tri- fluoromethyl, Y is I, Br, Cl, or mono-, di- or tri- fluoromethyl and Z is H or F. In further or additional embodiments, G is $R_{1d}$ and $R^0$ is F, Cl, methyl, ethyl, methoxy, ethoxy, or 2- methoxy-ethoxy.

In further or additional embodiments, G is $R_{1d}$, $R^0$ is F, Cl, methyl, ethyl, methoxy, ethoxy, or 2- methoxy-ethoxy and X is F, Cl, or $CH_3$. In further or additional embodiments, G is $R_{1d}$, $R^0$ is F, Cl, methyl, ethyl, methoxy, ethoxy, or 2-methoxy-ethoxy, X is F, Cl, or $CH_3$ and Y is I, Br, Cl, or mono-, di- or tri- fluoromethyl. In further or additional embodiments, G is $R_{1d}$, $R^0$ is F, Cl, methyl, ethyl, methoxy, ethoxy, or 2- methoxy-ethoxy, X is F, Cl, or $CH_3$, Y is I, Br, Cl, or mono-, di- or tri- fluoromethyl and Z is H or F. In further or additional embodiments, G is $R_{1d}$ and $R^0$ is H; X is F, Cl, $CH_3$, or mono-, di- or tri- fluoromethyl. In further or additional embodiments, G is $R_{1d}$, $R^0$ is H; X is F, Cl, $CH_3$, or mono-, di- or tri- fluoromethyl and Y is I, Br, Cl, or mono-, di- or tri- fluoromethyl. In further or additional embodiments, G is $R_{1d}$, $R^0$ is H; X is F, Cl, $CH_3$, or mono-, di- or tri- fluoromethyl, Y is I, Br, Cl, or mono-, di- or tri- fluoromethyl and Z is H or F.

In further or additional embodiments, G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is $C_1$-$C_6$ cycloalkyl. In further or additional embodiments, G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is $C_1$-$C_6$ cycloalkyl and B is H. In further or additional embodiments, G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is $C_1$-$C_6$ cycloalkyl and B is methyl, ethyl, 2-hydroxyethyl, *n*-propyl, 3- hydroxypropyl, 2,3-dihydroxypropyl, 3,4-dihydroxybutyl, isopropyl, l-methyl-2-hydroxy ethyl, n-butyl, sec-butyl, isobutyl, or 2-hydroxymethyl-3-hydroxy propyl.

In further or additional embodiments, G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is $C_1$-$C_6$ cycloalkyl and B is 2,3-dihydroxypropyl or 3,4-dihydroxybutyl. In further or additional embodiments, G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is $C_1$-$C_6$ cycloalkyl and B is 2,3-dihydroxypropyl or 3,4-dihydroxybutyl, in which the chiral carbon in B is in the R configuration. In further or additional embodiments, G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is $C_1$-$C_6$ cycloalkyl and B is 2,3-dihydroxypropyl or 3,4-dihydroxybutyl, in which the chiral carbon in B is in the S configuration. In further or additional embodiments, G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is $C_1$-$C_6$ cycloalkyl and B is methyl, optionally substituted with one OH group, or $C_2$-$C_4$ alkyl, optionally substituted with one or two OH groups. In further or additional embodiments, G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is $C_1$-$C_6$ cycloalkyl and $R^0$ is fluoro, chloro, methyl, ethyl, propyl, isopropyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, cyclopropyl, cyclobutyl, fluoromethyl, methoxy, fluoromethoxy, methylamino or dimethylamino. In further or additional embodiments, G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is $C_1$-$C_6$ cycloalkyl and $R^0$ is F, Cl, methyl, ethyl, methoxy, ethoxy, or 2-methoxy-ethoxy. In further or additional embodiments, G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is $C_1$-$C_6$ cycloalkyl and $R^0$ is H; X is F, Cl, $CH_3$, or mono-, di- or tri- fluoromethyl.

In further or additional embodiments, the invention provides a composition comprising a compound of formula I, where G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is $C_1$-$C_6$ cycloalkyl and B is 2,3-dihydroxypropyl or 3,4-dihydroxybutyl, in which the chiral carbon in B is in the R configuration, which is substantially free of the S isomer. In further or additional

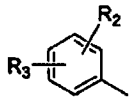
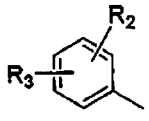
embodiments, the invention provides a composition comprising a compound of formula I, where G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is $C_1$-$C_6$ cycloalkyl and B is 2,3-dihydroxypropyl, in which the chiral carbon in B is in the R configuration, which is substantially free of the S isomer. In further or additional embodiments, the invention provides a composition comprising a compound of formula I, where G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is $C_1$-$C_6$ cycloalkyl and B is 3,4-dihydroxybutyl, in which the chiral carbon in B is in the R configuration, which is substantially free of the S isomer. In further or additional embodiments, the invention provides a composition comprising a compound of formula I, where G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is $C_1$-$C_6$ cycloalkyl and B is 2,3-dihydroxypropyl or 3,4-dihydroxybutyl, in which the chiral carbon in B is in the S configuration, which is substantially free of the R isomer. In further or additional embodiments, the invention provides a composition comprising a compound of formula I, where G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is $C_1$-$C_6$ cycloalkyl and B is 2,3-dihydroxypropyl, in which the chiral carbon in B is in the S configuration, which is substantially free of the R isomer. In further or additional embodiments, the invention provides a composition comprising a compound of formula I, where G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is $C_1$-$C_6$ cycloalkyl and B is 3,4-dihydroxybutyl, in which the chiral carbon in B is in the S configuration, which is substantially free of the R isomer.

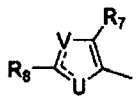
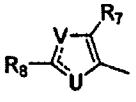
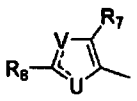
In further or additional embodiments, G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is cyclopropyl. In further or additional embodiments, G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is cyclopropyl and B is H. In further or additional embodiments, G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is cyclopropyl and B is methyl, ethyl, 2-hydroxyethyl, *n*-propyl, 3- hydroxypropyl, 2,3-dihydroxypropyl, 3,4-dihydroxybutyl, isopropyl, l-methyl-2-hydroxy ethyl, n-butyl, sec-butyl, isobutyl, or 2-hydroxymethyl-3-hydroxy propyl. In further or additional embodiments, G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is cyclopropyl and B is 2,3-dihydroxypropyl or 3,4-dihydroxybutyl. In further or additional embodiments, G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is cyclopropyl and B is 2,3-dihydroxypropyl or 3,4-dihydroxybutyl, in which the chiral carbon in B is in the R configuration. In further or additional embodiments, G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is cyclopropyl and B is 2,3-dihydroxypropyl or 3,4-dihydroxybutyl, in which the chiral carbon in B is in the S configuration. In further or additional embodiments, G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is cyclopropyl and B is methyl, optionally substituted with one OH group, or $C_2$-$C_4$ alkyl, optionally substituted with one or two OH groups. In further or additional embodiments, G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is cyclopropyl and $R^0$ is fluoro, chloro, methyl, ethyl, propyl, isopropyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, cyclopropyl, cyclobutyl, fluoromethyl, methoxy, fluoromethoxy, methylamino or dimethylamino. In further or additional embodiments, G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is cyclopropyl and $R^0$ is F, Cl, methyl, ethyl, methoxy, ethoxy, or 2-methoxy-ethoxy. In further or additional embodiments, G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is cyclopropyl and $R^0$ is H; X is F, Cl, $CH_3$, or mono-, di- or tri- fluoromethyl.

In further or additional embodiments, the invention provides a composition comprising a compound of formula I, where G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is cyclopropyl and B is 2,3-dihydroxypropyl or 3,4-dihydroxybutyl, in which the chiral carbon in B is in the R configuration, which is substantially free of the S isomer. In further or additional embodiments, the invention provides a composition comprising a compound of formula I, where G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is cyclopropyl and B is 2,3-dihydroxypropyl, in which the chiral carbon in B is in the R configuration, which is substantially free of the S isomer. In further or additional embodiments, the invention provides a composition comprising a compound of formula I, where G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is cyclopropyl and B is 3,4-dihydroxybutyl, in which the chiral carbon in B is in the R configuration, which is substantially free of the S isomer. In further or additional embodiments, the invention provides a composition comprising a compound of formula I, where G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is cyclopropyl and B is 2,3-dihydroxypropyl or 3,4-dihydroxybutyl, in which the chiral carbon in B is in the S configuration, which is substantially free of the R isomer. In further or additional embodiments, the invention provides a composition comprising a compound of formula I, where G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is cyclopropyl and B is 2,3-

dihydroxypropyl, in which the chiral carbon in B is in the S configuration, which is substantially free of the R isomer. In further or additional embodiments, the invention provides a composition comprising a compound of formula I, where G is $R_{1d}$ where $R_{1d}$ is C(A)(A') is cyclopropyl and B is 3,4-dihydroxybutyl, in which the chiral carbon in B is in the S configuration, which is substantially free of the R isomer.

In some embodiments, G is $R_{1e}$ and n is 1. In further or additional embodiments, G is $R_{1e}$, $R^0$ is H, $R_{4-6}$ are H, $R_2$ and $R_3$ are, independently, H, F, Cl, Br, $CH_3$, $CH_2F$, $CHF_2$, $CF_3$, O $CH_3$, $OCH_2F$, $OCHF_2$, $OCF_3$, ethyl, *n*-propyl, isopropyl, cyclopropyl, isobutyl, *sec*-butyl, *tert*-butyl, and methylsulfonyl, X is F and Y is I.

In some embodiments, G is $Ar_1$ where $Ar_1$is phenyl optionally substituted with one group selected from acetamido, amidinyl, cyano, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, l,3,4-oxadiazol-2-yl, 5-methyl-l,3,4-oxadiazolyl, 1,3,4-thiadiazolyI, 5 -methyl- 1,3,4- thiadiazolyl, lH-tetrazolyl, N-morpholylcarbonylamino, N-morpholylsulfonyl, N-pyrrolidinylcarbonylamino, and methylsulfonyl, optionally substituted with 1-3 substituents selected independently from F, Cl, and $CH_3$. In further or additional embodiments, G is $Ar_1$ where $Ar_1$is phenyl optionally substituted with one group selected from acetamido, amidinyl, cyano, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, l,3,4-oxadiazol-2-yl, 5-methyl-l,3,4-oxadiazolyl, 1,3,4-thiadiazolyI, 5 -methyl- 1,3,4- thiadiazolyl, lH-tetrazolyl, N-morpholylcarbonylamino, N-morpholylsulfonyl, N- pyrrolidinylcarbonylamino, and methylsulfonyl, optionally substituted with 1-3 substituents selected independently from F, Cl, and $CH_3$, $R^0$ is H, X is F, Cl, or methyl and Y is Br, I, $CF_3$, $C_1$-$C_3$ alkyl, $C_2$-$C_3$ alkenyl, $C_2$-$C_3$ alkynyl, cyclopropyl, O $CH_3$, $OCH_2CH_3$ or $SCH_3$. In some embodiments, G is $Ar_1$ where $Ar_1$ is  and where $R_2$ and $R_3$ are, independently, H, F, Cl, $CH_3$, $CF_3$, $OCH_3$. In further or additional embodiments, G is $Ar_1$ where $Ar_1$ is  and where $R_2$ and $R_3$ are, independently, H, F, Cl, $CH_3$, $CF_3$, $OCH_3$, X is F or $CH_3$, Y is I, Br, or Cl; and Z is F. In further or additional embodiments, G is $Ar_1$ where $Ar_1$is phenyl or mono-substituted phenyl. In further or additional embodiments, G is $Ar_1$ where $Ar_1$is phenyl or mono-substituted phenyl, X is F or $CH_3$, Y is I, Br, or Cl, Z is F; and $R^0$ is F, methyl, ethyl, methoxy, or 2-methoxy-ethoxy. In further or additional embodiments, G is $Ar_1$ where U is N or $CR_2$ and V is N. In further or additional embodiments, G is $Ar_1$ where U is N or $CR_2$ and V is CR. In further or additional embodiments, G is $Ar_1$ where U is N or $CR_2$, V is CR, $R^0$ is H, X is F, Cl, or methyl and Y is Br, I, $CF_3$, $C_1$-$C_3$ alkyl, $C_2$-$C_3$ alkenyl, $C_2$-$C_3$ alkynyl, cyclopropyl, $OCH_3$, $OCH_2CH_3$ or $SCH_3$.

In some embodiments, G is $Ar_2$ where $Ar_2$ is  where $R_7$ is H or methyl and $R_8$ is H, acetamido, methyl, F or Cl. In further or additional embodiments, G is $Ar_2$ where $Ar_2$ is  where $R_7$ is H or methyl, $R_8$ is H, acetamido, methyl, F or Cl, $R^0$ is H, X is F, Cl, or methyl, Y is Br, I, $CF_3$, $C_1$-$C_3$ alkyl, $C_2$-$C_3$ alkenyl, $C_2$-$C_3$ alkynyl, cyclopropyl, $OCH_3$, $OCH_2CH_3$ or $SCH_3$, and Z is F. In further or additional embodiments, G is $Ar_2$ where $Ar_2$ is  where U is S or O, V is CH=, and $R_8$ is H or $CH_3$, $R_7$ is H or methyl, $R_8$ is H, acetamido, methyl, F or Cl, $R^0$ is H, X is F, Cl, or methyl, Y is Br, I, $CF_3$, $C_1$-$C_3$ alkyl, $C_2$-$C_3$ alkenyl, $C_2$-$C_3$ alkynyl, cyclopropyl, $OCH_3$, $OCH_2CH_3$

or $SCH_3$ and Z is F. In further or additional embodiments, $R^0$ is H. In further or additional embodiments, $R^0$ is H, X is F or Cl and Y is Br, I, $CH_2CH_3$ or $SCH_3$

In some embodiments, G is $Ar_3$ where U is -O-.

In further or additional embodiments, G is $R_{1a}$, where $R_{1a}$ is defined as above. In further or additional embodiments, G is $R_{1a}$, and $R^0$ is H, where $R_{1a}$ is defined as above. In further or additional embodiments, G is $R_{1a}$ and $R^0$ is as defined above, other than H, and $R_{1a}$ is defined as above. In further or additional embodiments, G is $R_{1a}$, where $R_{1a}$ is methyl, monohalomethyl, $C_1$-$C_3$ alkoxymethyl, or cyclopropoxymethyl. In further or additional embodiments, G is $R_{1a}$, where $R_{1a}$ is methyl, monohalomethyl, $C_1$-$C_3$ alkoxymethyl, or cyclopropoxy methyl and where $R^0$ is F, Cl, $C_1$-$C_3$ alkyl, monochloro $C_1$-$C_3$ alkyl, $C_1$-$C_3$ alkoxy, trifluoro methoxy, or 2-methoxy-ethoxy.

In further or additional embodiments, G is $R_{1b}$, where $R_{1b}$ is defined as above. In further or additional embodiments, G is $R_{1b}$, and $R^0$ is H, where $R_{1b}$ is defined as above. In further or additional embodiments, G is $R_{1b}$, $R^0$ is H and Z is F, where $R_{1b}$ is defined as above. In further or additional embodiments, G is $R_{1b}$ and $R^0$ is as defined above, other than H, and $R_{1b}$ is defined as above. In further or additional embodiments, G is $R_{1b}$, where $R_{1b}$ is isopropyl, 2-butyl, 2-pentyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, all optionally substituted with 1 or 2 substituents selected independently from F, Cl, OH, and $OCH_3$; Y is Br, I, methyl, or trifluoromethyl. In further or additional embodiments, G is $R_{1b}$, where $R_{1b}$ is isopropyl, 2-butyl, 2-pentyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, optionally substituted with 1 or 2 substituents selected independently from F, Cl, OH, and $OCH_3$; Y is Br, I, methyl, or trifluoromethyl; and $R^0$ is F, Cl, $C_1$-$C_3$ alkyl, monochloro $C_1$-$C_3$ alkyl, $C_1$-$C_3$ alkoxy, trifluoromethoxy, or 2-methoxy-ethoxy. In further or additional embodiments, G is $R_{1b}$, where $R_{1b}$ is isopropyl, 2-butyl, 2-pentyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, all optionally substituted with one Cl or with 1 or 2 OH groups; and Y is Br, I, methyl, or trifluoromethyl. In further or additional embodiments, G is $R_{1b}$, where $R_{1b}$ is isopropyl, 2-butyl, 2-pentyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, all optionally substituted with one Cl or with 1 or 2 OH groups; Y is Br, I, methyl, or trifluoromethyl; and $R^0$ is F, Cl, $C_1$-$C_3$ alkyl, monochloro $C_1$-$C_3$ alkyl, $C_1$-$C_3$ alkoxy, trifluoromethoxy, or 2-methoxy-ethoxy.

In further or additional embodiments, G is $R_{1c}$, where $R_{1c}$ is defined as above. In further or additional embodiments, G is $R_{1c}$, and $R^0$ is H, where $R_{1c}$ is defined as above. In further or additional embodiments, G is $R_{1c}$ and $R^0$ is as defined above, other than H, and $R_{1c}$ is defined as above. In further or additional embodiments, G is $R_{1c}$, and $R^0$ is H, where $R_{1c}$ is $(CH_2)_nO_mR'$, where m is 0 or 1, n is 2 or 3 when m is 1, and n is 1 or 2 when m is 0, and R' is $C_1$-$C_6$ alkyl, optionally substituted with 1-3 substituents selected independently from F, Cl, OH, $OCH_3$, $OCH_2CH_3$, and $C_3$-$C_6$ cycloalkyl. In another more specific subgeneric embodiment, m is zero, n is 1 or 2, and R' is $C_1$-$C_4$ alkyl, optionally substituted as described above. In another more specific subgeneric embodiment, m is 1, n is 2 or 3, and R' is $C_1$-$C_4$ alkyl, optionally substituted as described above. In a still more specific subgeneric embodiment, m is zero, n is 1 or 2, and R' is $C_1$-$C_4$ alkyl, optionally substituted with 1 -3 groups selected from OH, $OCH_3$, Cl, and cyclopropyl.

In further or additional embodiments, G is $R_{1d}$, where $R_{1d}$ is defined as above. In further or additional embodiments, G is $R_{1d}$, and $R^0$ is H, where $R_{1d}$ is defined as above. In further or additional embodiments, G is $R_{1d}$ and $R^0$ is as defined above, other than H, and $R_{1d}$ is defined as above. In further or additional embodiments, G is $R_{1d}$, and $R^0$ is H, where $R_{1d}$ is C(A)(A')(B)- where B, A, and A' are, independently, H or $C_{1-4}$ alkyl, optionally substituted with one or two OH groups or halogen atoms, or A and $A^1$, together with the carbon atom to which they are attached, form a 3- to 6-member saturated ring, said ring optionally containing one or two heteroatoms selected, independently, from O, N, and S and optionally substituted with one or two groups selected independently from methyl, ethyl, fluoro, chloro, bromo and iodo.

In further or additional embodiments, G is $R_{1e}$, where $R_{1e}$ is defined as above. In further or additional embodiments, G is $R_{1e}$, and $R^0$ is H, where $R_{1e}$ is defined as above. In further or additional embodiments, G is $R_{1e}$ and $R^0$ is as defined above, other than H, and $R_{1e}$ is defined as above.

In further or additional embodiments, G is $Ar_1$, where $Ar_1$is defined as above. In further or additional embodiments, G is $Ar_1$, and $R^0$ is H, where $Ar_1$is defined as above. In further or additional embodiments, G is $Ar_1$and $R^0$ is as defined above, other than H, and $Ar_1$is defined as above.

In further or additional embodiments, G is $Ar_2$, where $Ar_2$ is defined as above. In further or additional embodiments, G is $Ar_2$, and $R^0$ is H, where $Ar_2$ defined as above. In further or additional embodiments, G is $Ar_2$ and $R^0$ is as defined above, other than H, and $Ar_2$ is defined as above.

In further or additional embodiments, X is F, Cl, or $CH_3$; Y is I, Br, Cl, $CF_3$ or $C_1$-$C_3$ alkyl, and Z is H or F. In further or additional embodiments, X is F, Cl, or $CH_3$: Y is I, Br, Cl, $CF_3$, or $C_1$-$C_3$ alkyl, Z is H or F, and $R^0$ is halogen, $C_1$-$C_6$ alkyl, monohalo $C_1$-$C_6$ alkyl, $C_3$-$C_6$ cycloalkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, phenyl, monosubstituted phenyl, $OR_3$, O-C(=O)$R_4$, or C(=O)$OR_5$. In further or additional embodiments, X is F, Cl, or $CH_3$: Y is I, Br, Cl, $CF_3$, or $C_1$-$C_3$ alkyl, Z is H or F, and $R^0$ is furyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrrolyl, or pyrazolyl. In further or additional embodiments, X is F, Cl, or $CH_3$: Y is I, Br, Cl, $CF_3$, or $C_1$-$C_3$ alkyl, Z is H or F, and $R^0$ is F, Cl, $C_1$-$C_4$ alkyl, $C_1$-$C_3$ alkoxy, trifluoromethoxy, or 2- methoxy-ethoxy.

In another more specific subgeneric embodiment, $R_{1d}$ is cycloalkyl or 1-alkyl-cycloalkyl, in which the 1-alkyl group is optionally substituted with one or two OH groups or with one or two halogen atoms.

In another more specific subgeneric embodiment, $R^0$ is halogen, $C_1$-$C_6$ alkyl, monohalo $C_1$-$C_6$ alkyl, $C_3$-$C_6$ cycloalkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, phenyl, monosubstituted phenyl, $OR_3$, O-C(=O)$R_4$, or C(=O)$OR_5$; and $R_{1d}$ is cycloalkyl or 1-alkyl-cycloalkyl, in which the 1-alkyl group is optionally substituted with one or two OH groups or with one or two halogen atoms.

In another more specific subgeneric embodiment, $R^0$ is furyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrrolyl, or pyrazolyl; and $R_{1d}$ is cycloalkyl or 1-alkyl-cycloalkyl, in which the 1-alkyl group is optionally substituted with one or two OH groups or one or two halogen atoms.

In another more specific subgeneric embodiment, $R_{1d}$ is cycloalkyl or 1-alkyl-cycloalkyl, in which the 1-alkyl group is optionally substituted with one or two OH groups, and where Y is Br, I, methyl, or trifluoromethyl. In another more specific subgeneric embodiment, $R_{1d}$ is cycloalkyl or 1-alkyl-cycloalkyl, in which the 1-alkyl group is optionally substituted with one or two fluorine or chlorine atoms, and where Y is Br, I, methyl, or trifluoromethyl. In another more specific subgeneric embodiment, $R_{1d}$ is cycloalkyl or (1 -alley l)-cycloalkyl, in which the 1-alkyl group is optionally substituted with one or two OH groups, and where $R^0$ is F, Cl, $C_1$-$C_3$ alkyl, monochloro $C_1$-$C_3$ alkyl, $C_1$-$C_3$ alkoxy, trifluoromethoxy, or 2-methoxy-ethoxy. In another more specific subgeneric embodiment, $R_{1d}$ is tetrahydrofuryl, tetrahydrothienyl, pyrrolidyl, piperidyl, piperazinyl, or morpholyl, each optionally substituted as described above, and where Y is Br, I, methyl, or trifluoromethyl. In another more specific subgeneric embodiment, $R_{1d}$ is oxazolidinyl, thiazolidinyl, isoxazolidinyl, isothiazolidinyl, tetrahydrofuryl, tetrahydrothienyl, pyrrolidyl, piperidyl, piperazinyl, or morpholyl, each optionally substituted as described above, and where Y is Br, I, methyl, or trifluoromethyl. In another more specific subgeneric embodiment, $R_{1d}$ is cyclopropyl or l-alkyl-cyclopropyl, in which the 1-alkyl group is optionally substituted with one or two OH groups, and where $R^0$ is F, Cl, methyl, ethyl, chloromethyl, $C_1$-$C_2$ alkoxy, trifluoromethoxy, or 2-methoxy-ethoxy. In an even more specific embodiment, $R_{1d}$ is l-(monohydroxyalkyl) cycloalkyl. In another more specific embodiment, $R_{1d}$ is l-(monohydroxyalkyl) cycloalkyl, where $R^0$ is F, Cl, methyl, ethyl, chloromethyl, $C_1$-$C_2$ alkoxy, trifluoromethoxy, or 2-methoxy-ethoxy. In an even more specific embodiment, $R_{1d}$ is l-

(dihydroxyalkyl) cycloalkyl. In another more specific embodiment, $R_{1d}$ is l-(dihydroxyalkyl) cycloalkyl, where $R^0$ is F, Cl, methyl, ethyl, chloromethyl, $C_1$-$C_2$ alkoxy, trifluoromethoxy, or 2-methoxy-ethoxy.

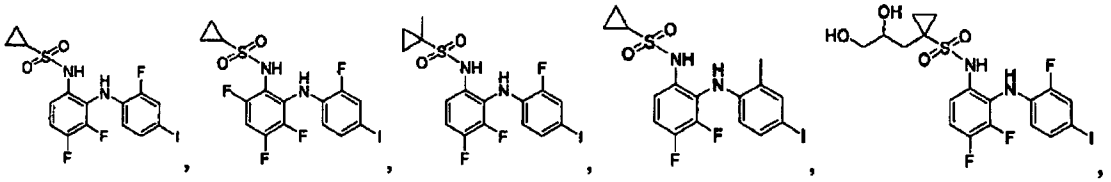
In a more specific subgeneric embodiment U is $CR_2$ and V is N. In another more specific, subgeneric embodiment, U and V are both N. In a more specific, subgeneric embodiment, U is $CR_2$ and V is $CR_3$.

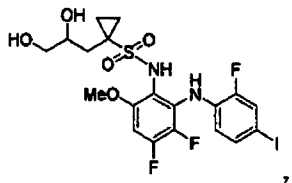
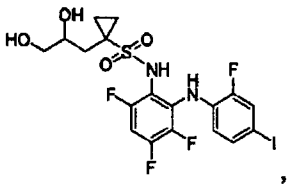
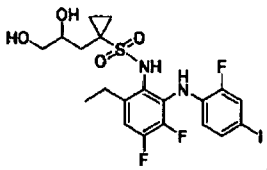
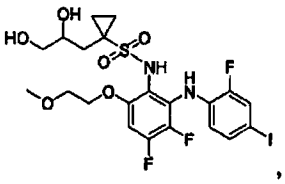
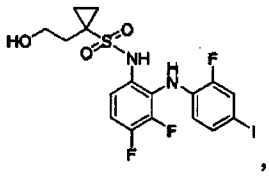
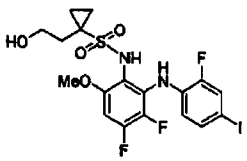
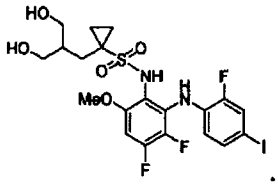
In a still more specific subgeneric embodiment, this invention provides a compound of formula I, where G is $Ar_1$ and $Ar_1$ is phenyl or monosubstituted phenyl, $R^0$ is F, methyl, ethyl, $C_1$-$C_3$ alkoxy, trifluoromethoxy, or 2-methoxy-ethoxy; X is F, Cl, or $CH_3$; Y is I; and Z is F. In another subgeneric embodiment, this invention provides a compound of formula I, where G is $Ar_1$, where $Ar_1$ is phenyl or monosubstituted phenyl, $R^0$ is halogen, $C_1$-$C_6$ alkyl, $C_3$-$C_6$ cycloalkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, all such alkyl, cycloalkyl, alkenyl, and alkynyl groups optionally substituted with 1-3 substituents selected independently from halogen, OH, CN, cyanomethyl, nitro, phenyl, and trifluoromethyl; or $R^0$ is phenyl, $OR_3$, furyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrrolyl, or pyrazolyl. In a more specific subgeneric embodiment, this invention provides a compound of formula I, where A is $Ar_1$, where $Ar_1$ is phenyl or monosubstituted phenyl, $R^0$ is F, Cl, $C_1$-$C_3$ alkyl, $C_1$-$C_3$ alkoxy, 2-methoxyethoxy, $C_2$-$C_3$ alkenyl, $C_2$-$C_3$ alkynyl, trifluoromethyl, phenyl, furyl, or thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrrolyl, or pyrazolyl; X is F, Cl, or methyl; Y is I, Br, Cl, $CF_3$, or $C_1$-$C_3$ alkyl; and Z is F.

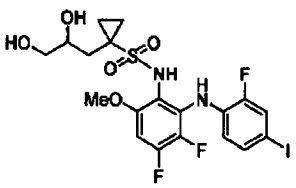
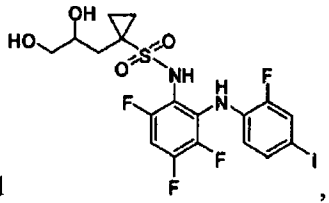
In another still more specific subgeneric embodiment, this invention provides a compound of formula I, where G is $Ar_1$, where $Ar_1$ is phenyl or monosubstituted phenyl, $R^0$ is H; X is F, Cl, or $CH_3$; Y is Br or I; and Z is F.

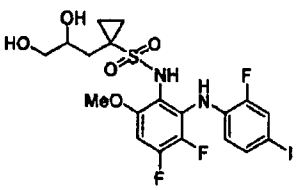
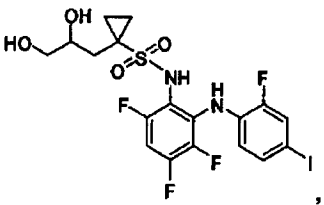
In another subgeneric embodiment his invention provides a compound of formula I, where G is $Ar_2$, where $Ar_2$ is 2-thienyl, 2-furyl, 3 -thienyl, 3 -furyl, 2-pyrrolyl, or 3 -pyrrolyl, all optionally substituted with methoxycarbonyl, methylcarbamoyl, acetamido, acetyl, methyl, ethyl, trifluoromethyl, or halogen. In a more specific subgeneric embodiment his invention provides a compound of formula I, where G is $Ar_2$, where $Ar_2$ is 2-thienyl, 2-furyl, 3-thienyl, 3-furyl, 2-pyrrolyl, or 3- pyrrolyl, all optionally substituted with methoxycarbonyl, methylcarbamoyl, acetamido, acetyl, methyl, ethyl, trifluoromethyl, or halogen; $R^0$ is other than H; X is F, Cl, or $CH_3$: Y is I, Br, Cl, $CF_3$, or $C_1$-$C_3$ alkyl, and Z is H or F. In another subgeneric embodiment this invention provides a compound of formula I, where G is $Ar_2$, where $Ar_2$ is 2-thienyl, 2-furyl, 3-thienyl, 3-furyl, 2-pyrrolyl, or 3-pyrrolyl, all optionally substituted with methoxycarbonyl, methylcarbamoyl, acetamido, acetyl, methyl, ethyl, trifluoromethyl, or halogen; $R^0$ is F, Cl, $C_1$-$C_3$ alkyl, monochloro $C_1$-$C_3$ alkyl, $C_1$-$C_3$ alkoxy, trifluoromethoxy, methyloxy-methoxy, or 2-methoxy-ethoxy; X is F, Cl, or $CH_3$: Y is I, Br, Cl, $CF_3$, or $C_1$-$C_3$ alkyl, and Z is H or F. In another subgeneric embodiment his invention provides a compound of formula I, where G is $Ar_2$, where $Ar_2$ is 2-thienyl, 2-furyl, 3-thienyl, 3-furyl, 2-pyrrolyl, or 3-pyrrolyl, all optionally substituted with methoxycarbonyl, methylcarbamoyl, acetamido, acetyl, methyl, ethyl, trifluoromethyl, or halogen; $R^0$ is H; X is F, Cl, or $CH_3$: Y is I, Br, Cl, $CF_3$, or $C_1$-$C_3$ alkyl, and Z is H or F. In another subgeneric embodiment his invention provides a compound of formula I, where G is $Ar_2$, where $Ar_2$ is thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrrolyl, or pyrazolyl, all optionally substituted with methoxycarbonyl, methylcarbamoyl, acetamido, acetyl, methyl, ethyl, trifluoromethyl, or halogen; $R^0$ is H or methoxy; X is F, Cl, or $CH_3$: Y is I, Br, Cl, $CF_3$, or $C_1$-$C_3$ alkyl, and Z is H or F.

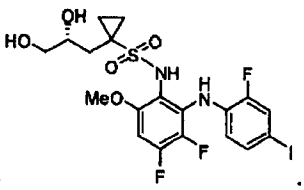
In some embodiments, the compound of formula (I), or a pharmaceutical salt thereof, is selected from

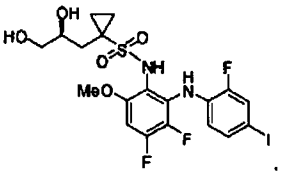


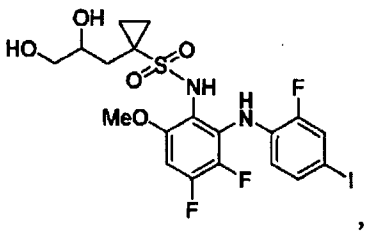
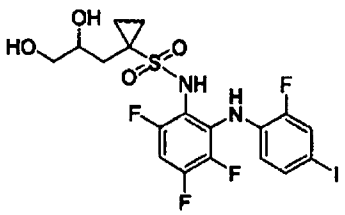






and


In some embodiments, the invention provides a compound of formula I, or a pharmaceutical salt thereof, selected from:

and

, where the 2-OH carbon is in the R configuration.

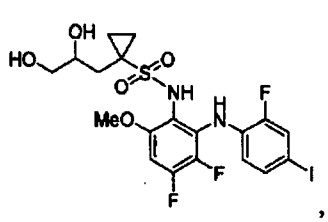
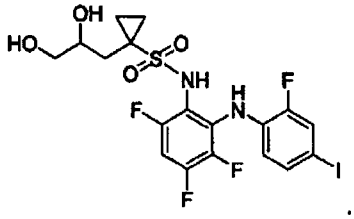
In some embodiments, the invention provides a compound of formula I, or a pharmaceutical salt thereof, selected from:

and

, where the 2-OH carbon is in the S configuration.

In further or additional embodiments, the compound of formula (I), or a pharmaceutical salt thereof, is

.

In further or additional embodiments, the compound of formula (I), or a pharmaceutical salt thereof, is

.

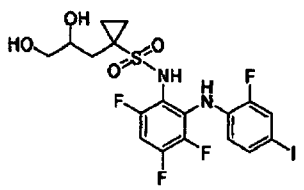
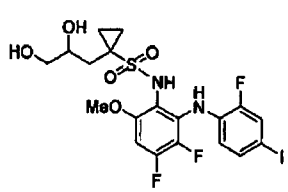
In some embodiments, the invention provides a composition comprising a compound of formula I, selected from those shown below, where the 2-OH carbon is in the R configuration, substantially free of the S- isomer.

,

.

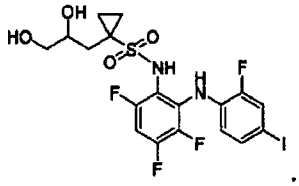
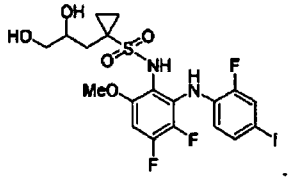
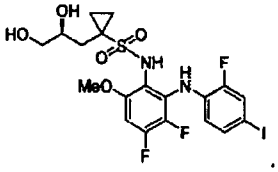
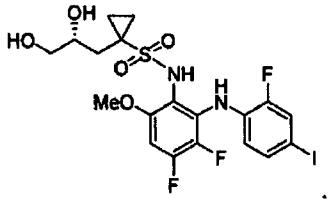
In some embodiments, the invention provides a composition comprising a compound of formula I, selected from those shown below, where the 2-OH carbon is in the S configuration, substantially free of the R- isomer.


,

.

In some embodiments, this invention provides a compound of formula I, where Y is phenyl, pyridyl, or pyrazolyl. In another subgeneric embodiment, this invention provides a compound of formula I, where Y is substituted phenyl, pyridyl, or pyrazolyl. In yet another subgeneric embodiment, this invention provides a compound of formula I, where Y is Br or I. In one subgeneric embodiment, this invention provides a compound of formula I, where G is 1-piperidyl, 2-piperidyl, 3-piperidyl, or 4-piperidyl. In another subgeneric embodiment, this invention provides a compound of formula I, where G is 1-piperazyl or 2-piperazyl. In another subgeneric embodiment, this invention provides a compound of formula I, where G is morpholyl. In another subgeneric embodiment, this invention provides a compound of formula I, where G is N-methyl-2-aminoethyl. In one subgeneric embodiment, this invention provides a compound of formula I, where G is N-methyl-3-amino-n-propyl. In another subgeneric embodiment, this invention provides a compound of formula I, where G is $(CH_3)_2N\text{-}CH_2CH_2\text{-}NH\text{-}(CH_2)_n\text{-}$, where n is 1, 2, or 3. In another subgeneric embodiment, this invention provides a compound of formula I, where G is $(CH_3CH_2)_2N\text{-}CH_2CH_2\text{-}NH\text{-}(CH_2)_n\text{-}$, where n is 1 or 2. In a more specific subgeneric embodiment, this invention provides a compound of formula I, where G is 1-piperidyl, 2-piperidyl, 3-piperidyl, or 4-piperidyl; $R^o$ is H, halo, or methoxy; X is F; and Y is I. In another more specific subgeneric embodiment, this invention provides a compound of formula I, where G is 1-piperazyl or 2-piperazyl; $R^o$ is H, halo, or methoxy; X is F; and Y is I In another more specific subgeneric embodiment, this invention provides a compound of formula I, where G is morpholyl; $R^o$ is H, halo, or methoxy; X is F; and Y is I. In another more specific subgeneric embodiment, this invention provides a compound of formula I, where G is N-methyl-2-aminoethyl; $R^o$ is H, halo, or methoxy; X is F; and Y is I In another more specific subgeneric embodiment, this invention provides a compound of formula I, where G is N-methyl-3-amino-n-propyl; $R^o$ is H, halo, or methoxy; X is F; and Y is I. In another more specific subgeneric embodiment, this invention provides a compound of formula I, where G is $(CH_3)_2N\text{-}CH_2CH_2\text{-}NH\text{-}(CH_2)_n\text{-}$, where n is 1, 2, or 3; $R^o$ is H, halo, or methoxy; X is F; and Y is I. In another more specific subgeneric embodiment, this invention provides a compound of formula I, where G is $(CH_3CH_2)_2N\text{-}CH_2CH_2\text{-}NH\text{-}(CH_2)_n\text{-}$, where n is 1 or 2; $R^o$ is H, halo, or methoxy; X is F; and Y is I.

In some embodiments, the invention provides a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, amide, tautomer or prodrug thereof. In some embodiments the pharmaceutical composition further comprises at least one pharmaceutically acceptable carrier.

In some embodiments, the invention provides a pharmaceutical composition comprising a compound selected from:  and  , or a pharmaceutically acceptable salt, solvate, polymorph, ester, amide, tautomer or prodrug thereof. In some embodiments, the pharmaceutical composition further comprises at least one pharmaceutically acceptable carrier. In some embodiments, the compound is in the R

configuration. In some embodiments, the compound is in the R configuration, substantially free of the S- isomer. In some embodiments, the compound is in the S configuration. In some embodiments, the compound is in the S configuration, substantially free of the R- isomer. In some embodiments, the compound is:  . In some embodiments, the compound is:  . In some embodiments, the compound is:  . In some embodiments, the compound is:  .

**Tables With Non-limiting Examples of Compounds of Formula I**

The tables below show examples of individual compounds provided or contemplated by this invention. These examples should in no way be construed as limiting.

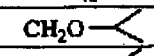
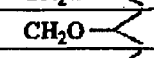
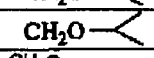
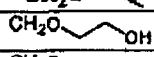
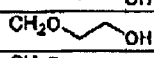
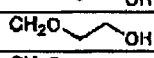
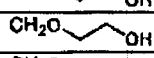
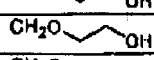
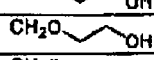
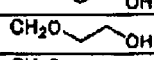
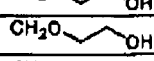
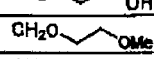
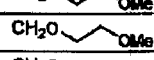
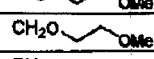
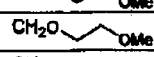
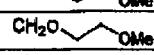
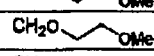
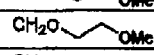
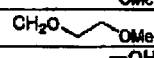
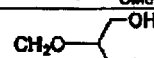
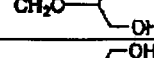
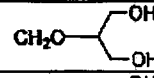
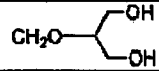
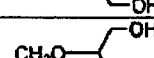
Table 1 shows embodiments of this invention which are compounds of formula I, wherein $R^0$ is as defined herein, G is $R_{1a}$ where $R_{1a}$ is as defined in the table and X, Y and Z are defined in the table.

**Table 1**

| $R_{1a}$ | X | Y |
|---|---|---|
| | | |
| $CH_3$ | F | I |
| $CH_3$ | Cl | I |
| $CH_3$ | F | Br |
| $CH_3$ | Cl | Br |
| $CH_3$ | F | $CH_3$ |
| $CH_3$ | Cl | $CH_3$ |
| $CH_3$ | F | $CF_3$ |
| $CH_3$ | Cl | $CF_3$ |
| $CH_3$ | F | C≡CH |
| $CH_3$ | Cl | C≡CH |
| $CH_3$ | F | $SCH_3$ |
| $CH_3$ | Cl | $SCH_3$ |
| $CH_3$ | F | $(CH_2)_2CH_3$ |
| $CH_3$ | Cl | $(CH_2)_2CH_3$ |
| $CH_3$ | F | $CH_2CH_3$ |
| $CH_3$ | Cl | $CH_2CH_3$ |
| $CH_3$ | F | $CH_2OH$ |
| $CH_3$ | Cl | $CH_2OH$ |
| $CH_3$ | F | ▷ |
| $CH_3$ | Cl | ▷ |
| $CH_3$ | $CH_3$ | $CH=CH_2$ |
| $CH_3$ | $CH_3$ | C≡CH |
| $CH_3$ | $CH_3$ | $SCH_3$ |
| $CH_2F$ | F | I |

| $R_{1a}$ | X | Y |
|---|---|---|
| $CH_2F$ | Cl | I |
| $CH_2F$ | F | Br |
| $CH_2F$ | Cl | Br |
| $CH_2F$ | F | $CH_3$ |
| $CH_2F$ | Cl | $CH_3$ |
| $CH_2F$ | F | $CF_3$ |
| $CH_2F$ | Cl | $CF_3$ |
| $CF_3$ | F | I |
| $CF_3$ | Cl | I |
| $CF_3$ | F | Br |
| $CF_3$ | Cl | Br |
| $CF_3$ | F | $CH_3$ |
| $CF_3$ | Cl | $CH_3$ |
| $CF_3$ | F | $CF_3$ |
| $CF_3$ | Cl | $CF_3$ |
| $CH_2Cl$ | F | I |
| $CH_2Cl$ | Cl | I |
| $CH_2Cl$ | F | Br |
| $CH_2Cl$ | Cl | Br |
| $CH_2Cl$ | F | $CH_3$ |
| $CH_2Cl$ | Cl | $CH_3$ |
| $CH_2Cl$ | F | $CF_3$ |
| $CH_2Cl$ | Cl | $CF_3$ |
| $CHCl_2$ | F | I |
| $CHCl_2$ | Cl | I |

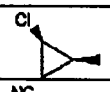
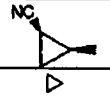
| $R_{1a}$ | X | Y |
|---|---|---|
| $CHCl_2$ | F | Br |
| $CHCl_2$ | Cl | Br |
| $CHCl_2$ | F | $CH_3$ |
| $CHCl_2$ | Cl | $CH_3$ |
| $CHCl_2$ | F | $CF_3$ |
| $CHCl_2$ | Cl | $CF_3$ |
| $CCl_3$ | F | I |
| $CCl_3$ | Cl | I |
| $CCl_3$ | F | Br |
| $CCl_3$ | Cl | Br |
| $CCl_3$ | F | $CH_3$ |
| $CCl_3$ | Cl | $CH_3$ |
| $CCl_3$ | F | $CF_3$ |
| $CCl_3$ | Cl | $CF_3$ |
| $CH_2OH$ | F | I |
| $CH_2OH$ | Cl | I |
| $CH_2OH$ | F | Br |
| $CH_2OH$ | Cl | Br |
| $CH_2OH$ | F | $CH_3$ |
| $CH_2OH$ | Cl | $CH_3$ |
| $CH_2OH$ | F | $CF_3$ |
| $CH_2OH$ | Cl | $CF_3$ |
| $CH_2OMe$ | F | I |
| $CH_2OMe$ | Cl | I |
| $CH_2OMe$ | F | Br |
| $CH_2OMe$ | Cl | Br |
| $CH_2OMe$ | F | $CH_3$ |
| $CH_2OMe$ | Cl | $CH_3$ |
| $CH_2OMe$ | F | $CF_3$ |
| $CH_2OMe$ | Cl | $CF_3$ |
| $CH_2OMe$ | F | C≡CH |
| $CH_2OMe$ | Cl | $SCH_3$ |
| $CH_2OMe$ | $CH_3$ | $CF_3$ |
| $CH_2OMe$ | $CH_3$ | C≡CH |
| $CH_2OEt$ | F | I |
| $CH_2OEt$ | Cl | I |
| $CH_2OEt$ | F | Br |
| $CH_2OEt$ | Cl | Br |
| $CH_2OEt$ | F | $CH_3$ |
| $CH_2OEt$ | Cl | $CH_3$ |
| $CH_2OEt$ | F | $CF_3$ |
| $CH_2OEt$ | Cl | $CF_3$ |
| $CH_2O$-◁ | F | I |
| $CH_2O$-◁ | Cl | I |
| $CH_2O$-◁ | F | Br |
| $CH_2O$-◁ | Cl | Br |
| $CH_2O$-◁ | F | $CH_3$ |
| $CH_2O$-◁ | Cl | $CH_3$ |
| $CH_2O$-◁ | F | $CF_3$ |
| $CH_2O$-◁ | Cl | $CF_3$ |
|  | F | I |
|  | Cl | I |
|  | F | Br |
|  | Cl | Br |
|  | F | $CH_3$ |

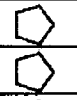
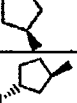
| $R_{1a}$ | X | Y |
|---|---|---|
|  | Cl | $CH_3$ |
|  | F | $CF_3$ |
|  | Cl | $CF_3$ |
|  | F | I |
|  | Cl | I |
|  | F | Br |
|  | Cl | Br |
|  | F | $CH_3$ |
|  | Cl | $CH_3$ |
|  | F | $CF_3$ |
|  | Cl | $CF_3$ |
|  | F | I |
|  | Cl | I |
|  | F | Br |
|  | Cl | Br |
|  | F | $CH_3$ |
|  | Cl | $CH_3$ |
|  | F | $CF_3$ |
|  | Cl | $CF_3$ |
|  | F | I |
|  | Cl | I |
|  | F | Br |
|  | Cl | Br |
|  | F | $CH_3$ |
|  | Cl | $CH_3$ |
|  | F | $CF_3$ |
|  | Cl | $CF_3$ |
| $CH_3$ | F | phenyl |
| $CH_3$ | Cl | phenyl |
| $CH_3$ | $CH_3$ | phenyl |
| $CH_3$ | F | 3-pyridyl |
| $CH_3$ | Cl | 3-pyridyl |
| $CH_3$ | $CH_3$ | 4-pyridyl |
| $CH_3$ | F | pyrazolyl |
| $CH_3$ | Cl | pyrazolyl |
| $CH_3$ | F | 4-pyridyl |
| $CH_3$ | Cl | 4-pyridyl |
| $CH_3$ | $CH_3$ | 2-($CH_3$-$SO_2$-NH)-phenyl |
| $CH_3$ | $CH_3$ | 3-($CH_3$-$SO_2$-NH)-phenyl |
| $CH_3$ | Cl | 3-($CH_3$-$SO_2$-NH)-phenyl |

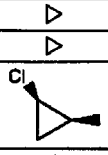
| $R_{1a}$ | X | Y |
|---|---|---|
| $CH_3$ | F | 3-($CH_3$-$SO_2$-NH)-phenyl |

Table 2 shows embodiments of this invention which are compounds of formula I, wherein $R^0$ is as defined herein, G is $R_{1b}$ where $R_{1b}$ is as defined in the table and X, Y and Z are defined in the table.

**Table 2**

| $R_{1b}$ | X | Y | Z |
|---|---|---|---|
| ▷ | F | I | F |
| ▷ | Cl | I | F |
| ▷ | F | Br | F |
| ▷ | Cl | Br | F |
| ▷ | F | $CH_3$ | F |
| ▷ | Cl | $CH_3$ | F |
| ▷ | F | $CF_3$ | F |
| ▷ | Cl | $CF_3$ | F |
| ▷ | F | C≡CH | F |
| ▷ | Cl | C≡CH | F |
| ▷ | F | $SCH_3$ | F |
| ▷ | Cl | $SCH_3$ | F |
| ▷ | F | $CH_2OH$ | F |
| ▷ | Cl | $CH_2OH$ | F |
| ▷ | F | $(CH_2)_3OH$ | F |
| ▷ | Cl | $(CH_2)_3OH$ | F |
| ▷ | F | $(CH_2)_2CH_3$ | F |
| ▷ | Cl | $(CH_2)_2CH_3$ | F |
| ▷ | F | $CH_2CH_3$ | F |
| ▷ | Cl | $CH_2CH_3$ | F |
| ▷ | F | $(CH_2)_2CH_3$ | F |
| ▷ | Cl | $(CH_2)_2CH_3$ | F |
| ▷ | $CH_3$ | I | F |
| ▷ | $CH_3$ | Br | F |
| ▷ | $CH_3$ | $CH_3$ | F |
| ▷ | $CH_3$ | $CF_3$ | F |
| ▷ | $CH_3$ | $CH_2CH_3$ | F |
| ▷ | $CH_3$ | $(CH_2)_2CH_3$ | F |
| ▷ | $CH_3$ | C≡CH | F |
| ▷ | $CH_3$ | $SCH_3$ | F |
|  | $CH_3$ | $(CH_2)_2CH_3$ | F |
|  | $CH_3$ | I | F |
| ▷ | F | $CH=CH_2$ | F |
| ▷ | Cl | $CH=CH_2$ | F |
| ▷ | $CH_3$ | $CH=CH_2$ | F |
| ▷ | F | ▷ | F |
| ▷ | F | $OCH_3$ | F |
| ▷ | Cl | $(CH_2)_2CH_2OH$ | F |
| ◇ | F | I | F |
| | | | F |
| ◇ | Cl | I | F |
| ◇ | F | Br | F |
| ◇ | Cl | Br | F |
| ◇ | F | $CH_3$ | F |
| ◇ | Cl | $CH_3$ | F |
| ◇ | F | $CF_3$ | F |
| ◇ | Cl | $CF_3$ | F |

| $R_{1b}$ | X | Y | Z |
|---|---|---|---|
|  | F | I | F |
|  | Cl | I | F |
|  | F | Br | F |
|  | Cl | Br | F |
|  | F | $CH_3$ | F |
|  | Cl | $CH_3$ | F |
|  | F | $CF_3$ | F |
|  | Cl | $CF_3$ | F |
|  | Cl | ▷ | F |
|  | F | $(CH_2)_2CH_3$ | F |
|  | Cl | C≡CH | F |
|  | $CH_3$ | $SCH_3$ | F |
|  | Cl | $CF_3$ | F |
|  | $CH_3$ | $CH_3$ | F |
|  | F | $CH_2OH$ | F |
|  | Cl | $(CH_2)_3OH$ | F |
|  | F | $OCH_2CH_3$ | F |
| ⬡ | F | I | F |
| ⬡ | Cl | I | F |
| ⬡ | F | Br | F |
| ⬡ | Cl | Br | F |
| ⬡ | F | $CH_3$ | F |
| ⬡ | Cl | $CH_3$ | F |
| ⬡ | F | $CF_3$ | F |
| ⬡ | Cl | $CF_3$ | F |
| | | | |
| ▷ | F | phenyl | F |
| ▷ | Cl | phenyl | F |
| ▷ | F | 3-pyridyl | F |
| ▷ | Cl | 3-pyridyl | F |
| ▷ | F | pyrazol-4-yl | F |
| ▷ | Cl | pyrazol-4-yl | F |

| $R_{1b}$ | X | Y | Z |
|---|---|---|---|
|  | F | 4-pyridyl | F |
|  | Cl | 4-pyridyl | F |
|  | F | 1-methyl-pyrazol-4-yl | F |
|  | Cl | 1-methyl-pyrazol-4-yl | F |
|  | F | pyrazol-3-yl | F |
|  | Cl | pyrazol-3-yl | F |
|  | F | 2-($CH_3$-$SO_2$-NH)-phenyl | F |
|  | Cl | 2-($CH_3$-$SO_2$-NH)-phenyl | F |
|  | F | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
|  | Cl | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
|  | $CH_3$ | 2-($CH_3$-$SO_2$-NH)-phenyl | F |
|  | $CH_3$ | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
|  | F | 4-$CF_3O$-phenyl | F |
|  | Cl | 4-$CF_3O$-phenyl | F |
|  | $CH_3$ | 4-$CF_3O$-phenyl | F |
|  | Cl | 2-($CH_3$-$SO_2$-NH)-phenyl | F |
|  | F | phenyl | F |
|  | | phenyl | |
|  | Cl | 3-pyridyl | F |
|  | F | 3-pyridyl | F |
|  | Cl | pyrazol-4-yl | F |
|  | F | pyrazol-4-yl | F |
|  | Cl | 4-pyridyl | F |
|  | F | 4-pyridyl | F |
|  | Cl | 1-methyl-pyrazol-4-yl | F |
|  | $CH_3$ | 1-methyl-pyrazol-4-yl | F |
|  | F | pyrazol-3-yl | F |
|  | Cl | pyrazol-3-yl | F |
|  | F | 2-($CH_3$-$SO_2$-NH)-phenyl | F |
|  | Cl | 2-($CH_3$-$SO_2$-NH)-phenyl | F |
|  | F | phenyl | F |
|  | Cl | phenyl | F |
|  | F | 3-pyridyl | F |
|  | Cl | 3-pyridyl | F |
|  | Cl | pyrazol-3-yl | F |

105

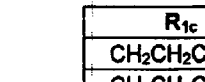
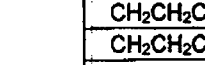
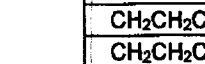
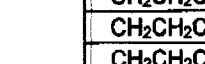
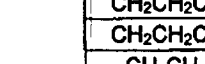
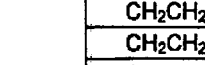
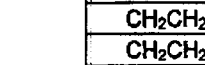
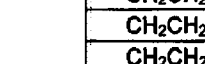
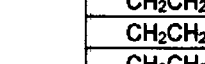
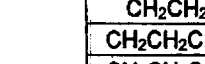
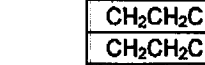
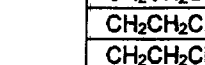
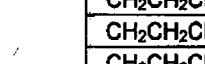
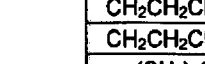
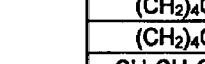
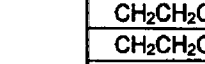
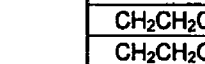
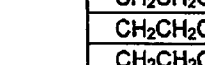
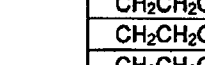
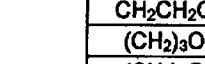
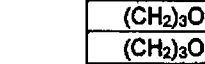
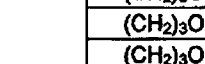
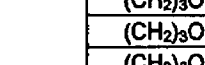
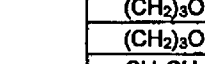
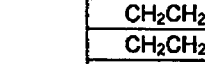
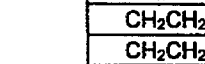
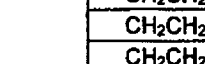
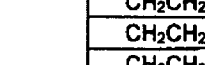
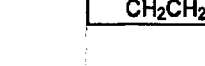
Table 3 shows embodiments of this invention which are compounds of formula I, wherein $R^0$ is as defined herein, G is $R_{1c}$ where $R_{1c}$ is as defined in the table and X, Y and Z are defined in the table.

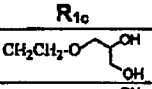
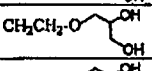
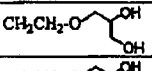
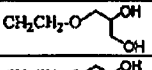
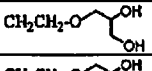
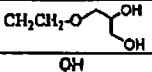
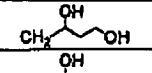
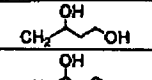
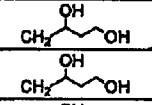
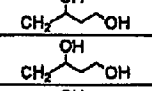
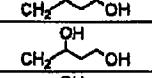
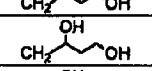
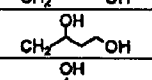
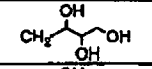
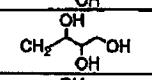
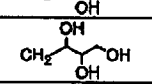
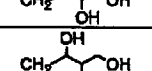
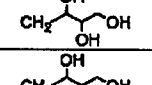
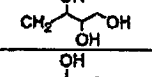
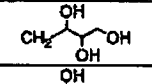
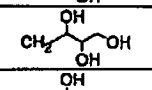
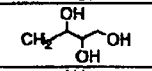
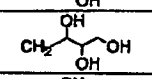
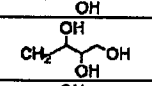
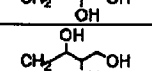
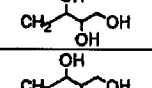
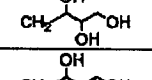
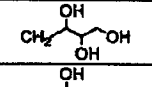
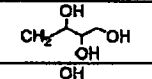
**Table 3**

| $R_{1c}$ | X | Y | Z |
|---|---|---|---|
| $CH_2CH_3$ | F | I | F |
| $CH_2CH_3$ | Cl | I | F |
| $CH_2CH_3$ | F | Br | F |
| $CH_2CH_3$ | Cl | Br | F |
| $CH_2CH_3$ | F | $CH_3$ | F |
| $CH_2CH_3$ | Cl | $CH_3$ | F |
| $CH_2CH_3$ | F | $CF_3$ | F |
| $CH_2CH_3$ | Cl | $CF_3$ | F |
| $CH_2CH_3$ | $CH_3$ | $CH_3$ | F |
| $CH_2CH_3$ | $CH_3$ | $CH_3$ | F |
| $CH_2CH_3$ | $CH_3$ | C≡CH | F |
| $CH_2CH_3$ | $CH_3$ | $SCH_3$ | F |
| $CH_2CH_3$ | F | C≡CH | F |
| $CH_2CH_3$ | Cl | $SCH_3$ | F |
| $CH_2CH_3$ | F | ▷ | F |
| $CH_2CH_3$ | Cl | ▷ | F |
| $CH_2CH_3$ | $CH_3$ | ▷ | F |
| $CH(CH_3)_2$ | F | $OCH_3$ | F |
| $CH(CH_3)_2$ | Cl | $OCH_3$ | F |
| $CH(CH_3)_2$ | F | I | F |
| $CH(CH_3)_2$ | Cl | I | F |
| $CH(CH_3)_2$ | F | Br | F |
| $CH(CH_3)_2$ | Cl | Br | F |
| $CH(CH_3)_2$ | F | $CH_3$ | F |
| $CH(CH_3)_2$ | Cl | $CH_3$ | F |
| $CH(CH_3)_2$ | F | $CH_2CH_3$ | F |
| $CH(CH_3)_2$ | Cl | $CH_2CH_3$ | F |
| $CH(CH_3)_2$ | $CH_3$ | $CH_2CH_3$ | F |
| $CH(CH_3)_2$ | Cl | $CH_2CH_3$ | F |
| $CH(CH_3)_2$ | Fl | $CH(CH_3)_2$ | F |
| $CH(CH_3)_2$ | Cl | $CH(CH_3)_2$ | F |
| $CH(CH_3)_2$ | F | $CF_3$ | F |
| $CH(CH_3)_2$ | Cl | $CH_3$ | F |
| $CH(CH_3)_2$ | $CH_3$ | Br | F |
| $CH(CH_3)_2$ | $CH_3$ | C≡CH | F |
| $CH(CH_3)_2$ | $CH_3$ | $SCH_3$ | F |
| $CH(CH_3)_2$ | $CH_3$ | ▷ | F |
| $CH(CH_3)_2$ | F | $CH_2OH$ | F |
| $CH(CH_3)_2$ | Cl |  | F |
| *n*-butyl | F | I | F |
| *n*-butyl | Cl | I | F |
| *n*-butyl | F | Br | F |
| *n*-butyl | Cl | Br | F |
| *n*-butyl | F | $CH_3$ | F |
| *n*-butyl | Cl | $CH_3$ | F |
| *n*-butyl | F | $OCH_3$ | F |
| *n*-butyl | Cl | $OCH_3$ | F |
| *n*-butyl | $CH_3$ | $OCH_3$ | F |
| *n*-butyl | Cl | $OCH_2CH_3$ | F |
| *n*-butyl | F | $OCH_2CH_3$ | F |

| $R_{1c}$ | X | Y | Z |
|---|---|---|---|
| *n*-butyl | $CH_3$ | $OCH_2CH_3$ | F |
| *n*-butyl | F | $OCH_2CH_2OH$ | F |
| *n*-butyl | F | $CF_3$ | F |
| *n*-butyl | Cl | $CF_3$ | F |
| *sec*-butyl | F | I | F |
| *sec*-butyl | Cl | I | F |
| *sec*-butyl | F | Br | F |
| *sec*-butyl | Cl | Br | F |
| *sec*-butyl | F | $CH_3$ | F |
| *sec*-butyl | Cl | $CH_3$ | F |
| *sec*-butyl | F | $CF_3$ | F |
| *sec*-butyl | Cl | $CF_3$ | F |
| $CH_2CF_3$ | F | I | F |
| $CH_2CF_3$ | Cl | I | F |
| $CH_2CF_3$ | F | Br | F |
| $CH_2CF_3$ | Cl | Br | F |
| $CH_2CF_3$ | F | $CH_3$ | F |
| $CH_2CF_3$ | Cl | $CH_3$ | F |
| $CH_2CF_3$ | F | $CF_3$ | F |
| $CH_2CF_3$ | Cl | $CF_3$ | F |
| $CH_2CCl_3$ | F | I | F |
| $CH_2CCl_3$ | Cl | I | F |
| $CH_2CCl_3$ | F | Br | F |
| $CH_2CCl_3$ | Cl | Br | F |
| $CH_2CCl_3$ | F | $CH_3$ | F |
| $CH_2CCl_3$ | Cl | $CH_3$ | F |
| $CH_2CCl_3$ | F | $CF_3$ | F |
| $CH_2CCl_3$ | Cl | $CF_3$ | F |
| $CH_2$-◁ | F | I | F |
| $CH_2$-◁ | Cl | I | F |
| $CH_2$-◁ | F | Br | F |
| $CH_2$-◁ | Cl | Br | F |
| $CH_2$-◁ | F | $CH_3$ | F |
| $CH_2$-◁ | Cl | $CH_3$ | F |
| $CH_2$-◁ | F | $CF_3$ | F |
| $CH_2$-◁ | Cl | $CF_3$ | F |
| $CH_2CH_2F$ | F | I | F |
| $CH_2CH_2F$ | Cl | I | F |
| $CH_2CH_2F$ | F | Br | F |
| $CH_2CH_2F$ | Cl | Br | F |
| $CH_2CH_2F$ | F | $CH_3$ | F |
| $CH_2CH_2F$ | Cl | $CH_3$ | F |
| $CH_2CH_2F$ | F | $CF_3$ | F |
| $CH_2CH_2F$ | Cl | $CF_3$ | F |
| $CH_2CH_2Cl$ | F | I | F |
| $CH_2CH_2Cl$ | Cl | I | F |
| $CH_2CH_2Cl$ | F | Br | F |
| $CH_2CH_2Cl$ | Cl | Br | F |
| $CH_2CH_2Cl$ | F | $CH_3$ | F |
| $CH_2CH_2Cl$ | Cl | $CH_3$ | F |
| $CH_2CH_2Cl$ | F | $CF_3$ | F |
| $CH_2CH_2Cl$ | Cl | $CF_3$ | F |

| $R_{1c}$ | X | Y | Z |
|---|---|---|---|
| $CH_2CH_2CH_2Cl$ | F | I | F |
| $CH_2CH_2CH_2Cl$ | Cl | I | F |
| $CH_2CH_2CH_2Cl$ | F | Br | F |
| $CH_2CH_2CH_2Cl$ | Cl | Br | F |
| $CH_2CH_2CH_2Cl$ | F | $CH_3$ | F |
| $CH_2CH_2CH_2Cl$ | Cl | $CH_3$ | F |
| $CH_2CH_2CH_2Cl$ | F | $CF_3$ | F |
| $CH_2CH_2CH_2Cl$ | Cl | $CF_3$ | F |
| $CH_2CH_2OH$ | F | I | F |
| $CH_2CH_2OH$ | Cl | I | F |
| $CH_2CH_2OH$ | F | Br | F |
| $CH_2CH_2OH$ | Cl | Br | F |
| $CH_2CH_2OH$ | F | $CH_3$ | F |
| $CH_2CH_2OH$ | Cl | $CH_3$ | F |
| $CH_2CH_2OH$ | F | $CF_3$ | F |
| $CH_2CH_2OH$ | Cl | $CF_3$ | F |
| $CH_2CH_2CH_2OH$ | F | I | F |
| $CH_2CH_2CH_2OH$ | Cl | I | F |
| $CH_2CH_2CH_2OH$ | F | Br | F |
| $CH_2CH_2CH_2OH$ | Cl | Br | F |
| $CH_2CH_2CH_2OH$ | F | $CH_3$ | F |
| $CH_2CH_2CH_2OH$ | Cl | $CH_3$ | F |
| $CH_2CH_2CH_2OH$ | F | $CF_3$ | F |
| $CH_2CH_2CH_2OH$ | Cl | $CF_3$ | F |
| $(CH_2)_4OH$ | F | I | F |
| $(CH_2)_4OH$ | Cl | I | F |
| $(CH_2)_4OH$ | F | Br | F |
| $(CH_2)_4OH$ | Cl | Br | F |
| $(CH_2)_4OH$ | F | $CH_3$ | F |
| $(CH_2)_4OH$ | Cl | $CH_3$ | F |
| $(CH_2)_4OH$ | F | $CF_3$ | F |
| $(CH_2)_4OH$ | Cl | $CF_3$ | F |
| $CH_2CH_2OCH_3$ | F | I | F |
| $CH_2CH_2OCH_3$ | Cl | I | F |
| $CH_2CH_2OCH_3$ | F | Br | F |
| $CH_2CH_2OCH_3$ | Cl | Br | F |
| $CH_2CH_2OCH_3$ | F | $CH_3$ | F |
| $CH_2CH_2OCH_3$ | Cl | $CH_3$ | F |
| $CH_2CH_2OCH_3$ | F | $CF_3$ | F |
| $CH_2CH_2OCH_3$ | Cl | $CF_3$ | F |
| $(CH_2)_3OCH_3$ | F | I | F |
| $(CH_2)_3OCH_3$ | Cl | I | F |
| $(CH_2)_3OCH_3$ | F | Br | F |
| $(CH_2)_3OCH_3$ | Cl | Br | F |
| $(CH_2)_3OCH_3$ | F | $CH_3$ | F |
| $(CH_2)_3OCH_3$ | Cl | $CH_3$ | F |
| $(CH_2)_3OCH_3$ | F | $CF_3$ | F |
| $(CH_2)_3OCH_3$ | Cl | $CF_3$ | F |
| $CH_2CH_2OEt$ | F | I | F |
| $CH_2CH_2OEt$ | Cl | I | F |
| $CH_2CH_2OEt$ | F | Br | F |
| $CH_2CH_2OEt$ | Cl | Br | F |
| $CH_2CH_2OEt$ | F | $CH_3$ | F |
| $CH_2CH_2OEt$ | Cl | $CH_3$ | F |
| $CH_2CH_2OEt$ | F | $CF_3$ | F |
| $CH_2CH_2OEt$ | Cl | $CF_3$ | F |

| $R_{1c}$ | X | Y | Z |
|---|---|---|---|
|  | F | I | F |
|  | Cl | I | F |
|  | F | Br | F |
|  | Cl | Br | F |
|  | F | $CH_3$ | F |
|  | Cl | $CH_3$ | F |
|  | F | $CF_3$ | F |
|  | Cl | $CF_3$ | F |
|  | F | I | F |
|  | Cl | I | F |
|  | F | Br | F |
|  | Cl | Br | F |
|  | F | $CH_3$ | F |
|  | Cl | $CH_3$ | F |
|  | F | $CF_3$ | F |
|  | Cl | $CF_3$ | F |
| $CH_2CH_2CH_2OEt$ | F | I | F |
| $CH_2CH_2CH_2OEt$ | Cl | I | F |
| $CH_2CH_2CH_2OEt$ | F | Br | F |
| $CH_2CH_2CH_2OEt$ | Cl | Br | F |
| $CH_2CH_2CH_2OEt$ | F | $CH_3$ | F |
| $CH_2CH_2CH_2OEt$ | Cl | $CH_3$ | F |
| $CH_2CH_2CH_2OEt$ | F | $CF_3$ | F |
| $CH_2CH_2CH_2OEt$ | Cl | $CF_3$ | F |
|  | F | I | F |
|  | Cl | I | F |
|  | F | Br | F |
|  | Cl | Br | F |
|  | F | $CH_3$ | F |
|  | Cl | $CH_3$ | F |
|  | F | $CF_3$ | F |
|  | Cl | $CF_3$ | F |
|  | F | I | F |
|  | Cl | I | F |
|  | F | Br | F |
|  | Cl | Br | F |
|  | F | $CH_3$ | F |
|  | Cl | $CH_3$ | F |
|  | F | $CF_3$ | F |
|  | Cl | $CF_3$ | F |
|  | F | I | F |
|  | Cl | I | F |

| $R_{1c}$ | X | Y | Z |
|---|---|---|---|
|  | F | Br | F |
|  | Cl | Br | F |
|  | F | $CH_3$ | F |
|  | Cl | $CH_3$ | F |
|  | F | $CF_3$ | F |
|  | Cl | $CF_3$ | F |
|  | F | I | F |
|  | Cl | I | F |
|  | F | Br | F |
|  | Cl | Br | F |
|  | F | $CH_3$ | F |
|  | Cl | $CH_3$ | F |
|  | F | $CF_3$ | F |
|  | Cl | $CF_3$ | F |
|  | F | I | F |
|  | Cl | I | F |
|  | $CH_3$ | I | F |
|  | F | Br | F |
|  | Cl | Br | F |
|  | $CH_3$ | Br | F |
|  | F | $CH_3$ | F |
|  | Cl | $CH_3$ | F |
|  | $CH_3$ | $CH_3$ | F |
|  | F | C≡CH | F |
|  | F | $SCH_3$ | F |
|  | F | $CH_2CH_2CH_3$ | F |
|  | Cl | $CH_2CH(OH)CH_3$ | F |
|  | F | $CH(CH_3)_2$ | F |
|  | Cl | $CF_3$ | F |
| $CH_2CH_3$ | F | phenyl | F |
| $CH_2CH_3$ | Cl | phenyl | F |
| $CH_2CH_3$ | F | phenyl | F |

| $R_{1c}$ | X | Y | Z |
|---|---|---|---|
| $CH_2CH_3$ | Cl | 3-pyridyl | F |
| $CH_2CH_3$ | F | 3-pyridyl | F |
| $CH_2CH_3$ | Cl | 4-pyridyl | F |
| $CH_2CH_3$ | F | pyrazolyl | F |
| $CH_2CH_3$ | Cl | pyrazolyl | F |
| $CH_2CH_3$ | $CH_3$ | 4-pyridyl | F |
| $CH_2CH_3$ | $CH_3$ | 4-pyridyl | F |
| $CH_2CH_3$ | $CH_3$ | 2-($CH_3$-$SO_2$-NH)-phenyl | F |
| $CH_2CH_3$ | $CH_3$ | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
| $CH_2CH_3$ | F | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
| $CH_2CH_3$ | Cl | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
| $CH_2CH_3$ | F | phenyl | F |
| $CH_2CH_3$ | Cl | phenyl | F |
| $CH_2CH_3$ | $CH_3$ | phenyl | F |
| | | 3-pyridyl | |
| $CH(CH_3)_2$ | F | 3-pyridyl | F |
| $CH(CH_3)_2$ | Cl | 4-pyridyl | F |
| $CH(CH_3)_2$ | F | pyrazolyl | F |
| $CH(CH_3)_2$ | Cl | pyrazolyl | F |
| $CH(CH_3)_2$ | F | 4-pyridyl | F |
| $CH(CH_3)_2$ | Cl | 4-pyridyl | F |
| $CH(CH_3)_2$ | F | 2-($CH_3$-$SO_2$-NH)-phenyl | F |
| $CH(CH_3)_2$ | Cl | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
| $CH(CH_3)_2$ | F | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
| $CH(CH_3)_2$ | Cl | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
| $CH(CH_3)_2$ | $CH_3$ | phenyl | F |
| $CH(CH_3)_2$ | Cl | phenyl | F |
| $CH(CH_3)_2$ | Fl | phenyl | F |
| $CH(CH_3)_2$ | Cl | 3-pyridyl | F |
| | | 3-pyridyl | |
| $CH(CH_3)_2$ | F | 4-pyridyl | F |
| $CH(CH_3)_2$ | Cl | pyrazolyl | F |
| $CH(CH_3)_2$ | $CH_3$ | pyrazolyl | F |
| $CH(CH_3)_2$ | $CH_3$ | 4-pyridyl | F |
| $CH(CH_3)_2$ | $CH_3$ | 4-pyridyl | F |
| $CH(CH_3)_2$ | $CH_3$ | 2-($CH_3$-$SO_2$-NH)-phenyl | F |
| $CH(CH_3)_2$ | F | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
| $CH(CH_3)_2$ | Cl | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
| | | 3-($CH_3$-$SO_2$-NH)-phenyl | |
| *n*-butyl | F | phenyl | F |
| *n*-butyl | Cl | phenyl | F |
| *n*-butyl | F | phenyl | F |
| *n*-butyl | Cl | 3-pyridyl | F |
| *n*-butyl | F | 3-pyridyl | F |
| *n*-butyl | Cl | 4-pyridyl | F |
| *n*-butyl | F | pyrazolyl | F |

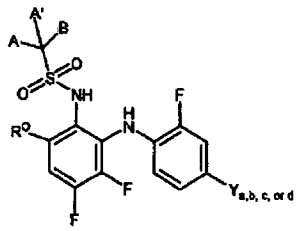
| $R_{1c}$ | X | Y | Z |
|---|---|---|---|
| *n*-butyl | Cl | pyrazolyl | F |
| *n*-butyl | $CH_3$ | 4-pyridyl | F |
| *n*-butyl | Cl | 4-pyridyl | F |
| *n*-butyl | F | 2-($CH_3$-$SO_2$-NH)-phenyl | F |
| *n*-butyl | $CH_3$ | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
| *n*-butyl | F | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
| | | 3-($CH_3$-$SO_2$-NH)-phenyl | |
| *n*-butyl | F | phenyl | F |
| *n*-butyl | Cl | phenyl | F |
| | | phenyl | |
| *sec*-butyl | F | 3-pyridyl | F |
| *sec*-butyl | Cl | 3-pyridyl | F |
| *sec*-butyl | F | 4-pyridyl | F |
| *sec*-butyl | Cl | pyrazolyl | F |
| *sec*-butyl | F | pyrazolyl | F |
| *sec*-butyl | Cl | 4-pyridyl | F |
| *sec*-butyl | F | 4-pyridyl | F |
| sec-butyl | Cl | $CF_3$ | F |
| $CH_2CF_3$ | F | phenyl | F |
| $CH_2CF_3$ | Cl | phenyl | F |
| $CH_2CF_3$ | F | phenyl | F |
| $CH_2CF_3$ | Cl | 3-pyridyl | F |
| $CH_2CF_3$ | F | 3-pyridyl | F |
| $CH_2CF_3$ | Cl | 4-pyridyl | F |
| $CH_2CF_3$ | F | pyrazolyl | F |
| $CH_2CF_3$ | Cl | pyrazolyl | F |
| | | 4-pyridyl | |
| $CH_2CCl_3$ | F | 4-pyridyl | F |
| $CH_2CCl_3$ | Cl | 2-($CH_3$-$SO_2$-NH)-phenyl | F |
| $CH_2CCl_3$ | F | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
| $CH_2CCl_3$ | Cl | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
| $CH_2CCl_3$ | F | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
| $CH_2CCl_3$ | Cl | phenyl | F |
| $CH_2CCl_3$ | F | phenyl | F |
| $CH_2CCl_3$ | Cl | phenyl | F |
| | | 3-pyridyl | |
| $CH_2$-◁ | F | 3-pyridyl | F |
| $CH_2$-◁ | Cl | 4-pyridyl | F |
| $CH_2$-◁ | F | pyrazolyl | F |
| $CH_2$-◁ | Cl | pyrazolyl | F |
| $CH_2$-◁ | F | 4-pyridyl | F |
| $CH_2$-◁ | Cl | 4-pyridyl | F |
| $CH_2$-◁ | F | 2-($CH_3$-$SO_2$-NH)-phenyl | F |
| $CH_2$-◁ | Cl | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
| | | 3-($CH_3$-$SO_2$-NH)-phenyl | |
| $CH_2CH_2F$ | F | 3-($CH_3$-$SO_2$-NH)-phenyl | F |

| $R_{1c}$ | X | Y | Z |
|---|---|---|---|
| $CH_2CH_2F$ | Cl | phenyl | F |
| $CH_2CH_2F$ | F | phenyl | F |
| $CH_2CH_2F$ | Cl | phenyl | F |
| $CH_2CH_2F$ | F | 3-pyridyl | F |
| $CH_2CH_2F$ | Cl | 3-pyridyl | F |
| $CH_2CH_2F$ | F | 4-pyridyl | F |
| $CH_2CH_2F$ | Cl | pyrazolyl | F |
| | | pyrazolyl | |
| $CH_2CH_2Cl$ | F | 4-pyridyl | F |
| $CH_2CH_2Cl$ | Cl | 4-pyridyl | F |
| $CH_2CH_2Cl$ | F | 2-($CH_3$-$SO_2$-NH)-phenyl | F |
| $CH_2CH_2Cl$ | Cl | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
| $CH_2CH_2Cl$ | F | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
| $CH_2CH_2Cl$ | Cl | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
| $CH_2CH_2Cl$ | F | phenyl | F |
| $CH_2CH_2Cl$ | Cl | phenyl | F |
| | | phenyl | |
| $CH_2CH_2CH_2Cl$ | F | 3-pyridyl | F |
| $CH_2CH_2CH_2Cl$ | Cl | 3-pyridyl | F |
| $CH_2CH_2CH_2Cl$ | F | 4-pyridyl | F |
| $CH_2CH_2CH_2Cl$ | Cl | pyrazolyl | F |
| $CH_2CH_2CH_2Cl$ | F | pyrazolyl | F |
| $CH_2CH_2CH_2Cl$ | Cl | 4-pyridyl | F |
| $CH_2CH_2CH_2Cl$ | F | 4-pyridyl | F |
| $CH_2CH_2CH_2Cl$ | Cl | 2-($CH_3$-$SO_2$-NH)-phenyl | F |
| | | 3-($CH_3$-$SO_2$-NH)-phenyl | |
| $CH_2CH_2OH$ | F | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
| $CH_2CH_2OH$ | Cl | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
| $CH_2CH_2OH$ | F | phenyl | F |
| $CH_2CH_2OH$ | Cl | phenyl | F |
| $CH_2CH_2OH$ | F | phenyl | F |
| $CH_2CH_2OH$ | Cl | 3-pyridyl | F |
| $CH_2CH_2OH$ | F | 3-pyridyl | F |
| $CH_2CH_2OH$ | Cl | 4-pyridyl | F |
| | | pyrazolyl | |
| $CH_2CH_2CH_2OH$ | F | pyrazolyl | F |
| $CH_2CH_2CH_2OH$ | Cl | 4-pyridyl | F |
| $CH_2CH_2CH_2OH$ | F | 4-pyridyl | F |
| $CH_2CH_2CH_2OH$ | Cl | 2-($CH_3$-$SO_2$-NH)-phenyl | F |
| $CH_2CH_2CH_2OH$ | F | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
| $CH_2CH_2CH_2OH$ | Cl | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
| $CH_2CH_2CH_2OH$ | F | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
| $CH_2CH_2CH_2OH$ | Cl | phenyl | F |
| | | phenyl | |
| $(CH_2)_4OH$ | F | phenyl | F |
| $(CH_2)_4OH$ | Cl | 3-pyridyl | F |

| $R_{1c}$ | X | Y | Z |
|---|---|---|---|
| $(CH_2)_4OH$ | F | 3-pyridyl | F |
| $(CH_2)_4OH$ | Cl | 4-pyridyl | F |
| $(CH_2)_4OH$ | F | pyrazolyl | F |
| $(CH_2)_4OH$ | Cl | pyrazolyl | F |
| $(CH_2)_4OH$ | F | 4-pyridyl | F |
| $(CH_2)_4OH$ | Cl | 4-pyridyl | F |
| | | 2-($CH_3$-$SO_2$-NH)-phenyl | |
| $CH_2CH_2OCH_3$ | F | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
| $CH_2CH_2OCH_3$ | Cl | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
| $CH_2CH_2OCH_3$ | F | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
| $CH_2CH_2OCH_3$ | Cl | phenyl | F |
| $CH_2CH_2OCH_3$ | F | phenyl | F |
| $CH_2CH_2OCH_3$ | Cl | phenyl | F |
| $CH_2CH_2OCH_3$ | F | 3-pyridyl | F |
| $CH_2CH_2OCH_3$ | Cl | 3-pyridyl | F |
| | | 4-pyridyl | |
| $(CH_2)_3OCH_3$ | F | pyrazolyl | F |
| $(CH_2)_3OCH_3$ | Cl | pyrazolyl | F |
| $(CH_2)_3OCH_3$ | F | 4-pyridyl | F |
| $(CH_2)_3OCH_3$ | Cl | 4-pyridyl | F |
| $(CH_2)_3OCH_3$ | F | 2-($CH_3$-$SO_2$-NH)-phenyl | F |
| $(CH_2)_3OCH_3$ | Cl | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
| $(CH_2)_3OCH_3$ | F | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
| $(CH_2)_3OCH_3$ | Cl | 3-($CH_3$-$SO_2$-NH)-phenyl | F |
| | | phenyl | |
| $CH_2CH_2OEt$ | F | phenyl | F |
| $CH_2CH_2OEt$ | Cl | phenyl | F |
| $CH_2CH_2OEt$ | F | 3-pyridyl | F |
| $CH_2CH_2OEt$ | Cl | 3-pyridyl | F |
| $CH_2CH_2OEt$ | F | 4-pyridyl | F |
| $CH_2CH_2OEt$ | Cl | pyrazolyl | F |
| $CH_2CH_2OEt$ | F | pyrazolyl | F |
| $CH_2CH_2OEt$ | Cl | 4-pyridyl | F |

Tables 4a and 4b show embodiments of this invention which are compounds of formula I, where G = $R_{1d}$, Z is F, X is F and $R_{1d}$ and $R^0$ are defined in the table. Each line in the table corresponds to five species which differ only at position Y.

**Table 4a**




$Y_a = CH_3$; $Y_b$ = Br; $Y_c$ = I; $Y_d$ = Cl;

| CMPD # | A, A' | B | $R^0$ |
|---|---|---|---|
| 1(a-d) | H, H | H | $OCH_3$ |
| 2(a-d) | H, H | H | $NHCH_3$ |
| 3(a-d) | H, H | H | $CH_2CH_3$ |
| 4(a-d) | H, H | H | $CH_2CH=CH_2$ |
| 5(a-d) | H, H | H | CN |
| 6(a-d) | H, H | H | $CF_3$ |
| 7(a-d) | H, H | H | F |
| 8(a-d) | H, H | H | $C_6H_6$ |
| 9(a-d) | H, H | $-CH_2CH(OH)CH_2OH$ | $OCH_3$ |
| 10(a-d) | H, H | $-CH_2CH(OH)CH_2OH$ | $NHCH_3$ |
| 11(a-d) | H, H | $-CH_2CH(OH)CH_2OH$ | $CH_2CH_3$ |
| 12(a-d) | $-(CH_2)_2-$ | $-CH_2(C_3H_5)$ | $OCH_3$ |
| 13(a-d) | $-(CH_2)_2-$ | $-CH_2(C_3H_5)$ | $NHCH_3$ |
| 14(a-d) | $-(CH_2)_2-$ | $-CH_2(C_3H_5)$ | $CH_2CH_3$ |
| 15(a-d) | $-(CH_2)_2-$ | $CH_3$ | F |
| 16(a-d) | $-(CH_2)_2-$ | $-CH_2CH_2OH$ | F |
| 17(a-d) | $-(CH_2)_2-$ | $-(CH_2)_2CH(OH)CH_2OH$ | F |
| 18(a-d) | $CH_3$, H | $-(CH_2)_2CH(OH)CH_2OH$ | F |
| 19(a-d) | $-(CH_2)_2-$ | $CH_3$ | $OCH_3$ |
| 20(a-d) | $-(CH_2)_2-$ | $-CH_2CH_2OH$ | $OCH_3$ |
| 21(a-d) | $-(CH_2)_2-$ | $-(CH_2)_2CH(OH)CH_2OH$ | $OCH_3$ |
| 22(a-d) | $CH_3$, H | $-(CH_2)_2CH(OH)CH_2OH$ | $OCH_3$ |
| 23(a-d) | $-(CH_2)_2-$ | $CH_3$ | H |
| 24(a-d) | $-(CH_2)_2-$ | $-CH_2CH_2OH$ | H |
| 25(a-d) | $-(CH_2)_2-$ | $-(CH_2)_2CH(OH)CH_2OH$ | H |
| 26(a-d) | $CH_3$, H | $-(CH_2)_2CH(OH)CH_2OH$ | H |
| 27(a-d) | H, H | H | $OCH_3$ |
| 28(a-d) | H, H | H | $NHCH_3$ |
| 29(a-d) | H, H | H | $CH_2CH_3$ |
| 30(a-d) | H, H | H | $CH_2CH=CH_2$ |
| 31(a-d) | H, H | H | CN |
| 32(a-d) | H, H | H | $CF_3$ |
| 33(a-d) | H, H | H | F |
| 34(a-d) | H, H | H | $C_6H_6$ |
| 35(a-d) | H, H | $-CH_2CH(OH)CH_2OH$ | $OCH_3$ |
| 36(a-d) | H, H | $-CH_2CH(OH)CH_2OH$ | $NHCH_3$ |
| 37(a-d) | H, H | $-CH_2CH(OH)CH_2OH$ | $CH_2CH_3$ |
| 38(a-d) | $-(CH_2)_2-$ | $-CH_2(C_3H_5)$ | $OCH_3$ |
| 39(a-d) | $-(CH_2)_2-$ | $-CH_2(C_3H_5)$ | $NHCH_3$ |
| 40(a-d) | $-(CH_2)_2-$ | $-CH_2(C_3H_5)$ | $CH_2CH_3$ |
| 41(a-d) | $-(CH_2)_2-$ | $CH_3$ | F |

| CMPD # | A, A' | B | $R^0$ |
|---|---|---|---|
| 42(a-d) | $-(CH_2)_2-$ | $-CH_2CH_2OH$ | F |
| 43(a-d) | $-(CH_2)_2-$ | $-(CH_2)_2CH(OH)CH_2OH$ | F |
| 44(a-d) | $CH_3$, H | $-(CH_2)_2CH(OH)CH_2OH$ | F |
| 45(a-d) | $-(CH_2)_2-$ | $CH_3$ | $OCH_3$ |
| 46(a-d) | $-(CH_2)_2-$ | $-CH_2CH_2OH$ | $OCH_3$ |
| 47(a-d) | $-(CH_2)_2-$ | $-(CH_2)_2CH(OH)CH_2OH$ | $OCH_3$ |
| 48(a-d) | $CH_3$, H | $-(CH_2)_2CH(OH)CH_2OH$ | $OCH_3$ |
| 49(a-d) | $-(CH_2)_2-$ | $CH_3$ | H |
| 50(a-d) | $-(CH_2)_2-$ | $-CH_2CH_2OH$ | H |
| 51(a-d) | $-(CH_2)_2-$ | $-(CH_2)_2CH(OH)CH_2OH$ | H |
| 52(a-d) | $CH_3$, H | $-(CH_2)_2CH(OH)CH_2OH$ | H |

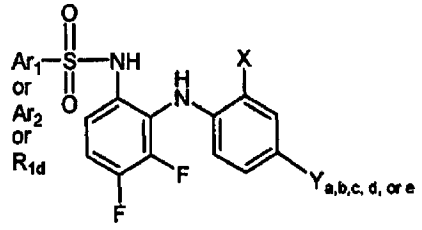
**Table 4b**

| CMPD # | A, A' | B | $R^0$ |
|---|---|---|---|
| 1(a-d) | H, H | H | 2-furanyl |
| 2(a-d) | H, H | H | 1,2,3 triazolyl-4-yl |
| 3(a-d) | H, H | H | 4-imidazolyl |
| 4(a-d) | H, H | H | 2-furanyl |
| 5(a-d) | H, H | H | 1,2,3 triazolyl-4-yl |
| 6(a-d) | H, H | H | 4-imidazolyl |
| 7(a-d) | H, H | $-(CH_2)_2CH(OH)CH_2OH$ | 2-furanyl |
| 8(a-d) | H, H | $-(CH_2)_2CH(OH)CH_2OH$ | 1,2,3 triazolyl-4-yl |
| 9(a-d) | H, H | $-(CH_2)_2CH(OH)CH_2OH$ | 4-imidazolyl |
| 10(a-d) | $-(CH_2)_2-$ | $-CH_2(C_3H_5)$ | 2-furanyl |
| 11(a-d) | $-(CH_2)_2-$ | $-CH_2(C_3H_5)$ | 1,2,3 triazolyl-4-yl |
| 12(a-d) | $-(CH_2)_2-$ | $-CH_2(C_3H_5)$ | 4-imidazolyl |
| 13(a-d) | $-(CH_2)_2-$ | $CH_3$ | 4-thiazolyl |
| 14(a-d) | $-(CH_2)_2-$ | $-CH_2CH_2OH$ | 4-thiazolyl |
| 15(a-d) | $-(CH_2)_2-$ | $-(CH_2)_2CH(OH)CH_2OH$ | 4-thiazolyl |
| 16(a-d) | $CH_3$, H | $-(CH_2)_2CH(OH)CH_2OH$ | 4-thiazolyl |
| 17(a-d) | $-(CH_2)_2-$ | $CH_3$ | 2-oxazolyl |
| 18(a-d) | $-(CH_2)_2-$ | $-CH_2CH_2OH$ | 2-oxazolyl |
| 19(a-d) | $-(CH_2)_2-$ | $-(CH_2)_2CH(OH)CH_2OH$ | 2-oxazolyl |
| 20(a-d) | $CH_3$, H | $-(CH_2)_2CH(OH)CH_2OH$ | 2-oxazolyl |
| 21(a-d) | H, H | H | 2-furanyl |
| 22(a-d) | H, H | H | 1,2,3 triazolyl-4-yl |
| 23(a-d) | H, H | H | 4-imidazolyl |
| 24(a-d) | H, H | H | 2-furanyl |
| 25(a-d) | H, H | H | 1,2,3 triazolyl-4-yl |
| 26(a-d) | H, H | H | 4-imidazolyl |
| 27(a-d) | H, H | $-CH_2CH(OH)CH_2OH$ | 2-furanyl |
| 28(a-d) | H, H | $-CH_2CH(OH)CH_2OH$ | 1,2,3 triazolyl-4-yl |
| 29(a-d) | H, H | $-CH_2CH(OH)CH_2OH$ | 4-imidazolyl |
| 30(a-d) | $-(CH_2)_2-$ | $-CH_2(C_3H_5)$ | 2-furanyl |
| 31(a-d) | $-(CH_2)_2-$ | $-CH_2(C_3H_5)$ | 1,2,3 triazolyl-4-yl |
| 32(a-d) | $-(CH_2)_2-$ | $-CH_2(C_3H_5)$ | 4-imidazolyl |
| 33(a-d) | $-(CH_2)_2-$ | $CH_3$ | 4-thiazolyl |
| 34(a-d) | $-(CH_2)_2-$ | $-CH_2CH_2OH$ | 4-thiazolyl |
| 35(a-d) | $-(CH_2)_2-$ | $-(CH_2)_2CH(OH)CH_2OH$ | 4-thiazolyl |

| CMPD # | A, A' | B | $R^0$ |
|---|---|---|---|
| 36(a-d) | $CH_3$, H | -$(CH_2)_2CH(OH)CH_2OH$ | 4-thiazolyl |
| 37(a-d) | -$(CH_2)_2$- | $CH_3$ | 2-oxazolyl |
| 38(a-d) | -$(CH_2)_2$- | -$CH_2CH_2OH$ | 2-oxazolyl |
| 39(a-d) | -$(CH_2)_2$- | -$(CH_2)_2CH(OH)CH_2OH$ | 2-oxazolyl |
| 40(a-d) | $CH_3$, H | -$(CH_2)_2CH(OH)CH_2OH$ | 2-oxazolyl |

Table 5a shows embodiments of this invention which are compounds of formula I, where G is $Ar_1$, $Ar_2$ or $R_{1d}$, and where $R^0$ is H, Z is F and G and X are defined in the table. Each line in the table corresponds to five species ($Y_a$, $Y_b$, $Y_c$, $Y_d$ and $Y_e$) which differ only at position Y, where $Y_a = SCH_3$; $Y_b$ = Br; $Y_c$ = I; $Y_d$ = Cl; $Y_e = CH_3$.

**Table 5a**




$Y_a = SCH_3$; $Y_b$ = Br; $Y_c$ = I; $Y_d$ = Cl; $Y_e = CH_3$

| Compound # | G = $R_{1d}$, $Ar_1$, or $Ar_2$ | X |
|---|---|---|
| 1 (a-e) | phenyl | Cl |
| 2 (a-e) | phenyl | F |
| 3 (a-e) | 2-F-phenyl | Cl |
| 4 (a-e) | 2-F-phenyl | F |
| 5 (a-e) | 3-F-phenyl | Cl |
| 6 (a-e) | 3-F-phenyl | F |
| 7 (a-e) | 4-F-phenyl | Cl |
| 8 (a-e) | 4-F-phenyl | F |
| 9 (a-e) | 2,4-di-F-phenyl | Cl |
| 10 (a-e) | 2,4-di-F-phenyl | F |
| 11 (a-e) | 2,5-di-F-phenyl | Cl |
| 12 (a-e) | 2,5-di-F-phenyl | F |
| 13 (a-e) | 2,6-di-F-phenyl | Cl |
| 14 (a-e) | 2,6-di-F-phenyl | F |
| 15 (a-e) | 3,4-di-F-phenyl | Cl |
| 16 (a-e) | 3,4-di-F-phenyl | F |
| 17 (a-e) | 3,5-di-F-phenyl | Cl |
| 18 (a-e) | 3,5-di-F-phenyl | F |
| 19 (a-e) | 2,6-di-F-phenyl | Cl |
| 20 (a-e) | 2,6-di-F-phenyl | F |
| 21 (a-e) | 2,3,4-tri-F-phenyl | Cl |
| 22 (a-e) | 2,3,4-tri-F-phenyl | F |
| 23 (a-e) | 3,4,5-tri-F-phenyl | Cl |
| 24 (a-e) | 3,4,5-tri-F-phenyl | F |
| 25 (a-e) | penta-F-phenyl | Cl |
| 26 (a-e) | penta-F-phenyl | F |
| 27 (a-e) | 3-Cl-4-F-phenyl | Cl |
| 28 (a-e) | 3-Cl-4-F-phenyl | F |
| 29 (a-e) | 2-Cl-4-F-phenyl | Cl |
| 30 (a-e) | 2-Cl-4-F-phenyl | F |

| Compound # | G = $R_{1d}$, $Ar_1$, or $Ar_2$ | X |
|---|---|---|
| 31 (a-e) | 2-F-3-Cl-phenyl | Cl |
| 32 (a-e) | 2-F-3-Cl-phenyl | F |
| 33 (a-e) | 2-F-4-Cl-phenyl | Cl |
| 34 (a-e) | 2-F-4-Cl-phenyl | F |
| 35 (a-e) | 2-F-5-Cl-phenyl | Cl |
| 36 (a-e) | 2-F-5-Cl-phenyl | F |
| 37 (a-e) | 3-cyano-4-F-phenyl | Cl |
| 38 (a-e) | 3-cyano-4-F-phenyl | F |
| 39 (a-e) | 2-Cl-phenyl | Cl |
| 40 (a-e) | 2-Cl-phenyl | F |
| 41 (a-e) | 3-Cl-phenyl | Cl |
| 42 (a-e) | 3-Cl-phenyl | F |
| 43 (a-e) | 4-Cl-phenyl | Cl |
| 44 (a-e) | 4-Cl-phenyl | F |
| 45 (a-e) | 2,3-di-Cl-phenyl | Cl |
| 46 (a-e) | 2,3-di-Cl-phenyl | F |
| 47 (a-e) | 2,5-di-Cl-phenyl | Cl |
| 48 (a-e) | 2,5-di-Cl-phenyl | F |
| 49 (a-e) | 2,6-di-Cl-phenyl | Cl |
| 50 (a-e) | 2,6-di-Cl-phenyl | F |
| 51 (a-e) | 3,5-di-Cl-phenyl | Cl |
| 52 (a-e) | 3,5-di-Cl-phenyl | F |
| 53 (a-e) | 2,4-di-Cl-phenyl | Cl |
| 54 (a-e) | 2,4-di-Cl-phenyl | F |
| 55 (a-e) | 3,4-di-Cl-phenyl | Cl |
| 56 (a-e) | 3,4-di-Cl-phenyl | F |
| 57 (a-e) | 2,4,6-tri-Cl-phenyl | Cl |
| 58 (a-e) | 2,4,6-tri-Cl-phenyl | F |
| 59 (a-e) | 2-Cl-4-$CF_3$-phenyl | Cl |
| 60 (a-e) | 2-Cl-4-$CF_3$-phenyl | F |

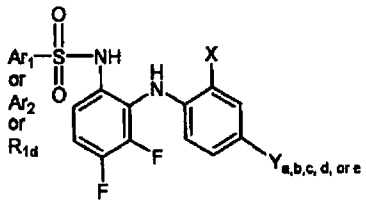
113

| Compound # | G = $R_{1d}$, $Ar_1$, or $Ar_2$ | X |
|---|---|---|
| 61 (a-e) | 2-$CF_3$-phenyl | Cl |
| 62 (a-e) | 2-$CF_3$-phenyl | F |
| 63 (a-e) | 3-$CF_3$-phenyl | Cl |
| 64 (a-e) | 3-$CF_3$-phenyl | F |
| 65 (a-e) | 4-$CF_3$-phenyl | Cl |
| 66 (a-e) | 4-$CF_3$-phenyl | F |
| 67 (a-e) | 2-$CF_3O$ phenyl | Cl |
| 68 (a-e) | 2-$CF_3O$ phenyl | F |
| 69 (a-e) | 3-$CF_3O$ phenyl | Cl |
| 70 (a-e) | 3-$CF_3O$ phenyl | F |
| 71 (a-e) | 4-$CF_3O$ phenyl | Cl |
| 72 (a-e) | 4-$CF_3O$ phenyl | F |
| 73 (a-e) | 2-$CHF_2O$ phenyl | Cl |
| 74 (a-e) | 2-$CHF_2O$ phenyl | F |
| 75 (a-e) | 2-methyl-5-nitro-phenyl | Cl |
| 76 (a-e) | 2-methyl-5-nitro-phenyl | F |
| 77 (a-e) | 2-cyano-phenyl | Cl |
| 78 (a-e) | 2-cyano-phenyl | F |
| 79 (a-e) | 3-cyano-phenyl | Cl |
| 80 (a-e) | 3-cyano-phenyl | F |
| 81 (a-e) | 4-cyano-phenyl | Cl |
| 82 (a-e) | 4-cyano-phenyl | F |
| 83 (a-e) | 4-methoxy-phenyl | Cl |
| 84 (a-e) | 4-methoxy-phenyl | F |
| 85 (a-e) | 3,4-dimethoxy-phenyl | Cl |
| 86 (a-e) | 3,4-dimethoxy-phenyl | F |
| 87 (a-e) | 3-carbamyl-phenyl | Cl |
| 88 (a-e) | 3-carbamyl-phenyl | F |
| 89 (a-e) | 3-carboxyl-phenyl | Cl |
| 90 (a-e) | 3-carboxyl-phenyl | F |
| 91 (a-e) | 3-(N,N-dimethylcarbamoyl)phenyl | Cl |
| 92 (a-e) | 3-(N,N-dimethylcarbamoyl)phenyl | F |
| 93 (a-e) | 4-methylsulfonyl-phenyl | Cl |
| 94 (a-e) | 4-methylsulfonyl-phenyl | F |
| 95 (a-e) | 3-(1,3,4 oxadiazol-2-yl)phenyl | Cl |
| 96 (a-e) | 3-(1,3,4 oxadiazol-2-yl)phenyl | F |
| 97 (a-e) | 3-(1,3,4 thiadiazol-2-yl)phenyl | Cl |
| 98 (a-e) | 3-(1,3,4 thiadiazol-2-yl)phenyl | F |
| 99 (a-e) | 3-(5-methyl-1-1,3,4-oxadiazol)phenyl | Cl |
| 100 (a-e) | 3-(5-methyl-1-1,3,4-oxadiazol)phenyl | F |
| 101 (a-e) | 3-(5-methyl-1-1,3,4-thiadiazol)phenyl | Cl |
| 102 (a-e) | 3-(5-methyl-1-1,3,4-thiadiazol)phenyl | F |
| 103 (a-e) | 3-amidinyl-phenyl | Cl |
| 104 (a-e) | 3-amidinyl-phenyl | F |
| 105 (a-e) | 3-(1H-tetrazolyl)phenyl | Cl |
| 106 (a-e) | 3-(1H-tetrazolyl)phenyl | F |
| 107 (a-e) | 4-acetamido-phenyl | Cl |
| 108 (a-e) | 4-acetamido-phenyl | F |
| 109 (a-e) | 3-Cl-4-[(N-morpholinylcarbonyl)amino]phenyl | Cl |
| 110 (a-e) | 3-Cl-4-[(N-morpholinylcarbonyl)amino]phenyl | F |

| Compound # | G = $R_{1d}$, $Ar_1$, or $Ar_2$ | X |
|---|---|---|
| 111 (a-e) | 3-Cl-4-[(N-pyrrolidinylcarbonyl)amino]phenyl | Cl |
| 112 (a-e) | 3-Cl-4-[(N-pyrrolidinylcarbonyl)amino]phenyl | F |
| 113 (a-e) | 3,5-dimethylisoxazolyl | Cl |
| 114 (a-e) | 3,5-dimethylisoxazolyl | F |
| 115 (a-e) | 4-(N-morpholinylsulfonyl)phenyl | Cl |
| 116 (a-e) | 4-(N-morpholinylsulfonyl)phenyl | F |
| 117 (a-e) | 3-F-benzyl | Cl |
| 118 (a-e) | 3-F-benzyl | F |
| 119 (a-e) | 4-F-benzyl | Cl |
| 120 (a-e) | 4-F-benzyl | F |
| 121 (a-e) | 3-F-phenyl-ethyl | Cl |
| 122 (a-e) | 3-F-phenyl-ethyl | F |
| 123 (a-e) | 4-F-phenyl-ethyl | Cl |
| 124 (a-e) | 4-F-phenyl-ethyl | F |
| 125 (a-e) | 8-quinolinyl | Cl |
| 126 (a-e) | 8-quinolinyl | F |
| 127 (a-e) | 2-thienyl | Cl |
| 128 (a-e) | 2-thienyl | F |
| 129 (a-e) | 2,3-di-Cl-thien-5-yl | Cl |
| 130 (a-e) | 2,3-di-Cl-thien-5-yl | F |
| 131 (a-e) | 1,3,5 trimethyl-1H-pyrazolyl | Cl |
| 132 (a-e) | 1,3,5 trimethyl-1H-pyrazolyl | F |
| 133 (a-e) | 1,3-dimethyl-5-Cl-1H-pyrazolyl | Cl |
| 134 (a-e) | 1,3-dimethyl-5-Cl-1H-pyrazolyl | F |
| 135 (a-e) | 1-methyl-3$CF_3$-1H-pyrazol-4-yl | Cl |
| 136 (a-e) | 1-methyl-3$CF_3$-1H-pyrazol-4-yl | F |
| 137 (a-e) | 2-acetamido-4-methyl-thiazol-5-yl | Cl |
| 138 (a-e) | 2-acetamido-4-methyl-thiazol-5-yl | F |
| 139 (a-e) | 2,4-dimethyl-thiazol-5-yl | Cl |
| 140 (a-e) | 2,4-dimethyl-thiazol-5-yl | F |
| 141 (a-e) | 1,2-dimethyl-1H-imidazol-4-yl | Cl |
| 142 (a-e) | 1,2-dimethyl-1H-imidazol-4-yl | F |

Table 5b shows embodiments of this invention which are compounds of formula I, where G is $Ar_1$, $Ar_2$ or $R_{1d}$, and where $R^0$ is H, Z is F and G and X are defined in the table. Each line in the table corresponds to five species ($Y_a$, $Y_b$, $Y_c$, $Y_d$ and $Y_e$) which differ only at position Y, where $Y_a$ = phenyl; $Y_b$ = 3-substituted phenyl; $Y_c$ = 3-pyridyl; $Y_d$ = 4-pyridyl; $Y_e$ = 3-pyrazolyl.

**Table 5b**




$Y_a$ = phenyl; $Y_b$ = 3-substituted phenyl; $Y_c$ = 3-pyridyl; $Y_d$ = 4-pyridyl; $Y_e$ = 3-pyrazolyl

| Compound # | G = $R_{1d}$, $Ar_1$, or $Ar_2$ | X |
|---|---|---|
| 1 (a-e) | phenyl | Cl |
| 2 (a-e) | phenyl | F |
| 3 (a-e) | 2-F-phenyl | Cl |
| 4 (a-e) | 2-F-phenyl | F |
| 5 (a-e) | 3-F-phenyl | Cl |
| 6 (a-e) | 3-F-phenyl | F |
| 7 (a-e) | 4-F-phenyl | Cl |
| 8 (a-e) | 4-F-phenyl | F |
| 9 (a-e) | 2,4-di-F-phenyl | Cl |
| 10 (a-e) | 2,4-di-F-phenyl | F |
| 11 (a-e) | 2,5-di-F-phenyl | Cl |
| 12 (a-e) | 2,5-di-F-phenyl | F |
| 13 (a-e) | 2,6-di-F-phenyl | Cl |
| 14 (a-e) | 2,6-di-F-phenyl | F |
| 15 (a-e) | 3,4-di-F-phenyl | Cl |
| 16 (a-e) | 3,4-di-F-phenyl | F |
| 17 (a-e) | 3,5-di-F-phenyl | Cl |
| 18 (a-e) | 3,5-di-F-phenyl | F |
| 19 (a-e) | 2,6-di-F-phenyl | Cl |
| 20 (a-e) | 2,6-di-F-phenyl | F |
| 21 (a-e) | 2,3,4-tri-F-phenyl | Cl |
| 22 (a-e) | 2,3,4-tri-F-phenyl | F |
| 23 (a-e) | 3,4,5-tri-F-phenyl | Cl |
| 24 (a-e) | 3,4,5-tri-F-phenyl | F |
| 25 (a-e) | penta-F-phenyl | Cl |
| 26 (a-e) | penta-F-phenyl | F |
| 27 (a-e) | 3-Cl-4-F-phenyl | Cl |
| 28 (a-e) | 3-Cl-4-F-phenyl | F |
| 29 (a-e) | 2-Cl-4-F-phenyl | Cl |
| 30 (a-e) | 2-Cl-4-F-phenyl | F |
| 31 (a-e) | 2-F-3-Cl-phenyl | Cl |
| 32 (a-e) | 2-F-3-Cl-phenyl | F |
| 33 (a-e) | 2-F-4-Cl-phenyl | Cl |
| 34 (a-e) | 2-F-4-Cl-phenyl | F |
| 35 (a-e) | 2-F-5-Cl-phenyl | Cl |
| 36 (a-e) | 2-F-5-Cl-phenyl | F |
| 37 (a-e) | 3-cyano-4-F-phenyl | Cl |
| 38 (a-e) | 3-cyano- 4-F-phenyl | F |
| 39 (a-e) | 2-Cl-phenyl | Cl |
| 40 (a-e) | 2-Cl-phenyl | F |

| Compound # | G = $R_{1d}$, $Ar_1$, or $Ar_2$ | X |
|---|---|---|
| 41 (a-e) | 3-Cl-phenyl | Cl |
| 42 (a-e) | 3-Cl-phenyl | F |
| 43 (a-e) | 4-Cl-phenyl | Cl |
| 44 (a-e) | 4-Cl-phenyl | F |
| 45 (a-e) | 2,3-di-Cl-phenyl | Cl |
| 46 (a-e) | 2,3-di-Cl-phenyl | F |
| 47 (a-e) | 2,5-di-Cl-phenyl | Cl |
| 48 (a-e) | 2,5-di-Cl-phenyl | F |
| 49 (a-e) | 2,6-di-Cl-phenyl | Cl |
| 50 (a-e) | 2,6-di-Cl-phenyl | F |
| 51 (a-e) | 3,5-di-Cl-phenyl | Cl |
| 52 (a-e) | 3,5-di-Cl-phenyl | F |
| 53 (a-e) | 2,4-di-Cl-phenyl | Cl |
| 54 (a-e) | 2,4-di-Cl-phenyl | F |
| 55 (a-e) | 3,4-di-Cl-phenyl | Cl |
| 56 (a-e) | 3,4-di-Cl-phenyl | F |
| 57 (a-e) | 2,4,6-tri-Cl-phenyl | Cl |
| 58 (a-e) | 2,4,6-tri-Cl-phenyl | F |
| 59 (a-e) | 2-Cl-4-$CF_3$-phenyl | Cl |
| 60 (a-e) | 2-Cl-4-$CF_3$-phenyl | F |
| 61 (a-e) | 2-$CF_3$-phenyl | Cl |
| 62 (a-e) | 2-$CF_3$-phenyl | F |
| 63 (a-e) | 3-$CF_3$-phenyl | Cl |
| 64 (a-e) | 3-$CF_3$-phenyl | F |
| 65 (a-e) | 4-$CF_3$-phenyl | Cl |
| 66 (a-e) | 4-$CF_3$-phenyl | F |
| 67 (a-e) | 2-$CF_3O$ phenyl | Cl |
| 68 (a-e) | 2-$CF_3O$ phenyl | F |
| 69 (a-e) | 3-$CF_3O$ phenyl | Cl |
| 70 (a-e) | 3-$CF_3O$ phenyl | F |
| 71 (a-e) | 4-$CF_3O$ phenyl | Cl |
| 72 (a-e) | 4-$CF_3O$ phenyl | F |
| 73 (a-e) | 4-$CHF_2O$-phenyl | Cl |
| 74 (a-e) | 4-$CHF_2O$-phenyl | F |
| 75 (a-e) | 2-methyl-5-nitro-phenyl | Cl |
| 76 (a-e) | 2-methyl-5-nitro-phenyl | F |
| 77 (a-e) | 2-cyano-phenyl | Cl |
| 78 (a-e) | 2-cyano-phenyl | F |
| 79 (a-e) | 3-cyano-phenyl | Cl |
| 80 (a-e) | 3-cyano-phenyl | F |

| Compound # | G = $R_{1d}$, $Ar_1$, or $Ar_2$ | X |
|---|---|---|
| 81 (a-e) | 4-cyano-phenyl | Cl |
| 82 (a-e) | 4-cyano-phenyl | F |
| 83 (a-e) | 4-methoxy-phenyl | Cl |
| 84 (a-e) | 4-methoxy-phenyl | F |
| 85 (a-e) | 3,4-dimethoxy-phenyl | Cl |
| 86 (a-e) | 3,4-dimethoxy-phenyl | F |
| 87 (a-e) | 3-carbamyl-phenyl | Cl |
| 88 (a-e) | 3-carbamyl-phenyl | F |
| 89 (a-e) | 3-carboxyl-phenyl | Cl |
| 90 (a-e) | 3-carboxyl- phenyl | F |
| 91 (a-e) | 3-(N,N-dimethylcarbamoyl)phenyl | Cl |
| 92 (a-e) | 3-(N,N-dimethylcarbamoyl)phenyl | F |
| 93 (a-e) | 4-methylsulfonyl-phenyl | Cl |
| 94 (a-e) | 4-methylsulfonyl-phenyl | F |
| 95 (a-e) | 3-(1,3,4 oxadiazol-2-yl)phenyl | Cl |
| 96 (a-e) | 3-(1,3,4 oxadiazol-2-yl)phenyl | F |
| 97 (a-e) | 3-(1,3,4 thiadiazol-2-yl)phenyl | Cl |
| 98 (a-e) | 3-(1,3,4 thiadiazol-2-yl)phenyl | F |
| 99 (a-e) | 3-(5-methyl-1,3,4-oxadiazol)phenyl | Cl |
| 100 (a-e) | 3-(5-methyl-1,3,4-oxadiazol)phenyl | F |
| 101 (a-e) | 3-(5-methyl-1,3,4-thiadiazol)phenyl | Cl |
| 102 (a-e) | 3-(5-methyl-1,3,4-thiadiazol)phenyl | F |
| 103 (a-e) | 3-amidinyl-phenyl | Cl |
| 104 (a-e) | 3-amidinyl-phenyl | F |
| 105 (a-e) | 3-(1H-tetrazolyl)phenyl | Cl |
| 106 (a-e) | 3-(1H-tetrazolyl)phenyl | F |
| 107 (a-e) | 4-acetamido-phenyl | Cl |
| 108 (a-e) | 4-acetamido-phenyl | F |
| 109 (a-e) | 3-Cl-4-[(N-morpholinylcarbonyl) amino]phenyl | Cl |
| 110 (a-e) | 3-Cl-4-[(N-morpholinylcarbonyl) amino]phenyl | F |
| 111 (a-e) | 3-Cl-4-[(N-pyrrolidinylcarbonyl) amino]phenyl | Cl |
| 112 (a-e) | 3-Cl-4-[(N-pyrrolidinylcarbonyl) amino]phenyl | F |
| 113 (a-e) | 3,5-dimethylisoxazolyl | Cl |
| 114 (a-e) | 3,5-dimethylisoxazolyl | F |
| 115 (a-e) | 4-(N-morpholinylsulfonyl)phenyl | Cl |
| 116 (a-e) | 4-(N-morpholinylsulfonyl)phenyl | F |
| 117 (a-e) | 3-F-benzyl | Cl |
| 118 (a-e) | 3-F-benzyl | F |
| 119 (a-e) | 4-F-benzyl | Cl |
| 120 (a-e) | 4-F-benzyl | F |
| 121 (a-e) | 3-F-phenyl-ethyl | Cl |
| 122 (a-e) | 3-F-phenyl-ethyl | F |
| 123 (a-e) | 4-F-phenyl-ethyl | Cl |
| 124 (a-e) | 4-F-phenyl-ethyl | F |
| 125 (a-e) | 8-quinolinyl | Cl |
| 126 (a-e) | 8-quinolinyl | F |
| 127 (a-e) | 2-thienyl | Cl |
| 128 (a-e) | 2-thienyl | F |
| 129 (a-e) | 2,3-di-Cl-thien-5-yl | Cl |
| 130 (a-e) | 2,3-di-Cl-thien-5-yl | F |
| 131 (a-e) | 1,3,5 trimethyl-1H-pyrazolyl | Cl |
| 132 (a-e) | 1,3,5 trimethyl-1H-pyrazolyl | F |
| 133 (a-e) | 1,3-dimethyl-5-Cl-1H-pyrazolyl | Cl |
| 134 (a-e) | 1,3-dimethyl-5-Cl-1H-pyrazolyl | F |
| 135 (a-e) | 1-methyl-3-$CF_3$-1H-pyrazol-4-yl | Cl |
| 136 (a-e) | 1-methyl-3-$CF_3$-1H-pyrazol-4-yl | F |
| 137 (a-e) | 2-acetamido-4-methyl-thiazol-5-yl | Cl |
| 138 (a-e) | 2-acetamido-4-methyl-thiazol-5-yl | F |
| 139 (a-e) | 2,4-dimethyl-thiazol-5-yl | Cl |
| 140 (a-e) | 2,4-dimethyl-thiazol-5-yl | F |
| 141 (a-e) | 1,2-dimethyl-1H-imidazol-4-yl | Cl |
| 142 (a-e) | 1,2-dimethyl-1H-imidazol-4-yl | F |
| 143 (a-e) | 1-(2-hydroxyethyl) cyclopropyl | F |
| 144 (a-e) | 1-(3-hydroxypropyl) cyclopropyl | F |
| 145 (a-e) | 1-(2,3-dihydroxypropyl) cyclopropyl | F |
| 146 (a-e) | 1-(3,4-dihydroxybutyl) cyclopropyl | F |
| 147 (a-e) | 1-(2,3-dihydroxypropyl) cyclobutyl | F |

16

***Synthetic Procedures***

In another aspect, methods for synthesizing the compounds described herein are provided. In some embodiments, the compounds described herein can be made by the methods described below. The procedures and examples below are intended to illustrate those methods. Neither the procedures nor the examples should be construed as limiting the invention in any way. Compounds described herein may also be synthesized using standard synthetic techniques known to those of skill in the art or using methods known in the art in combination with methods described herein. In additions, solvents, temperatures and other reaction conditions presented herein may vary according to the practice and knowledge of those of skill in the art.

The starting materials for the synthesis of the compounds as described herein may be obtained from commercial sources, such as Aldrich Chemical Co. (Milwaukee, Wis.), Sigma Chemical Co. (St. Louis, Mo.), or the starting materials can be synthesized. The compounds described herein, and other related compounds having different substituents can be synthesized using techniques and materials known to those of skill in the art, such as described, for example, in March, ADVANCED ORGANIC CHEMISTRY 4th Ed., (Wiley 1992); Carey and Sundberg, ADVANCED ORGANIC CHEMISTRY 4th Ed., Vols. A and B (Plenum 2000, 2001), and Green and Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS 3rd Ed., (Wiley 1999) (all of which are incorporated by reference in their entirety). General methods for the preparation of compound as disclosed herein may be derived from known reactions in the field, and the reactions may be modified by the use of appropriate reagents and conditions, as would be recognized by the skilled person, for the introduction of the various moieties found in the formulae as provided herein. As a guide the following synthetic methods may be utilized.

Formation of Covalent Linkages by Reaction of an Electrophile with a Nucleophile

The compounds described herein can be modified using various electrophiles or nucleophiles to form new functional groups or substituents. The table below entitled "Examples of Covalent Linkages and Precursors Thereof" lists selected examples of covalent linkages and precursor functional groups which yield and can be used as guidance toward the variety of electrophiles and nucleophiles combinations available. Precursor functional groups are shown as electrophilic groups and nucleophilic groups.

| Covalent Linkage Product | Electrophile | Nucleophile |
|---|---|---|
| Carboxamides | Activated esters | Amines/anilines |
| Carboxamides | Acyl azides | Amines/anilines |
| Carboxamides | Acyl halides | Amines/anilines |
| Esters | Acyl halides | Alcohols/phenols |
| Esters | Acyl nitriles | Alcohols/phenols |
| Carboxamides | Acyl nitriles | Amines/anilines |
| Imines | Aldehydes | Amines/anilines |
| Hydrazones | Aldehydes or ketones | Hydrazines |
| Oximes | Aldehydes or ketones | Hydroxylamines |
| Alkyl amines | Alkyl halides | Amines/anilines |
| Esters | Alkyl halides | Carboxylic acids |
| Thioethers | Alkyl halides | Thiols |
| Ethers | Alkyl halides | Alcohols/phenols |
| Thioethers | Alkyl sulfonates | Thiols |
| Esters | Alkyl sulfonates | Carboxylic acids |
| Ethers | Alkyl sulfonates | Alcohols/phenols |
| Esters | Anhydrides | Alcohols/phenols |
| Carboxamides | Anhydrides | Amines/anilines |
| Thiophenols | Aryl halides | Thiols |
| Aryl amines | Aryl halides | Amines |
| Thioethers | Aziridines | Thiols |

| Boronate esters | Boronates | Glycols |
|---|---|---|
| Carboxamides | Carboxylic acids | Amines/anilines |
| Esters | Carboxylic acids | Alcohols |
| Hydrazines | Hydrazides | Carboxylic acids |
| *N*-acylureas or Anhydrides | Carbodiimides | Carboxylic acids |
| Esters | Diazoalkanes | Carboxylic acids |
| Thioethers | Epoxides | Thiols |
| Thioethers | Haloacetamides | Thiols |
| Ammotriazines | Halotriazines | Amines/anilines |
| Triazinyl ethers | Halotriazines | Alcohols/phenols |
| Amidines | Imido esters | Amines/anilines |
| Ureas | Isocyanates | Amines/anilines |
| Urethanes | Isocyanates | Alcohols/phenols |
| Thioureas | Isothiocyanates | Amines/anilines |
| Thioethers | Maleimides | Thiols |
| Phosphite esters | Phosphoramidites | Alcohols |
| Silyl ethers | Silyl halides | Alcohols |
| Alkyl amines | Sulfonate esters | Amines/anilines |
| Thioethers | Sulfonate esters | Thiols |
| Esters | Sulfonate esters | Carboxylic acids |
| Ethers | Sulfonate esters | Alcohols |
| Sulfonamides | Sulfonyl halides | Amines/anilines |
| Sulfonate esters | Sulfonyl halides | Phenols/alcohols |

*Examples of Covalent Linkages and Precursors Thereof*

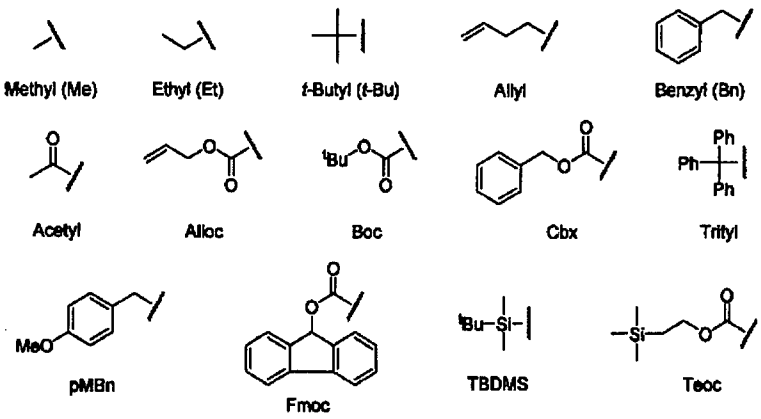
Use of Protecting Groups

In the reactions described, it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Protecting groups are used to block some or all reactive moieties and prevent such groups from participating in chemical reactions until the protective group is removed. In some embodiments, each protective group is removable by a different means. Protective groups that are cleaved under totally disparate reaction conditions fulfill the requirement of differential removal. Protective groups can be removed by acid, base, and hydrogenolysis. Groups such as trityl, dimethoxytrityl, acetal and t-butyldimethylsilyl are acid labile and may be used to protect carboxy and hydroxy reactive moieties in the presence of amino groups protected with Cbz groups, which are removable by hydrogenolysis, and Fmoc groups, which are base labile. Carboxylic acid and hydroxy reactive moieties may be blocked with base labile groups such as, but not limited to, methyl, ethyl, and acetyl in the presence of amines blocked with acid labile groups such as t-butyl carbamate or with carbamates that are both acid and base stable but hydrolytically removable.

Carboxylic acid and hydroxy reactive moieties may also be blocked with hydrolytically removable protective groups such as the benzyl group, while amine groups capable of hydrogen bonding with acids may be blocked with base labile groups such as Fmoc. Carboxylic acid reactive moieties may be protected by conversion to simple ester compounds as exemplified herein, or they may be blocked with oxidatively-removable protective groups such as 2,4-dimethoxybenzyl, while co-existing amino groups may be blocked with fluoride labile silyl carbamates.

Allyl blocking groups are useful in then presence of acid- and base- protecting groups since the former are stable and can be subsequently removed by metal or pi-acid catalysts. For example, an allyl-blocked carboxylic acid can be deprotected with a Pd-catalyzed reaction in the presence of acid labile t-butyl carbamate or base-labile acetate amine protecting groups. Yet another form of protecting group is a resin to which a compound or intermediate may be attached. As long as the residue is attached to the resin, that functional group is blocked and cannot react. Once released from the resin, the functional group is available to react.

Protecting or blocking groups may be selected from:

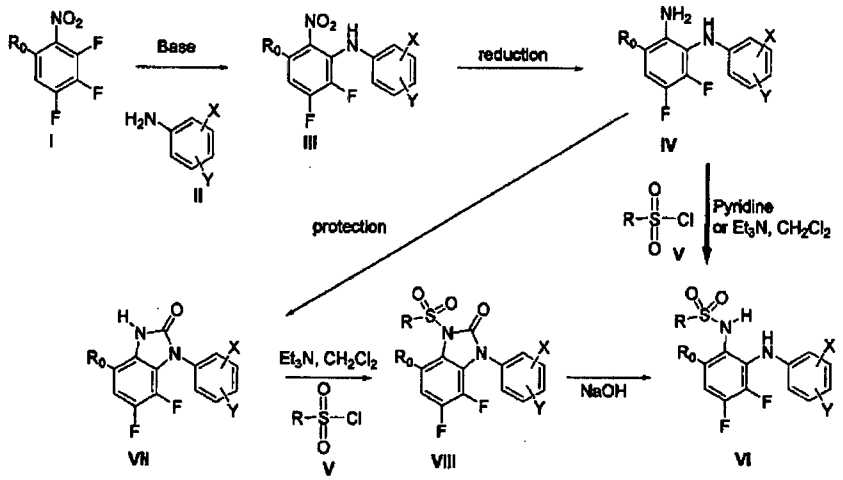



Other protecting groups, plus a detailed description of techniques applicable to the creation of protecting groups and their removal are described in Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999, and Kocienski, Protective Groups, Thieme Verlag, New York, NY, 1994, which are incorporated herein by reference in their entirety.

Making compounds of formula I

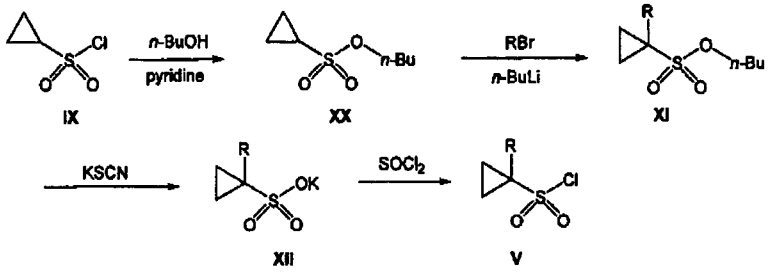
Compounds of this invention can be made by a variety of methods. The procedures below are intended to illustrate those methods, and the examples given are intended to illustrate the scope of this invention. Neither the methods not the examples should be construed as limiting the invention in any way.

I. The preparation of compound of formula VI is outlined below



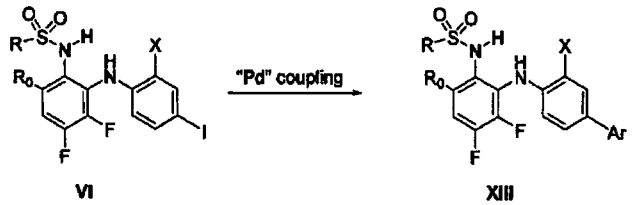

Scheme I above illustrates a method for making the sulfonamide derivatives of formula VI. 1,2 Diamine derivative (formula IV) can be easily prepared in two steps from the desired nitro derivatives (formula I). Compounds of formula IV can be reacted with the sulfonyl chloride derivatives (formula V, see next scheme) to form the desired sulfonamide. Alternatively, the 1,2 diamine derivatives IV can be protected to for an imidazolidone (formula VII), before being reacted with the corresponding sulfonyl chloride. Deprotection of the 1,2 diamine VIII under basic conditions provided the desired material VI.

**II.** The general route to synthesis compound of general formula V is outlined below



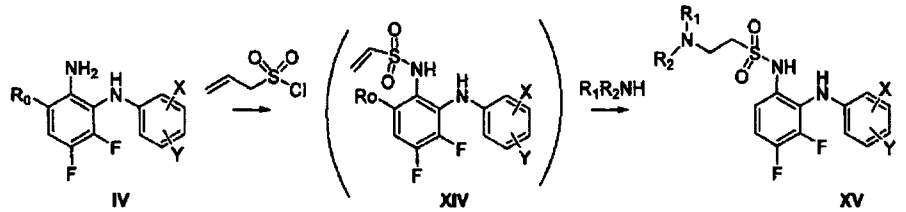

Scheme II above shows one example of the preparation of complex sulfonyl chloride. Compound XX can be synthesized from IX, alkylated, and converted to the potassium salt XII. Treatment of the salt with $SOCl_2$ or $POCl_3$ affords the desired compounds. Other more specific procedures to prepare unique sulfonyl chloride derivatives are reported in the experimental section.

**III.** The general route to synthesis compound of general formula XIII is outlines Scheme 3.




Scheme III above illustrates the preparation of sulfonamide derivatives of general formula XIII. For example, these compounds can be easily obtained by reacting the compound VI with a boronic acid using a palladium catalyst under Suzuki conditions.

**IV.** The general route to synthesis compound of general formula XIII is outlines Scheme 4.




Scheme IV above illustrates the preparation of sulfonamide derivatives of general formula XV. The vinyl sulfonamide (XIV) is reacted with amines to form derivatives of general formulas XV.

***Further Forms of Compounds of Formula I***

Isomers of compounds of formula I

The compounds described herein may exist as geometric isomers. The compounds described herein may possess one or more double bonds. The compounds presented herein include all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the corresponding mixtures thereof. In some situations, compounds may exist as tautomers. The compounds described herein include all possible tautomers within the formulas described herein. The compounds described herein may possess one or more chiral centers and each center may exist in the R or S configuration. The compounds described herein include all diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. In additional embodiments of the compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion may also be useful for the applications described herein. The compounds described herein can be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. Resolution of enantiomers can

be carried out using covalent diastereomeric derivatives of the compounds described herein, or dissociable complexes may be used (e.g., crystalline diastereomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chiral chromatography, or separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions," John Wiley And Sons, Inc., 1981, herein incorporated by reference in its entirety.

Labeled compounds of formula I

Also described herein are isotopically-labeled compounds of formula I and methods of treating disorders. For example, the invention provides for methods of treating diseases, by administering isotopically-labeled compounds of formula I. The isotopically-labeled compounds of formula I can be administered as pharmaceutical compositions. Thus, compounds of formula I also include isotopically-labeled compounds, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chloride, such as $^{2}H$, $^{3}H$, $^{13}C$, $^{14}C$, $^{15}N$, $^{18}0$, $^{17}O$, $^{31}P$, $^{32}P$, $^{35}S$, $^{18}F$, and $^{36}Cl$, respectively. Compounds described herein, pharmaceutically acceptable salts, thereof which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds of formula I, for example those into which radioactive isotopes such as $^{3}H$ and $^{14}C$ are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i. e., $^{3}H$ and carbon-14, i. e., $^{14}C$, isotopes are often easily prepared and detectabilited. Further, substitution with heavier isotopes such as deuterium, i. e., $^{2}H$, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be desirable in some circumstances. Isotopically labeled compounds and pharmaceutically acceptable salts thereof can generally be prepared by carrying out procedures described herein, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

The compounds described herein may be labeled by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

Pharmaceutically acceptable salts of compounds of formula I

Also described herein are pharmaceutically acceptable salts of compounds of formula I and methods of treating disorders. For example, the invention provides for methods of treating diseases, by administering pharmaceutically acceptable salts of compounds of formula I. The pharmaceutically acceptable salts of compounds of formula I can be administered as pharmaceutical compositions.

Thus, the compounds described herein can be prepared as pharmaceutically acceptable salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, for example an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base. Base addition salts can also be prepared by reacting the free acid form of the compounds described herein with a pharmaceutically acceptable inorganic or organic base, including, but not limited to organic bases such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like and inorganic bases such as aluminum hydroxide, calcium hydroxide, potassium

hydroxide, sodium carbonate, sodium hydroxide, and the like. In addition, the salt forms of the disclosed compounds can be prepared using salts of the starting materials or intermediates.

Further, the compounds described herein can be prepared as pharmaceutically acceptable salts formed by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid, including, but not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid metaphosphoric acid, and the like; and organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, Q-toluenesulfonic acid, tartaric acid, trifluoroacetic acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, arylsulfonic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1 -carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, and muconic acid.

Solvates of compounds of formula I

Also described herein are solvates of compounds of formula I and methods of treating disorders. For example, the invention provides for methods of treating diseases, by administering solvates of compounds of formula I. The solvates of compounds of formula I can be administered as pharmaceutical compositions.

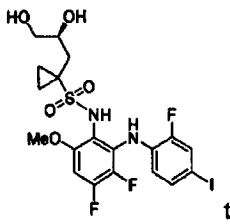
Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and may be formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of the compounds described herein can be conveniently prepared or formed during the processes described herein. By way of example only, hydrates of the compounds described herein can be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents including, but not limited to, dioxane, tetrahydrofuran or methanol. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

Polymorphs of compounds of formula I

Also described herein are polymorphs of compounds of formula I and methods of treating disorders. For example, the invention provides for methods of treating diseases, by administering polymorphs of compounds of formula I. The polymorphs of compounds of formula I can be administered as pharmaceutical compositions.

Thus, the compounds described herein include all their crystalline forms, known as polymorphs. Polymorphs include the different crystal packing arrangements of the same elemental composition of a compound. Polymorphs may have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and solubility. Various factors such as the recrystallization solvent, rate of crystallization, and storage temperature may cause a single crystal form to dominate.

**Crystalline Polymorph Form of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide**

The invention also relates to a crystalline polymorph form A of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-l-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide:  that exhibits a specific powder x-ray diffraction pattern. In some embodiments, the powder x-ray diffraction pattern contains at least about 50% of the peaks shown in **FIG. 5**. In some embodiments, the powder x-ray diffraction pattern contains at least about 70% of the peaks shown in **FIG. 5**. In some embodiments, the powder x-ray diffraction pattern contains at least about 90% of the peaks shown in **FIG. 5**. In some embodiments, the powder x-ray diffraction pattern is substantially the same the powder x-ray diffraction pattern shown in **FIG. 5**.

The invention also relates to a crystalline polymorph form A of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-l-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide that exhibits a specific differential scanning calorimetry pattern. In some embodiments, the specific differential scannin calorimetry patern is substantially the same as the differential scanning calorimetry pattern shown in **FIG. 6**. In some embodiments the crystalline polymorph form A has a melting point onset as determined by differential scanning calorimetry at about 143°C.

The invention also relates to a polymorphic form of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-l-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide made by a method comprising the step of crystallizing amorphous N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-l-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide from a solvent. The invention also relates to a polymorphic form of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-l-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide made by a method comprising the step of crystallizing amorphous N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-l-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide from a mixture of hexane and ethyl acetate.

The invention also relates to pharmaceutical compositions comprising an effective amount of crystalline polymorph form A of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-l-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide and a pharmaceutically acceptable carrier or vehicle. Other aspects of the invention relate to a pharmaceutical composition comprising the crystalline polymorph form A and at least one excipient or carrier.

The crystalline polymorph form A of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-l-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide is useful for treating or preventing cancer or an inflammatory disease. The invention further relates to methods for treating or preventing cancer or an inflammatory disease, comprising administering an effective amount of a crystalline polymorph form A of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-l-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide to a subject in need thereof. Yet other aspects of the invention relate to methods for the treatment or prophylaxis of an inflammatory disease comprising administering to a subject in need thereof an effective amount of the crystalline polymorph. Further aspects of the invention relate to methods for the treatment or prophylaxis of a proliferative disease comprising administering to a subject in need thereof an effective amount of the crystalline polymorph.

Prodrugs of compounds of formula I

Also described herein are prodrugs of compounds of formula I and methods of treating disorders. For example, the invention provides for methods of treating diseases, by administering prodrugs of compounds of formula I. The prodrugs of compounds of formula I can be administered as pharmaceutical compositions.

Prodrugs are generally drug precursors that, following administration to a subject and subsequent absorption, are converted to an active, or a more active species via some process, such as conversion by a metabolic pathway. Some prodrugs have a chemical group present on the prodrug that renders it less active and/or confers solubility or some other property to the drug. Once the chemical group has been cleaved and/or modified from the prodrug the active drug is generated. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. An example, without limitation, of a prodrug would be a compound as described herein which is administered as an ester (the "prodrug") to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water-solubility is beneficial. A further example of a prodrug might be a short peptide (polyamino acid) bonded to an acid group where the peptide is metabolized to reveal the active moiety.

Prodrugs may be designed as reversible drug derivatives, for use as modifiers to enhance drug transport to site-specific tissues. The design of prodrugs to date has been to increase the effective water solubility of the therapeutic compound for targeting to regions where water is the principal solvent. See, e.g., Fedorak et al., *Am. J. Physiol.*, 269:G210-218 (1995); McLoed et al., *Gastroenterol*, 106:405-413 (1994); Hochhaus et al., *Biomed. Chrom.*, 6:283-286 (1992); J. Larsen and H. Bundgaard, *Int. J. Pharmaceutics*, 37, 87 (1987); J. Larsen et al., *Int. J. Pharmaceutics*, 47, 103 (1988); Sinkula et al., *J. Pharm. Sci.*, 64:181-210 (1975); T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems*, Vol. 14 of the A.C.S. Symposium Series; and Edward B. Roche, *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, 1987, all incorporated herein in their entirety.

Additionally, prodrug derivatives of compounds described herein can be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier et al., (1994), Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985). By way of example only, appropriate prodrugs can be prepared by reacting a non-derivatized compound of formula I with a suitable carbamylating agent, such as, but not limited to, 1,1-acyloxyalkylcarbanochloridate, para-nitrophenyl carbonate, or the like. Prodrug forms of the herein described compounds, wherein the prodrug is metabolized *in vivo* to produce a derivative as set forth herein are included within the scope of the claims. Indeed, some of the herein-described compounds may be a prodrug for another derivative or active compound.

In some embodiments, prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e. g., two, three or four) amino acid residues is covalently joined through an amide or ester bond to a free amino, hydroxy or carboxylic acid group of compounds of the present invention. The amino acid residues include but are not limited to the 20 naturally occurring amino acids commonly designated by three letter symbols and also includes 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvaline, beta-alanine, gamma-aminobutyric acid, cirtulline, homocysteine, homoserine, ornithine and methionine sulfone. Additional types of prodrugs are also encompassed.

Compounds of formula I having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. For instance, free carboxyl groups can be derivatized as amides or alkyl esters. Free hydroxy groups may be derivatized using groups including but not limited to hemisuccinates, phosphate esters, dimethylaminoacetates, and phosphoryloxymethyloxycarbonyls, as outlined in *Advanced Drug Delivery Reviews* **1996**, *19*, 115. Carbamate prodrugs of hydroxy and amino groups are also included, as are carbonate prodrugs, sulfonate esters and sulfate esters of hydroxy groups.

Derivatization of hydroxy groups as (acyloxy) methyl and (acyloxy) ethyl ethers wherein the acyl group may be an alkyl ester, optionally substituted with groups including but not limited to ether, amine and carboxylic acid functionalities, or where the acyl group is an amino acid ester as described above, are also encompassed. Prodrugs of this type are described in *J. Med. Chem.* **1996**, *39*, 10. Free amines can also be derivatized as amides, sulfonamides or phosphonamides. All of these prodrug moieties may incorporate groups including but not limited to ether, amine and carboxylic acid functionalities.

Sites on the aromatic ring portions of compounds of formula I may be susceptible to various metabolic reactions, therefore incorporation of appropriate substituents on the aromatic ring structures, can reduce, minimize or eliminate this metabolic pathway.

***Pharmaceutical Compositions***

Described herein are pharmaceutical compositions. In some embodiments, the pharmaceutical compositions comprise an effective amount of a compound formula I, or a pharmaceutically acceptable salt, thereof. In some embodiments, the pharmaceutical compositions comprise an effective amount of a compound formula I, or a pharmaceutically acceptable salt, solvate, polymorph, ester, amide, tautomer, prodrug, hydrate, or derivative thereof and at least one pharmaceutically acceptable carrier. In some embodiments the pharmaceutical compositions are for the treatment of disorders. In some embodiments the pharmaceutical compositions are for the treatment of disorders in a mammal. In some embodiments the pharmaceutical compositions are for the treatment of disorders in a human.

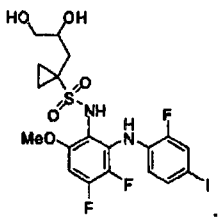
In further aspects, the present invention is directed to a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, amide, tautomer or prodrug thereof. In some embodiments, the pharmaceutical compositions further comprise a pharmaceutically acceptable carrier. Such compositions may contain adjuvants, excipients, and preservatives, agents for delaying absorption, fillers, binders, adsorbents, buffers, disintegrating agents, solubilizing agents, other carriers, and other inert ingredients. Methods of formulation of such compositions are well-known in the art.

In some embodiments, the pharmaceutical composition is in a form suitable for oral administration. In further or additional embodiments, the pharmaceutical composition is in the form of a tablet, capsule, pill, powder, sustained release formulation, solution, suspension, for parenteral injection as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

In further or additional embodiments, the pharmaceutical composition is in unit dosage forms suitable for single administration of precise dosages. In further or additional embodiments the amount of compound of formula I is in the range of about 0.001 to about 1000 mg/kg body weight/day. In further or additional embodiments the amount of compound of formula I is in the range of about 0.5 to about 50 mg/kg/day. In further or additional embodiments the amount of compound of formula I is about 0.001 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.002 to about 6 g/day. In further or additional embodiments the amount of compound of formula I is about 0.005 to about 5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.01 to about 5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.02 to about 5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.05 to about 2.5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.1 to about 1 g/day. In further or additional embodiments, dosage levels below the lower limit of the aforesaid range may be more than adequate. In further or additional embodiments, dosage levels above the upper limit of the aforesaid range may be required.

In further or additional embodiments the compound of formula I is administered in a single dose, once daily. In further or additional embodiments the compound of formula I is administered in multiple doses, more than once per day. In further or additional embodiments the compound of formula I is administered twice daily. In further or additional embodiments the compound of formula I is administered three times per day. In further or additional embodiments the compound of formula I is administered four times per day. In further or additional embodiments the compound of formula I is administered more than four times per day. In some embodiments, the pharmaceutical composition is for administration to a mammal. In further or additional embodiments, the mammal is human.

In further or additional embodiments, the pharmaceutical composition further comprises a pharmaceutical carrier, excipient and/or adjuvant. In further or additional embodiments, the pharmaceutical composition further comprises at least one therapeutic agent. In further or additional embodiments, the therapeutic agent is selected from the group of cytotoxic agents, anti-angiogenesis agents and anti-neoplastic agents. In further or additional embodiments, the anti-neoplastic agent is selected from the group of consisting of alkylating agents, anti-metabolites, epidophyllotoxins; antineoplastic enzymes, topoisomerase inhibitors, procarbazines, mitoxantrones, platinum coordination complexes, biological response modifiers and growth inhibitors, hormonal/anti-hormonal therapeutic agents, and haematopoietic growth factors. In further or additional embodiments, the therapeutic agent is taxol, bortezomib or both. In further or additional embodiments, the pharmaceutical composition is administered in combination with an additional therapy. In further or additional embodiments, the additional therapy is radiation therapy, chemotherapy, surgery, or any combination thereof. In further or additional embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable salt of a compound of formula I.



The invention also relates to a composition comprising . In some embodiments, the 2-OH carbon on the compound is in the R configuration. In some embodiments, composition is substantially free of the S-isomer of the compound. In some embodiments, the compound contains less than 10% of the S- isomer of the compound. In some embodiments, the compound contains less than 5% of the S- isomer of the compound. In some embodiments, the compound contains less than 1% of the S- isomer of the compound. In some embodiments, the compound is in the R configuration.

In some embodiments, the 2-OH carbon on the compound is in the S configuration. In some embodiments, composition is substantially free of the R- isomer of the compound. In some embodiments, the compound contains less than 10% of the R- isomer of the compound. In some embodiments, the compound contains less than 5% of the R-isomer of the compound. In some embodiments, the compound contains less than 1% of the R- isomer of the compound. In some embodiments, the compound is in the S configuration.

In some embodiments, the composition contains at least about 50% of a compound which exhibits a powder x-ray diffraction pattern comprising at least 50% of the peaks identified in the powder x-ray diffraction pattern shown in FIG. 5. In some embodiments, the powder x-ray diffraction pattern comprises at least 70% of the peaks identified in the powder x-ray diffraction pattern shown in FIG. 5. In some embodiments, the powder x-ray diffraction pattern comprises at least 90% of the peaks identified in the In some embodiments, the powder x-ray diffraction pattern substantially the same as the powder x-ray diffraction pattern shown in FIG. 5.

In some embodiments, the composition contains at least about 75% of a compound which exhibits a powder x-ray diffraction pattern comprising at least 50% of the peaks identified in the powder x-ray diffraction pattern shown in FIG. 5. In some embodiments, the powder x-ray diffraction pattern comprises at least 70% of the peaks identified in the powder x-ray diffraction pattern shown in FIG. 5. In some embodiments, the powder x-ray diffraction pattern comprises at least 90% of the peaks identified in the In some embodiments, the powder x-ray diffraction pattern substantially the same as the powder x-ray diffraction pattern shown in FIG. 5.

In some embodiments, the composition contains at least about 90% of a compound which exhibits a powder x-ray diffraction pattern comprising at least 50% of the peaks identified in the powder x-ray diffraction pattern shown in FIG. 5. In some embodiments, the powder x-ray diffraction pattern comprises at least 70% of the peaks identified in the powder x-ray diffraction pattern shown in FIG. 5. In some embodiments, the powder x-ray diffraction pattern comprises at least 90% of the peaks identified in the In some embodiments, the powder x-ray diffraction pattern substantially the same as the powder x-ray diffraction pattern shown in FIG. 5.

In some embodiments, substantially all of the compound in the composition exhibits a powder x-ray diffraction pattern comprising at least 50% of the peaks identified in the powder x-ray diffraction pattern shown in FIG. 5. In some embodiments, the powder x-ray diffraction pattern comprises at least 70% of the peaks identified in the powder x-ray diffraction pattern shown in FIG. 5. In some embodiments, the powder x-ray diffraction pattern comprises at least 90% of the peaks identified in the In some embodiments, the powder x-ray diffraction pattern substantially the same as the powder x-ray diffraction pattern shown in FIG. 5.

In some embodiments, the crystalline polymorph present in the composition has a melting point onset as determined by differential scanning calorimetry at about 143°C. In some embodiments, the crystalline polymorph is substantially free of water. In some embodiments, the crystalline polymorph is substantially free of solvent.

In some embodiments, the composition contains at least about 50% of a compound which exhibits a differential scanning calorimetry pattern substantially the same as the differential scanning calorimetry pattern shown in FIG. 6. In some embodiments, the crystalline polymorph has a melting point onset as determined by differential scanning calorimetry at about 143°C. In some embodiments, the crystalline polymorph is substantially free of water. In some embodiments, the crystalline polymorph is substantially free of solvent.

In some embodiments, the composition contains at least about 75% of a compound which exhibits a differential scanning calorimetry pattern substantially the same as the differential scanning calorimetry pattern shown in FIG. 6. In some embodiments, the crystalline polymorph has a melting point onset as determined by differential scanning calorimetry at about 143°C. In some embodiments, the crystalline polymorph is substantially free of water. In some embodiments, the crystalline polymorph is substantially free of solvent.

In some embodiments, the composition contains at least about 90% of a compound which exhibits a differential scanning calorimetry pattern substantially the same as the differential scanning calorimetry pattern shown in FIG. 6. In some embodiments, the crystalline polymorph has a melting point onset as determined by differential scanning calorimetry at about 143°C. In some embodiments, the crystalline polymorph is substantially free of water. In some embodiments, the crystalline polymorph is substantially free of solvent.

In some embodiments, substantially all the compound in the composition exhibits a differential scanning calorimetry pattern substantially the same as the differential scanning calorimetry pattern shown in FIG. 6. In some embodiments, the crystalline polymorph has a melting point onset as determined by differential scanning calorimetry at about 143°C. In some embodiments, the crystalline polymorph is substantially free of water. In some embodiments, the crystalline polymorph is substantially free of solvent.

In some embodiments, the polymorphic form of N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-l-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide made by a method comprising the step of crystallizing amorphous N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-l-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide. In some embodiments, the crystallization step comprises crystallizing from a mixture of ethyl acetate and heptane, for example, a mixture of ethyl acetate and heptane is in a ratio of from about 1-4 parts ethyl acetate to about 2-10 parts heptane or more specifically, a ratio of from about 2 parts ethyl acetate to about 5 parts heptane.

In some embodiments, the compound is formulated for the immediate release of the compound. In some embodiments, the compound is formulated for the sustained release of the compound. In other embodiments, the compound is formulated for the extended release of the compound.

In some embodiments, the composition is in a tablet dosage form. In other embodiments, the composition is in a capsule dosage form. The composition can be made into a capsule or tablet dosage form and a wide range of alternative compositions and manufacturing approaches can be used, References: (1) Remington, The Science and Practice of Pharmacy, 20th Edition, 2000, (2) Pharmaceutical Dosage Forms Tablets Volumes 1-3, 1989 and (3) Modern Pharmaceuticals 4th Edition, 2002. A range of manufacturing approaches can be employed including dry blending, wet granulation, roller compaction, extrusion, spheronization, coating, and spray drying processes. Soft gel formulation and manufacturing approaches are also possible.

In some embodiments, the composition includes a filler or diluent. In various embodiments, the filler or diluent is selected from microcrystalline cellulose, silicified microcrystalline cellulose, lactose, mannitol, compressible sugar, calcium phosphate, calcium sulfate, calcium carbonate, calcium silicate and starch. In other embodiments, the filler or diluent is microcrystalline cellulose.

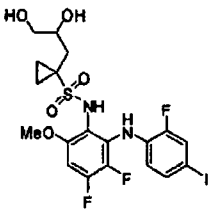
In some embodiments, the composition includes a disintegrant. In various embodiments, the disintegrant is selected from croscarmellose sodium, sodium starch glycolate, crospovidone, methylcellulose, alginic acid, sodium alginate, starch derivatives, betonite and veegum. In some embodiment, the disintegrant is croscarmellose sodium.

In some embodiments, the composition includes a lubricant. In various embodiments, the lubricant is selected from magnesium stearate, metallic stearates, talc, sodium stearyl fumarate and stearic acid. In some embodiments, the lubricant is magnesium stearate.

In some embodiments, the composition includes a wetting agent or surfactant. In various embodiments, the wetting agent or surfactant is selected from sodium lauryl sulfate, glycerol, sorbitan oleates, sorbitan stearates, polyoxyethylenated sorbitan laurate, palmitate, stearate, oleate or hexaolate, polyoxyethylene stearyl alcohol and sorbitan monolaurate. In some embodiments, the wetting agent or surfactant is sodium lauryl sulfate.

Additional excipients such as glidants, flavors, and colorants can also be added. Additional alternative excipients can be found in The Handbook of Pharmaceutical Excipients, 5th Edition, 2005 and the FDA Inactive Ingredient database.

The invention also relates to a composition comprising:

about 1mg of a compound of structure:  (as defined in any of the above embodiments);

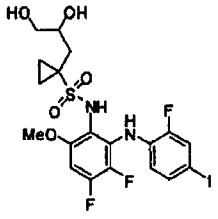
about 222.2mg of microcrystalline cellulose;

about 12.0mg of croscarmellose sodium;

about 2.4mg of sodium lauryl sulfate; and

about 2.4mg of magnesium stearate.

The invention also relates to a composition comprising:

about 10mg of a compound of structure:  (as defined in any of the above embodiments);

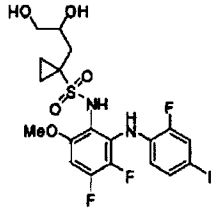
about 213.2mg of microcrystalline cellulose;

about 12.0mg of croscarmellose sodium;

about 2.4mg of sodium lauryl sulfate; and

about 2.4mg of magnesium stearate.

The invention also relates to a composition comprising:

about 20mg of a compound of structure:  (as defined in any of the above embodiments);

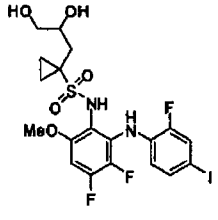
about 203.2mg of microcrystalline cellulose;

about 12.0mg of croscarmellose sodium;

about 2.4mg of sodium lauryl sulfate; and

about 2.4mg of magnesium stearate.

The invention also relates to a composition comprising:

about 40mg of a compound of structure:  (as defined in any of the above embodiments);

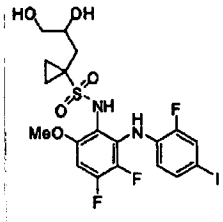
about 183.2mg of microcrystalline cellulose;

about 12.0mg of croscarmellose sodium;

about 2.4mg of sodium lauryl sulfate; and

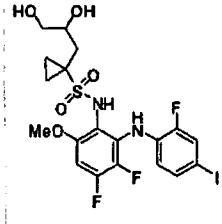
about 2.4mg of magnesium stearate.

The invention also relates to a composition comprising: about 0.4% by weight of a compound of structure:



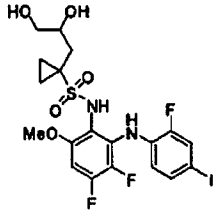
(as defined in any of the above embodiments), and about 99.6% by weight of a pharmaceutically acceptable carrier or vehicle. In some embodiments, the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose. In further or additional embodiments, the microcrystalline cellulose is about 92.6% by weight of the composition. In further or additional embodiments, the composition further comprises: about 5% by weight croscarmellose sodium; about 1% by weight sodium lauryl sulfate; and about 1% by weight magnesium stearate.

The invention also relates to a composition comprising: about 4.2% by weight of a compound of structure:



(as defined in any of the above embodiments); and about 95.8 % by weight of a pharmaceutically acceptable carrier or vehicle. In some embodiments, the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose. In further or additional embodiments, the microcrystalline cellulose is about 88.8% by weight of the composition. In further or additional embodiments, the composition further comprises: about 5% by weight croscarmellose sodium; about 1% by weight sodium lauryl sulfate; and about 1% by weight magnesium stearate.

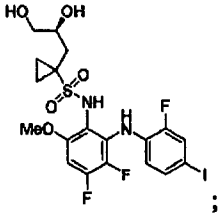
The invention also relates to a composition comprising: from about 2% to about 10% by weight of a compound of structure:



(as defined in any of the above embodiments); and from about 98% to about 90% by weight of a pharmaceutically acceptable carrier or vehicle. In some embodiments, the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose. In further or additional embodiments, the microcrystalline cellulose is from about 85% to about 95% by weight of the composition. In further or additional embodiments, the composition further comprises: from about 1% to about 6% by weight croscarmellose sodium; from about 0.1% to about 2% by weight sodium lauryl sulfate; and from about 0.25% to about 1.5% by weight magnesium stearate. In some embodiments, the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose. In further or additional embodiments, the microcrystalline cellulose is from about 85% to about 95% by weight of the composition. In further or additional embodiments, the composition further comprises: from about 1% to about 6% by weight croscarmellose sodium; and from about 0.25% to about 1.5% by weight magnesium stearate.

The invention also relates to a composition comprising:

about 1mg of a compound of structure:



;

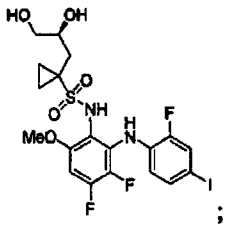
about 222.2mg of microcrystalline cellulose;

about 12.0mg of croscarmellose sodium;

about 2.4mg of sodium lauryl sulfate; and

about 2.4mg of magnesium stearate.

The invention also relates to a composition comprising:



about 10mg of a compound of structure: ;

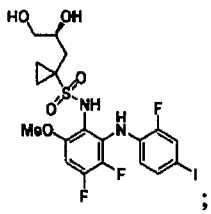
about 213.2mg of microcrystalline cellulose;

about 12.0mg of croscarmellose sodium;

about 2.4mg of sodium lauryl sulfate; and

about 2.4mg of magnesium stearate.

The invention also relates to a composition comprising:



about 20mg of a compound of structure: ;

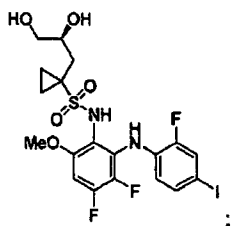
about 203.2mg of microcrystalline cellulose;

about 12.0mg of croscarmellose sodium;

about 2.4mg of sodium lauryl sulfate; and

about 2.4mg of magnesium stearate.

The invention also relates to a composition comprising:



about 40mg of a compound of structure: ;

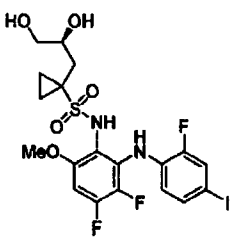
about 183.2mg of microcrystalline cellulose;

about 12.0mg of croscarmellose sodium;

about 2.4mg of sodium lauryl sulfate; and

about 2.4mg of magnesium stearate.

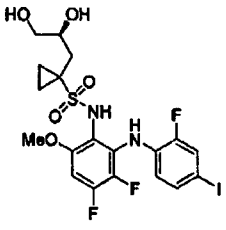
The invention also relates to a composition comprising: about 0.4% by weight of a compound of structure:



, and about 99.6% by weight of a pharmaceutically acceptable carrier or vehicle. In some

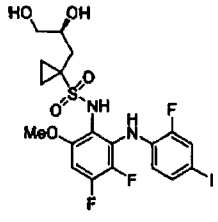
embodiments, the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose. In further or additional embodiments, the microcrystalline cellulose is about 92.6% by weight of the composition. In further or additional embodiments, the composition further comprises: about 5% by weight croscarmellose sodium; about 1% by weight sodium lauryl sulfate; and about 1% by weight magnesium stearate.

The invention also relates to a composition comprising: about 4.2% by weight of a compound of structure:



, and about 95.8 % by weight of a pharmaceutically acceptable carrier or vehicle. In some embodiments, the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose. In further or additional embodiments, the microcrystalline cellulose is about 88.8% by weight of the composition. In further or additional embodiments, the composition further comprises: about 5% by weight croscarmellose sodium; about 1% by weight sodium lauryl sulfate; and about 1% by weight magnesium stearate.

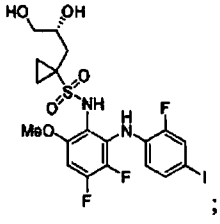
The invention also relates to a composition comprising: from about 2% to about 10% by weight of a compound of structure:



, and from about 98% to about 90% by weight of a pharmaceutically acceptable carrier or vehicle. In some embodiments, the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose. In further or additional embodiments, the microcrystalline cellulose is from about 85% to about 95% by weight of the composition. In further or additional embodiments, the composition further comprises: from about 1% to about 6% by weight croscarmellose sodium; from about 0.1% to about 2% by weight sodium lauryl sulfate; and from about 0.25% to about 1.5% by weight magnesium stearate. In some embodiments, the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose. In further or additional embodiments, the microcrystalline cellulose is from about 85% to about 95% by weight of the composition. In further or additional embodiments, the composition further comprises: from about 1% to about 6% by weight croscarmellose sodium; and from about 0.25% to about 1.5% by weight magnesium stearate.

The invention also relates to a composition comprising:

about 1mg of a compound of structure:



;

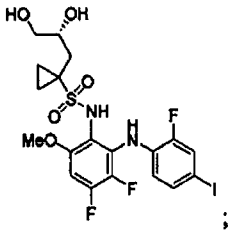
about 222.2mg of microcrystalline cellulose;

about 12.0mg of croscarmellose sodium;

about 2.4mg of sodium lauryl sulfate; and

about 2.4mg of magnesium stearate.

The invention also relates to a composition comprising:



about 10mg of a compound of structure: ;

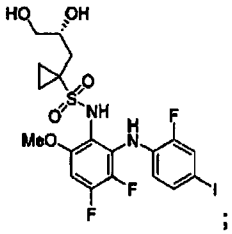
about 213.2mg of microcrystalline cellulose;

about 12.0mg of croscarmellose sodium;

about 2.4mg of sodium lauryl sulfate; and

about 2.4mg of magnesium stearate.

The invention also relates to a composition comprising:



about 20mg of a compound of structure: ;

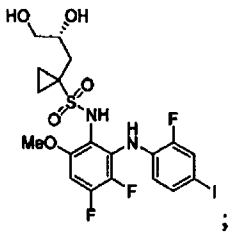
about 203.2mg of microcrystalline cellulose;

about 12.0mg of croscarmellose sodium;

about 2.4mg of sodium lauryl sulfate; and

about 2.4mg of magnesium stearate.

The invention also relates to a composition comprising:



about 40mg of a compound of structure: ;

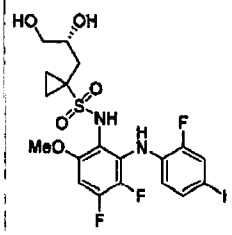
about 183.2mg of microcrystalline cellulose;

about 12.0mg of croscarmellose sodium;

about 2.4mg of sodium lauryl sulfate; and

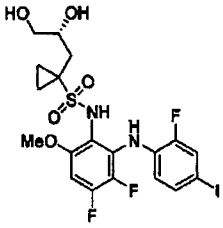
about 2.4mg of magnesium stearate.

The invention also relates to a composition comprising: about 0.4% by weight of a compound of structure:



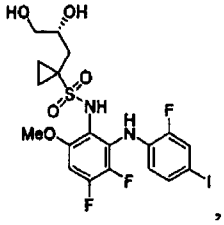
, and about 99.6% by weight of a pharmaceutically acceptable carrier or vehicle. In some embodiments, the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose. In further or additional embodiments, the microcrystalline cellulose is about 92.6% by weight of the composition. In further or additional embodiments, the composition further comprises: about 5% by weight croscarmellose sodium; about 1% by weight sodium lauryl sulfate; and about 1% by weight magnesium stearate.

The invention also relates to a composition comprising: about 4.2% by weight of a compound of structure:



, and about 95.8 % by weight of a pharmaceutically acceptable carrier or vehicle. In some embodiments, the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose. In further or additional embodiments, the microcrystalline cellulose is about 88.8% by weight of the composition. In further or additional embodiments, the composition further comprises: about 5% by weight croscarmellose sodium; about 1% by weight sodium lauryl sulfate; and about 1% by weight magnesium stearate.

The invention also relates to a composition comprising: from about 2% to about 10% by weight of a compound of structure:



, and from about 98% to about 90% by weight of a pharmaceutically acceptable carrier or vehicle. In some embodiments, the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose. In further or additional embodiments, the microcrystalline cellulose is from about 85% to about 95% by weight of the composition. In further or additional embodiments, the composition further comprises: from about 1% to about 6% by weight croscarmellose sodium; from about 0.1% to about 2% by weight sodium lauryl sulfate; and from about 0.25% to about 1.5% by weight magnesium stearate. In some embodiments, the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose. In further or additional embodiments, the microcrystalline cellulose is from about 85% to about 95% by weight of the composition. In further or additional embodiments, the composition further comprises: from about 1% to about 6% by weight croscarmellose sodium; and from about 0.25% to about 1.5% by weight magnesium stearate.

Also described herein are pharmaceutical compositions comprising an effective amount of a crystalline polymorph form A of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide. In some embodiments, the pharmaceutical compositions comprise an effective amount of a crystalline polymorph form A of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide, and at least one pharmaceutically acceptable carrier. In some embodiments the pharmaceutical compositions are for the treatment of disorders. In some embodiments the pharmaceutical compositions are for the treatment of disorders in a mammal. In some embodiments the pharmaceutical compositions are for the treatment of disorders in a human. In some embodiments the pharmaceutical compositions are for the treatment or prophylaxis of inflammatory diseases. In some embodiments the pharmaceutical compositions are for the treatment or prophylaxis of proliferative diseases.

***Methods of Use of the Compounds, Including Polymorph Forms, and the Compositions***

In other aspects, the present invention is directed to a method for achieving an effect in a patient comprising the administration of an effective amount of a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, amide, tautomer or prodrug thereof, to a patient, wherein the effect is selected from the group consisting of inhibition of various cancers, immunological diseases, and inflammatory diseases. In some embodiments, the compound or pharmaceutically acceptable salt, solvate, polymorph, ester, amide, tautomer or prodrug thereof is

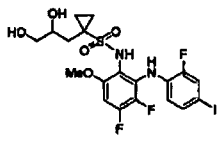
administered as a component of a composition that further comprises a pharmaceutically acceptable carrier or vehicle. In some embodiments, the effect is inhibition of various cancers. In further or additional embodiments, the effect is inhibition of immunological diseases. In further or additional embodiments, the effect is inhibition inflammatory diseases.

Any of the compositions described and claimed herein may be used in the methods provided in this section.

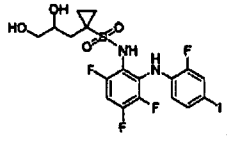
In some embodiments, the composition comprising a compound of formula I is administered in combination with an additional therapy. In further or additional embodiments, the additional therapy is radiation therapy, chemotherapy, or surgery or any combination thereof. In further or additional embodiments, the composition comprising a compound of formula I is administered in combination with at least one therapeutic agent.

In some embodiments, the composition is administered orally, intraduodenally, parenterally (including intravenous, subcutaneous, intramuscular, intravascular or by infusion), topically or rectally. In further or additional embodiments the amount of compound of formula I is in the range of about 0.001 to about 1000 mg/kg body weight/day. In further or additional embodiments the amount of compound of formula I is in the range of about 0.5 to about 50 mg/kg/day. In further or additional embodiments the amount of compound of formula I is about 0.001 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.01 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.02 to about 5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.05 to about 2.5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.1 to about 1 g/day. In further or additional embodiments, dosage levels below the lower limit of the aforesaid range may be more than adequate. In further or additional embodiments, dosage levels above the upper limit of the aforesaid range may be required.

In some embodiments of the compositions and methods provided herein, provided are MEK protein kinase inhibitors further comprising a compound of formula I, wherein the compound of formula I is present in an amount of about 0.1 mg to about 200 mg. In other embodiments, the MEK protein kinase inhibitor comprises a compound of formula I and is present in an amout of about 0.2 mg to about 100 mg. In other embodiments, the MEK protein kinase inhibitor comprises a compound of formula I and is present in an amout of about 0.3 mg to about 90 mg. In other embodiments, the MEK protein kinase inhibitor comprises a compound of formula I and is present in an amout of about 0.4 mg to about 80 mg. In other embodiments, the MEK protein kinase inhibitor comprises a compound of formula I and is present in an amout of about 0.5 mg to about 70 mg. In other embodiments, the MEK protein kinase inhibitor comprises a compound of formula I and is present in an amout of about 0.4 mg to about 80 mg. In other embodiments, the MEK protein kinase inhibitor comprises a compound of formula I and is present in an amout of about 0.5 mg to about 70 mg. In other embodiments, the MEK protein kinase inhibitor comprises a compound of formula I and is present in an amout of about 1 mg to about 60 mg. In other embodiments, the MEK protein kinase inhibitor comprises a compound of formula I and is present in an amout of about 1.5 mg to about 50 mg. In other embodiments, the MEK protein kinase inhibitor comprises a compound of formula I and is present in an amout of about 2 mg to about 45 mg. In other embodiments, the MEK protein kinase inhibitor comprises a compound of formula I and is present in an amout of about 2.5 mg to about 40 mg. In further embodiments, MEK protein kinase inhibitor further comprising the compound of

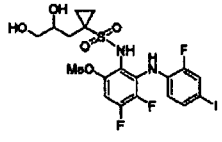


formula I present in the dosage amounts provided herein is selected from the group consisting of:

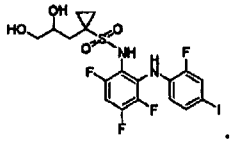


and .

In some embodiments of the compositions and methods provided herein, provided are MEK protein kinase inhibitors further comprising a compound of formula I, wherein the compound of formula I is present in an amount of about 0.1 mg, about 0.2 mg, about 0.25 mg, about 0.3 mg, about 0.4 mg, about 0.5 mg, about 0.6 mg, about 0.7 mg, about 0.8 mg, about 0.9 mg, about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 3.5 mg, about 4.0 mg, about 4.5 mg, about 5 mg, about 5.5 mg, about 6 mg, about 6.5 mg, about 7 mg, about 7.5 mg, about 8 mg, about 8.5 mg, about 9 mg, about 9.5 mg, about 10 mg, about 10.5 mg, about 11 mg, about 11.5 mg, about 12 mg, about 12.5 mg, and/or about 13 mg, about 14 mg, or about 15 mg. In further embodiments, the compound of formula I present in the dosage amounts provided herein is selected from the group consisting of:

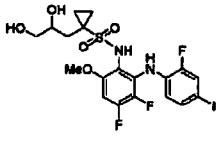


and

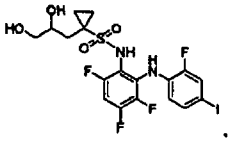


.

In some embodiments of the compositions and methods provided herein, provided are MEK protein kinase inhibitors further comprising a compound of formula I, wherein the compound of formula I is present in an amount of about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 175 mg, about 180 mg, about 190 mg, or about 200 mg. In further embodiments, the compound of formula I present in the dosage amounts provided herein is selected from the group consisting of:



and



.

In further or additional embodiments the compound of formula I is administered in a single dose, once daily. In further or additional embodiments the compound of formula I is administered in multiple doses, more than once per day. In further or additional embodiments the compound of formula I is administered twice daily. In further or additional embodiments the compound of formula I is administered three times per day. In further or additional embodiments the compound of formula I is administered four times per day. In further or additional embodiments the compound of formula I is administered more than four times per day. In some embodiments, the individual suffering from cancer is a mammal. In further or additional embodiments, the individual is a human. In further or additional embodiments, an effective amount of a composition comprising a pharmaceutically acceptable salt of a compound of formula I is administered.

In some aspects, the present invention is directed to a method of treating a disease in an individual suffering from said disease comprising administering to said individual an effective amount of a composition comprising a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof.

In other aspects, the present invention is directed to a method of treating a disorder in a mammal, comprising administering to said mammal a therapeutically effective amount of the compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof

In other aspects, the present invention is directed to a method of treating a disorder in a human, comprising administering to said mammal a therapeutically effective amount of the compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof.

MEK Modulated Disease and Disorders

Also described herein are methods of modulating MEK activity by contacting MEK with an amount of a compound of formula I sufficient to modulate the activity of MEK. Modulate can be inhibiting or activating MEK activity. In some embodiments, the invention provides methods of inhibiting MEK activity by contacting MEK with an amount of a compound of formula I sufficient to inhibit the activity of MEK. In some embodiments, the invention provides methods of inhibiting MEK activity in a solution by contacting said solution with an amount of a compound of formula I sufficient to inhibit the activity of MEK in said solution. In some embodiments, the invention provides methods of inhibiting MEK activity in a cell by contacting said cell with an amount of a compound described herein sufficient to inhibit the activity of MEK in said cell. In some embodiments, the invention provides methods of inhibiting MEK activity in a tissue by contacting said tissue with an amount of a compound described herein sufficient to inhibit the activity of MEK in said tissue. In some embodiments, the invention provides methods of inhibiting MEK activity in an organism by contacting said organism with an amount of a compound described herein sufficient to inhibit the activity of MEK in said organism. In some embodiments, the invention provides methods of inhibiting MEK activity in an animal by contacting said animal with an amount of a compound described herein sufficient to inhibit the activity of MEK in said animal. In some embodiments, the invention provides methods of inhibiting MEK activity in a mammal by contacting said mammal with an amount of a compound described herein sufficient to inhibit the activity of MEK in said mammal. In some embodiments, the invention provides methods of inhibiting MEK activity in a human by contacting said human with an amount of a compound described herein sufficient to inhibit the activity of MEK in said human.

Compounds of formula I, and compositions containing a compound of formula I, and pharmaceutically acceptable salts, solvates, polymorphs, esters, amides, tautomers or prodrugs thereof, may modulate the activity of MEK enzymes; and, as such, are useful for treating diseases or conditions in which aberrant MEK enzyme activity contributes to the pathology and/or symptoms of a disease or condition.

In some aspects, the present invention is directed to a method of treating a disorder or condition which is modulated by the MEK cascade in a mammal, including a human, comprising administering to said mammal an amount of the compound of formula I, or a pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof, effective to modulate said cascade. The appropriate dosage for a particular patient can be determined, according to known methods, by those skilled in the art.

In other aspects, the present invention is directed to a method for inhibiting a MEK enzyme. In some embodiments, the method comprises contacting said MEK enzyme with an amount of a composition comprising a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, amide, tautomer or prodrug thereof, sufficient to inhibit said enzyme, wherein said enzyme is inhibited. In further or additional embodiments the enzyme is at least about 1% inhibited. In further or additional embodiments the enzyme is at least about 2% inhibited. In

further or additional embodiments the enzyme is at least about 3% inhibited. In further or additional embodiments the enzyme is at least about 4% inhibited. In further or additional embodiments the enzyme is at least about 5% inhibited. In further or additional embodiments the enzyme is at least about 10% inhibited. In further or additional embodiments the enzyme is at least about 20% inhibited. In further or additional embodiments the enzyme is at least about 25% inhibited. In further or additional embodiments the enzyme is at least about 30% inhibited. In further or additional embodiments the enzyme is at least about 40% inhibited. In further or additional embodiments the enzyme is at least about 50% inhibited. In further or additional embodiments the enzyme is at least about 60% inhibited. In further or additional embodiments the enzyme is at least about 70% inhibited. In further or additional embodiments the enzyme is at least about 75% inhibited. In further or additional embodiments the enzyme is at least about 80% inhibited. In further or additional embodiments the enzyme is at least about 90% inhibited. In further or additional embodiments the enzyme is essentially completely inhibited. In further or additional embodiments the MEK enzyme is MEK kinase. In further or additional embodiments the MEK enzyme is MEK1. In further or additional embodiments the MEK enzyme is MEK2. In further or additional embodiments the contacting occurs within a cell. In further or additional embodiments the cell is a mammalian cell. In further or additional embodiments the mammalian cell is a human cell. In further or additional embodiments, the MEK enzyme is inhibited with a composition comprising a pharmaceutically acceptable salt of a compound of formula I.

In further or additional aspects, the present invention is directed to a method of treatment of a MEK mediated disorder in an individual suffering from said disorder comprising administering to said individual an effective amount of a composition comprising a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, amide, tautomer or prodrug thereof. In some embodiments, the composition comprising a compound of formula I is administered orally, intraduodenally, parenterally (including intravenous, subcutaneous, intramuscular, intravascular or by infusion), topically or rectally. In some embodiments, the pharmaceutical composition is in a form suitable for oral administration. In further or additional embodiments, the pharmaceutical composition is in the form of a tablet, capsule, pill, powder, sustained release formulations, solution, suspension, for parenteral injection as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. In further or additional embodiments, the pharmaceutical composition is in unit dosage forms suitable for single administration of precise dosages. In further or additional embodiments, the pharmaceutical composition further comprises a pharmaceutical carrier, excipient and/or adjuvant.

In further or additional embodiments the amount of compound of formula I is in the range of about 0.001 to about 1000 mg/kg body weight/day. In further or additional embodiments the amount of compound of formula I is in the range of about 0.5 to about 50 mg/kg/day. In further or additional embodiments the amount of compound of formula I is about 0.001 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.01 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.02 to about 5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.05 to about 2.5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.1 to about 1 g/day. In further or additional embodiments, dosage levels below the lower limit of the aforesaid range may be more than adequate. In further or additional embodiments, dosage levels above the upper limit of the aforesaid range may be required.

In further or additional embodiments the compound of formula I is administered in a single dose, once daily. In further or additional embodiments the compound of formula I is administered in multiple doses, more than once per day. In further or additional embodiments the compound of formula I is administered twice daily. In further or additional embodiments the compound of formula I is administered three times per day. In further or additional embodiments the compound of formula I is administered four times per day. In further or additional embodiments the compound of

formula I is administered more than four times per day. In some embodiments, the individual suffering from the MEK mediated disorder is a mammal. In further or additional embodiments, the individual is a human.

In some embodiments, the composition comprising a compound of formula I is administered in combination with an additional therapy. In further or additional embodiments, the additional therapy is radiation therapy, chemotherapy, surgery or any combination thereof. In further or additional embodiments, the composition comprising a compound of formula I is administered in combination with at least one therapeutic agent. In further or additional embodiments, the therapeutic agent is selected from the group of cytotoxic agents, anti-angiogenesis agents and anti-neoplastic agents. In further or additional embodiments, the anti-neoplastic agent is selected from the group of consisting of alkylating agents, anti-metabolites, epidophyllotoxins; antineoplastic enzymes, topoisomerase inhibitors, procarbazines, mitoxantrones, platinum coordination complexes, biological response modifiers and growth inhibitors, hormonal/anti-hormonal therapeutic agents, and haematopoietic growth factors. In further or additional embodiments, the therapeutic agent is selected from taxol, bortezomib or both.

In some embodiments, the MEK mediated disorder is selected from the group consisting of inflammatory diseases, infections, autoimmune disorders, stroke, ischemia, cardiac disorder, neurological disorders, fibrogenetic disorders, proliferative disorders, hyperproliferative disorders, non-cancer hyperproliferative disorders, tumors, leukemias, neoplasms, cancers, carcinomas, metabolic diseases, malignant disease, vascular restenosis, psoriasis, atherosclerosis, rheumatoid arthritis, osteoarthritis, heart failure, chronic pain, neuropathic pain, dry eye, closed angle glaucoma and wide angle glaucoma. In further or additional embodiments, the MEK mediated disorder is an inflammatory disease. In further or additional embodiments, the MEK mediated disorder is a hyperproliferative disease. In further or additional embodiments, the MEK mediated disorder is selected from the group consisting of tumors, leukemias, neoplasms, cancers, carcinomas and malignant disease. In further or additional embodiments, stomach cancer, brain cancer, breast cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, colorectal cancer or leukemia. In further or additional embodiments, the fibrogenetic disorder is scleroderma, polymyositis, systemic lupus, rheumatoid arthritis, liver cirrhosis, keloid formation, interstitial nephritis or pulmonary fibrosis. In further or additional embodiments, an effective amount of a composition comprising a pharmaceutically acceptable salt of a compound of formula I is administered.

The invention also relates to methods of modulating MEK activity by contacting MEK with an amount of a crystalline polymorph form A of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide sufficient to modulate the activity of MEK. Modulate can be inhibiting or activating MEK activity. In some embodiments, the invention provides methods of inhibiting MEK activity by contacting MEK with an amount of a crystalline polymorph form A of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide sufficient to inhibit the activity of MEK. In some embodiments, the invention provides methods of inhibiting MEK activity in a solution by contacting said solution with an amount of a crystalline polymorph form A of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide sufficient to inhibit the activity of MEK in said solution. In some embodiments, the invention provides methods of inhibiting MEK activity in a cell by contacting said cell with an amount of a crystalline polymorph form A of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide sufficient to inhibit the activity of MEK in said cell. In some embodiments, the invention provides methods of inhibiting MEK activity in a tissue by contacting said tissue with an amount of a crystalline polymorph form A of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide sufficient to inhibit the activity of MEK in said tissue. In some

embodiments, the invention provides methods of inhibiting MEK activity in an organism by contacting said organism with an amount of a crystalline polymorph form A of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide sufficient to inhibit the activity of MEK in said organism. In some embodiments, the invention provides methods of inhibiting MEK activity in an animal by contacting said animal with an ofamount a crystalline polymorph form A of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide sufficient to inhibit the activity of MEK in said animal. In some embodiments, the invention provides methods of inhibiting MEK activity in a mammal by contacting said mammal with an amount of a crystalline polymorph form A of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide sufficient to inhibit the activity of MEK in said mammal. In some embodiments, the invention provides methods of inhibiting MEK activity in a human by contacting said human with an amount of a crystalline polymorph form A of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide sufficient to inhibit the activity of MEK in said human.

Cancer

In other aspects, the present invention is directed to a method for the treatment, prevention or prophylaxis of cancer in an individual comprising administering to said individual an effective amount of a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, amide, tautomer or prodrug thereof. In some embodiments, the compound or pharmaceutically acceptable salt, solvate, polymorph, ester, amide, tautomer or prodrug thereof is administered as a component of a composition that further comprises a pharmaceutically acceptable carrier or vehicle. In further or additional embodiments, the cancer is brain cancer, breast cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, colorectal cancer, stomach cancer, or leukemia. In further or additional embodiments, the fibrogenetic disorder is scleroderma, polymyositis, systemic lupus, rheumatoid arthritis, liver cirrhosis, keloid formation, interstitial nephritis or pulmonary fibrosis. In further or additional embodiments, the cancer is brain cancer, breast cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, colorectal cancer, leukemia, melanoma, thyroid cancer, or basal cell carcinoma. In further or additional embodiments, the cancer is brain cancer or adrenocortical carcinoma. In further or additional embodiments, the cancer is breast cancer. In further or additional embodiments, the cancer is ovarian cancer. In further or additional embodiments, the cancer is pancreatic cancer. In further or additional embodiments, the cancer is prostate cancer. In further or additional embodiments, the cancer is renal cancer. In further or additional embodiments, the cancer is colorectal cancer. In further or additional embodiments, the cancer is myeloid leukemia. In further or additional embodiments, the cancer is glioblastoma. In further or additional embodiments, the cancer is follicular lymphona. In further or additional embodiments, the cancer is pre-B acute leukemia. In further or additional embodiments, the cancer is chronic lymphocytic B-leukemia. In further or additional embodiments, the cancer is mesothelioma. In further or additional embodiments, the cancer is small cell lung cancer. In some embodiments, the cancer is stomach cancer.

In some embodiments, the composition comprising a compound of formula I is administered in combination with an additional therapy. In further or additional embodiments, the additional therapy is radiation therapy, chemotherapy, surgery or any combination thereof. In further or additional embodiments, the composition comprising a compound of formula I is administered in combination with at least one therapeutic agent. In further or additional embodiments, the therapeutic agent is selected from the group of cytotoxic agents, anti-angiogenesis agents and anti-neoplastic agents. In further or additional embodiments, the anti-neoplastic agent is selected from the group of consisting of alkylating agents, anti-metabolites, epidophyllotoxins; antineoplastic enzymes, topoisomerase inhibitors, procarbazines, mitoxantrones,

platinum coordination complexes, biological response modifiers and growth inhibitors, hormonal/anti-hormonal therapeutic agents, and haematopoietic growth factors. In further or additional embodiments, the therapeutic agent is selected from taxol, bortezomib or both.

In further or additional embodiments the amount of compound of formula I is in the range of about 0.001 to about 1000 mg/kg body weight/day. In further or additional embodiments the amount of compound of formula I is in the range of about 0.5 to about 50 mg/kg/day. In further or additional embodiments the amount of compound of formula I is about 0.001 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.01 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.02 to about 5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.05 to about 2.5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.1 to about 1 g/day. In further or additional embodiments, dosage levels below the lower limit of the aforesaid range may be more than adequate. In further or additional embodiments, dosage levels above the upper limit of the aforesaid range may be required.

In some embodiments, the composition is administered orally, intraduodenally, parenterally (including intravenous, subcutaneous, intramuscular, intravascular or by infusion), topically or rectally. In further or additional embodiments the compound of formula I is administered in a single dose, once daily. In further or additional embodiments the compound of formula I is administered in multiple doses, more than once per day. In further or additional embodiments the compound of formula I is administered twice daily. In further or additional embodiments the compound of formula I is administered three times per day. In further or additional embodiments the compound of formula I is administered four times per day. In further or additional embodiments the compound of formula I is administered more than four times per day. In some embodiments, the individual suffering from cancer is a mammal. In further or additional embodiments, the individual is a human. In further or additional embodiments, an effective amount of a composition comprising a pharmaceutically acceptable salt of a compound of formula I is administered.

**Abnormal Cell Growth**

Also described herein are compounds, pharmaceutical compositions and methods for inhibiting abnormal cell growth. In some embodiments, the abnormal cell growth occurs in a mammal. Methods for inhibiting abnormal cell growth comprise administering an effective amount of a compound of formula I, or a pharmaceutically acceptable salt, solvate, polymorph, ester, amide, tautomer, prodrug, hydrate, or derivative thereof, wherein abnormal cell growth is inhibited. Methods for inhibiting abnormal cell growth in a mammal comprise administering to the mammal an amount of a compound of formula I, or a pharmaceutically acceptable salt, solvate, polymorph, ester, amide, tautomer, prodrug, hydrate, or derivative thereof, wherein the amounts of the compound, or salt, is effective in inhibiting abnormal cell growth in the mammal.

In some embodiments, the methods comprise administering an effective amount of a compound of formula I, or a pharmaceutically acceptable salt, solvate, polymorph, ester, amide, tautomer, prodrug, hydrate, or derivative thereof, in combination with an amount of a chemotherapeutic, wherein the amounts of the compound, or its salt, solvate, polymorph, ester, amide, tautomer, prodrug, hydrate, or derivative thereof and the chemotherapeutic are together effective in inhibiting abnormal cell growth. Many chemotherapeutics are presently known in the art and can be used in combination with the compounds of the invention. In some embodiments, the chemotherapeutic is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, and anti-androgens.

Also described are methods for inhibiting abnormal cell growth in a mammal comprising administering to the mammal an amount of a compound of formula I, or a pharmaceutically acceptable salt, solvate, polymorph, ester, amide, tautomer, prodrug, hydrate, or derivative thereof, in combination with radiation therapy, wherein the amounts of the compound, or its salt, solvate, polymorph, ester, amide, tautomer, prodrug, hydrate, or a derivative thereof is in combination with the radiation therapy effective in inhibiting abnormal cell growth or treating the hyperproliferative disorder in the mammal. Techniques for administering radiation therapy are known in the art, and these techniques can be used in the combination therapy described herein. The administration of the compound of formula I in this combination therapy can be determined as described herein.

The invention also relates to a method of and to a pharmaceutical composition of inhibiting abnormal cell growth in a mammal which comprises an amount of a compound of formula I, or a pharmaceutically acceptable salt, solvate, polymorph, ester, amide, tautomer, prodrug, hydrate, or derivative thereof, or an isotopically-labeled derivative thereof, and an amount of one or more substances selected from anti-angiogenesis agents, signal transduction inhibitors, and antiproliferative agents.

Anti-angiogenesis agents, such as MMP-2 (matrix-metalloprotienase 2) inhibitors, MMP-9 (matrix-metalloprotienase 9) inhibitors, and COX-11 (cyclooxygenase 11) inhibitors, can be used in conjunction with a compound of the present invention and pharmaceutical compositions described herein. Examples of useful COX-II inhibitors include CELEBREX™ (alecoxib), valdecoxib, and rofecoxib. Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172 (published October 24,1996), WO 96/27583 (published March 7,1996), European Patent Application No. 97304971.1 (filed July 8,1997), European Patent Application No. 99308617.2 (filed October 29, 1999), WO 98/07697 (published February 26,1998), WO 98/03516 (published January 29,1998), WO 98/34918 (published August 13,1998), WO 98/34915 (published August 13,1998), WO 98/33768 (published August 6,1998), WO 98/30566 (published July 16, 1998), European Patent Publication 606,046 (published July 13,1994), European Patent Publication 931, 788 (published July 28,1999), WO 90/05719 (published May 31,1990), WO 99/52910 (published October 21,1999), WO 99/52889 (published October 21, 1999), WO 99/29667 (published June 17,1999), PCT International Application No. PCT/IB98/01113 (filed July 21,1998), European Patent Application No. 99302232.1 (filed March 25,1999), Great Britain Patent Application No. 9912961.1 (filed June 3, 1999), United States Provisional Application No. 60/148,464 (filed August 12,1999), United States Patent 5,863, 949 (issued January 26,1999), United States Patent 5,861, 510 (issued January 19,1999), and European Patent Publication 780,386 (published June 25, 1997), all of which are incorporated herein in their entireties by reference. Some MMP-2 and MMP-9 inhibitors have little or no activity inhibiting MMP-1, while some selectively inhibit MMP-2 and/or AMP-9 relative to the other matrix-metalloproteinases (i. e., MAP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP- 7, MMP-8, MMP-10, MMP-ll, MMP-12, andMMP-13). Some specific examples of MMP inhibitors useful in the present invention are AG-3340, RO 32-3555, and RS 13-0830.

In other aspects, the present invention is directed to a method for degrading, inhibiting the growth of or killing a cancer cell comprising contacting said cell with an amount of a composition effective to degrade, inhibit the growth of or to kill said cell, the composition comprising a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, amide, tautomer or prodrug thereof. In some embodiments, the cancer cells comprise brain, breast, lung, ovarian, pancreatic, prostate, renal, or colorectal cancer cells.

In further or additional embodiments, the composition is administered with at least one therapeutic agent. In further or additional embodiments, the therapeutic agent is taxol, bortezomib or both. In further or additional embodiments, the therapeutic agent is selected from the group consisting of cytotoxic agents, anti-angiogenesis agents

and anti-neoplastic agents. In further or additional embodiments, the anti-neoplastic agents selected from the group of consisting of alkylating agents, anti-metabolites, epidophyllotoxins; antineoplastic enzymes, topoisomerase inhibitors, procarbazines, mitoxantrones, platinum coordination complexes, biological response modifiers and growth inhibitors, hormonal/anti-hormonal therapeutic agents, and haematopoietic growth factors.

In some embodiments, the cancer cells are degraded. In further or additional embodiments, 1% of the cancer cells are degraded. In further or additional embodiments, 2% of the cancer cells are degraded. In further or additional embodiments, 3% of the cancer cells are degraded. In further or additional embodiments, 4% of the cancer cells are degraded. In further or additional embodiments, 5% of the cancer cells are degraded. In further or additional embodiments, 10% of the cancer cells are degraded. In further or additional embodiments, 20% of the cancer cells are degraded. In further or additional embodiments, 25% of the cancer cells are degraded. In further or additional embodiments, 30% of the cancer cells are degraded. In further or additional embodiments, 40% of the cancer cells are degraded. In further or additional embodiments, 50% of the cancer cells are degraded. In further or additional embodiments, 60% of the cancer cells are degraded. In further or additional embodiments, 70% of the cancer cells are degraded. In further or additional embodiments, 75% of the cancer cells are degraded. In further or additional embodiments, 80% of the cancer cells are degraded. In further or additional embodiments, 90% of the cancer cells are degraded. In further or additional embodiments, 100% of the cancer cells are degraded. In further or additional embodiments, essentially all of the cancer cells are degraded.

In some embodiments, the cancer cells are killed. In further or additional embodiments, 1% of the cancer cells are killed. In further or additional embodiments, 2% of the cancer cells are killed. In further or additional embodiments, 3% of the cancer cells are killed. In further or additional embodiments, 4% of the cancer cells are killed. In further or additional embodiments, 5% of the cancer cells are killed. In further or additional embodiments, 10% of the cancer cells are killed. In further or additional embodiments, 20% of the cancer cells are killed. In further or additional embodiments, 25% of the cancer cells are killed. In further or additional embodiments, 30% of the cancer cells are killed. In further or additional embodiments, 40% of the cancer cells are killed. In further or additional embodiments, 50% of the cancer cells are killed. In further or additional embodiments, 60% of the cancer cells are killed. In further or additional embodiments, 70% of the cancer cells are killed. In further or additional embodiments, 75% of the cancer cells are killed. In further or additional embodiments, 80% of the cancer cells are killed. In further or additional embodiments, 90% of the cancer cells are killed. In further or additional embodiments, 100% of the cancer cells are killed. In further or additional embodiments, essentially all of the cancer cells are killed.

In further or additional embodiments, the growth of the cancer cells is inhibited. In further or additional embodiments, the growth of the cancer cells is about 1% inhibited. In further or additional embodiments, the growth of the cancer cells is about 2% inhibited. In further or additional embodiments, the growth of the cancer cells is about 3% inhibited. In further or additional embodiments, the growth of the cancer cells is about 4% inhibited. In further or additional embodiments, the growth of the cancer cells is about 5% inhibited. In further or additional embodiments, the growth of the cancer cells is about 10% inhibited. In further or additional embodiments, the growth of the cancer cells is about 20% inhibited. In further or additional embodiments, the growth of the cancer cells is about 25% inhibited. In further or additional embodiments, the growth of the cancer cells is about 30% inhibited. In further or additional embodiments, the growth of the cancer cells is about 40% inhibited. In further or additional embodiments, the growth of the cancer cells is about 50% inhibited. In further or additional embodiments, the growth of the cancer cells is about 60% inhibited. In further or additional embodiments, the growth of the cancer cells is about 70% inhibited. In further or additional embodiments, the growth of the cancer cells is about 75% inhibited. In further or additional embodiments, the

growth of the cancer cells is about 80% inhibited. In further or additional embodiments, the growth of the cancer cells is about 90% inhibited. In further or additional embodiments, the growth of the cancer cells is about 100% inhibited. In further or additional embodiments, a composition comprising a pharmaceutically acceptable salt of a compound of formula I is used.

Also described herein are methods for inhibiting abnormal cell growth. In some embodiments, the abnormal cell growth occurs in a mammal. Methods for inhibiting abnormal cell growth comprise administering an effective amount of a crystalline polymorph form A of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide, wherein abnormal cell growth is inhibited. Methods for inhibiting abnormal cell growth in a mammal comprise administering to the mammal an amount of a crystalline polymorph form A of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide, wherein the amount of a crystalline polymorph form A of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide is effective in inhibiting abnormal cell growth in the mammal.

In some embodiments, the methods comprise administering an effective amount of a crystalline polymorph form A of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide in combination with an amount of a chemotherapeutic, wherein the amounts of the crystalline polymorph form A of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide and of the chemotherapeutic are together effective in inhibiting abnormal cell growth.

Many chemotherapeutics are presently known in the art and can be used in combination with the compounds and compositions of the invention. In some embodiments, the chemotherapeutic is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, and anti-androgens.

In some embodiments, the methods for inhibiting abnormal cell growth in a mammal comprise administering to the mammal an amount of a crystalline polymorph form A of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide in combination with radiation therapy, wherein the amount of crystalline polymorph form A of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide in combination with the radiation therapy is effective in inhibiting abnormal cell growth. Techniques for administering radiation therapy are known in the art, and these techniques can be used in the combination therapy described herein.

**Treatment of a Hyperproliferative Disorder**

In other aspects, the present invention is directed to a method of treating a hyperproliferative disorder in a mammal, including a human, comprising administering to said mammal a therapeutically effective amount of the compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof.

In other aspects, the present invention is directed to a method for the treatment, prevention or prophylaxis of a proliferative disease in an individual comprising administering to said individual an effective amount of a compound of formula I, or a pharmaceutically acceptable salt, solvate, polymorph, ester, amide, tautomer or prodrug thereof. In some embodiments, the compound or pharmaceutically acceptable salt, solvate, polymorph, ester, amide, tautomer or prodrug thereof is administered as a component of a composition that further comprises a pharmaceutically acceptable carrier or vehicle. In some embodiments, the proliferative disease is cancer, psoriasis, restenosis, autoimmune disease, or

atherosclerosis. In further or additional embodiments, the proliferative disease is a hyperproliferative disease. In further or additional embodiments, the proliferative disease is selected from the group consisting of tumors, leukemias, neoplasms, cancers, carcinomas and malignant disease. In further or additional embodiments, the cancer is brain cancer, breast cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, stomach cancer, colorectal cancer or leukemia. In further or additional embodiments, the fibrogenetic disorder is scleroderma, polymyositis, systemic lupus, rheumatoid arthritis, liver cirrhosis, keloid formation, interstitial nephritis or pulmonary fibrosis. In further or additional embodiments, the cancer is brain cancer, breast cancer, lung cancer, ovarian cancer, stomach cancer, pancreatic cancer, prostate cancer, renal cancer, colorectal cancer or leukemia. In further or additional embodiments, the cancer is brain cancer or adrenocortical carcinoma. In further or additional embodiments, the cancer is breast cancer. In further or additional embodiments, the cancer is ovarian cancer. In further or additional embodiments, the cancer is pancreatic cancer. In further or additional embodiments, the cancer is prostate cancer. In further or additional embodiments, the cancer is renal cancer. In further or additional embodiments, the cancer is colorectal cancer. In further or additional embodiments, the cancer is myeloid leukemia. In further or additional embodiments, the cancer is glioblastoma. In further or additional embodiments, the cancer is follicular lymphona. In further or additional embodiments, the cancer is pre-B acute leukemia. In further or additional embodiments, the cancer is chronic lymphocytic B-leukemia. In further or additional embodiments, the cancer is mesothelioma. In further or additional embodiments, the cancer is small cell lung cancer. In some embodiments, the cancer is stomach cancer.

In some embodiments, the composition comprising a compound of formula I is administered in combination with an additional therapy. In further or additional embodiments, the additional therapy is radiation therapy, chemotherapy, surgery or a combination thereof. In further or additional embodiments, the composition comprising a compound of formula I is administered in combination with at least one therapeutic agent. In further or additional embodiments, the therapeutic agent is selected from the group of cytotoxic agents, anti-angiogenesis agents and anti-neoplastic agents. In further or additional embodiments, the anti-neoplastic agent is selected from the group of consisting of alkylating agents, anti-metabolites, epidophyllotoxins; antineoplastic enzymes, topoisomerase inhibitors, procarbazines, mitoxantrones, platinum coordination complexes, biological response modifiers and growth inhibitors, hormonal/anti-hormonal therapeutic agents, and haematopoietic growth factors. In further or additional embodiments, the therapeutic agent is selected from taxol, bortezomib or both.

In some embodiments, the composition is administered orally, intraduodenally, parenterally (including intravenous, subcutaneous, intramuscular, intravascular or by infusion), topically or rectally. In further or additional embodiments the amount of compound of formula I is in the range of about 0.001 to about 1000 mg/kg body weight/day. In further or additional embodiments the amount of compound of formula I is in the range of about 0.5 to about 50 mg/kg/day. In further or additional embodiments the amount of compound of formula I is about 0.001 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.01 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.02 to about 5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.05 to about 2.5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.1 to about 1 g/day. In further or additional embodiments, dosage levels below the lower limit of the aforesaid range may be more than adequate. In further or additional embodiments, dosage levels above the upper limit of the aforesaid range may be required.

In further or additional embodiments the compound of formula I is administered in a single dose, once daily. In further or additional embodiments the compound of formula I is administered in multiple doses, more than once per day. In further or additional embodiments the compound of formula I is administered twice daily. In further or additional

embodiments the compound of formula I is administered three times per day. In further or additional embodiments the compound of formula I is administered four times per day. In further or additional embodiments the compound of formula I is administered more than four times per day. In some embodiments, the individual suffering from the proliferative disease is a mammal. In further or additional embodiments, the individual is a human. In further or additional embodiments, an effective amount of a composition comprising a pharmaceutically acceptable salt of a compound of formula I is administered.

**Tumor Size**

In other aspects, the present invention is directed to a method of reducing the size of a tumor, inhibiting tumor size increase, reducing tumor proliferation or preventing tumor proliferation in an individual, comprising administering to said individual an effective amount of a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, amide, tautomer or prodrug thereof. In some embodiments, the compound or pharmaceutically acceptable salt, solvate, polymorph, ester, amide, tautomer or prodrug thereof is administered as a component of a composition that further comprises a pharmaceutically acceptable carrier or vehicle. In some embodiments, the size of a tumor is reduced. In further or additional embodiments, the size of a tumor is reduced by at least 1%. In further or additional embodiments, the size of a tumor is reduced by at least 2%. In further or additional embodiments, the size of a tumor is reduced by at least 3%. In further or additional embodiments, the size of a tumor is reduced by at least 4%. In further or additional embodiments, the size of a tumor is reduced by at least 5%. In further or additional embodiments, the size of a tumor is reduced by at least 10%. In further or additional embodiments, the size of a tumor is reduced by at least 20%. In further or additional embodiments, the size of a tumor is reduced by at least 25%. In further or additional embodiments, the size of a tumor is reduced by at least 30%. In further or additional embodiments, the size of a tumor is reduced by at least 40%. In further or additional embodiments, the size of a tumor is reduced by at least 50%. In further or additional embodiments, the size of a tumor is reduced by at least 60%. In further or additional embodiments, the size of a tumor is reduced by at least 70%. In further or additional embodiments, the size of a tumor is reduced by at least 75%. In further or additional embodiments, the size of a tumor is reduced by at least 80%. In further or additional embodiments, the size of a tumor is reduced by at least 85%. In further or additional embodiments, the size of a tumor is reduced by at least 90%. In further or additional embodiments, the size of a tumor is reduced by at least 95%. In further or additional embodiments, the tumor is eradicated. In some embodiments, the size of a tumor does not increase.

In some embodiments, tumor proliferation is reduced. In some embodiments, tumor proliferation is reduced by at least 1 %. In some embodiments, tumor proliferation is reduced by at least 2 %. In some embodiments, tumor proliferation is reduced by at least 3 %. In some embodiments, tumor proliferation is reduced by at least 4 %. In some embodiments, tumor proliferation is reduced by at least 5 %. In some embodiments, tumor proliferation is reduced by at least 10 %. In some embodiments, tumor proliferation is reduced by at least 20 %. In some embodiments, tumor proliferation is reduced by at least 25 %. In some embodiments, tumor proliferation is reduced by at least 30 %. In some embodiments, tumor proliferation is reduced by at least 40 %. In some embodiments, tumor proliferation is reduced by at least 50 %. In some embodiments, tumor proliferation is reduced by at least 60 %. In some embodiments, tumor proliferation is reduced by at least 70 %. In some embodiments, tumor proliferation is reduced by at least 75 %. In some embodiments, tumor proliferation is reduced by at least 75 %. In some embodiments, tumor proliferation is reduced by at least 80 %. In some embodiments, tumor proliferation is reduced by at least 90 %. In some embodiments, tumor proliferation is reduced by at least 95 %. In some embodiments, tumor proliferation is prevented.

In some embodiments, the composition comprising a compound of formula I is administered in combination with an additional therapy. In further or additional embodiments, the additional therapy is radiation therapy, chemotherapy,

surgery or any combination thereof. In further or additional embodiments, the composition comprising a compound of formula I is administered in combination with at least one therapeutic agent. In further or additional embodiments, the therapeutic agent is selected from the group of cytotoxic agents, anti-angiogenesis agents and anti-neoplastic agents. In further or additional embodiments, the anti-neoplastic agent is selected from the group of consisting of alkylating agents, anti-metabolites, epidophyllotoxins; antineoplastic enzymes, topoisomerase inhibitors, procarbazines, mitoxantrones, platinum coordination complexes, biological response modifiers and growth inhibitors, hormonal/anti-hormonal therapeutic agents, and haematopoietic growth factors. In further or additional embodiments, the therapeutic agent is selected from taxol, bortezomib or both.

In some embodiments, the composition is administered orally, intraduodenally, parenterally (including intravenous, subcutaneous, intramuscular, intravascular or by infusion), topically or rectally. In further or additional embodiments the amount of compound of formula I is in the range of about 0.001 to about 1000 mg/kg body weight/day. In further or additional embodiments the amount of compound of formula I is in the range of about 0.5 to about 50 mg/kg/day. In further or additional embodiments the amount of compound of formula I is about 0.001 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.01 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.02 to about 5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.05 to about 2.5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.1 to about 1 g/day. In further or additional embodiments, dosage levels below the lower limit of the aforesaid range may be more than adequate. In further or additional embodiments, dosage levels above the upper limit of the aforesaid range may be required.

In further or additional embodiments the compound of formula I is administered in a single dose, once daily. In further or additional embodiments the compound of formula I is administered in multiple doses, more than once per day. In further or additional embodiments the compound of formula I is administered twice daily. In further or additional embodiments the compound of formula I is administered three times per day. In further or additional embodiments the compound of formula I is administered four times per day. In further or additional embodiments the compound of formula I is administered more than four times per day. In some embodiments, the individual suffering from cancer is a mammal. In further or additional embodiments, the individual is a human. In further or additional embodiments, an effective amount of a composition comprising a pharmaceutically acceptable salt of a compound of formula I is administered.

Inflammatory Disease

In other aspects, the present invention is directed to a method for the treatment, prevention or prohylaxis of an inflammatory disease in an individual comprising administering to said individual an effective amount of compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, amide, tautomer or prodrug thereof. In some embodiments, the compound or pharmaceutically acceptable salt, solvate, polymorph, ester, amide, tautomer or prodrug thereof is administered as a component of a composition that further comprises a pharmaceutically acceptable carrier or vehicle. In further or additional embodiments, the inflammatory disease is selected from chronic inflammatory diseases, rheumatoid arthritis, rheumatoid arthritis, spondyloarthropathies, ankylosing spondylitis, gout, tendonitis, bursitis, sciatica, gouty arthritis, osteoarthritis, juvenile arthritis, acute rheumatic arthritis, enteropathic arthritis, neuropathic arthritis, psoriatic arthritis, pyogenic arthritis, atherosclerosis, systemic lupus erythematosus, inflammatory bowel disease, irritable bowel syndrome, ulcerative colitis, reflux esophagitis, Crohn's disease, gastritis, asthma, allergies, respiratory distress syndrome, pancreatitis, chronic obstructive pulmonary disease, pulmonary fibrosis, psoriasis, eczema or scleroderma.

In some embodiments, the composition comprising a compound of formula I is administered in combination with an additional therapy. In further or additional embodiments, the composition comprising a compound of formula I is administered in combination with at least one therapeutic agent. In some embodiments, the composition is administered orally, intraduodenally, parenterally (including intravenous, subcutaneous, intramuscular, intravascular or by infusion), topically or rectally. In further or additional embodiments the amount of compound of formula I is in the range of about 0.001 to about 1000 mg/kg body weight/day. In further or additional embodiments the amount of compound of formula I is in the range of about 0.5 to about 50 mg/kg/day. In further or additional embodiments the amount of compound of formula I is about 0.001 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.01 to about 7 g/day. In further or additional embodiments the amount of compound of formula I is about 0.02 to about 5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.05 to about 2.5 g/day. In further or additional embodiments the amount of compound of formula I is about 0.1 to about 1 g/day. In further or additional embodiments, dosage levels below the lower limit of the aforesaid range may be more than adequate. In further or additional embodiments, dosage levels above the upper limit of the aforesaid range may be required.

In further or additional embodiments the compound of formula I is administered in a single dose, once daily. In further or additional embodiments the compound of formula I is administered in multiple doses, more than once per day. In further or additional embodiments the compound of formula I is administered twice daily. In further or additional embodiments the compound of formula I is administered three times per day. In further or additional embodiments the compound of formula I is administered four times per day. In further or additional embodiments the compound of formula I is administered more than four times per day. In some embodiments, the individual suffering from the inflammatory disease is a mammal. In further or additional embodiments, the individual is a human. In further or additional embodiments, an effective amount of a composition comprising a pharmaceutically acceptable salt of a compound of formula I is administered.

***Modes of Administration***

Described herein are compounds of formula I or a pharmaceutically acceptable salt solvate, polymorph, ester, amide, tautomer, prodrug, hydrate, or derivative thereof. Also described, are pharmaceutical compositions comprising a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, amide, tautomer, prodrug, hydrate, or derivative thereof. The compounds and compositions described herein may be administered either alone or in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice.

Also described herein are pharmaceutical compositions comprising crystalline polymorph N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide (Form A). The compounds and compositions described herein may be administered either alone or in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. Administration can be effected by any method that enables delivery of the compounds to the site of action. These methods include, though are not limited to delivery via enteral routes (including oral, gastric or duodenal feeding tube, rectal suppository and rectal enema), parenteral routes (injection or infusion, including intraarterial, intracardiac, intradermal, intraduodenal, intramedullary, intramuscular, intraosseous, intraperitoneal, intrathecal, intravascular, intravenous, intravitreal, epidural and subcutaneous), inhalational, transdermal, transmucosal, sublingual, buccal and topical (including epicutaneous, dermal, enema, eye drops, ear drops, intranasal, vaginal) administration, although the most suitable route may depend upon for example the condition and disorder of the recipient. Those of skill

in the art will be familiar with administration techniques that can be employed with the compounds and methods of the invention. By way of example only, compounds described herein can be administered locally to the area in need of treatment, by for example, local infusion during surgery, topical application such as creams or ointments, injection, catheter, or implant, said implant made for example, out of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. The administration can also be by direct injection at the site of a diseased tissue or organ.

Administration of the compounds and compositions described herein can be effected by any method that enables delivery of the compounds to the site of action. These methods include oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intraperitoneal, intramuscular, intravascular or infusion), topical, and rectal administration. For example, compounds described herein can be administered locally to the area in need of treatment. This may be achieved by, for example, but not limited to, local infusion during surgery, topical application, *e.g.*, cream, ointment, injection, catheter, or implant, said implant made, *e.g.*, out of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. The administration can also be by direct injection at the site (or former site) of a tumor or neoplastic or pre-neoplastic tissue. Those of ordinary skill in the art are familiar with formulation and administration techniques that can be employed with the compounds and methods of the invention, e.g., as discussed in Goodman and Gilman, The Pharmacological Basis of Therapeutics, current ed.; Pergamon; and Remington's, Pharmaceutical *Sciences* (current edition), Mack Publishing Co., Easton, Pa.

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous, intraarticular, and intramedullary), intraperitoneal, transmucosal, transdermal, rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association a compound of the subject invention or a pharmaceutically acceptable salt, solvate, polymorph, ester, amide, tautomer, prodrug, hydrate, or derivative thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

Pharmaceutical preparations which are useful for oral administration include tablets, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. Tablets may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with binders, inert diluents, or lubricating, surface active or dispersing agents. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. All formulations for oral administration should be in dosages suitable for such administration. The push-fit capsules or tablets can contain the active ingredient; in admixture with a filler such as microcrystalline cellulose, silicified microcrystalline cellulose, pregelatinized starch, lactose, dicalcium phosphate, or compressible sugar ; a binder

such as hypromellose, povidone or starch paste; a disintegrant such as croscarmellose sodium, crospovidone or sodium starch glycolate; a surfactant such as sodium lauryl sulfate and/or lubricants and processing aides such as talc,magnesium stearate, stearic acid or colloidal silicion dioxide and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions are useful, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or Dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in powder form or in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or sterile pyrogen-free water, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations for parenteral administration include aqueous and non-aqueous (oily) sterile injection solutions of the active compounds which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Pharmaceutical preparations may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, pastilles, or gels formulated in conventional manner. Such compositions may comprise the active ingredient in a flavored basis such as sucrose and acacia or tragacanth.

Pharmaceutical preparations may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter, polyethylene glycol, or other glycerides.

Pharmaceutical preparations may be administered topically, that is by non-systemic administration. This includes the application of a compound of the present invention externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

Pharmaceutical preparations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as gels, liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, for instance from 1% to 2% by weight of the formulation. It may however comprise as much as 10% w/w or may comprise less than 5% w/w, or from 0.1% to 1% w/w of the formulation.

Pharmaceutical preparations for administration by inhalation are conveniently delivered from an insufflator, nebulizer pressurized packs or other convenient means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Alternatively, for administration by inhalation or insufflation, pharmaceutical preparations may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form, in for example, capsules, cartridges, gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

It should be understood that in addition to the ingredients particularly mentioned above, the compounds and compositions described herein may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

***Formulations***

It should be noted that any of the compositions and compounds described herein may be used in any of the formulations discussed in this section, which is not intended to be limiting and should not be so construed.

The compounds or compositions described herein can be delivered in a vesicle, *e.g.*, a liposome (see, for example, Langer, *Science* **1990**, *249*,1527-1533; Treat et al., *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Bernstein and Fidler, Ed., Liss, N.Y., pp. 353-365, 1989).The compounds and pharmaceutical compositions described herein can also be delivered in a controlled release system. In one embodiment, a pump may be used (see, Sefton, 1987, CRC Crit. Ref. Biomed. Eng. 14:201; Buchwald et al. *Surgery*, **1980** *88*, 507; Saudek et al. *N. Engl. J. Med.* **1989**, *321*, (574). Additionally, a controlled release system can be placed in proximity of the therapeutic target. (See, Goodson, *Medical Applications of Controlled Release*, 1984, Vol. 2, pp. 115-138). The pharmaceutical compositions described herein can also contain the active ingredient in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, 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 preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents; fillers such as microcrystalline cellulose, silicified microcrystalline cellulose, pregelatinized starch, lactose, dicalcium phosphate, or compressible sugar ; binders such as hypromellose, povidone or starch paste; disintegrants such as croscarmellose sodium, crospovidone or sodium starch glycolate; a surfactant such as sodium lauryl sulfate and/or lubricants and processing aides such as talc, sodium croscarmellose, corn starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia, and lubricating agents, for example magnesium stearate, stearic acid or colloidal silicion dioxide and, optionally, talc. The tablets may be un-coated or coated by known techniques to mask the taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby

provide a sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropylmethyl-cellulose or hydroxypropylcellulose, or a time delay material such as ethyl cellulose, or cellulose acetate butyrate may be employed as appropriate. Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water soluble carrier such as polyethyleneglycol or an oil medium, for example peanut oil, liquid paraffin, or olive oil. The capsule and tablet dosage forms may be prepared by various processing techniques including dry blending and wet granulation techniques. In the dry blending method of manufacture the drug substance may be incorporated into the dosage form by dry blending with the excipients followed by encapsulation into a capsule shell or compression into a tablet form. The dry blending operation may be approached in a stepwise manner and include screening steps between the blending steps to facilitate formation of a uniform blend. In the wet granulation method of manufacture the drug substance may be added to the dry excipients and mixed prior to the addition of the binder solution or the drug substance may be dissolved and added as a solution as part of granulation. In the wet granulation technique the surfactant, if used, may be added to the dry excipients or added to the binder solution and incorporated in a solution form. Capsule dosage forms may also be manufactured by dissolving the drug substance in a material that can be filled into and is compatible with hard gelatin capsule shells that can be subsequently banded and sealed. Capsule and tablet dosage forms may also be produced by dissolving the drug substance in a material such a molten form of a high molecular weight polyethylene glycol and cooling to a solid form, milling and incorporating this material into conventional capsule and tablet manufacturing processes.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisol or alpha-tocopherol.

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 and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Pharmaceutical compositions may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening agents, flavoring agents, preservatives and antioxidants.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring and coloring agents and antioxidant.

Pharmaceutical compositions may be in the form of a sterile injectable aqueous solution. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. The sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the active ingredient is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then introduced into a water and glycerol mixture and processed to form a microemulsion. The injectable solutions or microemulsions may be introduced into a patient's blood-stream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of the instant compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS™ model 5400 intravenous pump. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. 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.

Pharmaceutical compositions may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the inhibitors with a suitable non-irritating excipient which 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, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

For topical use, creams, ointments, jellies, solutions or suspensions, *etc.*, containing a compound or composition of the invention are useful for topical administration. As used herein, topical application can include mouth washes and gargles.

Pharmaceutical compositions may be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association a compound of the subject invention or a pharmaceutically acceptable salt, ester, prodrug or solvate thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and

then, if necessary, shaping the product into the desired formulation. Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent, to those skilled in this art. To be administered in the form of transdermal delivery, the dosage form will, of course, be continuous rather than intermittent throughout the dosage regimen.

***Doses***

The amount of pharmaceutical compositions administered will firstly be dependent on the mammal being treated. In the instances where pharmaceutical compositions are administered to a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, sex, diet, weight, general health and response of the individual patient, the severity of the patient's symptoms, the precise indication or condition being treated, the severity of the indication or condition being treated, time of administration, route of administration, the disposition of the composition, rate of excretion, drug combination, and the discretion of the prescribing physician. Also, the route of administration may vary depending on the condition and its severity.The pharmaceutical composition may be in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, *e.g.*, an effective amount to achieve the desired purpose. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small amounts until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired. The amount and frequency of administration of the compounds described herein, and if applicable other therapeutic agents and/or therapies, will be regulated according to the judgment of the attending clinician (physician) considering such factors as described above. Thus the amount of pharmaceutical composition to be administered may vary widely. Administration may occur in an amount of between about 0.001 mg/kg of body weight to about 100 mg/kg of body weight per day (administered in single or divided doses), or at least about 0.1 mg/kg of body weight per day. A particular therapeutic dosage can include, *e.g.*, from about 0.01 mg to about 7000 mg of compound, or, *e.g.*, from about 0.05 mg to about 2500 mg. The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, from about 1 mg to 300 mg, or 10 mg to 200 mg, according to the particular application. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, e.g. by dividing such larger doses into several small doses for administration throughout the day. The amount administered will vary depending on the particular $IC_{50}$ value of the compound used. In combinational applications in which the compound is not the sole therapy, it may be possible to administer lesser amounts of compound and still have therapeutic or prophylactic effect.

Additional dosing is provided throughout the specification and claims.

***Dosage Forms***

The pharmaceutical composition may, for example, be in a form suitable for oral administration as a tablet, capsule, pill, powder, sustained release formulations, solution, suspension, for parenteral injection as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages. The pharmaceutical composition will include a conventional pharmaceutical carrier or excipient and a compound according to the invention as an active ingredient. In addition, it may include other medicinal or pharmaceutical agents, carriers, adjuvants, etc.

Exemplary parenteral administration forms include solutions or suspensions of active compounds in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

Suitable pharmaceutical carriers include inert diluents or fillers, water and various organic solvents. The pharmaceutical compositions may, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus for oral administration, tablets containing various excipients, such as citric acid may be employed together with various disintegrants such as starch, alginic acid and certain complex silicates and with binding agents such as sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tableting purposes. Solid compositions of a similar type may also be employed in soft and hard filled gelatin capsules, including lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration the active compound therein may be combined with various sweetening or flavoring agents, coloring matters or dyes and, if desired, emulsifying agents or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, or combinations thereof.

Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent, to those skilled in this art. For examples, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Ester, Pa., 18th Edition (1990).

***Combination Therapies***

The compounds described herein or a pharmaceutically acceptable salt, solvate, polymorph, ester, amide, tautomer, prodrug, hydrate, or derivative thereof may be administered as a sole therapy. The compounds described herein or a pharmaceutically acceptable salt, solvate, polymorph, ester, amide, tautomer, prodrug, hydrate, or derivative thereof may also be administered in combination with another therapy or therapies.

Also described herein is N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide (Form A) which may be administered as a sole therapy. Crystalline polymorph form A of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide may also be administered in combination with another therapy or therapies.

By way of example only, if one of the side effects experienced by a patient upon receiving one of the compounds described herein is hypertension, then it may be appropriate to administer an anti-hypertensive agent in combination with the compound. Or, by way of example only, the therapeutic effectiveness of one of the compounds described herein may be enhanced by administration of an adjuvant (i.e., by itself the adjuvant may only have minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). Or, by way of example only, the benefit experienced by a patient may be increased by administering one of the compounds described herein with another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit. By way of example only, in a treatment for diabetes involving administration of one of the compounds described herein, increased therapeutic benefit may result by also providing the patient with another therapeutic agent for diabetes. In any case, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient may simply be additive of the two therapeutic agents or the patient may experience a synergistic benefit.

Other therapies include, but are not limited to administration of other therapeutic agents, radiation therapy or both. In the instances where the compounds described herein are administered with other therapeutic agents, the compounds described herein need not be administered in the same pharmaceutical composition as other therapeutic agents, and may, because of different physical and chemical characteristics, be administered by a different route. For example, the compounds/compositions may be administered orally to generate and maintain good blood levels thereof, while the other

therapeutic agent may be administered intravenously. The determination of the mode of administration and the advisability of administration, where possible, in the same pharmaceutical composition, is well within the knowledge of the skilled clinician. The initial administration can be made according to established protocols known in the art, and then, based upon the observed effects, the dosage, modes of administration and times of administration can be modified by the skilled clinician. The particular choice of compound (and where appropriate, other therapeutic agent and/or radiation) will depend upon the diagnosis of the attending physicians and their judgment of the condition of the patient and the appropriate treatment protocol. Other therapeutic agents may include chemotherapeutic agents, such as anti-tumor substances, for example those selected from, mitotic inhibitors, for example vinblastine; alkylating agents, for example cis-platin, carboplatin and cyclophosphamide; anti-metabolites, for example 5-fluorouracil, cytosine arabinside and hydroxyurea, or, for example, an anti-metabolite disclosed in European Patent Application No. 239362 such as N- (5- [N- (3, 4-dihydro-2-methyl-4- oxoquinazolin-6-yhnethyl)-N-methylamino]-2-thenoyl)-L-glutamic acid; growth factor inhibitors; cell cycle inhibitors; intercalating antibiotics, for example adriamycin and bleomycin; enzymes, for example, interferon; and anti-hormones, for example anti- estrogens such as Nolvadex™ (tamoxifen) or, for example anti-androgens such as Casodex™ (4'-cyano-3- (4-fluorophenylsulphonyl)-2-hydroxy-2-methyl-3'- (trifluoromethyl) propionanilide). Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of treatment.

The compounds and compositions described herein (and where appropriate chemotherapeutic agent and/or radiation) may be administered concurrently (*e.g.*, simultaneously, essentially simultaneously or within the same treatment protocol) or sequentially, depending upon the nature of the disease, the condition of the patient, and the actual choice of chemotherapeutic agent and/or radiation to be administered in conjunction (i.e., within a single treatment protocol) with the compound/composition.

In combinational applications and uses, the compound/composition and the chemotherapeutic agent and/or radiation need not be administered simultaneously or essentially simultaneously, and the initial order of administration of the compound/composition, and the chemotherapeutic agent and/or radiation, may not be important. Thus, the compounds/compositions of the invention may be administered first followed by the administration of the chemotherapeutic agent and/or radiation; or the chemotherapeutic agent and/or radiation may be administered first followed by the administration of the compounds/compositions of the invention. This alternate administration may be repeated during a single treatment protocol. The determination of the order of administration, and the number of repetitions of administration of each therapeutic agent during a treatment protocol, is well within the knowledge of the skilled physician after evaluation of the disease being treated and the condition of the patient. For example, the chemotherapeutic agent and/or radiation may be administered first, especially if it is a cytotoxic agent, and then the treatment continued with the administration of the compounds/compositions of the invention followed, where determined advantageous, by the administration of the chemotherapeutic agent and/or radiation, and so on until the treatment protocol is complete. Thus, in accordance with experience and knowledge, the practicing physician can modify each protocol for the administration of a compound/composition for treatment according to the individual patient's needs, as the treatment proceeds. The attending clinician, in judging whether treatment is effective at the dosage administered, will consider the general well-being of the patient as well as more definite signs such as relief of disease-related symptoms, inhibition of tumor growth, actual shrinkage of the tumor, or inhibition of metastasis. Size of the tumor can be measured by standard methods such as radiological studies, *e.g.*, CAT or MRI scan, and successive measurements can be used to judge whether or not growth of the tumor has been retarded or even reversed. Relief of disease-related symptoms such as pain, and improvement in overall condition can also be used to help judge effectiveness of treatment.

Specific, non-limiting examples of possible combination therapies include use of the compounds of the invention with agents found in the following pharmacotherapeutic classifications as indicated below. These lists should not be construed to be closed, but should instead serve as illustrative examples common to the relevant therapeutic area at present. Moreover, combination regimens may include a variety of routes of administration and should include oral, intravenous, intraocular, subcutaneous, dermal, and inhaled topical.

For the treatment of oncologic diseases, proliferative disorders, and cancers, compounds according to the present invention may be administered with an agent selected from the group comprising: aromatase inhibitors, antiestrogen, anti-androgen, corticosteroids, gonadorelin agonists, topoisomerase 1and 2 inhibitors, microtubule active agents, alkylating agents, nitrosoureas, antineoplastic antimetabolites, platinum containing compounds, lipid or protein kinase targeting agents, IMiDs, protein or lipid phosphatase targeting agents, anti-angiogenic agents, Akt inhibitors, IGF-I inhibitors, FGF3 modulators, mTOR inhibitors, Smac mimetics, HDAC inhibitors, agents that induce cell differentiation, bradykinin 1 receptor antagonists, angiotensin II antagonists, cyclooxygenase inhibitors, heparanase inhibitors, lymphokine inhibitors, cytokine inhibitors, IKK inhibitors, P38MAPK inhibitors, ARRY-797, HSP90 inhibitors, multlikinase inhibitors, bisphosphanates, rapamycin derivatives, anti-apoptotic pathway inhibitors, apoptotic pathway agonists, PPAR agonists, RAR agonists, inhibitors of Ras isoforms, telomerase inhibitors, protease inhibitors, metalloproteinase inhibitors, aminopeptidase inhibitors, SHIP activators - AQX-MN100, Humax-CD20 (ofatumumab), CD20 antagonists, IL2-diptheria toxin fusions.

For the treatment of oncologic diseases, proliferative disorders, and cancers, compounds according to the present invention may be administered with an agent selected from the group comprising: dacarbazine (DTIC), actinomycins $C_2$, $C_3$, D, and $F_1$, cyclophosphamide, melphalan, estramustine, maytansinol, rifamycin, streptovaricin, doxorubicin, daunorubicin, epirubicin, idarubicin, detorubicin, carminomycin, idarubicin, epirubicin, esorubicin, mitoxantrone, bleomycins A, $A_2$, and B, camptothecin, Irinotecan.RTM., Topotecan.RTM., 9-aminocamptothecin, 10,11 - methylenedioxycamptothecin, 9-nitrocamptothecin, bortezomib, temozolomide, TAS103, NPI0052, combretastatin, combretastatin A-2, combretastatin A-4, calicheamicins, neocarcinostatins, epothilones A B, C, and semi-synthetic variants, Herceptin.RTM., Rituxan.RTM., CD40 antibodies, asparaginase, interleukins, interferons, leuprolide, and pegaspargase, 5-fluorouracil, fluorodeoxyuridine, ptorafur, 5'-deoxyfluorouridine, UFT, MITC, S-1 capecitabine, diethylstilbestrol, tamoxifen, toremefine, tolmudex, thymitaq, flutamide, fluoxymesterone, bicalutamide, finasteride, estradiol, trioxifene, dexamethasone, leuproelin acetate, estramustine, droloxifene, medroxyprogesterone, megesterol acetate, aminoglutethimide, testolactone, testosterone, diethylstilbestrol, hydroxyprogesterone, mitomycins A, B and C, porfiromycin, cisplatin, carboplatin, oxaliplatin, tetraplatin, platinum-DACH, ormaplatin, thalidomide, lenalidomide, CI-973, telomestatin, CHIR258, Rad 001, SAHA, Tubacin, 17-AAG, sorafenib, JM-216, podophyllotoxin, epipodophyllotoxin, etoposide, teniposide, Tarceva.RTM., Iressa.RTM., Imatinib.RTM., Miltefosine.RTM., Perifosine.RTM., aminopterin, methotrexate, methopterin, dichloro-methotrexate, 6-mercaptopurine, thioguanine, azattuoprine, allopurinol, cladribine, fludarabine, pentostatin, 2-chloroadenosine, deoxycytidine, cytosine arabinoside, cytarabine, azacitidine, 5-azacytosine, gencitabine, 5-azacytosine-arabinoside, vincristine, vinblastine, vinorelbine, leurosine, leurosidine and vindesine, paclitaxel, taxotere and docetaxel.

For the treatment of inflammatory diseases or pain, compounds and pharmaceutically acceptable salts of the compounds according to the present invention may be administered with an agent selected from the group comprising: corticosteroids, non-steroidal anti-inflammatories, muscle relaxants and combinations thereof with other agents, anaesthetics and combinations thereof with other agents, expectorants and combinations thereof with other agents, antidepressants, anticonvulsants and combinations thereof; antihypertensives, opioids, topical cannabinoids, capsaicin,

betamethasone dipropionate (augmented and nonaugemnted), betamethasone valerate, clobetasol propionate, prednisone, methyl prednisolone, diflorasone diacetate, halobetasol propionate, amcinonide, dexamethasone, dexosimethasone, fluocinolone acetononide, fluocinonide, halocinonide, clocortalone pivalate, dexosimetasone, flurandrenalide, salicylates, ibuprofen, ketoprofen, etodolac, diclofenac, meclofenamate sodium, naproxen, piroxicam, celecoxib, cyclobenzaprine, baclofen, cyclobenzaprine/lidocaine, baclofen/cyclobenzaprine, cyclobenzaprine/lidocaine/ketoprofen, lidocaine, lidocaine/deoxy-D-glucose, prilocaine, EMLA Cream (Eutectic Mixture of Local Anesthetics (lidocaine 2.5% and prilocaine 2.5%), guaifenesin, guaifenesin/ketoprofen/cyclobenzaprine, amitryptiline, doxepin, desipramine, imipramine, amoxapine, clomipramine, nortriptyline, protriptyline, duloxetine, mirtazepine, nisoxetine, maprotiline, reboxetine, fluoxetine, fluvoxamine, carbamazepine, felbamate, lamotrigine, topiramate, tiagabine, oxcarbazepine, carbamezipine, zonisamide, mexiletine, gabapentin/clonidine, gabapentin/carbamazepine, carbamazepine/cyclobenzaprine, antihypertensives including clonidine, codeine, loperamide, tramadol, morphine, fentanyl, oxycodone, hydrocodone, levorphanol, butorphanol, menthol, oil of wintergreen, camphor, eucalyptus oil, turpentine oil; CB1/CB2 ligands, acetaminophen, infliximab, nitric oxide synthase inhibitors, particularly inhibitors of inducible nitric oxide synthase, PDE4 inhibitors – similar mechanism to Ibudilast (AV-411) , CDC-801, JNK inhibitors - CC-401, Combination TNF/PDE4 inhibitors – CDC-998, IL1 antagonists e.g. Anakinra – Kineret, AMG 108, (mAb) that targets IL-1, SHIP activators - AQX-MN100, C5 antagonists, C5a inhibitors, Pexelizumab, Pyrimidine synthesis inhibitors, lymphokine inhibitors, cytokine inhibitors, IKK inhibitors, P38MAPK inhibitors, ARRY-797, HSP90 inhibitors, multlikinase inhibitors, bisphosphanates, PPAR agonists, Cox1 and cox 2 inhibitors, Anti-CD4 therapy, B-cell inhibitors, COX/LOX dual inhibitors, Immunosuppressive agents, iNOS inhibitors, NSAIDs, sPLA2 inhibitors, Colchicine, allopurinol, oxypurinol, Gold, Ridaura – Auranofin, febuxostat, Puricase, PEG-uricase formulations, Benzbromarone, Long-acting beta-2 agonists (LABAs), salmeterol (Serevent Diskus) and formoterol (Foradil), Leukotriene modifiers include montelukast (Singulair) and zafirlukast (Accolate). Inhaled cromolyn (Intal) or nedocromil (Tilade), Theophylline. Short-acting beta-2 agonists, Ipratropium (Atrovent), Immunotherapy-(Allergy-desensitization shots), Anti-IgE monoclonal antibodies – Xolair, Common DMARDs include hydroxychloroquine (Plaquenil), the gold compound auranofin (Ridaura), sulfasalazine (Azulfidine), minocycline (Dynacin, Minocin) and methotrexate (Rheumatrex), leflunomide (Arava), azathioprine (Imuran), cyclosporine (Neoral, Sandimmune) and cyclophosphamide (Cytoxan), Antibiotics, CD80 antagonists, costimulatory factor antagonists, Humax-CD20 (ofatumumab); CD20 antagonists, MEK inhibitors, ,NF kappa B inhibitors, anti B-cell antibodies, denosumab, mAb that specifically targets the receptor activator of nuclear factor kappa B ligand (RANKL). IL17 inactivating anti-bodies, IL-17 receptor antagonists/inhibitors, CTLA inhibitors, CD20 inhibitors, soluble VEGFR-1 receptors, anti-VEGFR-1 receptor antibodies, anti-VEGF antibodies, integrin receptor antagonist, Selectin inhibitors, P-selectin and E-selectin inhibitors, Phospholipase A2 Inhibitors , Lipoxygenase Inhibitors, RANKL and RANK antagonists/antibodies, Osteoprotegerin antagonists, Lymphotoxin inhibitors, B-lymphocyte stimulator, MCP-1 inhibitors, MIF inhibitors, inhibitors of : CD2, CD3, CD4 , CD25 , CD40 and CD40 Ligand CD152 (CTLA4), Macrolide immunosuppressants, Selective inhibitors of nucleotide metabolism, Inhibitors of chemotaxis, CXC receptor and CXC ligand inhibitors, Chemokine Antagonists, leukocyte chemotaxis inhibitors Adhesion Molecule blockers, Selectins Lymphocyte Function Antigen-1 (LFA-1, CD11a) antagonists, Very Late Antigen-4 (VLA-4) antagonists, Matrix Metalloprotease Inhibitors, Elastase Inhibitors, Cathepsin Inhibitors.

For the treatment of ophthalmologic disorders and diseases of the eye, compounds and pharmaceutically acceptable salts of the compounds according to the present invention may be administered with an agent selected from the group comprising: beta-blockers, carbonic anhydrase inhibitors, .alpha.- and .beta.-adrenergic antagonists including

al-adrenergic antagonists, .alpha.2 agonists, miotics, prostaglandin analogs, corticosteroids, and immunosuppressant agents.

For the treatment of ophthalmologic disorders and diseases of the eye, compounds pharmaceutically acceptable salts of the compounds according to the present invention may be administered with an agent selected from the group comprising: timolol, betaxolol, levobetaxolol, carteolol, levobunolol, propranolol, brinzolamide, dorzolamide, nipradilol, iopidine, brimonidine, pilocarpine, epinephrine, latanoprost, travoprost, bimatoprost, unoprostone, dexamethasone, prednisone, methylprednisolone, azathioprine, cyclosporine, and immunoglobulins.

For the treatment of autoimmune disorders, compounds pharmaceutically acceptable salts of the compounds according to the present invention may be administered with an agent selected from the group comprising: corticosteroids, immunosuppressants, prostaglandin analogs and antimetabolites.

For the treatment of autoimmune disorders, compounds according to the present invention may be administered with an agent selected from the group comprising: dexamethasome, prednisone, methylprednisolone, azathioprine, cyclosporine, immunoglobulins, latanoprost, travoprost, bimatoprost, unoprostone, infliximab, rutuximab, methotrexate, non-steroidal anti-inflammatories, muscle relaxants and combinations thereof with other agents, anaesthetics and combinations thereof with other agents, expectorants and combinations thereof with other agents, antidepressants, anticonvulsants and combinations thereof; antihypertensives, opioids, topical cannabinoids, and other agents, such as capsaicin, betamethasone dipropionate (augmented and nonaugemnted), betamethasone valerate, clobetasol propionate, prednisone, methyl prednisolone, diflorasone diacetate, halobetasol propionate, amcinonide, dexamethasone, dexosimethasone, fluocinolone acetononide, fluocinonide, halocinonide, clocortalone pivalate, dexosimetasone, flurandrenalide, salicylates, ibuprofen, ketoprofen, etodolac, diclofenac, meclofenamate sodium, naproxen, piroxicam, celecoxib, cyclobenzaprine, baclofen, cyclobenzaprine/lidocaine, baclofen/cyclobenzaprine, cyclobenzaprine/lidocaine/ketoprofen, lidocaine, lidocaine/deoxy-D-glucose, prilocaine, EMLA Cream (Eutectic Mixture of Local Anesthetics (lidocaine 2.5% and prilocaine 2.5%), guaifenesin, guaifenesin/ketoprofen/cyclobenzaprine, amitryptiline, doxepin, desipramine, imipramine, amoxapine, clomipramine, nortriptyline, protriptyline, duloxetine, mirtazepine, nisoxetine, maprotiline, reboxetine, fluoxetine, fluvoxamine, carbamazepine, felbamate, lamotrigine, topiramate, tiagabine, oxcarbazepine, carbamezipine, zonisamide, mexiletine, gabapentin/clonidine, gabapentin/carbamazepine, carbamazepine/cyclobenzaprine, antihypertensives including clonidine, codeine, loperamide, tramadol, morphine, fentanyl, oxycodone, hydrocodone, levorphanol, butorphanol, menthol, oil of wintergreen, camphor, eucalyptus oil, turpentine oil; CB1/CB2 ligands, acetaminophen, infliximab; nitric oxide synthase inhibitors, particularly inhibitors of inducible nitric oxide synthase; and other agents, such as capsaicin. PDE4 inhibitors – similar mechanism to Ibudilast (AV-411) , CDC-801, JNK inhibitors - CC-401, Combination TNF/PDE4 inhibitors – CDC-998, IL1 antagonists e.g. Anakinra – Kineret, AMG 108, (mAb) that targets IL-1, SHIP activators - AQX-MN100, C5 antagonists, C5a inhibitors, Pexelizumab, Pyrimidine synthesis inhibitors, lymphokine inhibitors, cytokine inhibitors, IKK inhibitors, P38MAPK inhibitors, ARRY-797, HSP90 inhibitors, multlikinase inhibitors, bisphosphanates, PPAR agonists, Cox1 and cox 2 inhibitors, Anti-CD4 therapy, B-cell inhibitors, COX/LOX dual inhibitors, Immunosuppressive agents, iNOS inhibitors, NSAIDs, sPLA2 inhibitors, Colchicine, allopurinol, oxypurinol, Gold, Ridaura – Auranofin, febuxostat, Puricase, PEG-uricase formulations, Benzbromarone, Long-acting beta-2 agonists (LABAs), salmeterol (Serevent Diskus) and formoterol (Foradil), Leukotriene modifiers include montelukast (Singulair) and zafirlukast (Accolate). Inhaled cromolyn (Intal) or nedocromil (Tilade), Theophylline. Short-acting beta-2 agonists, Ipratropium (Atrovent), Immunotherapy-(Allergy-desensitization shots), Anti-IgE monoclonal antibodies – Xolair, Common DMARDs include hydroxychloroquine (Plaquenil), the gold compound auranofin (Ridaura), sulfasalazine

(Azulfidine), minocycline (Dynacin, Minocin) and methotrexate (Rheumatrex), leflunomide (Arava), azathioprine (Imuran), cyclosporine (Neoral, Sandimmune) and cyclophosphamide (Cytoxan), Antibiotics, CD80 antagonists, costimulatory factor antagonists, Humax-CD20 (ofatumumab); CD20 antagonists, MEK inhibitors, ,NF kappa B inhibitors, anti B-cell antibodies, denosumab, mAb that specifically targets the receptor activator of nuclear factor kappa B ligand (RANKL). IL17 inactivating anti-bodies, IL-17 receptor antagonists/inhibitors, CTLA inhibitors, CD20 inhibitors, soluble VEGFR-1 receptors, anti-VEGFR-1 receptor antibodies, anti-VEGF antibodies, integrin receptor antagonist, Selectin inhibitors, P-selectin and E-selectin inhibitors, Phospholipase A2 Inhibitors , Lipoxygenase Inhibitors, RANKL and RANK antagonists/antibodies, Osteoprotegerin antagonists, Lymphotoxin inhibitors, B-lymphocyte stimulator, MCP-1 inhibitors, MIF inhibitors, inhibitors of : CD2, CD3, CD4 , CD25 , CD40 and CD40 Ligand CD152 (CTLA4), Macrolide immunosuppressants, Selective inhibitors of nucleotide metabolism, Inhibitors of chemotaxis, CXC receptor and CXC ligand inhibitors, Chemokine Antagonists, leukocyte chemotaxis inhibitors Adhesion Molecule blockers, Selectins Lymphocyte Function Antigen-1 (LFA-1, CD11a) antagonists, Very Late Antigen-4 (VLA-4) antagonists, Matrix Metalloprotease Inhibitors, Elastase Inhibitors, Cathepsin Inhibitors.

For the treatment of metabolic disorders, compounds and pharmaceutically acceptable salts of the compounds according to the present invention may be administered with an agent selected from the group comprising: insulin, insulin derivatives and mimetics, insulin secretagogues, insulin sensitizers, biguanide agents, alpha-glucosidase inhibitors, insulinotropic sulfonylurea receptor ligands, protein tyrosine phosphatase-1B (PTP-1B) inhibitors, GSK3 (glycogen synthase kinase-3) inhibitors, GLP-1 (glucagon like peptide-1), GLP-1 analogs, DPPIV (dipeptidyl peptidase IV) inhibitors, RXR ligands sodium-dependent glucose co-transporter inhibitors, glycogen phosphorylase A inhibitors, an AGE breaker, PPAR modulators, LXR and FXR modulators, non-glitazone type PPARS agonist, selective glucocorticoid antagonists, metformin, Glipizide, glyburide, Amaryl, meglitinides, nateglinide, repaglinide, PT-112, SB-517955, SB4195052, SB-216763, NN-57-05441, NN-57-05445, GW-0791, AGN-.sup.194.sup.204, T-1095, BAY R3401, acarbose Exendin-4, DPP728, LAF237, vildagliptin , MK-0431, saxagliptin, GSK23A, pioglitazone, rosiglitazone, (R)-1-{4-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-benze- nesulfonyl}2,3-dihydro-1H-indole-2-carboxylic acid described in the patent application WO 03/043985, as compound 19 of Example 4, and GI-262570.

***Diseases***

Described herein are methods of treating a disease in an individual suffering from said disease comprising administering to said individual an effective amount of a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, amide, tautomer, prodrug, hydrate, or derivative thereof.

Also described herein are methods of treating a disease or disorder in an individual suffering from said disease or disorder comprising administering to said individual an effective amount of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide (Form A). The invention extends to the use of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide (Form A) in the manufacture of a medicament for treating a disease or disorder.

In some embodiments, the invention relates to the prophylaxis or treatment of any disease or disorder in which MEK kinase plays a role including, without limitation: oncologic, hematologic, inflammatory, ophthalmologic, neurological, immunologic, cardiovascular, and dermatologic diseases as well as diseases caused by excessive or unregulated pro-inflammatory cytokine production including for example excessive or unregulated TNF, IL-1, IL-6 and IL-8 production in a human, or other mammal. The invention extends to such a use and to the use of the compounds for the manufacture of a medicament for treating such cytokine-mediated diseases or disorders. Further, the invention

extends to the administration to a human an effective amount of a MEK inhibitor for treating any such disease or disorder.

Diseases or disorders in which MEK kinase plays a role, either directly or via pro-inflammatory cytokines including the cytokines TNF, IL-1, IL-6 and IL-8, include, without limitation: dry eye, glaucoma, autoimmune diseases, inflammatory diseases, destructive-bone disorders, proliferative disorders, neurodegenerative disorders, viral diseases, allergies, infectious diseases, heart attacks, angiogenic disorders, reperfusion/ischemia in stroke, vascular hyperplasia, organ hypoxia, cardiac hypertrophy, thrombin-induced platelet aggregation, and conditions associated with prostaglandin endoperoxidase synthetase-2 (COX-2).

In certain aspects of the invention, the disease is a hyperproliferative condition of the human or animal body, including, but not limited to cancer, hyperplasias, restenosis, inflammation, immune disorders, cardiac hypertrophy, atherosclerosis, pain, migraine, angiogenesis-related conditions or disorders, proliferation induced after medical conditions, including but not limited to surgery, angioplasty, or other conditions.

In further embodiments, said hyperproliferative condition is selected from the group consisting of hematologic and nonhematologic cancers. In yet further embodiments, said hematologic cancer is selected from the group consisting of multiple myeloma, leukemias, and lymphomas. In yet further embodiments, said leukemia is selected from the group consisting of acute and chronic leukemias. In yet further embodiments, said acute leukemia is selected from the group consisting of acute lymphocytic leukemia (ALL) and acute nonlymphocytic leukemia (ANLL). In yet further embodiments, said chronic leukemia is selected from the group consisting of chronic lymphocytic leukemia (CLL) and chronic myelogenous leukemia (CML). In further embodiments, said lymphoma is selected from the group consisting of Hodgkin's lymphoma and non-Hodgkin's lymphoma. In further embodiments, said hematologic cancer is multiple myeloma. In other embodiments, said hematologic cancer is of low, intermediate, or high grade. In other embodiments, said nonhematologic cancer is selected from the group consisting of: brain cancer, cancers of the head and neck, lung cancer, breast cancer, cancers of the reproductive system, cancers of the digestive system, pancreatic cancer, and cancers of the urinary system. In further embodiments, said cancer of the digestive system is a cancer of the upper digestive tract or colorectal cancer. In further embodiments, said cancer of the urinary system is bladder cancer or renal cell carcinoma. In further embodiments, said cancer of the reproductive system is prostate cancer.

Additional types of cancers which may be treated using the compounds and methods described herein include: cancers of oral cavity and pharynx, cancers of the respiratory system, cancers of bones and joints, cancers of soft tissue, skin cancers, cancers of the genital system, cancers of the eye and orbit, cancers of the nervous system, cancers of the lymphatic system, and cancers of the endocrine system. In certain embodiments, these cancer s may be selected from the group consisting of: cancer of the tongue, mouth, pharynx, or other oral cavity; esophageal cancer, stomach cancer, or cancer of the small intestine; colon cancer or rectal, anal, or anorectal cancer; cancer of the liver, intrahepatic bile duct, gallbladder, pancreas, or other biliary or digestive organs; laryngeal, bronchial, and other cancers of the respiratory organs; heart cancer, melanoma, basal cell carcinoma, squamous cell carcinoma, other non-epithelial skin cancer; uterine or cervical cancer; uterine corpus cancer; ovarian, vulvar, vaginal, or other female genital cancer; prostate, testicular, penile or other male genital cancer; urinary bladder cancer; cancer of the kidney; renal, pelvic, or urethral cancer or other cancer of the genito-urinary organs; thyroid cancer or other endocrine cancer; chronic lymphocytic leukemia; and cutaneous T-cell lymphoma, both granulocytic and monocytic.

Yet other types of cancers which may be treated using the compounds and methods described herein include: adenocarcinoma, angiosarcoma, astrocytoma, acoustic neuroma, anaplastic astrocytoma, basal cell carcinoma, blastoglioma, chondrosarcoma, choriocarcinoma, chordoma, craniopharyngioma, cutaneous melanoma,

161

cystadenocarcinoma, endotheliosarcoma, embryonal carcinoma, ependymoma, Ewing's tumor, epithelial carcinoma, fibrosarcoma, gastric cancer, genitourinary tract cancers, glioblastoma multiforme, hemangioblastoma, hepatocellular carcinoma, hepatoma, Kaposi's sarcoma, large cell carcinoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, medullary thyroid carcinoma, medulloblastoma, meningioma mesothelioma, myelomas, myxosarcoma neuroblastoma, neurofibrosarcoma, oligodendroglioma, osteogenic sarcoma, epithelial ovarian cancer, papillary carcinoma, papillary adenocarcinomas, parathyroid tumors, pheochromocytoma, pinealoma, plasmacytomas, retinoblastoma, rhabdomyosarcoma, sebaceous gland carcinoma, seminoma, skin cancers, melanoma, small cell lung carcinoma, squamous cell carcinoma, sweat gland carcinoma, synovioma, thyroid cancer, uveal melanoma, and Wilm's tumor.

Also described are methods for the treatment of a hyperproliferative disorder in a mammal that comprise administering to said mammal a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt, solvate, polymorph, ester, amide, tautomer, prodrug, hydrate, or derivative thereof, in combination with an anti-tumor agent. In some embodiments, the anti-tumor agent is selected from the group consisting of mitotic inhibitors, alkylating agents, anti- metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzyme inhibitors, topoisomerase inhibitors, biological response modifiers, anti- hormones, angiogenesis inhibitors, anti-androgens, SHIP activators - AQX-MN100, Humax-CD20 (ofatumumab), CD20 antagonists, IL2-diptheria toxin fusions.

The disease to be treated using the compounds, compositions and methods described herein may be a hematologic disorder. In certain embodiments, said hematologic disorder is selected from the group consisting of sickle cell anemia, myelodysplastic disorders (MDS), and myeloproliferative disorders. In further embodiments, said myeloproliferative disorder is selected from the group consisting of polycythemia vera, myelofibrosis and essential thrombocythemia.

The compounds, compositions and methods described herein may be useful as anti-inflammatory agents with the additional benefit of having significantly less harmful side effects. The compounds, compositions and methods described herein are useful to treat arthritis, including but not limited to rheumatoid arthritis, spondyloarthropathies, ankylosing spondylitis, gout, gouty arthritis, osteoarthritis, systemic lupus erythematosus, juvenile arthritis, acute rheumatic arthritis, enteropathic arthritis, neuropathic arthritis, psoriatic arthritis, and pyogenic arthritis. The compounds, compositions and methods described herein are also useful in treating osteoporosis and other related bone disorders. These compounds, compositions and methods described herein are also useful to treat gastrointestinal conditions such as reflux esophagitis, diarrhea, inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis. The compounds, compositions and methods described herein may also be used in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis. In addition, the compounds, compositions and methods described herein are also useful in organ transplant patients either alone or in combination with conventional immunomodulators. Yet further, the compounds, compositions and methods described herein are useful in the treatment of pruritis and vitaligo. In particular, compounds, compositions and methods described herein are useful in treating the particular inflammatory disease rheumatoid arthritis.

Further inflammatory diseases which may be prevented or treated include, without limitation: asthma, allergies, respiratory distress syndrome or acute or chronic pancreatitis. Furthermore, respiratory system diseases may be prevented or treated including but not limited to chronic obstructive pulmonary disease, and pulmonary fibrosis. In addition, MEK kinase inhibitors described herein are also associated with prostaglandin endoperoxidase synthetase-2 (COX-2) production. Pro-inflammatory mediators of the cyclooxygenase pathway derived from arachidonic acid, such as prostaglandins, are produced by inducible COX-2 enzyme. Regulation of COX-2 would regulate these pro-inflammatory mediators, which affect a wide variety of cells and are important and critical inflammatory mediators of a wide variety of

disease states and conditions. In particular, these inflammatory mediators have been implicated in pain, such as in the sensitization of pain receptors, and edema. Accordingly, additional MEK kinase-mediated conditions which may be prevented or treated include edema, analgesia, fever and pain such as neuromuscular pain, headache, dental pain, arthritis pain and pain caused by cancer.

Further, the disease to be treated by the compounds, compositions and methods described herein may be an ophthalmologic disorder. Ophthalmologic diseases and other diseases in which angiogenesis plays a role in pathogenesis, may be treated or prevented and include, without limitation, dry eye (including Sjogren's syndrome), macular degeneration, closed and wide angle glaucoma, retinal ganglion degeneration, occular ischemia, retinitis, retinopathies, uveitis, ocular photophobia, and of inflammation and pain associated with acute injury to the eye tissue. The compounds, compositions and methods described herein are useful to treat glaucomatous retinopathy and/or diabetic retinopathy. The compounds, compositions and methods described herein are also useful to treat post-operative inflammation or pain as from ophthalmic surgery such as cataract surgery and refractive surgery.. In further embodiments, said ophthalmologic disorder is selected from the group consisting of dry eye, closed angle glaucoma and wide angle glaucoma.

Further, the disease to be treated by the compounds, compositions and methods described herein may be an autoimmune disease. Autoimmune diseases which may be prevented or treated include, but are not limited to: rheumatoid arthritis, inflammatory bowel disease, inflammatory pain, ulcerative colitis, Crohn's disease, periodontal disease, temporomandibular joint disease, multiple sclerosis, diabetes, glomerulonephritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, hemolytic anemia, autoimmune gastritis, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, atopic dermatitis, graft vs. host disease, and psoriasis. Inflammatory diseases which may be prevented or treated include, but are not limited to: asthma, allergies, respiratory distress syndrome or acute or chronic pancreatitis. In particular, compounds, compositions and methods described herein are useful in treating the particular autoimmune diseases rheumatoid arthritis and multiple sclerosis.

Further, the disease to be treated by the compounds, compositions and methods described herein may be a dermatologic disorder. In certain embodiments, said dermatologic disorder is selected from the group including, without limitation, melanoma, basel cell carcinoma, squamous cell carcinoma, and other non-epithelial skin cancer as well as psoriasis and persistent itch, and other diseases related to skin and skin structure, may be treated or prevented with MEK kinase inhibitors of this invention.

Metabolic diseases which may be treated or prevented include, without limitation, metabolic syndrome, insulin resistance, and Type 1 and Type 2 diabetes. In addition, the compositions described herein may be useful to treat insulin resistance and other metabolic disorders such as atherosclerosis that are typically associated with an exaggerated inflammatory signaling.

The compounds, compositions and methods described herein are also useful in treating tissue damage in such diseases as vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephritis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, periodontis, hypersensitivity, swelling occurring after injury, ischemias including myocardial ischemia, cardiovascular ischemia, and ischemia secondary to cardiac arrest, and the like. The compounds, compositions and methods described herein may also be useful to treat allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, and atherosclerosis.

Further, the disease to be treated by the compounds, compositions and methods described herein may be a cardiovascular condition. In certain embodiments, said cardiovascular condition is selected from the group consisting of

atherosclerosis, cardiac hypertrophy, idiopathic cardiomyopathies, heart failure, angiogenesis-related conditions or disorders, and proliferation induced after medical conditions, including, but not limited to restenosis resulting from surgery and angioplasty.

Further, the disease to be treated by the compounds, compositions and methods described herein may be a neurological disorder. In certain embodiments, said neurologic disorder is selected from the group consisting of Parkinson's disease, Alzheimer's disease, Alzheimer's dementia, and central nervous system damage resulting from stroke, ischemia and trauma. In other embodiments, said neurological disorder is selected from the group consisting of epilepsy, neuropathic pain, depression and bipolar disorders.

Further, the disease to be treated by the compounds, compositions and methods described herein may cancer such as acute myeloid leukemia, thymus, brain, lung, squamous cell, skin, eye, retinoblastoma, intraocular melanoma, oral cavity and oropharyngeal, bladder, gastric, stomach, pancreatic, bladder, breast, cervical, head, neck, renal, kidney, liver, ovarian, prostate, colorectal, esophageal, testicular, gynecological, thyroid, CNS, PNS, AIDS related AIDS-Related (e.g. Lymphoma and Kaposi's Sarcoma) or Viral-Induced cancer. In some embodiments, the compounds and compositions are for the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (e. g., psoriasis), restenosis, or prostate (e. g., benign prostatic hypertrophy (BPH)).

Further, the disease to be treated by the compounds, compositions and methods described herein may pancreatitis, kidney disease (including proliferative glomerulonephritis and diabetes- induced renal disease), pain, a disease related to vasculogenesis or angiogenesis, tumor angiogenesis, chronic inflammatory disease such as rheumatoid arthritis, inflammatory bowel disease, atherosclerosis, skin diseases such as psoriasis, eczema, and scleroderma, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, tendonitis, bursitis, sciatica, glioma, melanoma, Kaposi's sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer in a mammal.

Further, the disease to be treated by the compounds, compositions and methods described herein may the prevention of blastocyte implantation in a mammal.

Patients that can be treated with the compounds described herein, or their pharmaceutically acceptable salts, solvate, polymorphs, esters, amides, tautomers, prodrugs, hydrates, or derivatives according to the methods of this invention include, for example, patients that have been diagnosed as having psoriasis; restenosis; atherosclerosis; BPH; breast cancer such as a ductal carcinoma in duct tissue in a mammary gland, medullary carcinomas, colloid carcinomas, tubular carcinomas, and inflammatory breast cancer; ovarian cancer, including epithelial ovarian tumors such as adenocarcinoma in the ovary and an adenocarcinoma that has migrated from the ovary into the abdominal cavity; uterine cancer; cervical cancer such as adenocarcinoma in the cervix epithelial including squamous cell carcinoma and adenocarcinomas; prostate cancer, such as a prostate cancer selected from the following: an adenocarcinoma or an adenocarinoma that has migrated to the bone; pancreatic cancer such as epitheliod carcinoma in the pancreatic duct tissue and an adenocarcinoma in a pancreatic duct; bladder cancer such as a transitional cell carcinoma in urinary bladder, urothelial carcinomas (transitional cell carcinomas), tumors in the urothelial cells that line the bladder, squamous cell carcinomas, adenocarcinomas, and small cell cancers; leukemia such as acute myeloid leukemia (AML), acute lymphocytic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, hairy cell leukemia, myelodysplasia, and myeloproliferative disorders; bone cancer; lung cancer such as non-small cell lung cancer (NSCLC), which is divided into squamous cell carcinomas, adenocarcinomas, and large cell undifferentiated carcinomas, and small cell lung cancer; skin cancer such as basal cell carcinoma, melanoma, squamous cell carcinoma and actinic keratosis, which is a skin condition that sometimes develops into squamous cell carcinoma; eye retinoblastoma; cutaneous or intraocular (eye)

melanoma; primary liver cancer (cancer that begins in the liver); kidney cancer; thyroid cancer such as papillary, follicular, medullary and anaplastic; AIDS-related lymphoma such as diffuse large B-cell lymphoma, B-cell immunoblastic lymphoma and small non-cleaved cell lymphoma; Kaposi's Sarcoma; viral-induced cancers including hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatocellular carcinoma; human lymphotropic virus-type 1 (HTLV-1) and adult T-cell leukemia/lymphoma; and human papilloma virus (HPV) and cervical cancer; central nervous system cancers (CNS) such as primary brain tumor, which includes gliomas (astrocytoma, anaplastic astrocytoma, or glioblastoma multiforme), Oligodendroglioma, Ependymoma, Meningioma, Lymphoma, Schwannoma, and Medulloblastoma; peripheral nervous system (PNS) cancers such as acoustic neuromas and malignant peripheral nerve sheath tumor (MPNST) including neurofibromas and schwannomas, malignant fibrous cytoma, malignant fibrous histiocytoma, malignant meningioma, malignant mesothelioma, and malignant mixed Müllerian tumor; oral cavity and oropharyngeal cancer such as, hypopharyngeal cancer, laryngeal cancer, nasopharyngeal cancer, and oropharyngeal cancer; stomach cancer such as lymphomas, gastric stromal tumors, and carcinoid tumors; testicular cancer such as germ cell tumors (GCTs), which include seminomas and nonseminomas, and gonadal stromal tumors, which include Leydig cell tumors and Sertoli cell tumors; thymus cancer such as to thymomas, thymic carcinomas, Hodgkin disease, non-Hodgkin lymphomas carcinoids or carcinoid tumors; rectal cancer; and colon cancer.

***Kits***

The compounds, compositions and methods described herein provide kits for the treatment of disorders, such as the ones described herein. These kits comprise a compound, compounds or compositions described herein in a container and, optionally, instructions teaching the use of the kit according to the various methods and approaches described herein. Such kits may also include information, such as scientific literature references, package insert materials, clinical trial results, and/or summaries of these and the like, which indicate or establish the activities and/or advantages of the composition, and/or which describe dosing, administration, side effects, drug interactions, or other information useful to the health care provider.. Such information may be based on the results of various studies, for example, studies using experimental animals involving in vivo models and studies based on human clinical trials. Kits described herein can be provided, marketed and/or promoted to health providers, including physicians, nurses, pharmacists, formulary officials, and the like. Kits may also, in some embodiments, be marketed directly to the consumer.

The compounds described herein can be utilized for diagnostics and as research reagents. For example, the compounds described herein, either alone or in combination with other compounds, can be used as tools in differential and/or combinatorial analyses to elucidate expression patterns of genes expressed within cells and tissues. As one non-limiting example, expression patterns within cells or tissues treated with one or more compounds are compared to control cells or tissues not treated with compounds and the patterns produced are analyzed for differential levels of gene expression as they pertain, for example, to disease association, signaling pathway, cellular localization, expression level, size, structure or function of the genes examined. These analyses can be performed on stimulated or unstimulated cells and in the presence or absence of other compounds which affect expression patterns.

Besides being useful for human treatment, the compounds and formulations of the present invention are also useful for veterinary treatment of companion animals (eg dogs, cats), exotic animals and farm animals (eg horses), including mammals, rodents, and the like.

The examples and preparations provided below further illustrate and exemplify the compounds of the present invention and methods of preparing such compounds. It is to be understood that the scope of the present invention is not limited in any way by the scope of the following examples and preparations.

165

## EXAMPLES

**General Exemplary Procedures for the Synthesis of Sulfonamides**

**Procedure A**: To a solution of the amine (1 eq) in anhydrous dichloromethane (3 mL/ mmole) was added anhydrous triethylamine (5 eq). To this solution was added the sulfonyl chloride (1 eq) and the solution was stirred at room temperature for 16 h. The solvent was evaporated and the residue was purified by flash column chromatography on silica.

**Procedure B**: To a stirred solution of the amine (1 eq) in anhydrous pyridine (5ml/mmole) was added the sulfonyl chloride (1 - 5 eq). The reaction mixture was stirred at 40 °C for 48 hours. The reaction mixture was partitioned with water and EtOAc. The organic layer was washed with brine, dried ($MGSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica.

**Procedure C**: Substitution of the iodo-atom:

A suspension containing 1 eq. aryl iodide, 1.5 equiv. of the boronic acid or boronic ester, 0.25 eq. $PdCl_2$(dppf) x DCM and 10 eq. anhydrous $K_2CO_3$ powder in a deoxygenated mixture of dioxane and water (3:1) was heated in a microwave reactor for 60 min at 115 °C. It was extracted using aq. $NH_4Cl$ / THF, and the organic fraction was dried using $Na_2SO_4$. The crude reaction products were purified using flash-column chromatography (Si, EtOAc / Hexanes, or $CHCl_3$ / MeOH). Yields: 20-40%.

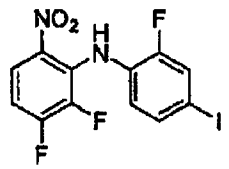
**Procedure D:** Synthesis of N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2-(alkylamino)ethanesulfonamide:

2-Chloro-ethanesulfonyl chloride (0.1 ml, 1 mmol) was added to a solution of 5,6-difluoro-$N^1$-(2-fluoro-4-iodophenyl)benzene-1,2-diamine (0.364 g, 1 mmol) and triethylamine (0.28 ml, 2 mmol) in $CH_2Cl_2$ (5 ml) and the reaction mixture was stirred at room temperature for 16h. Then it's treated with an excess amine (10 eq) either in solution or as a neat liquid. The reaction mixture stirred at room temperature for additional 6h. The reaction mixture diluted with $CH_2Cl_2$ (10 ml) and water (10 ml). The organic layer was sequentially washed with dil. HCl (2x20 ml, 2N) and saturated $NaHCO_3$ (2x10 ml) solution. Then the $CH_2Cl_2$ layer dried ($MgSO_4$) and evaporated to obtain the crude product. The impure product was purified under preparative HPLC conditions to obtain the pure products in 50-60 % yield.

Example 1

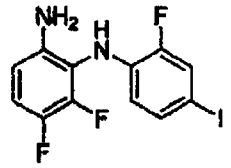
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)methanesulfonamide:**

**Step A:** 2,3-Difluoro-N-(2-fluoro-4-iodophenyl)-6-nitroaniline:



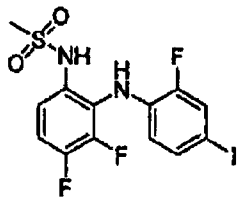

To a solution of 2-fluoro-4-iodoaniline (11.40 g, 47 mmol) in 100 ml anhydrous THF at 0°C, 47 ml of a 1M solution of LHMDS in THF (47 mmol) was added dropwise. The color of the solution turned dark purple. The solution was transferred *via* cannula to a dropping funnel, and the solution (containing the amine free base) was added in small portions to a solution of 2,3,4-trifluoronitrobenzene (8.321 g, 47.0 mmol) in anhydrous THF (50 ml) at 0°C. After completion of addition the mixture was stirred under argon at room temperature for 15 hours. The volume of the solvent was reduced, followed by extraction using ethyl acetate and brine. The organic layer was dried over sodium sulfate, the solvent was removed, and the obtained dark oil was purified by flash chromatography (EtOAc / hexane 1:5, $R_f = 0.58$) yielding the crude product, which became a brown solid upon drying *in vacuo* (yield: 6.23 g, 33.6%): $m/z = 393$ $[M-1]^-$.

**Step B:** 5,6-Difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine:



To a solution of nitro-diarylamine (6.23 g, 15.8 mmol) in 300 ml ethanol was added iron powder (13.74 g, 246 mmol) and ammonium chloride (13.59 g, 254 mmol) and the mixture was heated with stirring at 100°C oil bath temperature for 14 hours. It was filtered and the residue washed two times with ethanol. The ethanol was removed *in vacuo*, and the residue was extracted using ethyl acetate / 1M NaOH solution. During the extraction, more precipitate was formed which was filtered and discarded. The combined organic layers were washed with brine and dried over sodium sulfate. The solvent was removed, and the crude product was recrystallized from $CHCl_3$ / hexane (1:50). The product was obtained as brown needles (2.094 g, 66%,), $R_f$ = 0.44 (EtOAc / Hex 1:3), $^1$H-NMR (500 MHz, $CDCl_3$), δ = 7.40-7.38 (dd, 1H, *J* = 11.3 Hz, *J* = 1.5 Hz), 7.25-7.23 (d, 1H, *J* = 8.5 Hz), 6.97-6.92 (q, 1H, *J* = 9 Hz), 6.51-6.48 (m, 1H), 6.24-6.21 (t, 1H, *J* = 9 Hz), 5.3 (s, 1H, NH, br), 3.80 (s, 2H, $NH_2$, br), LRMS (ESI): *m/z* = 365 $[M+H]^-$.

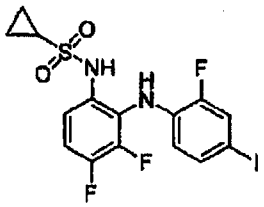
**Step C:** N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)methanesulfonamide:



According to the general procedure A, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with methanesulfonyl chloride to obtain the desired product. $^1$H NMR: (500 MHz, $CDCl_3$): δ = 7.38-7.37 (d, 1H), 7.35-7.34 (m, 1H), 7.27-7.26 (m, 1H), 7.20-7.0 (q, 1H), 6.68 (s, 1H, br), 6.15-6.12 (q, 1H), 5.65 (s, 1H, br), 2.95 (s, 3H); *m/z* = 441 $[M-1]^-$.

Example 2

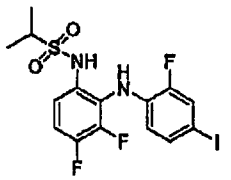
**2 N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)cyclopropanesulfonamide:**



According to the general procedure A, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with cyclopropanesulfonyl chloride to obtain the desired product. $^1$H NMR: (500 MHz, $CDCl_3$): δ = 7.38-7.37 (d, 1H), 7.35-7.34 (m, 1H), 121-1 Id (m, IH), 7.20-7.0 (q, 1H), 6.68 (s, 1H, br), 6.15-6.12 (q, 1H), 5.65 (s, 1H, br), 3.25-3.20 (m, 1H), 2.4-2.3 (m, 2H), 2.0-1.8 (m, 2H); *m/z* = 467 $[M-1]^-$.

Example 3

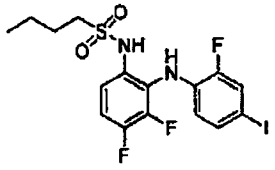
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)propane-2-sulfonamide:**



According to the general procedure A, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with isopropylsulfonyl chloride to obtain the desired product. Yield: 39%. $^1$H-NMR (500 MHz, $CDCl_3$): δ = 7.50-7.43 (m, 1H), 7.35-7.34 (m, 1H), 7.27-7.26 (m, 1H), 7.15-7.09 (q, 1H, *J* = 1.6 Hz), 6.62 (s, 1H, br), 6.22-6.18 (q, 1H, *J* = 1.5 Hz), 5.65 (s, 1H, br), 3.30-3.28 (m, 1H), 1.38-1.37 (d, 6H, *J* = 1.2 Hz); *m/z* = 469 $[M-I]^-$.

Example 4

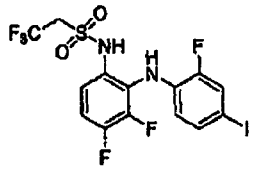
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)butane-l-sulfonamide:**



According to the general procedure A, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with n-butylsulfonyl chloride to obtain the desired product. Yield: 55%. $^1$H-NMR (500 MHz, $CDCl_3$): δ = 7.50-7.43 (m, 1H), 7.35-7.34 (m, 1H), 7.27-7.26 (m, 1H), 7.15-7.09 (q, 1H, *J* = 1.6 Hz), 6.62 (s, 1H, br), 6.22-6.18 (q, 1H, *J* = 1.5 Hz), 5.65 (s, 1H, br), 3.06-3.031 (t, 2H, *J* = 1.4 Hz), 1.75-1.71 (m, 2H), 1.38-1.36 (m, 2H), 0.87-0.86 (t, 3H, *J* = 1.3 Hz); *m/z* = 483 $[M-1]^-$.

Example 5

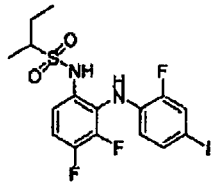
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2,2,2-trifluoro ethane sulfonamide:**



According to the general procedure A, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with 1,1,1-trifluoroethylsulfonyl chloride to obtain the desired product. Yield: 28%. *m/z* = 509 $[M-1]^-$.

Example 6

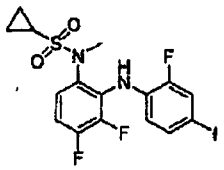
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)butane-2-sulfonaniide:**



According to the general procedure A, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with sec-butylsulfonyl chloride to obtain the desired product. Yield: 22%. $^1$H-NMR (500 MHz, MeOH[d4]): δ = 7.60-7.40 (m, 3H), 7.18-7.00 (q, 1H), 6.55-6.45 (m, 1H), 3.55-3.50 (m, 1H), 2.20-2.00 (m, 1H), 1.80-1.60 (m, 1H), 1.43-1.40 (d, 3H), 1.06-1.04 (t, 3H); *m/z* = 483 $[M-1]^-$.

Example 7

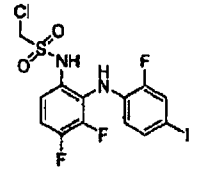
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-N-methyl cyclopropane sulfonamide:**



To a solution of N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)cyclopropane-sulfonamide (see Example 2) (283.9 mg, 0.61 mmol) in 3 ml anhydrous THF was added at -78°C a IM solution of LHMDS (0.6 ml, 0.6 mol) and the solution was stirred for 10 min at this temperature. Then, methyl iodide (0.8 ml, 1.824 g, 12.9 mmol) was added and the mixture was warmed to room temperature and stirred for 7 h. The solvent was removed and the residue extracted using EtOAc and brine. The organic fractions were dried using $Na_2SO_4$ and the solvent was removed. The obtained crude product was purified using flash-column chromatography (Si, EtOAc/Hexanes 1:2, $R_f$ = 0.45). Yield: 205 mg, 70%). $^1$H-NMR (500 MHz, $CDCl_3$): δ = 7.41-7.39 (d, 1H, *J* = 10 Hz), 7.30-7.29 (d, 1H, *J* = 8.0 Hz), 7.23-7.20 (m, 1H), 6.98-6.93 (q, 1H, *J* = 8.5 Hz), 6.60 (s, 1H, br), 6.51-6.47 (m, 1H), 3.23 (s, 3H), 2.46-2.42 (m, 1H), 1.19-1.16 (m, 2H), 1.04-1.02 (m, 2H); *m/z* = 481 $[M-1]^-$.

Example 8

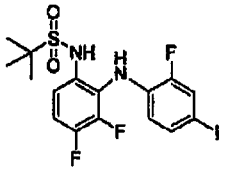
**1-Chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl) methane sulfonamide:**



According to the general procedure A, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with chloromethanesulfonyl chloride to obtain the desired product, *m/z* = 475 $[M-1]^-$.

Example 9

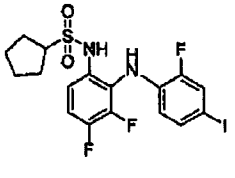
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2-methylpropane-2-sulfonamide:**



According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with 2-methylpropane-2-sulfonyl chloride (synthesized according to the literature procedure) to obtain the desired product. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.50 (m, 1H), 7.43 (dd, *J* = 1.8 & 10.5 Hz, 1H), 7.28 (br s, 1H), 7.10 (dd, *J* = 9.0 & 17.7 Hz, 1H), 6.48 (br s, $D_2O$ exchangeable, 1H), 6.19 (t, *J* = 7.8 & 9.6 Hz, 1H), 5.58 (br s, $D_2O$ exchangeable, 1H), 1.39 (s, 9H); *m/z* = 383 $[M-1]^-$.

Example 10

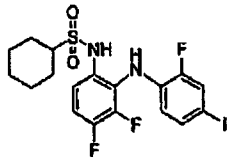
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)cyclopentanesulfonamide:**



According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with cyclopentanesulfonyl chloride to obtain the desired product $^1$H NMR (300 MHz, $CDCl_3$): δ 7.42 (dd, *J* = 2.1 & 10.5 Hz, 1H), 7.36 (ddd, *J* = 2.4, 4.8, & 9.3 Hz, 1H), 7.25 (m, 2H), 7.10 (dd, *J* = 9.6 & 17.7 Hz, 1H), 6.67 (br s, $D_2O$ exchangeable, 1H), 6.20 (dt, *J* = 1.5, 8.4 & 17.4 Hz, 1H), 3.53 (p, 1H), 1.80 (m, 8H); *m/z* = 495 $[M-1]^-$.

Example 11

**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)cyclohexanesulfonamide:**

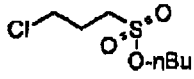


According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with cyclohexanesulfonyl chloride to obtain the desired product. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.43 (dd, $J$ = 1.5 & 10.2 Hz, 1H), 7.37 (ddd, $J$ = 2.4, 4.8 & 9.6 Hz, 1H), 7.27 (m, 1H), 7.11 (dd, $J$ = 9.3 & 18.0 Hz, 1H), 6.64 (br s, 1H), 6.18 (dt, $J$ = 1.5, 9.0 & 17.4 Hz, 1H), 5.63 (br s, 1H), 2.95 (triplet of triplet, 2.10-1.16 (m, 10H); $m/z$ = 509 $[M-1]^-$.

Example 12

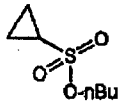
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-methylcyclopropane-1-sulfonamide:**

**Step A:** n-Butyl 3 -chloro-1-propanesulfonate:



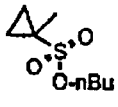
Triethylamine (28 ml, 200 mmol) in $CH_2Cl_2$ (50 ml) was slowly added to an ice-cooled solution of 3-chloro-1-propanesulfonyl chloride (36.6g, 200 mmol) and 1-butanol (18.4 g, 240 m mol) in $CH_2Cl_2$ (250 ml) and stirring was continued for 16h. The mixture was diluted with $CH_2Cl_2$ (200 ml), washed (aqueous HCl) and dried ($MgSO_4$) and the solvent was evaporated to obtain the titled product 1 (40.85 g, 95%) in crude form as slightly yellow oil which was used for the next reaction without further purification. $^1$H NMR ($CDCl_3$) δ 0.94 (t, $J$ = 7.5 Hz, 3H), 1.44 (sextet, 2H), 1.72 (quintet, 2H), 2.31 (quintet, 2H), 3.27(t, $J$ = 6.9 Hz, 2H), 3.68 (t, $J$ = 6.3 Hz), 4.23 (t, $J$ = 6.6 Hz, 2H).

**Step B:** 1-Butyl cyclopropanesulfonate:



Solutions of 1-butyl 3-chloro-1-propanesulfonate (4.6 g, 21.39 mmol in 25 ml THF) and of butyllithium (14.7 ml, 23.53 mmol, 1.6M, THF) were simultaneously added to THF (150 ml) at -78°C under nitrogen atmosphere. The solution was allowed to warm to 0°C and then quenched with water (2 ml). The volatiles evaporated under reduced pressure and the residue extracted with $CH_2Cl_2$ (150 ml). The extract was washed with water and dried ($MgSO_4$) and evaporated to give crude desired product (3.23 g, 78.22%) in almost pure form as pale yellow oil which was used for next step without further purification. $^1$H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, J = 7.5 Hz, 3H), 1.07 (m, 2H), 1.25 (m, 2H), 1.45(sextet, 2H), 1.74(quintet, 2H), 2.45 (heptet, 1H), 4.23 (t, J = 6.6 Hz, 2H).

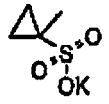
**Step C:** Butyl 1-Methyl-cyclopropanesulfonate:



To a solution of 1 -Butyl cyclopropanesulfonate (1 g, 5.58 mmol) in THF (15 ml) butyllithium solution ( 3.84 ml, 6,14 mmol, 1.6M, THF) was slowly added at -78°C under nitrogen atmosphere. After 15 minutes MeI (0.72 ml, 11.16 mmol) was added and the solution was allowed to warm to 0°C and quenched with water (1 ml). The volatiles evaporated under reduced pressure and the residue extracted with $CH_2Cl_2$ (100 ml). The extract was washed with water,

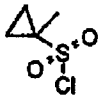
dried ($MgSO_4$) and evaporated. The residue was purified over silica gel chromatography (eluants: hexane/ $CH_2Cl_2$) to obtain the titled product (0.59 g, 55.0%) as a colorless oil. $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.84 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H), 1.43 (m, 4H), 1.53 (s, 3H), 1.74(m, 2H), 4.21 ((t, J = 6.6 Hz, 2H).

**Step D:** 1-Potassium 1-Methyl-cyclopropanesulfonate:



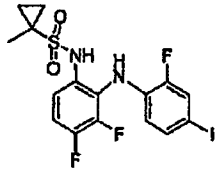
A mixture of 1-Butyl 1-Methyl-cyclopropanesulfonate (0.386 g, 2 mmol) and potassium thiocyanate (0.194 g, 2 mmol) in DME (5 ml) and water (5 ml) was refluxed for 16h. The volatiles were evaporated to obtain the crude sulfonate (0.348g, quantitative) which was dried under vacuum at 50°C for 16h. The crude product was used in the next reaction without further purification. $^1H$ NMR (300 MHz, $D_2O$) δ 0.56 (t, $J$ = 6.3 Hz, 2H), 0.96 (t, $J$ = 6.3 Hz, 2H), 1.26 (s, 3H).

**Step E:** 1-Methyl-cyclopropanesulfonylchloride:



A solution of 1-potassium 1-methyl-cyclopropanesulfonate (0.348 g, 2 mmol), thionyl chloride (5 ml) and DMF (5 drops) was refluxed at 60°C for 16h. The volatiles evaporated under reduced pressure and the residue extracted with $CH_2Cl_2$ (50 ml). The extract was washed with water, dried ($MgSO_4$) and evaporated to obtain the crude product as yellow gummy oil which was used in the next reaction without further purification.

**Step F:** N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-methylcyclopropane-1-sulfonamide:

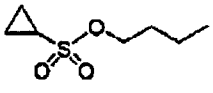


According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with 1-methyl-cyclopropanesulfonylchloride to obtain the desired product. $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.42 (dd, $J$ = 1.8 & 10.5 Hz, 1H), 7.36 (ddd, $J$ = 2.4, 4.5 & 9.0 Hz, 1H), 7.27 (d, $J$ = 6.0 Hz, 1H), 7.07 (dd, $J$ = 9.3 & 17.7 Hz, 1H), 6.24 (dt, $J$ = 2.1, 8.7 & 17.4 Hz, 1H), 5.86 (br s, 1H), 1.43 (s, 3H), 1.33 (t, $J$ = 5.4 Hz, 2H), 0.75 (dd, $J$ = 5.1 & 6.3 Hz, 2H); $m/z$ = 481 $[M-1]^-$.

Example 13

**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide:**

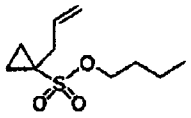
**Step A:** Butyl cyclopropanesulfonate:



Cyclopropanesulfonyl chloride (5 g, 35 mmol, 1 eq) was dissolved in an excess BuOH (20 ml), the reaction mixture was cooled at -10°C and pyridine (5.8 mL, 70 mmol, 2 eq) was slowly added dropwise. The mixture was slowly warmed at room temperature and stirred overnight. The solvent was removed under reduced pressure and the resulting white solid was dissolved in $CHCl_3$. The organic phase was washed with water, brine and dried (MgSO4) and

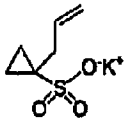
concentrated to give an oil (4.8 g, 24.9 mmol, 71%). $^1$H NMR (300 MHz, $CDCl_3$): δ 4.25 (t, 2H), 2.46 (m, 1H), 1.74 (m, 2H), 1.45 (m, 2H), 1.25 (dd, 2H), 1.09 (dd, 2H), .93 (t, 3H).

**Step B:** Butyl 1-allylcyclopropane-1-sulfonate:



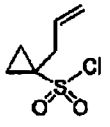
To a solution of 1-butyl cyclopropanesulfonate (4.8 g, 24.9 mmol) in THF at -78°C was added simultaneously butyllithium solution (15.6 ml, 24.9 mmol, 1.6M, THF) and allyl iodide (24.9 mmol) under nitrogen atmosphere. The reaction mixture was stirred 2 hours at -78°C and 3 hours at room temperature. The volatiles were evaporated under reduced pressure and the residue extracted with $CH_2Cl_2$ (100 ml). The extract was washed with water, dried ($MgSO_4$) and evaporated. The residue was purified over silica gel chromatography (eluants: hexane/ $CH_2Cl_2$) to obtain the titled product (3.75 g, 69.0%) as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$): δ 5.6 (m, 1H), 5.13-5.08 (t, 2H), 4.21 (t, 2H), 2.65 (d, 2H), 1.7 (m, 2H), 1.4 (m, 4H), .93 (m, 5H).

**Step C:** Potassium 1-allylcyclopropane-1-sulfonate:



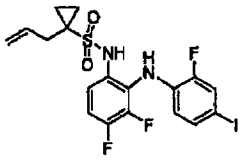
A mixture of 1-butyl 1-methyl-cyclopropanesulfonate (3.75 g, 17.2 mmol) and potassium thiocyanate (1.7 g, 17.2 mmol) in DME (20 ml) and water (20 ml) was refluxed for 16h. The volatiles were evaporated to obtain the crude sulfonate (3.44g, quantitative) which was dried under vacuum at 50°C for 16h. The crude product was used in the next reaction without further purification. $^1$H NMR ($CDCl_3$): δ 5.6 (m, 1H), 4.91-4.85 (dd, 2H), 2.471-2.397 (d, 2H), 0.756 (m, 2H), 0.322 (m, 2H).

**Step D:** 1-allylcyclopropane-1-sulfonyl chloride:



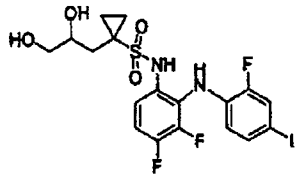
A solution of potassium 1-allylcyclopropane-1-sulfonate (3.44 g, 17.2 mmol), thionyl chloride (10 ml) and DMF (5 drops) was refluxed at 60°C for 16h. The volatiles evaporated under reduced pressure and the residue extracted with $CH_2Cl_2$ (50 ml). The extract was washed with water, dried ($MgSO_4$) and evaporated to obtain the crude product as yellow gummy oil which was washed with hexane and used in the next reaction without further purification (2.7 g, 15 mmol, 87%). $^1$HNMR (300 MHz, $CDCl_3$): δ 5.728 (m, 1H), 5.191 (t, 2H), 2.9 (d, 2H), 0.756 (m, 2H), 0.322 (m, 2H).

**Step E:** 1-allyl-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)cyclopropane-1-sulfonamide:



According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with 1-allylcyclopropane-1-sulfonyl chloride to obtain the desired product. *m/z* = 507 $[M-1]^-$.

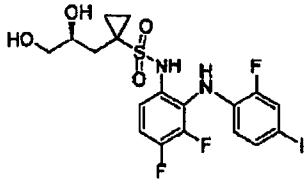
**Step F:** N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide:



1-Allyl-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)cyclopropane-1-sulfonamide (0,77 g, 1.52 mmol) and 4-methylmorpholine N-oxide (0,18 g, 1.52 mmol) were dissolved in THF (50 mL). Osmium tetroxide was added at room temperature (0.152 mmol, 0.965 mL, 4% in $H_2O$) and the reaction mixture was stirred at room temperature for 16 hours. EtOAc was added, the organic phase was washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified over silica gel chromatography (eluants: EtOAc/ MeOH) to obtain the titled product (0.65 g, 79%). $^1$H NMR (300 MHz, $CDCl_3$ + $D_2O$): δ 7.38 (dd, $J$ = 1.8 & 10.5 Hz, 1H), 7.36 (ddd, $J$ = 2.4, 5.1 & 9.3 Hz, 1H), 7.25 (d, $J$ = 8.7 Hz, 1H), 7.02 (dd, $J$ = 9.0 & 17.7 Hz, 1H), 6.27 (dt, $J$ = 3.0, 8.7 & 17.4 Hz, 1H), 3.92 (m, 1H), 3.54 (dd, $J$ = 3.9 & 11.1 Hz, 1H), 3.39 (dd, $J$ = 6.6 & 11.1 Hz, 1H), 2.16 (dd, $J$ = 9.6 & 15.9 Hz, 1H), 1.59 (d, $J$ = 14.1 Hz, 1H), 1.41 (m, 1H), 1.26 (m, 1H), 0.83 (m, 2H); $m/z$ = 542 $[M-1]^-$.

Example 14

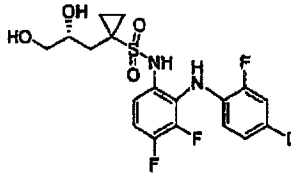
**(S)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide:**



The pure S isomer was obtained by chiral HPLC separation of the racemic mixture (example 13). $^1$H NMR (300 MHz, $CDCl_3$ + $D_2O$): δ 7.38 (dd, $J$ = 1.8 & 10.5 Hz, 1H), 7.36 (ddd, $J$ = 2.4, 5.1 & 9.3 Hz, 1H), 7.25 (d, $J$ = 8.7 Hz, 1H), 7.02 (dd, $J$ = 9.0 & 17.7 Hz, 1H), 6.27 (dt, $J$ = 3.0, 8.7 & 17.4 Hz, 1H), 3.92 (m, 1H), 3.54 (dd, $J$ = 3.9 & 11.1 Hz, 1H), 3.39 (dd, $J$ = 6.6 & 11.1 Hz, 1H), 2.16 (dd, $J$ = 9.6 & 15.9 Hz, 1H), 1.59 (d, $J$ = 14.1 Hz, 1H), 1.41 (m, 1H), 1.26 (m, 1H), 0.83 (m, 2H); $m/z$ = 542 $[M-1]^-$.

Example 15

**(R)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide:**

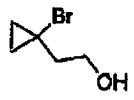


The pure R isomer was obtained by chiral HPLC separation of the racemic mixture (example 13). $^1$H NMR (300 MHz, $CDCl_3$ + $D_2O$): δ 7.38 (dd, $J$ = 1.8 & 10.5 Hz, 1H), 7.36 (ddd, $J$ = 2.4, 5.1 & 9.3 Hz, 1H), 7.25 (d, $J$ = 8.7 Hz, 1H), 7.02 (dd, $J$ = 9.0 & 17.7 Hz, 1H), 6.27 (dt, $J$ = 3.0, 8.7 & 17.4 Hz, 1H), 3.92 (m, 1H), 3.54 (dd, $J$ = 3.9 & 11.1 Hz, 1H), 3.39 (dd, $J$ = 6.6 & 11.1 Hz, 1H), 2.16 (dd, $J$ = 9.6 & 15.9 Hz, 1H), 1.59 (d, $J$ = 14.1 Hz, 1H), 1.41 (m, 1H), 1.26 (m, 1H), 0.83 (m, 2H); $m/z$ = 542 $[M-1]^-$.

Example 16

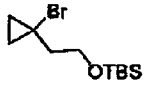
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-(2-hydroxyethyl)cyclopropane-1-sulfonamide:**

**Step A:** 2-d -bromocyclopropyl)ethanol:



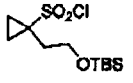

To a solution of neat diethyl zinc (3.3 ml, 3.977 g, 30 mmol) in 100 ml anhydrous DCM was added very slowly trifluoroacetic acid (2.31 ml, 3.4188 g, 30 mmol) dropwise at 0°C. (Caution: Violent gas evolution, exothermic!). After completed addition of the TFA, the suspension was stirred for 20 min at the same temperature, followed by the addition of diiodo methane (2.45 ml, 8.134 g, 30.4 mmol). It was further stirred at 0°C for 20 min, and then a solution of 3-bromobut-3-en-1-ol (1 ml, 1.523 g, 10.1 mmol) in 10 ml DCM was added at the same temperature. After complete addition, the mixture was warmed to room temperature and stirred for 4 hours. The mixture was quenched with 100 ml MeOH and 40 ml brine, and it was further stirred for 30 min. The solvents were reduced, and the residue extracted using $CHCl_3$ / aq. $NH_4Cl$. The organic layers were collected, washed with brine and water, and the solvent was removed to give 2-(1-bromocyclopropyl)-ethanol in sufficient purity (1.6564 g, 100%). $^1$H-NMR (500 MHz, $CDCl_3$): δ = 3.90-3.83 (t, 2H), 1.91-1.87 (t, 2H), 1.71 (s, 1H, br), 1.14-1.09 (m, 2H), 0.83-0.79 (m, 2H).

**Step B:** TBS protected 2-(1-bromocyclopropyl)ethanol:



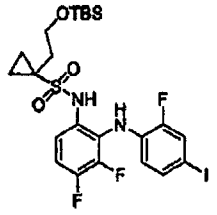

To a solution of the cyclopropyl alcohol (Step A) (1.303 g, 7.95 mmol) in 30 ml anhydrous DCM was added anhydrous pyridine (1.2 ml, 1,1736 g, 14.8 mmol) and TBSOTf (2.7 ml, 3.1077 g, 11.76 mol) and the solution was stirred at room temperature for 16h. It was extracted with $CHCl_3$ / brine and the organic fraction was dried with $MgSO_4$. The solvent was reduced and the crude product purified using flash-column chromatography (Si, $CHCl_3$ / hexanes 1:10, $R_f$ = 0.4). Yield: 0.796 g, 36%. $^1$H-NMR (500 MHz, $CDCl_3$): δ = 3.95-3.75 (t, 2H), 1.95-1.85 (t, 2H), 1.15-1.05 (m, 2H), 0.95-0.80 (m, HH), 0.15-0.05 (s, 6H).

**Step C:** TBS protected 2-(1-chlorosulfonylcyclopropyl)ethanol:



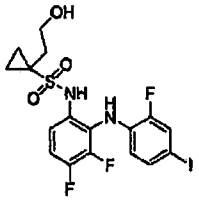

To a solution of the cyclopropyl bromide prepared in step B (1.1227 g, 4.04 mmol) in 15 ml anhydrous diethyl ether was added a 1.7 M solution of t-BuLi in pentane (4.8 ml, 8.16 mmol) at -78°C. The solution was stirred for 30 min at this temperature, and was then transferred via a transfer canola into a solution of freshly distilled sulfuryl chloride (0.65 ml, 1.029 g, 8.1 mmol) in 8 ml diethyl ether at -78°C. The yellow suspension was warmed to room temperature. The solvent was removed, and the residue was dried *in vacuo* to remove excessive sulfuryl chloride. Then, the residue was extracted two times with hexane, and after filtration the solvent was evaporated *in vacuo* to give the sulfonyl chloride in sufficient purity as a colorless oil. Yield: 870 mg (72%). $^1$H-NMR (300 MHz, $CDCl_3$): δ = 3.95-3.85 (t, 2H), 2.35-2.25 (t, 2H), 1.80-1.70 (m, 2H), 1.45-1.38 (m, 2H), 0.90 (s, 9H), 0.10 (s, 6H).

**Step D:** TBS-protected N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-(2-hydroxyethyl)cyclopropane-1-sulfonamide:



According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with the cyclpropylsulfonyl chloride prepared in step C to obtain the desired product. $^1$H-NMR (300 MHz, $CDCl_3$): δ = 7.44-7.39 (dd, 1H), 7.32-7.24 (m, 2H), 7.1-6.98 (q, 1H), 6.34-6.24 (m, 1H), 6.16 (s, 1H, br), 3.85-3.75 (t, 2H), 2.15-2.00 (t, 2H), 1.35-1.20 (m, 2H), 0.95-0.75 (m, 1 1H), 0.10 (s, 6H); *m/z* = 625 $[M-1]^-$.

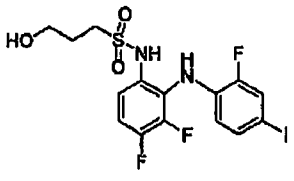
**Step E:** N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-(2-hydroxyethyl)cyclopropane-1-sulfonamide:



To a solution of the TBS-protected sulfonamide prepared in step D (21 mg, 0.033 mmol) in 1 ml THF was added 0.1 ml aq.1.2N HCl solution at 0°C and the solution was stirred for 2 h. The solvents were reduced and the residue was extracted using aq. $NaHCO_3$ solution and EtOAc. The organic fractions were dried with $MgSO_4$ and the volatiles were removed. The crude product was purified using flash-column chromatography (Si, $CHCl_3$ / MeOH 10:1, $R_f$ = 0.45) to give the pure product. Yield: 16.9 mg (100%). $^1$H-NMR (300 MHz, $CDCl_3$): δ = 7.44-7.39 (dd, 1H), 7.32-7.24 (m, 2H), 7.1-6.98 (q, 1H), 6.34-6.24 (m, 1H), 6.16 (s, 1H, br), 3.85-3.75 (t, 2H), 2.15-2.00 (t, 2H), 1.35-1.20 (m, 2H), 0.95-0.85 (m, 2H); *m/z* = 511 $[M-1]^-$.

Example 17

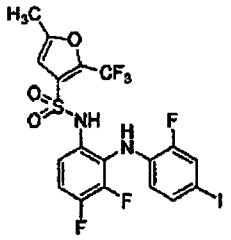
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-3-hydroxypropane-1-sulfonamide:**



To a solution of 3-chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-propane- 1-sulfonamide (69.4 mg, 0.138 mmol) in a mixture of 8 ml 1,4-dioxane and 2 ml $H_2O$ was added KOH powder (0.674 g, 12.0 mmol) and the mixture was heated to the reflux temperature for 3 days. It was extracted using EtOAc / brine, the organic fraction was dried with $Na_2SO_4$ and the volatiles were removed. The residue was purified using flash-column chromatography (Si, DCM / MeOH 5:1, $R_f$ = 0.3). Yield: 41 mg (62%). $^1$H-NMR (500 MHz, MeOH [d4]): δ = 7.38- 7.21 (d, 1H), 7.23-7.21 (d, 1H), 7.06-7.00 (q, 1H), 6.52-6.50 (m, 1H), 6.17-6.13 (t, 1H), 3.30-3.27 (t, 2H), 2.86-2.83 (t, 2H), 2.05-2.00 (m, 2H); *m/z* = 485 $[M-1]^-$.

Example 18

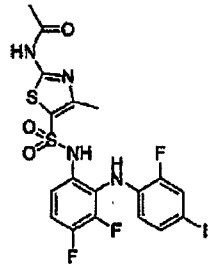
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2-methyl-5- (trifluoromethyl)furan-3-sulfonamide:**



According to the general procedure B, 5,6-difiuoro-N1-(2-fiuoro-4-iodophenyl)benzene-1,2-diamine (0.182 mmol) was reacted with 2-methyl-5-(trifluoromethyl)furan-3-sulfonyl chloride (0.5 mmol) to form N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2-methyl-5-(trifluoromethyl)furan-3-sulfonamide. $^1$H NMR ($CDCl_3$) δ 2.2 (s, 3H), 5.3 (s, 1H), 6.0 (dt, 1H), 6.8 (s, 1H), 6.95 (s, 1H), 7.0-7.3 (m, 3H), 7.4 (dd, 1H).

Example 19

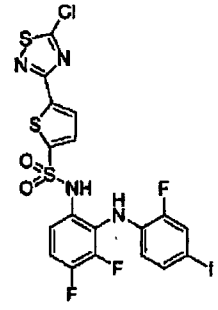
**N-(5-(N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)sulfamoyl)-methylthiazol-2-yl)acetamide:**



According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine (0.182 mmol) was reacted with 2-acetamido-4-methylthiazole-5-sulfonyl chloride (0.5 mmol) to obtain N-(5-(N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)sulfamoyl)-4-methylthiazol-2-yl)acetamide . $^1$H NMR ($CDCl_3$) δ 2.1 (s, 3H), 2.2 (s, 3H), 5.9 (dt, 1H), 6.05 (s, 1H), 7.0-7.6 (m, 3H), 7.4 (dd, 1H), 8.0 (s, 1H).

Example 20

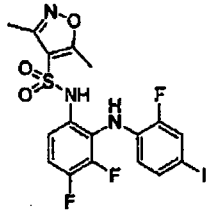
**5-(5-Chloro-1,2,4-thiadiazol-3-yl)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl) thiophene-2-sulfonamide:**



According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine (0.182 mmol) was reacted with 5-(5-chloro-1,2,4-thiadiazol-3-yl)thiophene-2-sulfonyl chloride (0.5 mmol) to obtain 5-(5-chloro-1,2,4-thiadiazol-3-yl)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)thiophene-2-sulfonamide. $^1$H NMR (300 MHz, $CDCl_3$) δ 5.8 (dt, 1H), 5.95 (s, 1H), 6.95 (d, 1H),7.4 (m, 2H), 7.6 (d, 1H), 7.8 (s, 1H).

Example 21

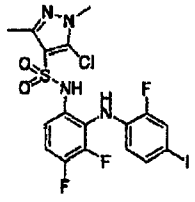
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-3,5dimethylisoxazole-4-sulfonamide:**



According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl) benzene-1,2-diamine (0.182 mmol) was reacted with 3,5-dimethylisoxazole-4-sulfonyl chloride (0.5 mmol) to obtain N-(3,4-difluoro-2-(2-fluoro-4-iodophenyl amino)phenyl)-3,5dimethylisoxazole-4-sulfonamide. $^1$H NMR (300 MHz, $CDCl_3$)) δ 2.2 (s, 3H), 2.4 (s, 3H), 5.8 (s, 1H), 6.0 (dt, 1H), 5.95 (s, 1H), 6.9 (s, 1H),7.0 (q, 1H), 7.2 (m, 3H), 7.4 (dd, 1H).

Example 22

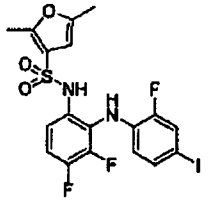
**5-Chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1,3-dimethyl- lH-pyrazole-4-sulfonamide:**



According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl) benzene-1,2-diamine (0.182 mmol) was reacted with 5-chloro-1,3-dimethyl-lH-pyrazole-4-sulfonyl chloride (0.5 mmol) to obtain 5-chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino) phenyl)-1,3-dimethyl-lH-pyrazole-4-sulfonamide. $^1$H NMR (300 MHz, $CDCl_3$)) δ 2.1 (s, 3H), 3.6 (s, 3H), 5.8 (s, 1H), 5.95 (dt, 1H), 7.0 (q, 1H), 7.2 (d, 1H), 7.3 (m, 2H), 7.4 (dd, 1H).

Example 23

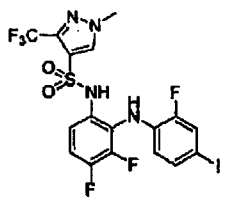
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2,5-dimethylfuran-3-sulfonamide:**



According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl) benzene-1,2-diamine (0.182 mmol) was reacted with 2,5-dimethylfuran-3-sulfonyl chloride (0.5 mmol) to obtain N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino) phenyl)-2,5-dimethylfuran-3-sulfonamide. $^1$H NMR (300 MHz, $CDCl_3$)) δ 2.2 (s, 3H), 2.3 (s, 3H), 5.8 (s, 1H), 6.0 (dt, 1H), 6.8 (s, 1H), 7.0 (q, 1H), 7.2 (d, 1H), 7.3 (m, 2H), 7.4 (dd, 1H).

Example 24

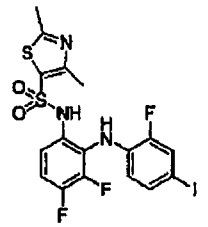
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-l-methyl-3-(trifluoromethyl)-lH-pyrazole-4-sulfonamide:**



According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl) benzene-1,2-diamine (0.182 mmol) was reacted with 1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-sulfonyl chloride (0.5 mmol) to obtain N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-sulfonamide. $^1$H NMR (300 MHz, $CDCl_3$)) δ 3.8 (s, 3H), 5.7 (s, 1H), 6.0 (dt, 1H), 7.0 (q, 1H), 7.2 (m, 2H), 7.4 (dd, 1H), 7.8 (s, 1H).

Example 25

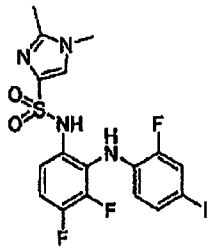
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2,4-dimethylthiazole-5-sulfonamide:**



According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl) benzene-1,2-diamine (0.182 mmol) was reacted with 2,4-dimethylthiazole-5-sulfonyl chloride (0.5 mmol) to obtain N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2,4-dimethylthiazole-5-sulfonamide. $^1$H NMR (300 MHz, $CDCl_3$)) δ 2.3 (s, 3H), 2.6 (s, 3H), 5.7 (s, 1H), 5.9 (dt, 1H), 7.1 (q, 1H), 7.2 (d, 1H), 7.3 (m, IH), 7.4 (d, 1H), 7.4 (s, 1H).

Example 26

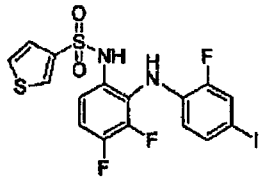
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1,2-dimethyl-1H-imidazole-4-sulfonamide:**



According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with 1,2-dimethyl-1H-imidazole-4-sulfonyl chloride to obtain the title compound. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.95 (br s, 1H), 7.37 (dd, $J$ = 1.8 & 10.8 Hz, 1H), 7.32-7.14 (m, 3H), 6.98 (dd, $J$ = 9.6 & 17.7 Hz, 1H), 5.87 (dt, $J$ = 4.2, 9.0 & 17.4 Hz, 1H), 5.55 (br s, 1H), 3.49 (s, 3H), 2.31 (s, 3H).

Example 27

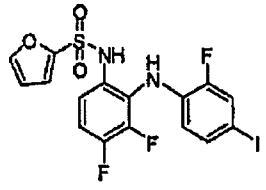
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)thiophene-3-sulfonamide:**



According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with thiophene-3-sulfonyl chloride to obtain the title compound. $^1$H NMR (300 MHz, $CDCl_3$): δ 8.00 (dd, $J$ = 1.2 & 3.3 Hz, 1H), 7.45 (dd, $J$ = 0.9 & 5.1 Hz, 1H), 7.35 (m, 2H), 7.27 (m, 2H), 6.91 (dd, $J$ = 9.3 & 17.1 Hz, 1H), 6.64 (ddd, $J$ = 2.1, 4.8 & 8.7 Hz, 1H), 6.34 (dt, $J$ = 5.4, 8.7 & 14.1 Hz, 1H), 5.98 (br d, $J$ = 2.1 Hz, $D_2O$ exchangeable, 1H).

Example 28

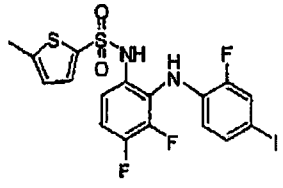
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)furan-2-sulfonamide:**



According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with furan-2-sulfonyl chloride to obtain the title compound. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.53 (br s, $D_2O$ exchangeable, 1H), 7.38 (dd, $J$ = 1.8 & 10.5 Hz, 1H), 7.30 (d, $J$ = 8.4 Hz, 1H), 7.21 (d, $J$ = 3.0 Hz, 1H), 6.96 (dd, $J$ = 8.7 & 16.5 Hz, 1H), 6.87 (ddd, $J$ = 1.8, 5.1 & 9.0 Hz, 1H), 6.53 (dd, $J$ = 1.8 & 3.6 Hz, 1H), 6.44 (dt, $J$ = 5.1, 8.7 & 13.8 Hz, 1H), 6.22 (br s, $D_2O$ exchangeable, 1H).

Example 29

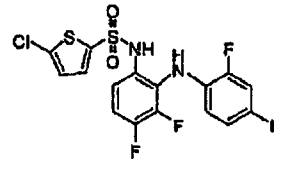
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-5-methylthiophene-2- sulfonamide:**



According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with 5-methylthiophene-2-sulfonyl chloride to obtain the title compound. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.34 (dd, $J$ = 0.9 & 10.2 Hz, 1H), 7.30 (ddd, $J$ = 2.1, 4.8 & 9.0 Hz, 1H), 7.25 (d, $J$ = 3.9 Hz, 1H), 7.07 (m, 2H), 6.65 (dd, $J$ = 1.2 & 3.9 Hz, 1H), 5.89 (dt, $J$ = 2.4, 8.7 & 17.4 Hz, 1H), 5.54 (br s, $D_2O$ exchangeable, 1H), 2.46 (s, 3H).

Example 30

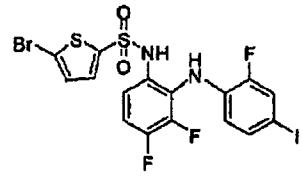
**5-Chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)thiophene-2-sulfonamide:**



According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene1,2-diamine was reacted with 5-chlorothiophene-2-sulfonyl chloride to obtain the title compound. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.38 (dd, $J$ = 1.5 & 10.2 Hz, 1H), 7.32 (ddd, $J$ = 2.1, 5.1 & 9.3 Hz, 1H), 7.25 (d, $J$ = 3.9 Hz, 1H), 7.10 (dd, $J$ = 9.0 & 18.6 Hz, 3H), 6.84 (d, $J$ = 4.2 Hz, 1H), 5.86 (dt, $J$ = 1.8, 8.7 & 17.4 Hz, 1H), 5.49 (br s, $D_2O$ exchangeable, 1H).

Example 31

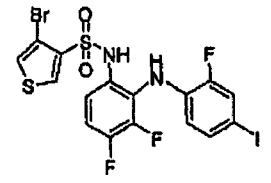
**5-Bromo-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)thiophene-2-sulfonamide:**



According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene1,2-diamine was reacted with 5-bromothiophene-2-sulfonyl chloride to obtain the title compound. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.39-7.29 (m, 2H), 7.20-7.05 (m, 3H), 6.96 (d, $J$ = 3.6 Hz, 1H), 5.85(dt, $J$ = 2.1, 9.0 & 17.4 Hz, 1H), 5.54 (br s, 1H).

Example 32

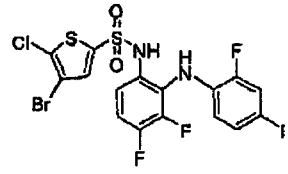
**4-Bromo-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)thiophene-3-sulfonamide:**



According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene1,2-diamine was reacted with 4-bromothiophene-3-sulfonyl chloride to obtain the title compound. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.48 (br m, 2H), 7.39 (dd, $J$ = 1.8 & 10.5 Hz, 1H), 7.28 (ddd, $J$ = 2.4, 4.8 & 9.0 Hz, 1H), 7.17 (d, $J$ = 8.4 Hz, 1H), 7.02 (m, 1H), 6.02 (dt, $J$ = 2.4, 8.7 & 17.4 Hz, 1H), 5.68 (br s, 1H).

Example 33

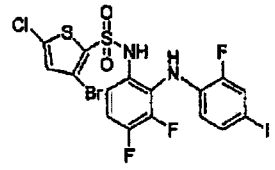
**4-Bromo-5-chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)thiophene-2- sulfonamide:**



According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene1,2-diamine was reacted with 4-bromo-5-chlorothiophene-2-sulfonyl chloride to obtain the title compound. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.42-7.34 (m, 2H), 7.25 (br m, 3H), 7.13 (dd, $J$ = 9.0 & 17.1 Hz, 1H), 6.02 (dt, $J$ = 2.4, 6.6 & 17.4 Hz, 1H), 5.52 (br s, 1H).

Example 34

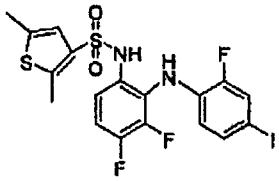
**3-Bromo-5-chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino) phenyl)thiophene-2- sulfonamide:**



According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene1,2-diamine was reacted with 3-bromo-5-chlorothiophene-2-sulfonyl chloride to obtain the title compound. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.41 (dd, $J$ = 2.1 & 10.5 Hz, 1H), 7.35 (br m, 2H), 7.31 (dd, $J$ = 2.1 & 4.2 Hz, 1H), 7.19 (d, $J$ = 8.7 Hz, 1H), 7.08 (dd, $J$ = 9.0 & 17.4 Hz, 1H), 6.02(dt, $J$ = 2.1, 8.4 & 17.1 Hz, 1H), 5.59 (br s, 1H).

Example 35

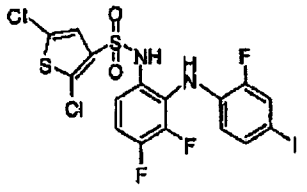
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2,5-dimethylthiophene-3-sulfonamide:**



According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene1,2-diamine was reacted with 2,5-dimethylthiophene-3-sulfonyl chloride to obtain the title compound. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.39 (dd, $J$ = 1.8 & 10.2 Hz, 1H), 7.24-7.16 (br m, 2H), 7.13 (dd, $J$ = 9.0 & 17.4 Hz, 1H), 6.77 (d, $J$ = 9.6 Hz, 1H), 5.98 (dt, $J$ = 2.4, 8.7 & 17.4 Hz, 1H), 5.55 (br s, 1H), 2.33 (s, 6H).

Example 36

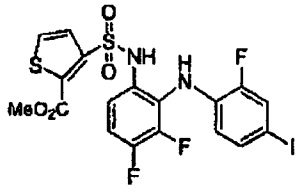
**2,5-Dichloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)thiophene-3-sulfonamide:**



According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene1,2-diamine was reacted with 2,5-dichlorothiophene-3-sulfonyl chloride to obtain the title compound. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.41(dd, $J$ = 1.5 & 10.5 Hz, 1H), 7.28-7.20 (m, 2H), 7.08 (dd, $J$ = 9.0 & 17.4 Hz, 2H), 6.99 (s, 1H), 6.03 (dt, $J$ = 2.1, 8.7 & 17.4 Hz, 1H), 5.56 (br s, 1H).

Example 37

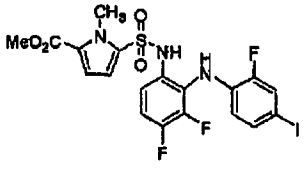
**Methyl 3-(N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl) sulfamoyl)thiophene-2-carboxylate:**



According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl) benzene 1,2-diamine was reacted with methyl 3-(chlorosulfonyl)thiophene-2-carboxylate to obtain the title compound. $^1$H NMR (300 MHz, $CDCl_3$): δ 8.58 (s, 1H), 7.43 (dd, $J$ = 5.1 & 10.8 Hz, 2H), 7.35 (dd, $J$ = 1.8 & 10.2 Hz, 1H), 7.31 (ddd, $J$ = 2.1, 4.2 & 9.3 Hz, 1H), 7.04 (m, 2H), 5.88 (dt, $J$ = 2.7, 8.7 & 17.4 Hz, 1H), 5.65 (br s, 1H), 3.85 (s, 3H).

Example 38

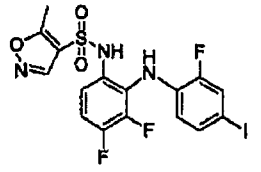
**Methyl 5-(N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)sulfamoyl)-1-methyl- 1H-pyrrole-2-carboxylate:**



According to the general procedure B, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene1,2-diamine was reacted with methyl 5-(chlorosulfonyl)-1-methyl-1H-pyrrole-2-carboxylate to obtain the title compound. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.37 (dd, $J$ = 1.8 & 10.5 Hz, 1H), 7.29 (m, 2H), 7.12-6.94 (m, 4H), 5.87 (dt, $J$ = 1.8, 8.4 & 17.4 Hz, 1H), 5.56 (br s, 1H), 3.65 (s, 3H), 3.75 (s, 3H).

Example 39

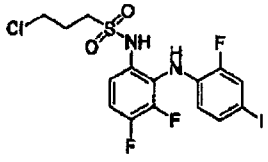
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-5-methylisoxazole-4-sulfonamide:**



According to the general procedure A, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene1,2- diamine was reacted with the corresponding sulfonyl chloride to obtain the title compound. Yield: 22%. *m/z*= 508 [M-1]$^-$.

Example 40

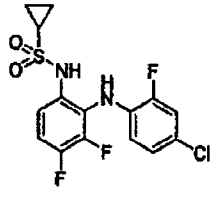
**3-Chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)propane-l-sulfonamide:**



According to the general procedure A, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with 3-chloropropane-l-sulfonyl chloride to obtain the desired product. $^1$H NMR (500 MHz, $CDCl_3$): δ = 7.39-7.38 (d, 1H), 7.35-7.34 (m, 1H), 7.27-7.26 (m, 1H), 7.10-7.0 (q, 1H), 6.63 (s, 1H, br), 6.15-6.11 (q, 1H), 5.60 (s, 1H, br), 3.60-3.56 (t, 2H), 3.22-3.20 (m, 2H), 2.22-2.16 (m, 2H).

Example 41

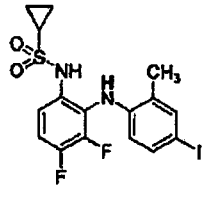
**N-(2-(4-chloro-2-fluorophenylamino)-3,4-difluorophenyl) cyclopropanesulfonamide:**



See example 1. $^1$H NMR (300 MHz, $CDCl_3$) δ 0.85-0.95 (m, 2H), 1.05-1.15 (ra, 2H), 2.2-2.4 (m, 1H), 5.8 (s, 1H), 6.3 (t, 1H), 6.6-7.4 (m, 5H); *m/z* = 375 [M-1]$^-$.

Example 42

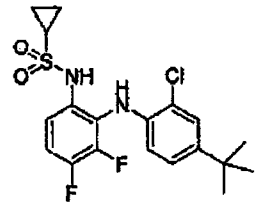
**N-(3,4-difluoro-2-(4-iodo-2-methylphenylamino)phenyl)cyclopropanesulfonamide:**



See example 1. $^1$H NMR ($CDCl_3$) δ 0.80-1.0 (m, 2H), 1.05-1.20 (m, 2H), 1.55 (s, 3H), 2.4-2.5 (m, 1H), 5.6 (s, 1H), 6.2 (dd, 1H), 6.4 (s, 1H), 7.1 (q, 1H), 7.3-7.4 (m, 2H), 7.5 (s, 1H); *m/z* = 463 [M-1]$^-$.

Example 43

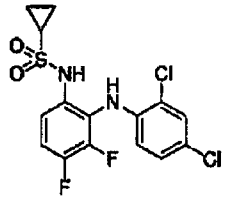
**N-(2-(4-tert-butyl-2-chlorophenylamino)-3,4-difluorophenyl) cyclopropanesulfonamide:**



See example 1. $^1$H NMR (300 MHz, $CDCl_3$) δ 0.9-1.0 (m, 2H), 1.05-1.20 (m, 2H), 1.3 (s, 9H), 2.4-2.5 (m, 1H), 5.8 (s, 1H), 6.3 (dd, 1H), 6.6 (s, 1H), 7.0-7.2 (m, 2H), 7.3-7.4 (m, 2H); *m/z* = 413 $[M-1]^-$.

Example 44

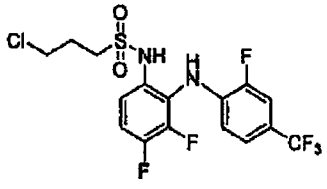
**N-(2-(2,4-dichlorophenylamino)-3,4-difluorophenyl)cyclopropanesulfonamide:**



See example 1. $^1$H NMR (300 MHz, $CDCl_3$) δ 0.9-1.0 (m, 2H), 1.05-1.20 (m, 2H), 2.4-2.5 (m, 1H), 6.0 (s, 1H), 6.3 (dd, 1H), 6.6 (s, 1H), 7.0-7.2 (m, 2H), 7.3-7.4 (m, 2H); *m/z* = 392 $[M-1]^-$.

Example 45

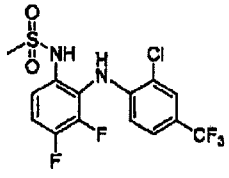
**3-Chloro-N-(3,4-difluoro-2-(2-fluoro-4-trifluoromethyl) phenylamino)phenyl)propane- 1-sulfonamide:**



See example 1. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.39-7.26 (m, 2H), 7.25 (m, 1H), 7.18 (dd, *J* = 9.0 & 17.7 Hz, 1H), 6.78 (br s, $D_2O$ exchangeable, 1H), 6.50 (t, *J* = 8.1 Hz, 1H), 6.00 (br d, $D_2O$ exchangeable, *J* = 1.5 Hz, 1H), 3.63 (t, *J* = 6.0 & 6.3 Hz, 2H), 3.29 (t, *J* = 7.2 & 7.8 Hz, 2H), 2.26 (quintet, 2H); *m/z* = 445 $[M-1]^-$.

Example 46

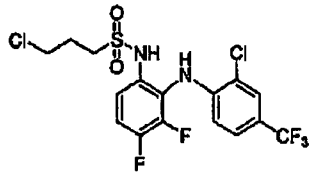
**N-(3,4-difluoro-2-(2-chloro-4-trifluoromethyl)phenylamino)methanesulfonamide:**



See example 1. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, *J* =7.8 Hz, 1H), 7.33 (m, 2H), 7.19 (dd, *J* = 9.3 & 17.4 Hz, 1H), 6.90 (br s, $D_2O$ exchangeable, 1H), 6.45 (dd, *J* = 1.5 & 8.4 Hz, 1H), 6.39 (br s, $D_2O$ exchangeable, 1H), 3.02 (s, 3H); *m/z* = 399 $[M-1]^-$.

Example 47

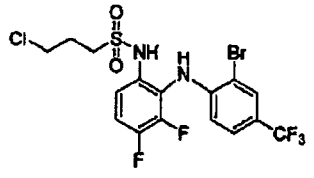
**3-Chloro-N-(3,4-difluoro-2-(2-chloro-4-trifluoromethyl) phenylamino)phenyl)propane-1-sulfonamide:**



See example 1. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, $J$ = 1.5 Hz, 1H), 7.36 (m, 2H), 7.19 (dd, $J$ = 9.0 & 17.4 Hz, 1H), 6.91 (br s, $D_2O$ exchangeable, 1H), 6.50 (dd, $J$ = 8.4 & 1.5 Hz, 1H), 6.37 (s, $D_2O$ exchangeable, 1H), 3.62 (t, $J$ = 6.0 Hz, 2H), 3.29 (t, $J$ = 7.5 & 7.8 Hz, 2H), 2.27 (quintet, 2H); $m/z$ = 462 $[M-1]^-$.

Example 48

**3-Chloro-N-(3,4-difluoro-2-(2-bromo-4-trifluoromethyl) phenylamino)phenyl)propane-1-sulfonamide:**

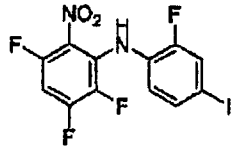


See example 1. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.38 (m, 2H), 7.20 (dd, $J$ = 9.0 & 17.7 Hz, 1H), 6.62 (br s, $D_2O$ exchangeable, 1H), 6.43 (d, $J$ = 8.4 Hz, 1H), 6.23 (s, $D_2O$ exchangeable, 1H), 3.65 (t, $J$ = 6.0 Hz, 2H), 3.30 (t, $J$ = 7.5 Hz, 2H), 2.28 (quintet, 2H); $m/z$ = 506 $[M-1]^-$.

Example 49

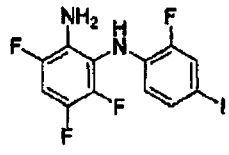
**Cyclopropanesulfonic acid (3,4,6-trifluoro-2-(2-fluoro-4-iodo-phenylamino)-phenyl)-amide:**

**Step A**: (2-Fluoro-4-iodo-phenyl)-(2,3,5-trifluoro-6-nitro-phenyl)-amine:



A stirred solution of 2-fluoro-4-iodoaniline (3.64 gm, 15.37 mmol) in dry THF (100 ml) under nitrogen was cooled to -78°C and a solution of 1.0 M lithium hexa methyl disilazide ($LiN(SiMe_3)_2$) "LHMDS" (15.37 ml, 15.37 mmol) was added slowly. This reaction mixture was kept stirring at -78°C for another hour and then 2,3,4,6-tetrafluoronitrobenzene was added. The reaction mixture was allowed to warm to room temperature and stirring continued for another 16 hours. Ethyl acetate (200 ml) was added to the reaction mixture and was washed with water. Organic layer was dried over sodium sulfate and further purified by column chromatography to provide yellow solid (3.75 gm, yield: 59.24%). M-H$^+$: 410.9. $^1$H NMR (DMSO, 300 MHz): 6.85 (t, 1H); 7.38 (d, 1H); 7.62 (m, 2H); 8.78 (s, 1H).

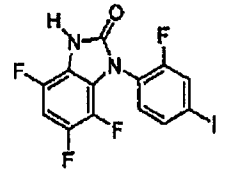
**Step B**: 3,4,6-Trifluoro-$N^2$-(2-Fluoro-4-iodo-phenyl)-benzene-1,2-diamine:



To the stirred solution of (2-fluoro-4-iodo-phenyl)-(2,3,5-trifluoro-6-nitro-phenyl)-amine 3 (5.2 gm, 12.62 mmol) in EtOH (200 ml), ammonium chloride (10.12 gm, 189.3 mmol) and iron powder (10.57 gm, 189.3 mmol) was added. This reaction mixture was kept stirring at reflux for 16 hours. Reaction mixture was allowed to cool and was filtered over celite and concentrated to dryness. The residue obtained was taken into EtOAc and was washed with water. The

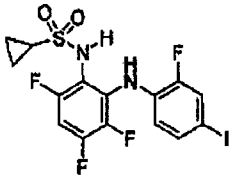
EtOAc layer was dried over sodium sulfate and further purified by crystallization from EtOH to provide off-white solid (3.2 gm, yield: 66.39%). M-H$^+$: 381.1. $^1$H NMR (DMSO, 300 MHz): 5.0 (s, 2H); 6.2 (t, 1H); 7,2 - 7.3 (m, 2H); 7.45 (s, 1H); 7.5 (d, 1H).

**Step C:** 4.6.7-Trifluoro-l-(2-Fluoro-4-iodo-phenyl)-1,3,-dihydrobenzoimidazole-2- one:



To the stirred solution of 3,4,6-trifluoro-N2-(2-Fluoro-4-iodo-phenyl)-benzene-1,2- diamine 3 (0.285 gm, 0.74 mmol) in $CH_2Cl_2$ (2 ml), 1,1'-carbonyldiimidazole (0.125 gm, 0.75 mmol) was added. This reaction mixture was kept stirring at room temperature for 16 hours when product precipitated out. The white solid was filtered and used further without any purification. (0.2 gm, yield: 65.85%): *m/z* = 407 [M-1]$^-$.

**Step D/E:** Cyclopropanesulfonic acid (3,4,6-trifluoro-2-(2-fluoro-4-iodo-phenylamino)-phenyl)-amide:

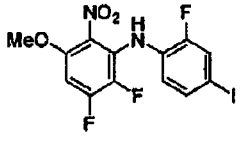


A stirred solution of 4,6,7-trifluoro-l-(2-fluoro-4-iodo-phenyl)-1,3,- dihydrobenzimidazol-2-one (0.2 gm, 0.41 mmol) in dry THF (4 ml) under nitrogen was cooled to -78°C and a solution of 1.0 M LiHMDS (0.41 ml, 0.41 mmol) was added slowly. (2 ml) followed by addition of cyclopropanesulfonyl chloride (0.050 ml, 0.49 mmol). This reaction mixture was kept stirring at room temperature for 16 hours, concentrated to dryness and was taken into EtOAc. The EtOAc was washed with water, dried over sodium sulfate and concentrated to dryness. The residue obtained l-cyclopropanesulfonyl-4,5,7-trifluoro-3-(2- fluoro-4-iodo-phenyl)-1,3-dihydro-benzimidazol-2-one **5** was taken into dioxane (2 ml) and to this 1.0 N NaOH (0.5ml) was added and kept stirring at room 50°C for 16 hours. TLC indicated incomplete reaction, the product was purified by HPLC to provide off-white solid (4.4 mg) M+H$^+$: 484.7, M-H$^+$: 486.7. $^1$H NMR ($CDCl_3$, 300 MHZ): 0.9 - 1.1 - (m, 2H); 1.1 - 1.2 (m, 2H); 2.45 - 2.55 (m, 1H); 6.05 (s, 1H); 6.44 - 6.54 (m, 1 H); 7.1 (s, 1H); 7.4 - 7.7 (d, 1H); 7.38 - 7.44 (dd, 1H); *m/z* = 485 [M-1]$^-$.

Example 50

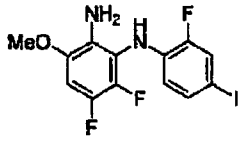
**N-(3,4-difluoro-2-(4-fluoro-2-iodophenylamino)-6-ethoxyphenyl) cyclopropane sulfonamide:**

**Step A:** (2J-Difluoro-5-methoxy-6-nitro-phenyl)-(2-fluoro-4-iodo-phenyl)-amine:



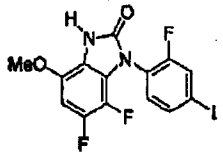
A stirred solution of (2-fluoro-4-iodo-phenyl)-(2,3,5-trifluoro-6-nitro-phenyl)-amine (1.23 gm, 3 mmol) in dry THF (25 ml) under nitrogen was cooled to -78°C and a solution of 25% NaOMe (0.68 ml, 0.3 mmol) was added slowly. Reaction mixture was allowed to warm to room temperature and stirring continued for another 16 hours. TLC indicated incomplete reaction. Ethyl acetate (100 ml) was added to the reaction mixture and was washed with water. Organic layer was dried over sodium sulfate and further purified by column chromatography to provide yellow solid (0.6 gm, yield: 47.6%). *m/z* = 424 [M=H]$^+$.

**Step B:** 5,6-Difluoro-N1-(4-fluoro-2-iodophenyl)-3-methoxybenzene-1,2-diamine:



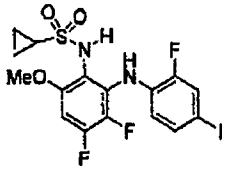
To the stirred solution of (2,3-difluoro-5-methoxy-6-nitro-phenyl)-(2-fluoro-4-iodo-phenyl)-amine (0.57 gm, 1.34 mmol) in EtOH (20 ml), ammonium chloride (1.18 gm, 20.16 mmol) and iron powder (1.15 gm, 21.44 mmol) was added. This reaction mixture was kept stirring at reflux for 16 hours. Reaction mixture was allowed to cool and was filtered over celite and concentrated to dryness. The residue obtained was taken into EtOAc and was washed with water. The EtOAc layer was dried over sodium sulfate and further purified by crystallization from EtOH to provide off-white solid (0.47 gm, yield: 90.3%). M-H$^+$: 393.2. $^1$H NMR (DMSO, 300 MHz): 3.76 (s, 3H); 6.1 (t, 1H); 6.8 - 7.0 (m, 1H); 7.2 (d, 1H); 7.35 (s, 1H); 7.42 (d, 1H).

**Step C:** 6,7-Difluoro-1-(4-fluoro-2-iodophenyl)-4-methoxy-1H-benzo[d]imidazol-2(3H)-one:



To the stirred solution of 5,6-difluoro-N1-(4-fluoro-2-iodophenyl)-3-methoxybenzene-1,2-diamine (0.17 gm, 0.43 mmol) in $CH_2Cl_2$ (2 ml), 1,1'-Carbonyldiimidazole (0.085 gm, 0.53 mmol) was added. This reaction mixture was kept stirring at room temperature for 16 hours when product precipitated out. The white solid was filtered and used further without any purification. (0.089 gm); *m/z* = 419 [M-1]$^-$.

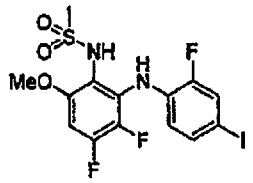
**Step D/F:** N-(3,4-difluoro-2-(4-fluoro-2-iodophenylamino)-6-methoxyphenyl)cyclopropanesulfonamide:



A stirred solution of 1-(cyclopropylsulfonyl)-4,5-difluoro-3-(2-fluoro-4-iodophenyl)-7-methoxy-1H-benzo[d]imidazol-2(3H)-one (0.89 gm, 0.17 mmol) in dry THF (4 ml) under nitrogen was cooled to -78°C and a solution of 1.0 M LiHMDS (0.17 ml, 0.17 mmol) was added slowly. (2 ml) followed by addition of cyclopropanesulfonyl chloride (0.021 ml, 0.21 mmol). This reaction mixture was kept stirring at room temperature for 16 hours, concentrated to dryness and was taken into EtOAc. The EtOAc was washed with water, dried over sodium sulfate and concentrated to dryness. The resulting 1-(cyclopropylsulfonyl)-4,5- difluoro-3-(2-fluoro-4-iodophenyl)-7-methoxy-1H-benzo[d]imidazol-2(3H)-one was taken into dioxane (2 ml) and to this 1.0 N NaOH (0.5ml) was added and kept stirring at room 50°C for 16 hours. TLC indicated incomplete reaction, the product was purified by HPLC to provide off-white solid (2.5 mg) M+H$^+$: 484.7, M-H$^+$: 497.3. $^1$H NMR ($CDCl_3$, 300 MHz): 0.85 - 0.95 (m, 2H); 1.05 - 1.15 (m, 2H); 2.4 - 2.5 (m, 1H); 3.9 (s, 3H); 6.1 (s, 1H); 6.4 - 6.6 (m, 2 H); 7.3 (m, 1H); 7.35 - 7.4 (dd, 1H); *m/z* = 497 [M-1]$^-$.

Example 51

**Methylsulfonic acid (3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-6-methoxy-phenyl)-amide:**

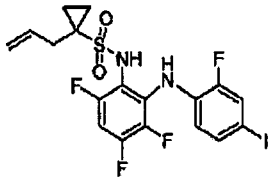


A stirred solution of 5,6-difluoro-N1-(4-fluoro-2-iodophenyl)-3-methoxybenzene-1,2-diamine (0.150 gm, 0.38 mmol) in dry $CH_2Cl_2$ (4 ml), TEA (.264 ml, 1.9 mmol) and methanesulfonyl chloride was added slowly. This reaction mixture was kept stirring at room temperature for 16 hours, TLC indicated incomplete reaction along with starting material two products were observed. The reaction mixture was washed with water, organic layer was dried over sodium sulfate and concentrated to dryness, the product was purified by column chromatography. The minor product was found to be the expected compound (6.4 mg). M-H$^+$: 471.5. $^1$H NMR ($CDCl_3$, 300 MHz): 3.9 (s, 3H); 6.05 (s, 1H); 6.4 - 6.5 (m, 1H); 6.5 - 6.6 (m, 1H); 7.2 (s, 1H); 7.28 (d, 1H); 7.35 - 7.4 (d, 1H); *m/z* = 471 [M-1]$^-$.

Example 52

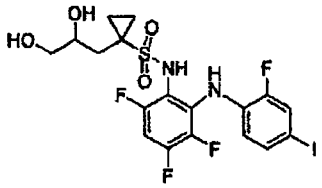
**l-(2,3-Dihydroxy-propyl)-cyclopropanesulfonic acid [3,4,6-trifluoro-2-(4-fluoro-2-iodo-phenylamino)-phenyl]-amide:**

**Step A:** 1-Allyl-cyclopropanesulfonic acid [3,4,6-trifluoro-2-(2-fluoro-4-iodo-phenylamino)phenyl]-amide:



According to the general procedure B, 1-allyl-cyclopropanesulfonyl chloride was reacted with 3,5,6-trifluoro-N$^1$-(2-fluoro-4-iodophenyl)benzene-1,2-diamine to obtain the title product. $^1$H NMR ($CDCl_3$, 300 MHz): δ 7.41 (dd, 1H), 7.38 (dd, 1H), 7.09 (s, 1H), 6.78 (m, 1H), 6.49 (m, 1H), 5.96 (s, 1H), 5.86 (m, 1H), 5.18 (d, 2H), 2.76 (d, 2H), 1.23 (m, 2H), 0.872 (m, 2H).

**Step B:** 1-(2,3-Dihydroxypropyl)-N-(3,4,6-trifluoro-2-(2-fluoro-4-iodophenylamino)phenyl)cyclopropane-1-sulfonamide:

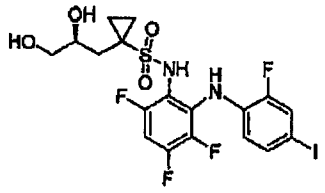


1-Allyl-cyclopropanesulfonic acid [3,4,6-trifluoro-2-(2-fluoro-4-iodo-phenyl amino)- phenyl]-amide (110 mg, 0.21 mmol) and 4-methylmorpholine N-oxide (24.6 mg, 0.21 mmol) was dissolved in THF (8 mL). Osmium tetroxide was added at room temperature (0.021 mmol, 0.153 mL, 4% in $H_2O$) and the reaction mixture was stirred at room temperature for 16 hours. EtOAc was added, the organic phase was washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified over silica gel chromatography (eluants: EtOAc/ MeOH) to obtain the titled product (0.89 g, 75 %). $^1$H NMR ($CDCl_3$, 300 MHz): δ 7.39 (dd, J = 1.5 & 10.6 Hz, 1H), 7.29 (d, J = 8.8 Hz, IH), 7.28 (s, 1H), 6.97 (s, 1H), 6.76 (m, 1H), 6.49 (m, 1H), 4.13 (m, 1H), 3.66 (dd, J = 3.7 & 11.4 Hz, 1H), 3.53 (dd. J = 6.7 & 11.2

Hz, 1H), 2.50(dd, J = 10.0 & 16.1 Hz, 1H), 1.6 (m,lH), 1.46 (m, 1H), 1.28 (m, 1H), 1.20 (m, 2H), 0.92 (m, 2H); *m/z* = 559 $[M-1]^-$.

Example 53

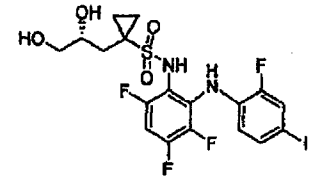
**(S)-1-(2,3-dihydroxypropyl)-N-(3,4,6-trifluoro-2-(2-fluoro-4-iodophenylamino)phenyl)cyclopropane-1-sulfonamide:**



The pure S isomer was obtained by chiral HPLC separation of the racemic mixture (example 52). $^1$H NMR ($CDCl_3$, 300 MHz): δ 7.39 (dd, J = 1.5 & 10.6 $Hz_5$ 1H), 7.29 (d, J = 8.8 Hz, 1H), 7.28 (s, 1H), 6.97 (s, 1H), 6.76 (m, 1H), 6.49 (m, 1H), 4.13 (m, 1H), 3.66 (dd, J = 3.7 & 11.4 $Hz_5$ 1H), 3.53 (dd, J = 6.7 & 11.2 Hz, 1H), 2.50(dd, J = 10.0 & 16.1 Hz, 1H), 1.6 (m,lH), 1.46 (m, 1H), 1.28 (m, 1H), 1.20 (m, 2H), 0.92 (m, 2H); *m/z* = 559 $[M-1]^-$.

Example 54

**(R)-1-(2,3-dihydroxypropyl)-N-(3,4,6-trifluoro-2-(2-fluoro-4-iodophenylamino)phenyl)cyclopropane-1-sulfonamide:**

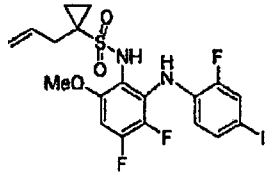


The pure R isomer was obtained by chiral HPLC separation of the racemic mixture (example 52). $^1$H NMR ($CDCl_3$, 300 MHz): δ 7.39 (dd, J = 1.5 & 10.6 Hz, 1H), 7.29 (d, J = 8.8 Hz, 1H), 7.28 (s, 1H), 6.97 (s, 1H), 6.76 (m, 1H), 6.49 (m, 1H), 4.13 (m, 1H), 3.66 (dd, J = 3.7 & 11.4 Hz, 1H), 3.53 (dd, J = 6.7 & 11.2 Hz, 1H), 2.50(dd, J = 10.0 & 16.1 Hz, 1H), 1.6 (m, lH), 1.46 (m, 1H), 1.28 (m, 1H), 1.20 (m, 2H), 0.92 (m, 2H); *m/z* = 559 $[M-1]^-$.

Example 55

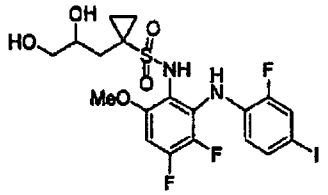
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide:**

**Step A:** 1-Allyl-N-3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)cyclopropane-1-sulfonamide:



According to the general procedure B, 1-allyl-cyclopropanesulfonyl chloride was reacted with 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)-3-methoxybenzene-1,2-diamine to obtain the title product. $^1$H NMR ($CDCl_3$, 300 MHz): δ 7.417 (dd, 1H), 7.309(s, 1H), 7.25 (m, 1H), 6.89 (m, 1H), 6.52(m, 1H), 6.427 (m, 1H), 6.03 (s, lH), 5.668 (m, 1H), 5.11 (t, 1H), 3.9 (s, 3H), 2.75 (d, 2H), 1.21 (m, 2H), 0.767 (m, 2H).

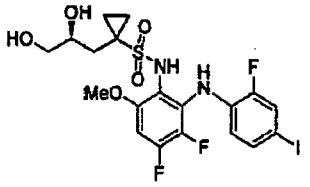
**Step B:** N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide:



1-Allyl-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl) cyclopropane-1-sulfonamide (97 mg, 0.18 mmol) and 4-methylmorpholine N-oxide (21 mg, 0.18 mmol) were dissolved in THF (8 mL). Osmium tetroxide was added at room temperature (0.018 mmol, 0.13 mL, 4% in $H_2O$) and the reaction mixture was stirred at room temperature for 16 hours. EtOAc was added, the organic phase was washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified over silica gel chromatography (eluants: EtOAc/ MeOH) to obtain the titled product (0.80 g, 78 %). $^1$H NMR ($CDCl_3$, 300 MHz): δ 7.38 (dd, J = 1.7 & 10.3 Hz,1H), 7.26 (m, 1H), 7.14 (s, 1H), 6.87 (s, 1H), 6.53 (dd, J = 6.8 & 11.4 Hz, 1H), 6.43 (m, 1H), 4.06 (m, 1H), 3.89 (s, 3H), 3.63 (dd, J = 3.7 & 11.1 Hz, 1H), 3.49 (dd, J = 6.4 & 11.1 Hz, 1H), 2.3 (dd, J = 9.7 & 16.1 Hz, 1H), 1.77 (dd, J = 1.9 & 16.0 Hz, 1H), 1.37 (m, 1H), 1.25 (m, 1H), 1.21 (m, 2H), 0.86 (m, 2H); *m/z* = 571 $[M-1]^-$.

Example 56

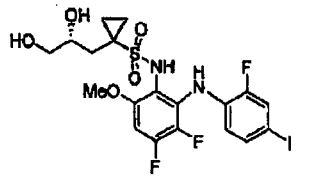
**(S)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide:**



The pure S isomer was obtained by chiral HPLC separation of the racemic mixture (example 55). $^1$H NMR ($CDCl_3$, 300 MHz): δ 7.38 (dd, J = 1.7 & 10.3 Hz,1H), 7.26 (m, 1H), 7.14 (s, 1H), 6.87 (s, 1H), 6.53 (dd, J = 6.8 & 11.4 Hz, 1H), 6.43 (m, 1H), 4.06 (m, 1H), 3.89 (s, 3H), 3.63 (dd, J = 3.7 & 11.1 Hz, 1H), 3.49 (dd, J = 6.4 & 11.1 Hz, 1H), 2.3 (dd, J = 9.7 & 16.1 Hz, 1H), 1.77 (dd, J = 1.9 & 16.0 Hz, 1H), 1.37 (m, 1H), 1.25 (m, 1H), 1.21 (m, 2H), 0.86 (m, 2H); *m/z* = 571 $[M-1]^-$.

Example 57

**(R)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide:**

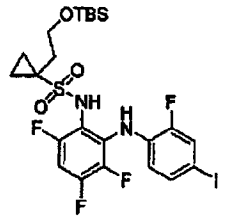


The pure R isomer was obtained by chiral HPLC separation of the racemic mixture (example 55). $^1$H NMR ($CDCl_3$, 300 MHz): δ 7.38 (dd, J = 1.7 & 10.3 Hz,1H), 7.26 (m, 1H), 7.14 (s, 1H), 6.87 (s, 1H), 6.53 (dd, J = 6.8 & 11.4 Hz, 1H), 6.43 (m, 1H), 4.06 (m, 1H), 3.89 (s, 3H), 3.63 (dd, J = 3.7 & 11.1 Hz, 1H), 3.49 (dd, J = 6.4 & 11.1 Hz, 1H), 2.3 (dd, J = 9.7 & 16.1 Hz, 1H), 1.77 (dd, J = 1.9 & 16.0 Hz, 1H), 1.37 (m, 1H), 1.25 (m, 1H), 1.21 (m, 2H), 0.86 (m, 2H); *m/z* = 571 $[M-1]^-$.

Example 58

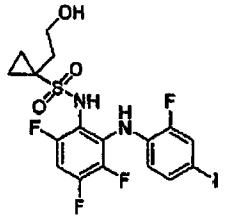
**1-(2-hydroxyethyl)-N-(3,4,6-trifluoro-2-(2-fluoro-4-iodophenylamino)phenyl) cyclopropane-1-sulfonamide:**

**Step A:** TBS-protected 1-(2-hydroxyethyl)-N-(3,4,6-trifluoro-2-(2-fluoro-4-iodophenylamino) phenyl) cyclopropane-1-sulfonamide:



According to the general procedure B, the sulfonyl chloride prepared in step C of example 16 was reacted with 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)-3-fluorobenzene-1,2- diamine to obtain the title product. Yield: 13%. $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ = 7.51 (s, 1H, br), 7.37-7.35 (d, 1H), 7.27-7.25 (d, 1H), 6.94 (s, 1H, br), 6.78-6.68 (m, 1H), 6.46-6.44 (m, 1H), 3.90-3.88 (t, 2H), 2.12-2.10 (t, 2H), 1.31-1.28 (m, 2H), 0.91-0.89 (m, 2H), 0.86 (s, 9H), 0.05 (s, 6H); *m/z* = 643 $[M-I]^-$

**Step B:** 1-(2-hydroxyethyl)-N-(3,4,6-trifluoro-2-(2-fluoro-4-iodophenylamino)-phenyl) cyclopropane-1-sulfonamide:

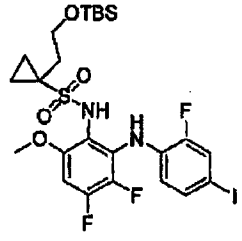


Same procedure as in step E, example 16. Yield: 100%. $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ = 7.51 (s, 1H, br), 7.37-7.35 (d, 1H), 7.27-7.25 (d, 1H), 6.94 (s, 1H, br), 6.78-6.68 (m, 1H), 6.46-6.44 (m, 1H), 3.90-3.88 (t, 2H), 2.12-2.10 (t, 2H), 1.31-1.28 (m, 2H), 0.91-0.89 (m, 2H); *m/z* = 529 $[M-1]^-$.

Example 59

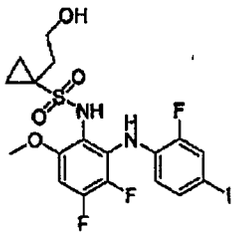
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2-hydroxyethyl)cyclopropane-1-sulfonamide:**

**Step A:** TBS-protected N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2-hydroxyethyl)cyclopropane-1-sulfonamide:



According to the general procedure B, the sulfonyl chloride prepared in step C of example 16 was reacted with 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)-3-methoxy-benzene- 1,2-diamine to obtain the title product. Yield: 37%. $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ = 7.40-7.34 (dd, 1H), 7.23-7.21 (m, 1H), 6.61 (s, 1H, br), 6.57-6.49 (dd, 1H), 6.48-6.39 (m, 1H), 3.9-3.7 (m, 5H), 2.15-2.05 (t, 2H), 1.30-1.20 (m, 2H), 0.95-0.80 (m, 11H), 0.05 (s, 6H); *m/z* = 655 $[M-1]^-$.

**Step B:** N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2-hydroxyethyl)cyclopropane-1-sulfonamide:

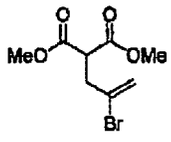


Same procedure as in step E, example 16. Yield: 100%. $^1$H-NMR (300 MHz, $CDCl_3$): δ = 7.40-7.34 (dd, 1H), 7.23-7.21 (m, 1H), 6.61 (s, 1H, br), 6.57-6.49 (dd, 1H), 6.48-6.39 (m, 1H), 3.9-3.7 (m, 5H), 2.15-2.05 (t, 2H), 1.30-1.20 (m, 2H), 0.95-0.80 (m, 2H); *m/z*= 541 $[M-1]^-$.

Example 60

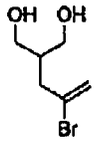
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(3-hydroxy-2-(hydroxymethyl)propyl)cyclopropane-1-sulfonamide:**

**Step A:** Dimethyl 2-(2-bromoallyl)malonate:



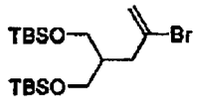
To a suspension of sodium hydride (5.0 g, 125 mmol) in HMPA (50 ml, distilled from calcium hydride) was added a solution of dimethyl malonate (11.7 ml, 100 mmol) in HMPA (5 ml) at 0°C under argon. The mixture was heated to 50°C and stirred 1 hour. Following this the solution was again cooled to 0°C, and a solution of 2,3-dibromopropene (12.2 ml, 100 mmol) in HMPA (5 ml) was added to the reaction mixture. Next, the solution was warmed to 40°C and stirred for 1 hour. The reaction mixture was quenched with aq. HCl (10%, 88 ml) and extracted with ether (3 x 45 ml). The organic fractions were collected, dried over $MgSO_4$, and the solvent was removed *in vacuo*. The crude oil was purified via silica gel chromatography (eluants: chloroform/hexane) to obtain the titled product as a colorless oil (16.3 g, 65%). $^1$H-NMR (300 MHz, $CDCl_3$) δ 5.70 (d, J = 1.8 Hz, 1 H), 5.48 (d, J = 1.8 Hz, 1H), 3.63 (t, J = 7.5 Hz, 1 H), 3.76 (s, 6 H), 3.04 (d, J = 7.5 Hz, 2 H).

**Step B:** 2-(2-Bromoallyl)propane-1,3-diol:



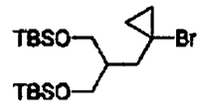
Lithium aluminum hydride (1.9 g, 7.65 mmol) was slurried in anhydrous diethyl ether (50 ml) and cooled to -78°C in a dry ice/acetone bath. A solution of the product from step A (0.639 g, 16.84 mmol) in dry ether (26 ml) was then added dropwise. After the malonate was added, the solution was allowed warm to room temperature and stirring was continued for 3 hours. The reaction was quenched with brine (50 ml), extracted with ethyl acetate (3 x 25 ml) and dried over $MgSO_4$. The solvent was removed *in vacuo* to give the desired product (1.3 g, 86%) which was used for the next step without further purification. $^1$H-NMR (300 MHz, $CDCl_3$) δ 5.66 (d, J = 1.2 Hz, 1 H), 5.48 (d, J = 1.5 Hz, 1H), 3.86 (m, 2 H), 3.73 (m, 2 H), 2.51 (d, J = 7.5 Hz, 2 H), 2.40 (br s, 2 H), 2.15 (m, 1 H).

**Step C:** Di-tert-butyldimethylsilyl protected 2-(2-bromoallyl)propane-1,3-diol:



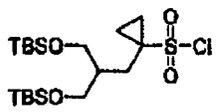

The product from step B (2.8 g, 14.20 mmol) was dissolved in anhydrous THF (140 ml). Anhydrous pyridine (2.5 ml, 31.24 mmol) was added, and the solution was cooled to 0°C. tert-Butyldimethylsilyltriflate (7.2 ml, 31.24 mmol) was added dropwise, and upon completion, the reaction solution was heated to 35°C. After stirring for 6 days, the reaction was quenched with 100 ml brine, extracted with ethyl acetate (3 x 50 ml) and dried over $MgSO_4$. The combined organic phases were evaporated to obtain the crude product (5.5 g, 91%) as a yellow oil which was used in the next step without further purification. $^1$H-NMR (300 MHz, $CDCl_3$) δ 5.54 (d, J = 0.9 Hz, 1 H), 5.40 (d, J = 1.2 Hz, 1H), 3.55 (d, J = 5.4, 4 H), 2.40 (d, J = 6.9 Hz, 2 H), 1.97 (m, 1 H), 0.85 (s, 18 H), 0.02 (s, 9 H).

**Step D:** Di-tert-butyldimethylsilyl protected 2-((1-bromocyclopropyl)methyl) propane-1,3-diol:



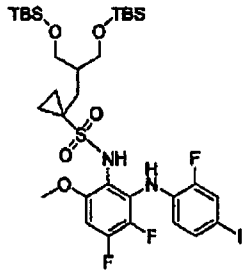

A reaction flask was charged with anhydrous $CH_2Cl_2$ (10 ml) and diethyl zinc (1.0 M in hexanes, 4.65 ml, 4.65 mmol) at 0°C. Trifluoroacetic acid (0.358 ml, 4.65 mmol) was added dropwise and the solution was allowed to stir for 20 minutes. Diiodomethane (0.375 ml, 4.65 mmol) was then added and the solution was stirred for another 20 minutes. Finally, the product from **step C** (0.492 g, 1.16 mmol) was added and the solution was allowed to warm to ambient temperature, stirring for 16 hours. The reaction was quenched with saturated aqueous $NH_4Cl$. The layers were partitioned and the aqueous phase was extracted with chloroform (3 x 5 ml). The combined organic phases were washed with brine (10 ml), dried over $MgSO_4$, and the volatiles were removed *in vacuo*. The resulting crude was purified via silica gel chromatography (eluants: chloroform/hexanes) to provide the product as a clear oil (0.280 g, 64%). $^1$H-NMR (300 MHz, $CDCl_3$) δ 3.66 (d, J = 5.4, 4 H), 2.08 (m, 1 H), 1.64 (d, J = 6.9, 2 H), 1.13 (m, 2 H), 0.88 (s, 18 H), 0.81 (m, 2 H), 0.04 (s, 9 H).

**Step E:** Di-tert-butyldimethylsilyl protected 1-(3-hydroxy-2-(hydroxymethyl)propyl)cyclopropane-1-sulfonyl chloride:



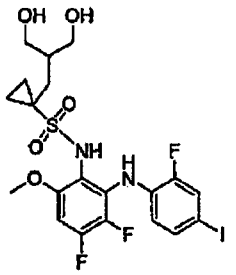

The product from step D (0.507 g, 1.16 mmol) was dissolved in anhydrous ether (6 ml) and the reaction solution was cooled to -78°C. Following this, tert-butyllithium (1.7 M in pentane, 1.50 ml, 2.55 mmol) was added dropwise over 5 minutes. After stirring for 0.5 hours, the lithiated product was transferred via cannula to a stirred solution of sulfuryl chloride (0.206 ml, 2.55 mmol) in dry ether (6 ml) at -78°C. Once the transfer is complete, the solution was allowed to warm to room temperature, the solvent was evaporated and the resulting white solid was slurried in dry hexanes. This slurry was immediately filtered through celite, and all volatiles were removed *in vacuo*. The resulting crude product (0.376 g, 71%) was isolated as a yellow oil and was used in the following step without further purification. $^1$H-NMR (300 MHz, $CDCl_3$) δ 3.60 (m, 4 H), 2.16 (m, 1 H), 2.03 (d, 2 H), 0.88 (s, 18 H), 0.04 (s, 9 H).

**Step F:** Di-tert-butyldimethylsilyl protected N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(3-hydroxy-2-(hydroxymethyl)propyl) cyclopropane-1-sulfonamide:




5,6-difluoro-N1-(2-fluoro-4-iodophenyl)-3-methoxybenzene-1,2-diamine (8.8 mg, 0.022 mmol) was dissolved in anhydrous pyridine (0.5 ml) under an argon atmosphere. The product from step E (20.5 mg, 0.045 mmol), dissolved in dry pyridine (0.5 ml), was added to the reaction flask and the mixture was heated at 80°C for 21 hours. The solvent was removed *in vacuo* and the resulting crude was purified via silica gel chromatography (eluents: ethyl acetate/hexanes) to provide the title compound (2.75 mg, 15%). *m/z* 813.5 (M-1).

**Step G:** N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(3-hydroxy-2-(hydroxymethyl)propyl)cyclopropane-1-sulfonamide:

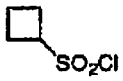



The product from step F (27.9 mg, 0.0342 mmol) was dissolved in THF (1 ml) and treated with aqueous HCl (1.2 N, 0.2 ml) at 0°C. The resulting solution was stirred for 4 hours. Following this, the reaction was quenched with saturated aqueous $NaHCO_3$, extracted with ethyl acetate, dried over $MgSO_4$ and the volatiles were removed *in vacuo*. The resulting crude was purified via silica gel chromatography (eluents: methanol/chloroform) followed by LC-MS purification to provide the title compound (11.8 mg, 59%). $^1$H-NMR (300 MHz, $CD_3OD$) δ 7.32 (dd, 1 H), 7.21 (d, 1 H), 6.76 (dd, 1 H), 6.33 (m, 1 H), 3.82 (s, 3 H), 3.52 (d, 4 H), 2.01 (m, 1 H), 1.88 (d, 2 H), 1.07 (m, 2 H), 0.75 (m, 2 H), *m/z* 585.3 $(M-1)^-$.

Example 61

**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl) cyclobutane sulfonamide:**

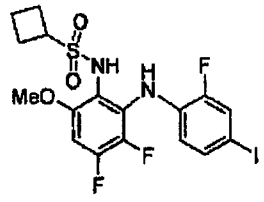
**Step A:** Cyclobutanesulfonyl chloride:




To a suspension of Mg turnings (0.790 g, 32.5 mmol) in 20 ml anhydrous diethyl ether was added a solution of cyclobutylbromide (1.8 ml, 2.5722 g, 19.1 mmol) in 20 ml diethyl ether in small portions with strong stirring. After the initial exothermic reaction had ceased, the mixture was further heated to the reflux temperature for 30 min. The suspension was cooled down to room temperature and the supernatant was added in small portions to an ice-cold solution of sulfuryl chloride (4.6 ml, 7.728 g, 57.2 mmol) in 30 ml anhydrous DCM. After complete addition, the suspension was warmed to room temperature and the volatiles were removed *in vacuo*. The residue was dried in oil-pump vacuo for 15 min, then it was extracted with hexane (150 ml). The hexane suspension was filtered and the hexane was removed in

vacuo to give the crude product as dark purple oil which was used for the next step without further purification. There is still some unreacted cyclopropylbromide present. Crude yield: 1.1 g (38%).

**Step B:** N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)cyclobutanesulfonamide:

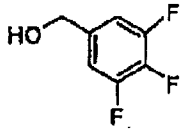


According to the general procedure B, the cyclobutylsulfonyl chloride prepared in the step above was reacted with 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)-3-methoxy-benzene- 1,2-diamine to obtain the title product. Yield: 75%. $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ = 7.44 (s, 1H, br), 7.41-7.36 (dd, 1H), 7.24-7.23 (m, 1H), 6.54-6.38 (m, 2H), 5.90 (s, 1H, br), 3.85-3.75 (m, 5H), 2.60-2.40 (m, 2H), 2.25-2.15 (m, 1H), 2.15-1.95 (m, 2H); *m/z* = 511 $[M-1]^-$.

Example 62

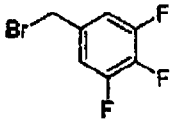
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methylphenyl)-1-(2,3- dihydroxypropyl)cyclopropane-1-sulfonamide:**

**Step A:** (3,4,5-Trifluorophenyl)methanol:



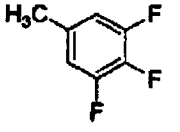
To a cooled (-5° C) solution of 3,4,5 -trifluorobenzaldehyde (7.0 g, 43.75 mmol) in a mixture ( 50 ml, 9:1) of THF and water $NaBH_4$ (1.662 g, 43.75 mmol) was slowly added in portions over a period of 30 min. The reaction mixture was allowed to attain room temperature over a period of 2h and carefully poured into ice-cold dil HCl (200 ml, IN). The oily layer was extracted into $CH_2Cl_2$ (250 ml) and the organic layer washed with water (200 ml), dried ($MgSO_4$) and evaporated. The crude product (7.08 g, quantitative) obtained was taken forward without further purification.

**Step B:** 5-(Bromomethyl)-1,2,3-trifluorobenzene:



To a solution of the (3,4,5-Trifluorophenyl)methanol (40 mmol) in $CH_2Cl_2$ (150 ml), a solution of thionyl bromide (6.16 ml, 80 mmol) in $CH_2Cl_2$ (50 ml) was added slowly. The reaction mixture stirred at room temperature for 16h and poured into ice-water (200 ml). The organic layer was separated and washed with saturated $NaHCO_3$ (2x200 ml), water (200 ml), dried ($MgSO_4$) and evaporated to obtain the corresponding bromo compound as a pale yellow oil in quantitative yield. The crude product was carried forward for the next reaction without further purification.

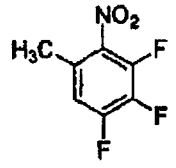
**Step C:** 1,2,3-Trifluoro-5-methylbenzene:



The above bromo compound (40 mmol) was mixed with triethylsilane (48 mmol) and the reaction mixture was treated with solid $PdCl_2$ (4 mmol) in small portions. After a few minutes a vigorous exothermic reaction was ensued and care was taken to reflux the contents of the flask by placing a reflux condenser. The reaction mixture was stirred at room

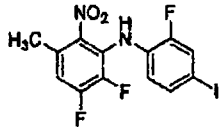
temperature for additional 6h and the contents were allowed to settle over 16h. Then the crude liquid product was decanted carefully and carried forward for the next reaction without further purification. It was assumed tat the reaction proceeds in quantitative yield.

**Step D:** 1,2,3-Trifluoro-5-methyl-4-nitrobenzene:



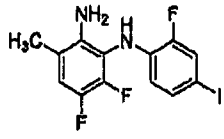
1,2,3-Trifluoro-5-methylbenzene (40 mmol) was added to conc. $H_2SO_4$ (50 ml) at 0-5° C. Then the reaction mixture was slowly treated with conc. $HNO_3$ (3.39 ml, 48.44 mmol, 90%) while maintaining the internal temperature below 20° C. The reaction mixture was stirred at room temperature for 16h and poured onto ice (300 g) and the oily layer was extracted with $CH_2Cl_2$ (2x125 ml). The organic layer was washed with water (2x200 ml), brine (200 ml) and dried ($MgSO_4$) and evaporated to obtain the crude product which was purified over flash silica gel chromatography to obtain the title product (6.5 g, 85%). $^1$H-NMR (300 MHz, $CDCl_3$): δ 6.96 (septet, 1H), 2.39 (s, 3H). $^{19}$FNMR ($CDCl_3$): δ -128.18, - 141.50, -159.05.

**Step E:** 2,3-Difluoro-N-(2-fluoro-4-iodophenyl)-5-methyl-6-nitroaniline:



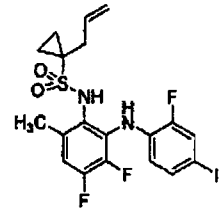
2-Fluoro-4-iodoaniline and 1,2,3-trifluoro-5-methyl-4-nitrobenzene were reacted using the condition described in Example 1 (Step A) to form the title compound. M-H$^+$: 407.9

**Step F:** 5,6-Difluoro-N1-(2-fluoro-4-iodophenyl)-3-methylbenzene-1,2-diamine:



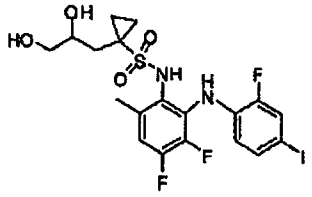
2,3-Difluoro-N-(2-fluoro-4-iodophenyl)-5-methyl-6-nitroaniline was reduced using the condition described in Example 1 (step B) to form the title compound. M-H$^+$: 377.4

**Step G:** 1-Allyl-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methylphenyl)cyclopropane-1-sulfonamide:



According to the general procedure B, 1-allyl-cyclopropanesulfonyl chloride (142 mg, 142 mg) was reacted with 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)-3-methylbenzene-1,2- diamine (150 mg, 0.4 mmol) to obtain the title product (100 mg, 47%); *m/z* = 521 [M-1]$^-$.

**Step H:** N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methylphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide:

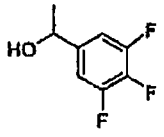


1-Allyl-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methylphenyl) cyclopropane-1-sulfonamide ( 150 mg, 0.29 mmol) and 4-methylmorpholine N-oxide (33 mg, 0.29 mmol) was dissolved in THF (5 mL). Osmium tetroxide was added at room temperature (0.029 mmol, 0.18 mL, 4% in $H_2O$) and the reaction mixture was stirred at room temperature for 16 hours. EtOAc was added, the organic phase was washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified over silica gel chromatography (eluants: EtOAc/ MeOH) to obtain the titled product (0.110 g, 68 %). $^1$H-NMR (300 MHz, $CDCl_3$): δ 7.07 (m, 1H), 6.97 (br m, 2H), 6.84 (m, 2H), 6.60 (br m, 2H), 3.98 (br m, 1H), 3.58 (m, 1H), 3.43 (m, 1H), 3.20 (d, $J$ = 3.9 Hz, 1H), 2.42 (s, 3H), 2.31 (dd, $J$ = 9.9 & 15.6 Hz, 1H), 2.01 (br t, 1H), 2.31 (dd, $J$ = 9.9 & 15.6 Hz, 1H), 1.66 (dd, $J$ = 2.1 & 15.9 Hz, 1H), 1.52 (m, 1H), 1.40 (m, 1H), 0.91 (m, 2H).

Example 63

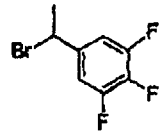
**1-(2,3-Dihydroxypropyl)-N-(6-ethyl-3,4-difluoro-2-(2-fluoro-4-iodophenylamino) phenyl) cyclopropane-1-sulfonamide:**

**Step A:** 1-(3,4,5-Trifluorophenyl)ethanol:



An ethereal solution (17.41 ml, 52.24 mmol, 3M) of MeMgBr was slowly added at - 78° C to a solution of 3,4,5-trifluorobenzaldehyde (6.96 g, 43.53 mmol) in THF (125 ml). The reaction mixture was stirred at room temperature for 16h and was cooled (0° C) and was quenched, sequentially, with excess ethyl acetate (10 ml) and water (5 ml). Excess anhydrous $MgSO_4$ (5 g) was added and stirred for 30 minutes at room temperature. The suspension was filtered over celite and the solids were washed with ethyl acetate (2x25 ml). The combined filtrate was evaporated to obtain the product in quantitative yield (7.65 g).

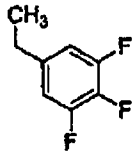
**Step B:** 5-(1-Bromoethyl)-1,2,3-trifluorobenzene:



To a solution of the 1-(3,4,5-Trifluorophenyl)ethanol: (7.65 g, 43.5 mmol) in $CH_2Cl_2$ (250 ml), a solution of thionyl bromide (18.1 g , 87 mmol) in $CH_2Cl_2$ (50 ml) was added slowly. The reaction mixture stirred at room temperature for 16h and poured into ice-water (200 ml). The organic layer was separated and washed with saturated $NaHCO_3$ (2x200 ml), water (200 ml), dried ($MgSO_4$) and evaporated to obtain the corresponding bromo compound as a pale yellow oil in quantitative yield (10.4 g). The crude product was carried forward for the next reaction without further purification.

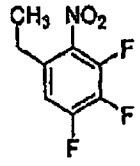
146

**Step C:** 5-Ethyl- 1,2,3 -trifluorobenzene:



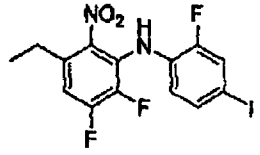
The above bromo compound (9.65 g, 40.4 mmol) was mixed with triethylsilane (41 mmol) and the reaction mixture was treated with solid $PdCl_2$ (177 mg, 4 mmol) in small portions. After a few minutes a vigorous exothermic reaction was ensued and care was taken to reflux the contents of the flask by placing a reflux condenser. The reaction mixture was stirred at room temperature for additional 6h and the contents were allowed to settle over 16h. Then the crude liquid product was decanted carefully and carried forward for the next reaction without further purification. It was assumed tat the reaction proceeds in quantitative yield.

**Step D:** 1-Ethyl-3,4,5-trifluoro-2-nitrobenzene:



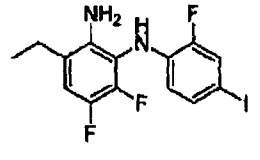
1,2,3-Trifluoro-5-methylbenzene (6.46 g, 40.4 mmol) was added to conc. $H_2SO_4$ (50 ml) at 0-5° C. Then the reaction mixture was slowly treated with conc. $HNO_3$ (3.39 ml, 48.44 mmol, 90%) while maintaining the internal temperature below 20° C. The reaction mixture was stirred at room temperature for 16h and poured onto ice (300 g) and the oily layer was extracted with $CH_2Cl_2$ (2x125 ml). The organic layer was washed with water (2x200 ml), brine (200 ml) and dried ($MgSO_4$) and evaporated to obtain the crude product which was purified over flash silica gel chromatography to obtain the title product (6.6 g, 79%). $^1H$ NMR ($CDCl_3$): δ 6.98 (septet, 1H), 2.68 (q, 2H), 1.26 (t, $J$ = 7.8 & 7.2 Hz, 3H).

**Step E:** 3-Ethyl-5,6-difluoro-N-(2-fluoro-4-iodophenyl)-2 nitroaniline:



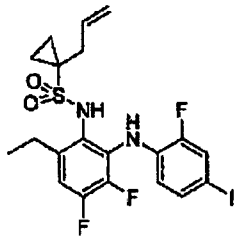
2-Fluoro-4-iodoaniline (2.05 g, 10 mmol) and 1-ethyl-3,4,5-trifluoro-2-nitrobenzene (2.37 g, 10 mmol) were reacted using the condition described in example 1 (Step A) to form the title compound (2.47 g, 60%); $m/z$ = 407 $[M-1]^-$.

**Step F:** 3-Ethyl-5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine:



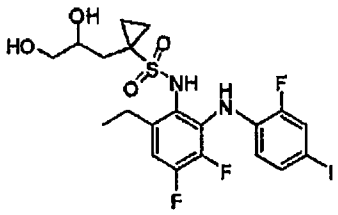
1,2,3-Trifluoro-5-methyl-4-nitrobenzene (2.47 g, 5.85 mmol) was reduced using the condition described in example 1 (Step B) to form the title compound. $M-H^+$: 393

**Step G:** l-Allyl-N-(6-ethyl-3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)cyclopropane-1-sulfonamide:



According to the general procedure B, l-allyl-cyclopropanesulfonyl chloride (230 mg, 1.27 mmol) was reacted with 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)-3-methylbenzene-1,2-diamine (100 mg, 0.255 mmol) to obtain the title product (72 mg, 53%); *m/z* = 535 [M-1].

**Step H:** 1-(2,3-Dihydroxypropyl)-N-(6-ethyl-3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)cyclopropane-1-sulfonamide:

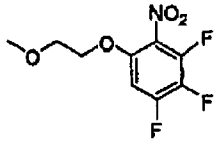


l-Allyl-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methylphenyl) cyclopropane-1-sulfonamide ( 70 mg, 0.13 mmol) and 4-methylmorpholine N-oxide (15 mg, 0.13 mmol) was dissolved in THF (2 mL). Osmium tetroxide was added at room temperature (0.013 mmol) 0.075 mL, 4% in $H_2O$) and the reaction mixture was stirred at room temperature for 16 hours. EtOAc was added, the organic phase was washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified over silica gel chromatography (eluants: EtOAc/MeOH) to obtain the titled product. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.38 (dd, *J* = 2.1 & 10.8 Hz, 1H), 7.27 (m, 2H), 7.12 (br s, 1H), 6.91 (dd, *J* = 8.1 & 10.8 Hz, 1H), 6.69 (br s, 1H), 6.36 (dt, *J* = 4.8, 8.7 & 13.5 Hz, 1H), 4.00 (m, 1H), 3.62 (dd, *J* = 3.6 & 10.5 Hz, 1H), 3.47 (br m, 2H), 2.81 (q, 2H), 2.40 (dd, *J* = 10.2 & 15.9 Hz, 1H), 1.73 (br m, 2H), 1.58 (m, 1H), 1.43 (m, 1H), 0.94 (m, 2H).

Example 64

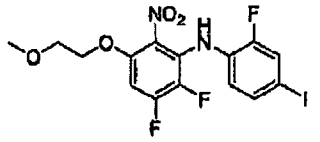
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-(2-methoxyethoxy)phenyl)-l-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide:**

**Step A:** 1,2,3-Trifluoro-5-(2-methoxyethoxy)-4-nitrobenzene:



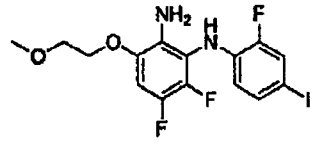
To a mixture of 3,4,5-trifluoro-2-nitrophenol (1.93, 10 mmol), $Ph_3P$ (3.93 g, 15 mmol), and 2-methoxy-ethanol (1.18 ml, 15 mmol) in anhydrous THF (25 ml) a solution of diisopropyl azodicarboxylate (2.91 ml, 15 mmol) in THF (5 ml) was added at 0° C and the reaction mixture was stirred at room temperature for 16h. The volatiles were evaporated and the residue was dissolved in $CH_2Cl_2$ (100 ml) and the organic layer was washed with water (100 ml), brine (100 ml) dried ($MgSO_4$) and evaporated. The residue obtained was purified over flash silica gel chromatography to obtain the titled product in 68% (1.70 g) yield. $^1$H NMR (300 MHz, $CDCl_3$): δ 6.78 (ddd, *J* = 2.4, 6.0, 11.7 Hz, 1H), 4.19 (t, *J* = 4.5 Hz, 2H), 3.72 (t, *J* = 4.5 Hz, 2H), 3.39 (s, 3H).

**Step B:** 2,3-Difluoro-N-(2-fluoro-4-iodophenyl)-5-(2-methoxyethoxy)-6-nitroaniline:



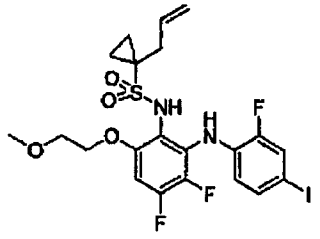
2-Fluoro-4-iodoaniline (1.6 g, 6.8 mmol) and 1,2,3-trifluoro-5-(2-methoxyethoxy)-4-nitrobenzene (1.7 g, 6.8 mmol) were reacted using the condition described in Example 1 (Step A) to form the title compound (1.02 g, 32%); *m/z* = 467 [M-1].

**Step C:** 5,6-Difluoro-N1-(2-fluoro-4-iodophenyl)-3-(2-methoxyethoxy)benzene-1,2-diamine:



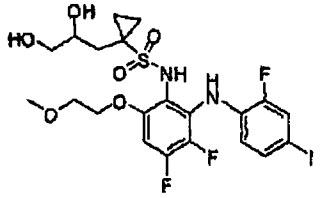
2,3-Difluoro-N-(2-fluoro-4-iodophenyl)-5-(2-methoxyethoxy)-6-nitroaniline (1.017 g, 2.17 mmol) was reduced using the condition described in Example 1 (Step B) to form the title compound; *m/z* = 337 [M-1].

**Step D:** 1-Allyl-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-(2-methoxyethoxy)phenyl)cyclopropane-1-sulfonamide:



According to the general procedure B, 1-allyl-cyclopropanesulfonyl chloride (450 mg, 2.5 mmol) was reacted with 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)-3-(2-methoxyethoxy)benzene-1,2-diamine (219 mg, 2.5 mmol) to obtain the title product (230 mg, 78%); *m/z* = 581 [M-1].

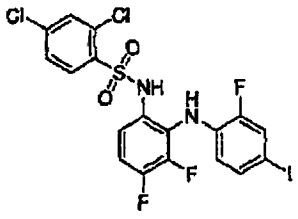
**Step E:** N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-(2-methoxyethoxy)phenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide:



1-allyl-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-(2-methoxyethoxy)phenyl)cyclopropane-1-sulfonamide (230 mg, 0.395 mmol) and 4-methylmorpholine N-oxide (46 mg, 0.395 mmol) was dissolved in THF (2 mL). Osmium tetroxide was added at room temperature (0.039 mmol, 0.25 mL, 4% in $H_2O$) and the reaction mixture was stirred at room temperature for 16 hours. EtOAc was added, the organic phase was washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified over silica gel chromatography (eluants: EtOAc/MeOH) to obtain the titled product. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.36 (dd, *J* = 1.8 & 10.5 Hz, 1H), 7.27 (m, 2H), 6.56 (dd, *J* = 6.9 & 11.4 Hz, 1H), 6.40 (dt, *J* = 5.7, 7.5 & 12.9 Hz, 1H), 4.17 (m, 2H), 4.01 (m, 1H), 3.78 (m, 2H), 3.60 (dd, *J* = 3.6 & 11.1 Hz, 1H), 3.47 (m, 1H), 3.45 (s, 3H), 2.36 (dd, *J* = 9.6 & 15.9 Hz, 1H), 1.78 (dd, *J* = 2.4 & 15.6 Hz, 1H), 1.45-1.25 (m, 2H), 0.89 (m, 2H).

Example 65

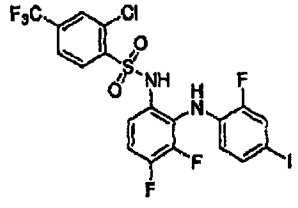
**2,4-dichloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl) benzene sulfonamide:**



Synthesized by method A using the appropriate sulfonyl chloride, *m/z* = 571 [M-1].

Example 66

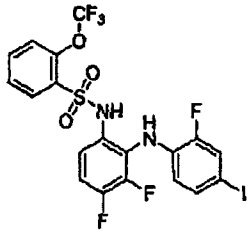
**2-chloro-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-4-(trifluoromethyl)benzenesulfonamide:**



Synthesized by method A using the appropriate sulfonyl chloride, *m/z* = 605 [M-1].

Example 67

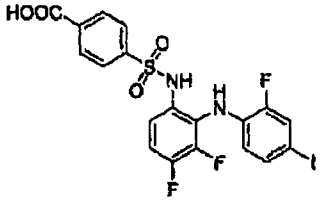
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2-(trifluoromethoxy) benzene sulfonamide:**



Synthesized by method A using the appropriate sulfonyl chloride, *m/z* = 587 [M-1].

Example 68

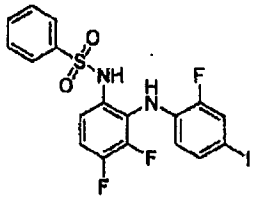
**4-(N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)sulfamoyl)benzoic acid:**



Synthesized by method A using the appropriate sulfonyl chloride, *m/z* = 584 [M-1].

Example 69

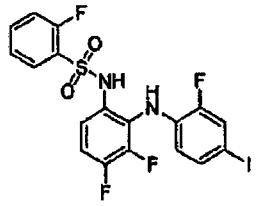
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)benzenesulfonamide:**



Synthesized by method A using the appropriate sulfonyl chloride, *m/z* = 503 [M-1].

Example 70

**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2-fluorobenzene sulfonamide:**



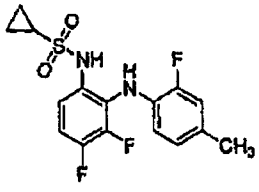
Synthesized by method A using the appropriate sulfonyl chloride, *m/z* = 521 [M-1].

**General procedure D:** substitution of the iodine atom:

A suspension containing 1 eq. aryl iodide, 1.5 equiv. of the boronic acid or boronic ester, 0.25 eq. $PdCl_2(dppf)$ x DCM and 10 eq. anhydrous $K_2CO_3$ powder in a deoxygenated mixture of dioxane and water (3:1) was heated in a microwave reactor for 60 min at 115°C. It was extracted using aq. $NH_4Cl$/THF, and the organic fraction was dried using $Na_2SO_4$. The crude reaction products were purified using flash-column chromatography (Si, EtOAc/Hexanes, or $CHCl_3$/MeOH). Yields: 20-40%.

Example 71

**N-(3,4-difluoro-2-(2-fluoro-4-methylphenylamino)phenyl)cyclopropanesulfonamide;**



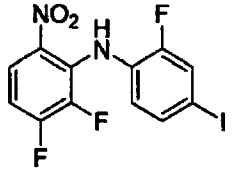
General procedure D: $^1$H-NMR (500 MHz, $CDCl_3$): δ = 7.38-7.36 (m, 1H), 7.06-7.03 (q, 1H), 6.92-6.90 (1H), 6.73-6.72 (d, 1H), 6.63 (s, 1H, br), 6.37-6.33 (t, 1H), 5.54 (s, 1H, br), 2.42-2.39 (m, 1H), 2.25 (s, 3H), 1.14-1.11 (m, 2H), 0.94-0.90 (m, 2H); *m/z* = 355 [M-1].

Where racemic mixtures of chiral compounds have been resolved into separate enantiomers, the phrase "substantially free" of the epimer, as used herein, means an enantiomeric excess of at least 90%.

Example 72

**N-(3,4-difluoro-2-(2-fluoro-4-(1H-pyrazol-4-yl)phenylamino)phenyl)cyclopropane sulfonamide**

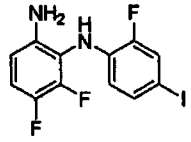
**Step A:** 2,3-Difluoro-N-(2-fluoro-4-iodophenyl)-6-nitroaniline:



To a solution of 2-fluoro-4-iodoaniline (11.40 g, 47 mmol) in 100 ml anhydrous THF at 0 °C, 47 ml of a 1M solution of LHMDS in THF (47 mmol) was added dropwise. The color of the solution turned dark purple. The solution was transferred via cannula to a dropping funnel, and the solution (containing the amine free base) was added in small portions to a solution of 2,3,4-trifluoronitrobenzene (8.321 g, 47.0 mmol) in anhydrous THF (50 ml) at 0 °C. After completion of addition the mixture was stirred under argon at room temperature for 15 hours. The volume of the solvent was reduced, followed by extraction using ethyl acetate and brine. The organic layer was dried over sodium sulfate, the solvent was removed, and the obtained dark oil was purified by flash

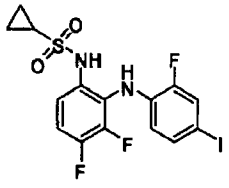
chromatography (EtOAc / hexane 1:5, $R_f = 0.58$) yielding the crude product, which became a brown solid upon drying *in vacuo* (yield: 6.23 g, 33.6%). *m/z* = 393 $[M-1]^-$.

**Step B:** 5,6-Difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine



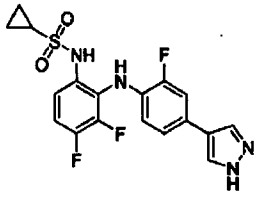
To a solution of nitro-diarylamine (6.23 g, 15.8 mmol) in 300 ml ethanol was added iron powder (13.74 g, 246 mmol) and ammonium chloride (13.59 g, 254 mmol) and the mixture was heated with stirring at 100 °C oil bath temperature for 14 hours. It was filtered and the residue washed two times with ethanol. The ethanol was removed *in vacuo*, and the residue was extracted using ethyl acetate / 1M NaOH solution. During the extraction, more precipitate was formed which was filtered and discarded. The combined organic layers were washed with brine and dried over sodium sulfate. The solvent was removed, and the crude product was recrystallized from $CHCl_3$ / hexane (1:50). The product was obtained as brown needles (2.094 g, 66%,). $R_f = 0.44$ (EtOAc / Hex 1:3). $^1$H-NMR (500 MHz, $CDCl_3$): δ = 7.40-7.38 (dd, 1H, *J* = 11.3 Hz, *J* = 1.5 Hz). 7.25-7.23 (d, 1H, *J* = 8.5 Hz), 6.97-6.92 (q, 1H, *J* = 9 Hz), 6.51-6.48 (m, 1H), 6.24-6.21 (t, 1H, *J* = 9 Hz), 5.3 (s, 1H, NH, br), 3.80 (s, 2H, $NH_2$, br); LRMS (ESI): *m/z* = 365 $[M+H]^+$.

**Step C:** N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)cyclopropane sulfonamide:



According to the general procedure A, 5,6-difluoro-N1-(2-fluoro-4-iodophenyl)benzene-1,2-diamine was reacted with cyclopropanesulfonyl chloride to obtain the desired product. (500 MHz, $CDCl_3$): δ = 7.38-7.37 (d, 1H), 7.35-7.34 (m, 1H), 7.27-7.26 (m, 1H), 7.20-7.0 (q, 1H), 6.68 (s, 1H, br), 6.15-6.12 (q, 1H), 5.65 (s, 1H, br), 3.25-3.20 (m, 1H), 2.4-2.3 (m, 2H), 2.0-1.8 (m, 2H); *m/z* = 467 $[M-1]^-$.

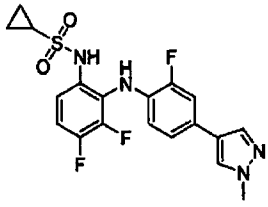
**Step D:** N-(3,4-difluoro-2-(2-fluoro-4-(1H-pyrazol-4-yl)phenylamino)phenyl) cyclopropanesulfonamide:



General procedure C : $^1$H-NMR (500 MHz, $CDCl_3$): δ = 8.00-7.90 (m, 2H), 7.30-7.20 (m, 2H), 7.15-7.10 (m, 1H), 7.05-7.00 (m, 1H), 6.70-6.60 (m, 1H), 2.40-2.35 (m, 1H), 1.05-1.0 (m, 2H), 0.95-0.85 (m, 2H); *m/z* = 407 $[M-1]^-$.

Example 73

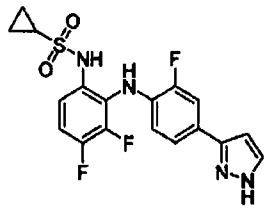
**N-(3,4-difluoro-2-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)phenylamino)phenyl) cyclopropanesulfonamide**



General procedure C : $^1$H-NMR (500 MHz, $CDCl_3$): δ = 7.95 (s, 1H), 7.75 (s, 1H), 7.30-7.20 (m, 2H), 7.15-7.10 (m, 1H), 7.05-7.00 (m, 1H), 6.70-6.60 (m, 1H), 3.95 (s, 3H), 2.40-2.35 (m, 1H), 1.05-1.0 (m, 2H), 0.95-0.85 (m, 2H); *m/z* = 421 $[M-1]^-$

Example 74

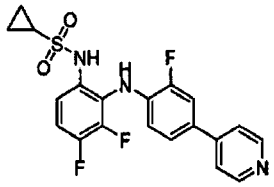
**N-(3,4-difluoro-2-(2-fluoro-4-(1H-pyrazol-3-yl)phenylamino)phenyl) cyclopropanesulfonamide**



General procedure C : $^1$H-NMR (500 MHz, $CDCl_3$): δ = 7.90 (s, 1H), 7.80 (s, 1H), 7.30-7.20 (m, 2H), 7.15-7.10 (m, 1H), 7.05-7.00 (m, 1H), 6.70-6.60 (m, 1H), 3.95 (s, 3H), 2.40-2.35 (m, 1H), 1.05-1.0 (m, 2H), 0.95-0.85 (m, 2H); *m/z* = 407 $[M-1]^-$

Example 75

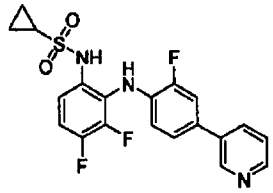
**N-(3,4-difluoro-2-(2-fluoro-4-(pyridin-4-yl)phenylamino)phenyl) cyclopropanesulfonamide**



General procedure C : $^1$H-NMR (500 MHz, $CDCl_3$): δ = 8.62-8.61 (d, 2H), 7.43-7.41 (m, 4H), 7.23-7.22 (m, 1H), 7.16-7.11 (q, 1H), 6.61-6.58 (t, 1H), 6.11 (s, 1H, br), 2.53-2.50 (m, 1H), 1.21-1.10 (m, 2H), 1.02-0.99 (m, 2H); *m/z* = 418 $[M-1]^-$.

Example 76

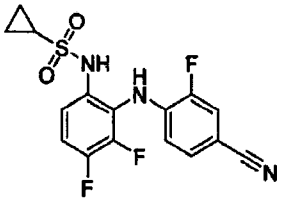
**N-(3,4-difluoro-2-(2-fluoro-4-(pyridin-3-yl)phenylamino)phenyl) cyclopropanesulfonamide**



General procedure C : $^1$H-NMR (500 MHz, [D6]-DMSO): δ = 9.45 (s, 1H), 8.91 (s, 1H), 8.54 (s, 1H), 8.07-8.06 (d, 1H), 7.76-7.70 (m, 2H), 7.46-7.34 (m, 2H), 7.34-7.33 (d, 2H), 6.80-6.78 (m, 1H), 0.86-0.79 (m, 4H); *m/z* = 418 $[M-1]^-$

Example 77

**N-(2-(4-cyano-2-fluorophenylamino)-3,4-difluorophenyl)cyclopropanesulfonamide**



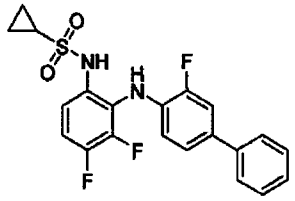
A suspension containing the aryl iodide (75.5 mg, 0.161 mmol), CuCN (46.6 mg, 0.520 mmol and $Pd(OAc)_2$ (0.47 mg) in 1 ml anhydrous DMF was heated to 130 °C for 60 min. in a microwave reactor. The mixture was extracted using

brine / THF, and the organic fractions were dried using $Na_2SO_4$. Subsequent flash-column chromatography gave the product as a dark red semi-solid ($R_f$ = 0.42 (EtOAc/Hexanes 1:1). Yield: 15 %.

*m/z* = 366 [M-1]$^-$.

Example 78

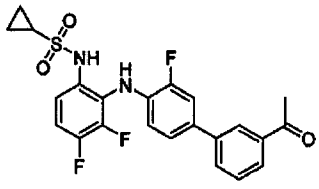
**N-(3,4-difluoro-2-(3-fluorobiphenyl-4-ylamino)phenyl)cyclopropanesulfonamide**



General procedure C : $^1$H-NMR (500 MHz, $CDCl_3$): δ = 7.55-7.53 (m, 2H), 7.45-7.3 (m, 5H), 7.20-7.15 (d, 1H), 7.13-7.10 (q, 1H), 6.70 (s, 1H, br),6.60-6.55 (t, 1H), 5.75 (s, 1H, br), 2.53-2.50 (m, 1H), 1.21-1.10 (m, 2H), 1.02-0.99 (m, 2H); *m/z* = 417 [M-1]$^-$.

Example 79

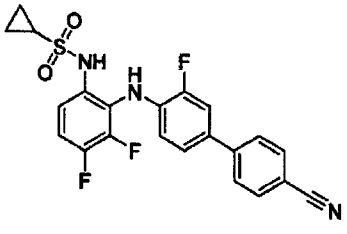
**N-(2-(3'-acetyl-3-fluorobiphenyl-4-ylamino)-3,4-difluorophenyl) cyclopropanesulfonamide**



General procedure C : $^1$H-NMR (500 MHz, $CDCl_3$): δ = 8.6 (s, 1H), 7.86-7.85 (d, 1H), 7.68-7.66 (d,1H), 7.49-7.46 (t, 1H), 7.38-7.33 (m, 2H), 7.20-7.18 (d, 1H), 7.09-7.03 (q, 1H), 6.90 (s, 1H, br), 6.57-6.54 (t, 1H), 5.90 (s, 1H), br), 2.61 (s, 3H), 2.46-2.43 (m, 1H), 1.15-1.13 (m, 2H), 0.94-0.91 (m, 2H); *m/z* = 459 [M-1]$^-$.

Example 80

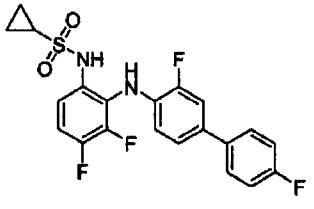
**N-(2-(4'-cyano-3-fluorobiphenyl-4-ylamino)-3,4-difluorophenyl) cyclopropanesulfonamide**



General procedure C : $^1$H-NMR (500 MHz, $CDCl_3$): δ = 7.68-7.66 (m, 2H), 7.58-7.57 (m, 2H), 7.38-7.35 (m, 2H), 7.20-7.18 (d, 1H), 7.18-7.02 (q, 1H), 6.67 (s, 1H, br), 6.58-6.54 (t, 1H), 5.99 (s, 1H, br), 2.47-2.44 (m, 1H), 1.15-1.13 (m, 2H), 0.94-0.91 (m, 2H); *m/z* = 442 [M-1]$^-$.

Example 81

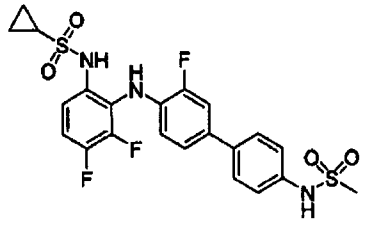
**N-(2-(3,4'-difluorobiphenyl-4-ylamino)-3,4-difluorophenyl)cyclopropanesulfonamide**



General procedure C : $^1$H-NMR (500 MHz, $CDCl_3$): δ = 7.44-7.37 (m, 3H), 7.29-7.27 (d, 1H), 7.11-7.05 (m, 4H), 6.70 (s, 1H, br), 6.53-6.50 (t, 1H), 5.81 (s, 1H, br), 2.47-2.44 (m, 1H), 1.15-1.13 (m, 2H), 0.94-0.91 (m, 2H); *m/z* = 435 [M-1]$^-$.

Example 82

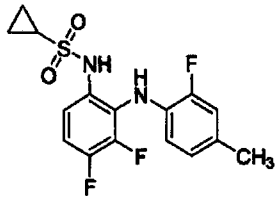
**N-(3,4-difluoro-2-(3-fluoro-4'-(methylsulfonamido)biphenyl-4-ylamino)phenyl) cyclopropanesulfonamide**



General procedure C : $^1$H-NMR (500 MHz, [D6]-DMSO): δ = 9.39 (s, 1H, br), 7.63-7.60 (m, 3H), 7.53-7.50 (d, 1H), 7.30-7.23 (m, 4H), 7.74-7.65 (m, 1H), 2.99 (s, 3H), 0.80-0.73 (m, 4H); *m/z* = 510 [M-1]$^-$.

Example 83

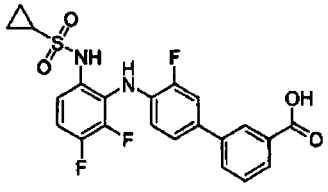
**N-(3,4-difluoro-2-(2-fluoro-4-methylphenylamino)phenyl)cyclopropanesulfonamide**



General procedure C : $^1$H-NMR (500 MHz, $CDCl_3$): δ = 7.38-7.36 (m, 1H), 7.06-7.03 (q, 1H), 6.92-6.90 (1H), 6.73-6.72 (d, 1H), 6.63 (s, 1H, br), 6.37-6.33 (t, 1H), 5.54 (s, 1H, br), 2.42-2.39 (m, 1H), 2.25 (s, 3H), 1.14-1.11 (m, 2H), 0.94-0.90 (m, 2H); *m/z* = 355 [M-1]$^-$.

Example 84

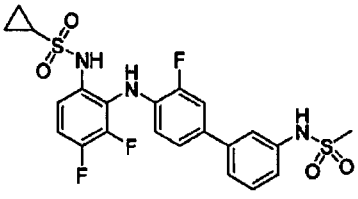
**4'-(6-(cyclopropanesulfonamido)-2,3-difluorophenylamino)-3'-fluorobiphenyl-3-carboxylic acid**



General procedure C : $^1$H-NMR (500 MHz, [D4]-MeOH): δ = 8.21 (s, 1H), 7.93-7.91 (d, 1H), 7.73-7.72 (d, 1H), 7.47-7.43 (m, 2H), 7.33-7.31 (d, 2H), 7.15-7.12 (q, 1H), 6.71-6.68 (m, 1H), 2.51-2.46 (m, 1H), 0.94-0.93 (m, 2H), 0.88-0.87 (m, 2H); *m/z* = 499 [M-1]$^-$.

Example 85

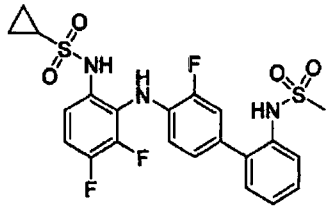
**N-(3,4-difluoro-2-(3-fluoro-3'-(methylsulfonamido)biphenyl-4-ylamino)phenyl) cyclopropanesulfonamide**



General procedure C : $^1$H-NMR (500 MHz, [D4]-MeOH): δ = 7.92 (s, 1H), 7.46-7.34 (m, 5H), 7.34-7.31 (d, 1H), 7.29-7.22 (m, 1H), 7.16-7.15 (q, 1H), 6.74-6.71 (m, 1H), 2.80 (s, 3H), 2.54-2.51 (m, 1H), 0.94-0.92 (m, 2H), 0.91-0.90 (m, 2H); *m/z* = 510 [M-1]$^-$.

Example 86

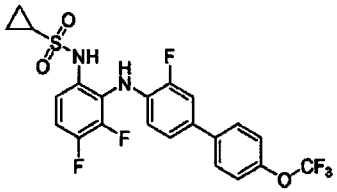
**N-(3,4-difluoro-2-(3-fluoro-2'-(methylsulfonamido)biphenyl-4-ylamino)phenyl) cyclopropanesulfonamide**



General procedure C : $^1$H-NMR (500 MHz, [D4]-MeOH): δ = 7.50-7.49 (d, 1H), 7.40-7.32 (m, 4H), 7.29-7.28 (d, 1H), 7.26-7.10 (m, 2H), 6.73-6.71 (m, 1H), 2.80 (s, 3H), 2.51-2.49 (m, 1H), 0.94-0.92 (m, 2H), 0.91-0.90 (m, 2H); *m/z* = 510 [M-1]$^-$.

Example 87

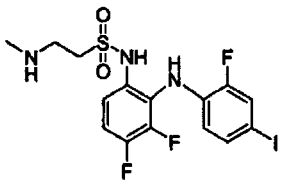
**N-(3,4-difluoro-2-(3-fluoro-4'-(trifluoromethoxy)biphenyl-4-ylamino)phenyl) cyclopropanesulfonamide**



General procedure C : $^1$H-NMR (500 MHz, [D4]-MeOH): δ = 7.69-7.67 (d, 2H), 7.46-7.43 (d, 1H), 7.36-7.33 (m, 4H), 7.30-7.29 (q, 1H), 6.73-6.72 (m, 1H), 2.51-2.49 (m, 1H), 0.94-0.92 (m, 2H), 0.91-0.90 (m, 2H); *m/z* = 501 [M-1]$^-$.

Example 88

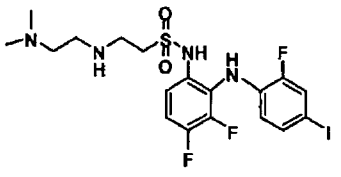
**N-(3,4-Difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2-(methylamino) ethanesulfonamide**



General procedure D. $^1$H NMR (300 MHz, $CDCl_3$): δ 9.01 (br s, $D_2O$ exchangeable, 1H), 7.36 (dd, *J* = 2.1 & 10.5 Hz, 1H), 7.27 (m, 1H), 7.17 (m, 1H), 7.03 (dd, *J* = 9.0 & 16.8 Hz, 1H), 6.48 (s, $D_2O$ exchangeable, 1H), 6.31 (dt, *J* = 3.0, 8.7 & 17.4 Hz, 1H), 3.45 (br t. 2H). 3.31 (br s, 2H), 2.65 (s. 3H). 1.80(br s, $D_2O$ exchangeable, 1H).

Example 89

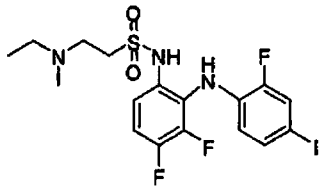
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2-(2-(dimethylamino)ethylamino) ethanesulfonamide**



General procedure D. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.35 (m, 1H), 7.25 (m, 1H), 7.18 (d, *J* = 8.7 Hz, 1H), 7.02 (dd, *J* = 8.7 & 18.0 Hz, 1H), 6.38 (m, 1H), 6.18 (dd, *J* = 8.7 & 17.1 Hz, 1H), 3.62 (t, *J* = 5.7 & 6.3 Hz, 2H), 3.35 (m, 2H), 3.26 (m, 2H), 3.26 (t, *J* = 5.7 & 6.6 Hz, 2H), 3.11 (t, *J* = 5.1 & 6.0 Hz, 2H), 2.85 (s, 6H).

Example 90

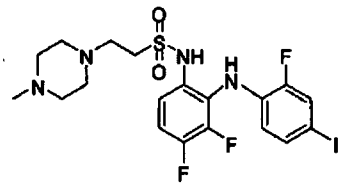
**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2-(ethyl(methyl)amino) ethanesulfonamide**



General procedure D. $^1$H NMR (300 MHz, ($CDCl_3$ + $D_2O$)): δ 7.39 (dd, $J$ = 1.5 & 10.5 Hz, 1H), 7.31 (m, 2H), 7.07 (dd, $J$ = 9.0 & 17.4 Hz, 1H), 6.30 (dt, $J$ = 2.4, 9.0 & 17.4 Hz, 1H), 3.55 (t, $J$ = 6.9 & 7.8 Hz, 2H), 3.38 (br t, $J$ = 6.0 & 8.7 Hz, 2H), 3.05 (q, 2H), 2.69 (s, 3H), 1.31 (t, $J$ = 7.2 Hz, 3H).

Example 91

**N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-2-(4-methylpiperazin-1-yl) ethanesulfonamide**



General procedure D. $^1$H NMR (300 MHz, $CD_3OD$): δ 7.45 (dd, $J$ = 2.1 & 10.8 Hz, 1H), 7.30 (m, 2H), 7.16 (dd, $J$ = 9.6 & 17.7 Hz, 1H), 6.39 (dt, $J$ = 3.3, 9.3 & 17.7 Hz, 1H), 3.26 (m, $J$ = 7.5 Hz, 2H), 3.10 (br m, 6H), 2.87 (s, 3H), 2.82 (t, $J$ = 7.5 Hz, 2H), 2.48 (br m, 4H).

***In vitro* Biological Activity**

Example 92

**Generation of IC50 Data**

Materials and preparation of reagents: Human GST-MEK1 and the constitutively active allele GST-MEK1$^{CA}$ (harboring the mutations Ser218Asp and Ser222Asp) were subcloned into the yeast expression vector pGEM4Z (Promega, Madison, WI) from the wild type human MEK1 cDNA. GST-MEK1$^{CA}$ was expressed in *Escherichia coli* and partially purified using Glutathione Sepharose 4B affinity resin (Amersham Pharmacia Biotech, Piscataway, NJ). The ERK2 allele was subcloned from MAPK2/Erk2 cDNA (wild type) in pUSEamp (Upstate Biotechnology, Inc., Waltham, MA) into the vector pET21a (Novagen, Madison, WI) resulting in an N-terminal histidine-tagged mouse ERK2 allele. ERK2 was expressed and purified to homogeneity [Zhang, 1993 #33]. Myelin basic protein (MBP) was purchased from Gibco BRL (Rockville, MD). EasyTides adenosine 5'-triphosphate (ATP) ([γ-$^{33}$P]) (NEN Perkin Elmer, Wellesley, MA) was the source of radiolabel for all kinase reactions. Activated Raf-1 (truncated) and activated MAPKinase 2/ERK2 were purchased from Upstate, Inc. (Lake Placid, NY). 4-20% Criterion Precast gels were purchased from Bio-Rad (Hercules, CA).

Determination of enzymatic activity: Compounds were diluted from dimethylsulfoxide (DMSO) stocks into 1xHMNDE (20 mM HEPES pH 7.2, 1 mM $MgCl_2$, 100 mM NaCl, 1.25 mM DTT, 0.2 mM EDTA). A typical 25-microliter assay contained 0.002 nanomoles MEK1$^{CA}$, 0.02 nanomoles ERK2, 0.25 nanomoles MBP, 0.25 nanomoles unlabeled ATP, and 0.1 μCi [γ$^{33}$P] ATP. The screening assay essentially comprised four additions. Five μl of diluted compound were dispensed to 96-well assay plates. Ten μl of 2.5x enzyme cocktail (MEK1$^{CA}$ and ERK2 only) were then added to each well followed by a pre-incubation for 30 minutes at ambient temperature. Ten μl of 2.5x substrate cocktail (labeled and unlabeled ATP plus MBP) were then added, followed by incubation for 60 minutes at ambient temperature.

Finally, 100 µl of 10% trichloroacetic acid (TCA) were added and incubated for 30 minutes at room temperature to halt the reaction and precipitate radiolabeled protein products. Reaction products were harvested on glass fiber 96 well filter plates prewetted with water and 1% pyrophosphate. The filter plate was then washed 5 times with water. Water was displaced by absolute ethanol and the plate was allowed to air dry for 30 minutes at room temperature. A back seal was applied manually and 40 µl of scintillation cocktail were dispensed to each well. A top seal was applied and the plate was counted in the TopCount for two seconds per well.

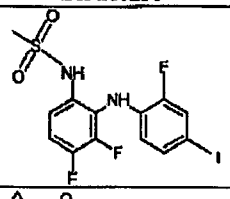
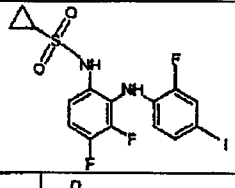
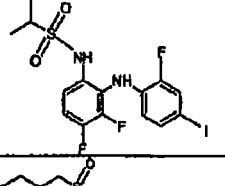
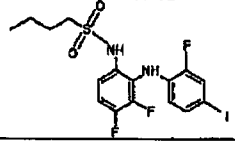
For certain experiments a truncated version of MEK that requires activation by Raf kinase were used.

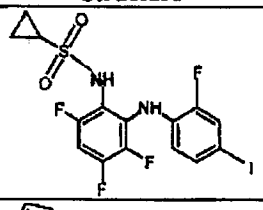
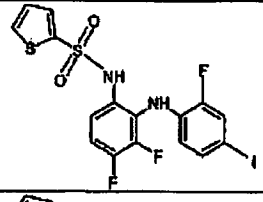
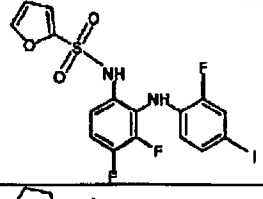
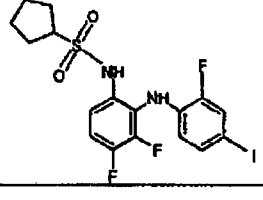
Example 93

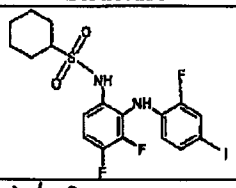
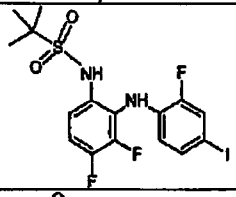
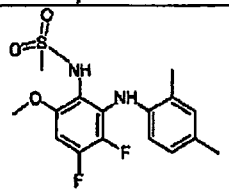
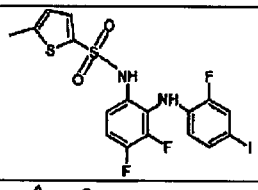
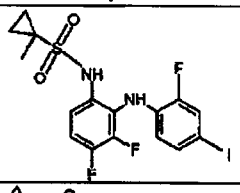
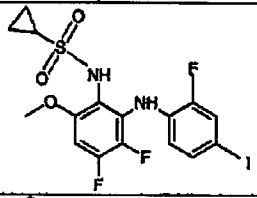
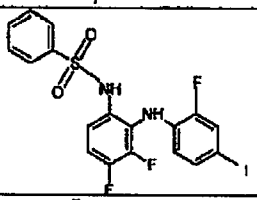
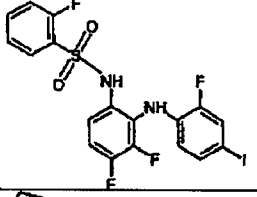
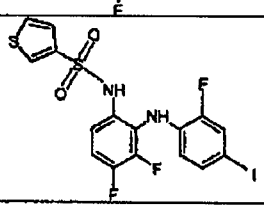
**Generation of EC50 Data**

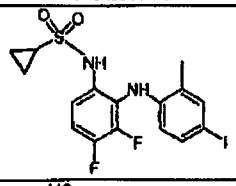
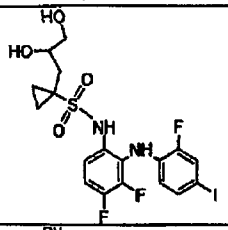
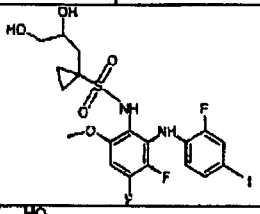
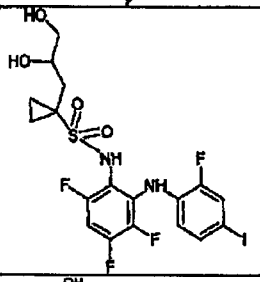
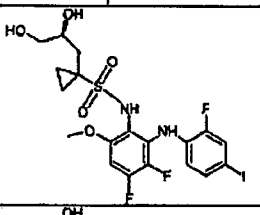
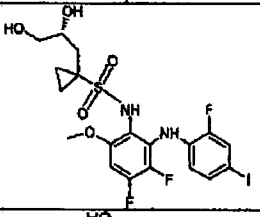
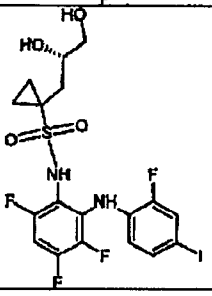
Effects of compounds in the cell were determined by Western blotting for phosphorylated ERK. MDA-MB-231 breast cancer cells were plated in a 48 well plate at 20,000 cells per well and grown in a 37° humidified $CO_2$ incubator. The following day, the growth media (DMEM + 10% fetal bovine serum) was removed and replaced with starve media (DMEM + 0.1% fetal bovine serum). Cells were incubated in the starve media for sixteen hours and then treated with a range of compound concentrations for thirty minutes. After incubation with compound, cells were stimulated with 100ng/ml EGF for five minutes. The cells were then lysed and analyzed by Western blot using a monoclonal antibody raised to phosphorylated ERK. The signal was amplified using a secondary antibody conjugated to a near -IR dye and detected on a Licor Odyssey scanner. The intensity of signal was quantitated and this data was used to generate dose response curves and EC50 calculations.

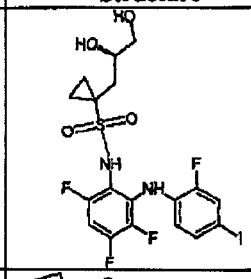
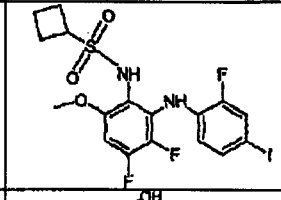
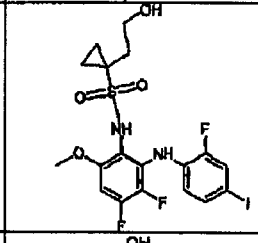
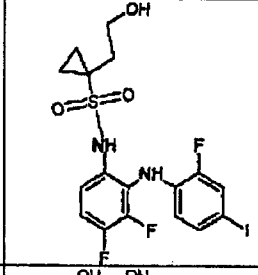
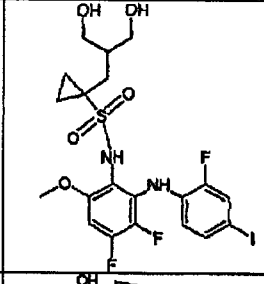
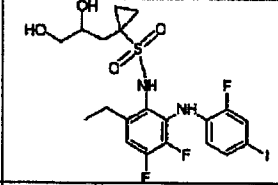
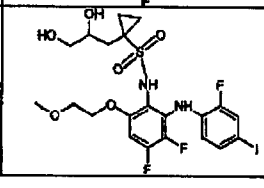
Legend: A, $EC_{50}$ = < 2.0nM; B, $EC_{50}$ = 2.0-15nM; C, $EC_{50}$ = 15nM-100nM;
D, $EC_{50}$ > 100nM, $IC_{50}$ < 20µM; F, $EC_{50}$ > 100nM, $IC_{50}$ > 20µM

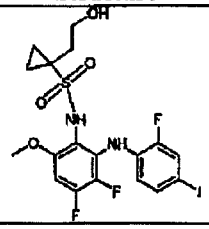
| Compound Number | Structure | Activity µM |
|---|---|---|
| 1000 |  | A |
| 1001 |  | A |
| 1002 |  | B |
| 1003 |  | C |

| Compound Number | Structure | Activity µM |
|---|---|---|
| 1004 |  | C |
| 1005 |  | C |
| 1006 |  | C |
| 1007 |  | C |

| Compound Number | Structure | Activity μM |
|---|---|---|
| 1008 |  | C |
| 1009 |  | C |
| 1010 |  | A |
| 1011 |  | C |
| 1012 |  | B |
| 1013 |  | B |
| 1014 |  | C |
| 1015 |  | D |
| 1016 |  | C |

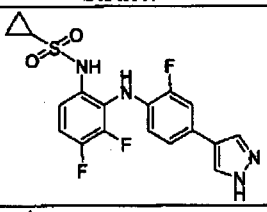
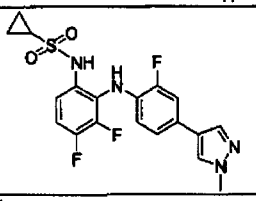
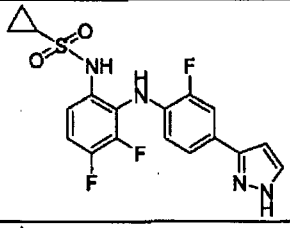
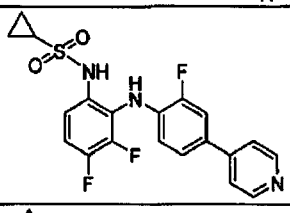
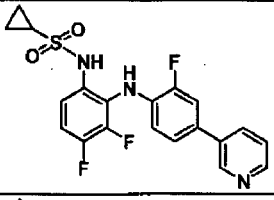
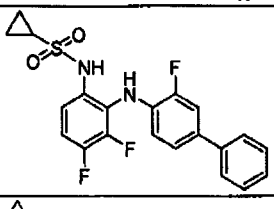
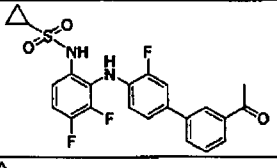
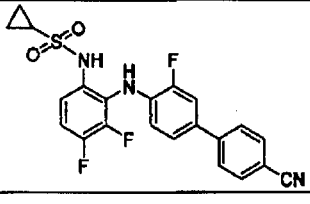
| Compound Number | Structure | Activity μM |
|---|---|---|
| 1017 |  | B |
| 1018 (Racemic) |  | A |
| 1019 (Racemic) |  | A |
| 1020 (Racemic) |  | A |
| 1021 (S isomer) Compound A |  | A |
| 1022 (R isomer) Compound B |  | B |
| 1023 (R isomer) |  | B |

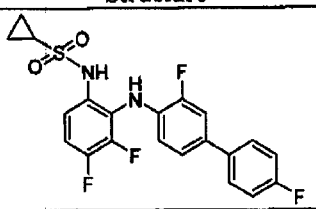
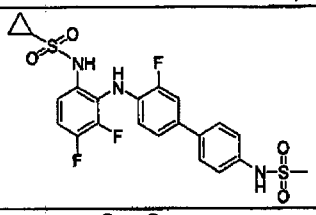
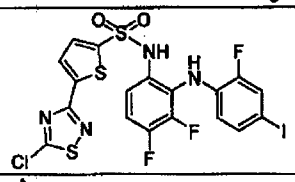
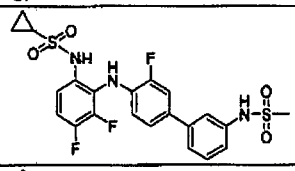
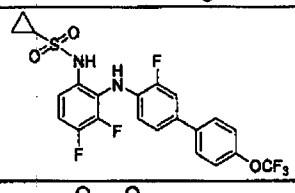
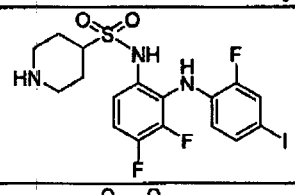
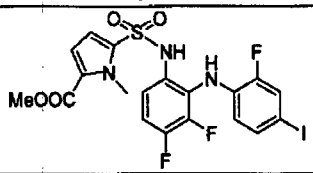
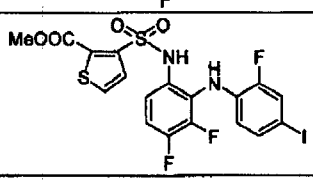
| Compound Number | Structure | Activity µM |
|---|---|---|
| 1024 (S isomer) |  | B |
| 1025 |  | B |
| 1026 |  | A |
| 1027 |  | A |
| 1028 |  | A |
| 1029 |  | C |
| 1030 |  | C |

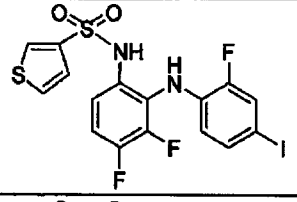
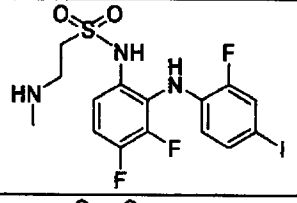
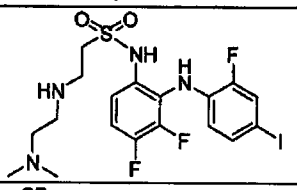
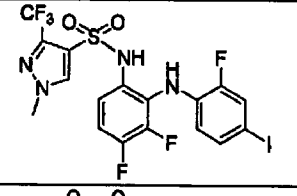
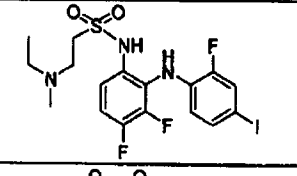
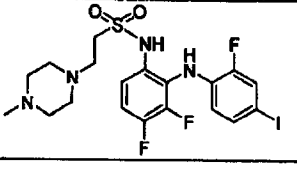
| Compound Number | Structure | Activity µM |
|---|---|---|
| 1031 |  | A |

210

Legend: A, $EC_{50}$ = < 2.0 nM; B, $EC_{50}$ = 2.0-15 nM; C, $EC_{50}$ = 15 nM-100 nM; D, $EC_{50}$ =100 nM – 200 nM; E, $EC_{50}$ > 200nM; ND = not yet determined

| CPD # | Structure | MDA pERK ELISA $EC_{50}$ |
|---|---|---|
| 0497618 |  | E |
| 0497620 |  | E |
| 0497654 |  | D |
| 0497688 |  | E |
| 0497689 |  | E |
| 0497692 |  | E |
| 0499266 |  | E |
| 0499267 |  | ND |

| CPD # | Structure | MDA pERK ELISA $EC_{50}$ |
|---|---|---|
| 0499268 |  | ND |
| 0499271 |  | E |
| 0530701 |  | D |
| 0530716 |  | ND |
| 0530717 |  | ND |
| 0561599 |  | C |
| 0561608 |  | C |
| 0620926 |  | E |

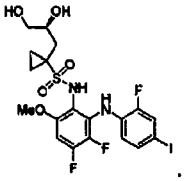
| CPD # | Structure | MDA pERK ELISA $EC_{50}$ |
|---|---|---|
| 0620927 |  | C |
| 0621002 |  | C |
| 0621016 |  | C |
| 0621026 |  | D |
| 0621029 |  | D |
| 0621030 |  | ND |

*In vivo* Biological Activity

Example 94

The compounds and compositions described herein are useful for the treatment or prophylaxis of one or more diseases including but not limited to cancer, inflammatory bowel disease (IBD), psoriasis and rheumatoid arthritis (RA). The compounds and compositions described herein are also useful for the once- or twice-daily oral treatment or prophylaxis of one or more diseases including but not limited to cancer, IBD, psoriasis and RA.

*In vivo* tests of the compound of the structure below (Compound A, prepared as described herein), are described in this example:



Human tumors were implanted in nu/nu mice. Compound A was administered orally for 14 days once tumors were approximately 100 $mm^3$ in size. Tumor growth inhibition (TGI) was determined after 14 days of treatment as the reduction in the size of tumors in treated groups versus vehicle controls. The time to endpoint (TTE) was calculated as the time for the tumor to reach the specified endpoint volume or the last day of the study, whichever came first. Treatment outcome was determined from percent tumor growth delay (%TGD), defined as the percent increase in median TTE of treated versus vehicle-treated control mice. Animals were also monitored for regression responses. Levels of pERK in tumors and brain were determined by Western blots and correlated with plasma levels of Compound A for the pharmacodynamic/pharmacokinetic study. A number of tumor models were evaluated with different doses and dosing regimens. Treatment with 25 or 50 mg/kg once daily (QD) showed statistically significant %TGD in A375 melanoma tumors, Colo205 colon cancer tumors, and A431 epidermoid tumors. Statistically significant TGI was observed for oral dosing at 25 mg/kg QD for these tumor models as well as in HT29 colon cancer tumors. The effect of different dosing regimens was evaluated in A375 xenografts. Although 100 mg/kg Compound A given orally once every two days showed statistically significant %TGD (91%), it was not as effective as QD treatments at 25 mg/kg (143% TGD) or 50 mg/kg (233% TGD). Twice daily (BID) dosing was also more effective than QD dosing as measured by %TGI. Dosing at 12.5 mg/kg BID resulted in 79.5% TGI compared to 51.7% for 25 mg/kg QD of Compound A. Dosing at 25 mg/kg BID resulted in 110.1% TGI compared to 69.9% TGI for 50 mg/kg QD. A pharmacodynamic/pharmacokinetic study in Colo205 xenografts show inhibition of pERK formation in tumors while minimal inhibition was observed in brain suggesting potent anti-tumor activity with limited CNS penetration.

Compound A is a potent inhibitor of MEK1/2 that suppresses tumor cell growth *in vitro* and *in vivo*. BRAF status determines sensitivity to growth inhibition by the compound in anchorage-dependent growth but not anchorage-independent growth or in xenografts. Maintaining adequate MEK inhibition throughout the dosing interval appears to be more important than peak levels due to the greater efficacy with more frequent dosing. Compound A has a favorable pk profile in humans, with the projected therapeutic dose, based on xenograft results, of 20-40mg/day in humans.

Example 94A

**Inhibition of Cancer Cell Growth ($GI_{50}$)**

Anchorage-dependent growth inhibition was measured using CellTiterGlo reagent after 48 hr treatment with Compound A of cells grown in 384-well plates. Anchorage- independent growth assays used MTS (methanethiosulfonate) reagent after 7 days treatment of cells grown in media containing 0.15% agarose or on non-binding plates (A431). Growth inhibition values ($GI_{50}$) are shown in the table below.

| Tumor Cell Line | BRAF | Anchorage-Dependent $GI_{50}$ | Anchorage-Independent $GI_{50}$ |
|---|---|---|---|

| | status | (nM ± sd) | (nM ± sd) |
|---|---|---|---|
| A375 Melanoma | V600E | 67 ± 12 | 68 ± 34 |
| Colo205 Colon | V600E | 74 ± 45 | 33 ± 16 |
| HT29 Colon | V600E | 70 ± 12 | Not determined |
| A431 Epidermoid | Normal | >10,000 | 65 ± 19 |

Example 94B

**Anti-Tumor Xenograft Activity**

Female nu/nu mice were implanted with A375 Melanoma, Colo205 Colon Tumor, A431 Epidermoid Tumor or HT-29 Colon Tumor cells, which were allowed to grow to 100-200 $mm^3$. Compound A or vehicle was administered orally (25mg/kg, 50mg/kg or 100mg/kg), once a day, for 14 days. Average tumor volumes were graphed for vehicle and treated groups and are shown in Fig. 1.

Example 94C

**Tumor Growth Inhibition (TGI) 25 mg/kg QD**

Tumor Growth Inhibition for the groups treated with 25 mg/kg Compound A were calculated for the indicated tumor xenografts. Tumor Growth Inhibition was measured at the end of once daily dosing for 14 days and calculated according to:

$$\%TGI = 100 \times 1 - \frac{(\text{treated tumor volume}_{final} - \text{tumor volume}_{initial})}{(\text{vehicle treated tumor volume}_{final} - \text{tumor volume}_{initial})}$$

The range for A375 and Colo205 represent values from 2 separate studies.

| Tumor Xenograft | % TGI | P value |
|---|---|---|
| A375 Melanoma | 52-72** | <0.001 |
| Colo205 Colon | 70-123** | <0.001 |
| HT29 Colon | 56 | <0.001 |
| A431 Epidermoid | 67 | <0.001 |

**Regressions noted during course of experiment

Example 94D

**$ED_{50}$ in Colo205 Xenografts**

Male nu/nu mice were implanted with Colo205 tumor cells. After 10 days animals were randomized by tumor size (range 126-256 $mm^3$) and treated with paclitaxel (IV, QODx5), vehicle or Compound A (PO, QDx14).

Pharmacokinetic parameters were obtained from dosing Balb/c mice with 25 mg/kg Compound A and extrapolating values for the lower dose groups and shown in the table below.

| Group | n | Treatment Regimen | | Initial Tumor Volume ($mm^3$) | Day 15 Tumor Volume ($mm^3$) | % TGI | $C_{max}$ (µg/mL) | $C_{min}$ (µg/mL) | AUC (µg-hr/mL) |
|---|---|---|---|---|---|---|---|---|---|
| | | Agent | mg/kg | | | | | | |
| 1 | 10 | Vehicle | - | 185±11.1 | 2093±174 | - | - | - | - |
| 2 | 10 | Paclitaxel | 30 | 184±9.8 | 113±9.6 | 104* | - | - | - |
| 3 | 10 | Compound A | 2.5 | 184±9.8 | 1187±127 | 47* | 0.99 | 0.003 | 5.5 |
| 4 | 10 | | 5 | 183.8±9.8 | 1175±104 | 48* | 1.97 | 0.006 | 11.0 |
| 5 | 10 | | 10 | 185.1±11.7 | 1045±160 | 55* | 3.94 | 0.012 | 22.0 |
| 6 | 10 | | 25 | 185.1±11.7 | 762±81 | 70* | 9.85 | 0.029 | 55.0 |

*P<0.001

Example 94E

**Tumor Growth Inhibition with A375 Xenografts**

A375 Xenograft mice were administered Compound A 50mg/kg QD, 25mg/kg BID, 50mg/kg QD and 12.5mg/kg BID. The %TGI was calculated and graphed and is shown in Fig. 2.

Example 94F

**Plasma Concentrations in Mice**

Female nu/nu mice were implanted with A375 tumor cells, which were allowed to grow to 100-200 $mm^3$. Compound A or vehicle was administered orally once a day (QD) or twice a day (BID) (50mg/kg QD, 25mg/kg BID, 50mg/kg QD and 12.5mg/kg BID). Tumor Growth Inhibition was measured at the end of once daily dosing for 14 days and calculated according to:

$$\%TGI = 100 \times 1 - \frac{(\text{treated tumor volume}_{final} - \text{tumor volume}_{initial})}{(\text{vehicle treated tumor volume}_{final} - \text{tumor volume}_{initial})}$$

| | | | | |
|---|---|---|---|---|
| AUC (µg·hr/ml) | 132.5 | 117.0 | 66.5 | 78.0 |
| $C_{max}$ (µg/ml) | 23.8 | 10.2 | 11.9 | 7.8 |
| $C_{min}$ (µg/ml) | 0.06 | 1.24 | 0.03 | 0.49 |
| $C_{min}$ Free Fraction (ng/ml) | 0.117 | 2.48 | 0.059 | 0.986 |

Statistical Significance = Logrank test

Example 94G

**Mouse Xenograft Tumors and Inhibition of Brain MEK Activity**

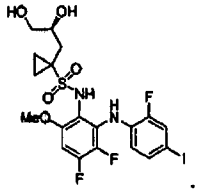
Female nu/nu mice implanted with Colo205 tumor cells were given a single dose of vehicle or Compound A at 2.5, 5, 10, or 25 mg/kg. Compound levels were determined in plasma samples and pERK levels were determined in tumor and brain samples collected at 2, 6, 12, and 24 hr post-dose. The pERK levels from Western blots were quantified using the LI-COR Odyssey, normalized to total ERK levels and compared to vehicle-treated levels to determine % MEK inhibition. MEK inhibition in tumor or brain for each mouse was graphed with the corresponding plasma concentration of Compound A in the animal. Non-linear regression gave an $EC_{50}$ of 73nM for MEK inhibition in tumors. The brain $EC_{50}$ was >5000 nM.

A graph of plasma concentration (log nM) against pERK % inhibition is shown in Fig. 3.

**Preparation of capsules**

Example 95A

Blue size 1 hard gelatin capsules were prepared containing a dry powder blend composition in 1 mg and 10 mg strengths of Compound A (see table shown in example 93 above) of structure:



Compound A was prepared as described herein, and then micronized using a fluid energy mill (Spiral Jet Mill, electronically grounded, with a grinding chamber diameter of 50mm; a 50°. 4 x 0.8mm nozzle ring; an injector nozzle diameter of 0.8mm and injector nozzle distance of 3mm).. Compound A and a portion of the microcrystalline cellulose were mixed and screened through a #20 mesh screen and added to a diffusion-tumble blender (V-blender). The remaining Microcrystalline Cellulose was screened through a #20 mesh screen, added to the materials in the blender and blended. The Croscarmellose Sodium and Sodium Lauryl Sulfate were screened through a #20 mesh screen, added to the materials in the blender and blended. The powder blend was passed through a rotating impeller mill (Quadro CoMil) and added back to the blender and blending continued. The Magnesium Stearate was screened through a #20 mesh screen and blended with the milled powder blend. The powder blend was filled into size 1 capsules. The 10 mg capsules were banded for identification.

The composition of the capsules is shown in the table below:

| Component | 1 mg capsule | 10 mg capsule |
|---|---|---|

| | mg/unit | % | mg/unit | % |
|---|---|---|---|---|
| Compound A | 1.0 | 0.4 | 10.0 | 4.2 |
| Microcrystalline Cellulose, NF (Avicel PH302) | 222.2 | 92.6 | 213.2 | 88.8 |
| Croscarmellose Sodium, NF (Ac-Di-Sol) | 12.0 | 5.0 | 12.0 | 5.0 |
| Sodium Lauryl Sulfate, NF | 2.4 | 1.0 | 2.4 | 1.0 |
| Magnesium Stearate, NF | 2.4 | 1.0 | 2.4 | 1.0 |
| Total[a] | 240.0 | 100.0 | 240.0 | 100.0 |
| Blue Size 1 Hard Gelatin Capsule Shell | 1 | | 1 | |

[a]Target fill weight adjusted based on actual potency of blend.

Typical batch formula for a 10,000 batch of 1 mg capsules were as follows:

| Batch Formula Components | Quantity per batch (g) (for 10,000 units) |
|---|---|
| Compound A | 10.0 |
| Microcrystalline Cellulose, NF (Avicel PH302) | 2222 |
| Croscarmellose Sodium, NF (Ac-Di-Sol) | 120.0 |
| Sodium Lauryl Sulfate, NF | 24.0 |
| Magnesium Stearate, NF | 24.0 |
| Total Fill Weight[a] | 2400 |
| Blue Size 1 Hard Gelatin Capsule Shell | 10,000 |

[a]Target fill weight adjusted based on actual potency of blend.

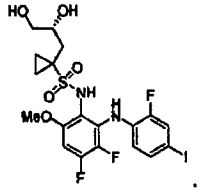
Typical batch formula for a 10,000 batch of 10 mg capsules were as follows:

| Batch Formula Components | Quantity per batch (g) (for 10,000 units) |
|---|---|
| Compound A | 100.0 |
| Microcrystalline Cellulose, NF (Avicel PH302) | 2132 |
| Croscarmellose Sodium, NF (Ac-Di-Sol) | 120.0 |
| Sodium Lauryl Sulfate, NF | 24.0 |
| Magnesium Stearate, NF | 24.0 |
| Total Fill Weight[a] | 2400 |
| Blue Size 1 Hard Gelatin Capsule Shell[b] | 10,000 |

[a]Target fill weight adjusted based on actual potency of blend.

Example 95B

Blue size 1 hard gelatin capsules are prepared containing a dry powder blend composition in 1 mg and 10 mg strengths of Compound B (see table shown in example 93 above) of structure:



Compound B is prepared as described herein, and micronized using a fluid energy mill (Spiral Jet Mill, electronically grounded, with a grinding chamber diameter of 50mm; a 50°. 4 x 0.8mm nozzle ring; an injector nozzle diameter of 0.8mm and injector nozzle distance of 3mm).. Compound B and a portion of the microcrystalline cellulose are mixed, screened through a #20 mesh screen and added to a diffusion-tumble blender (V-blender). The remaining Microcrystalline Cellulose is screened through a #20 mesh screen, added to the materials in the blender and blended. The Croscarmellose Sodium and Sodium Lauryl Sulfate are screened through a #20 mesh screen, added to the materials in the blender and blended. The powder blend is passed through a rotating impeller mill (Quadro CoMil), added back to the blender and blending continued. The Magnesium Stearate is screened through a #20 mesh screen and blended with the milled powder blend. The powder blend is filled into size 1 capsules. The 10 mg capsules are banded for identification.

The composition of the capsules is shown in the table below:

| Component | 1 mg capsule | 10 mg capsule |
|---|---|---|

| | mg/unit | % | mg/unit | % |
|---|---|---|---|---|
| Compound B | 1.0 | 0.4 | 10.0 | 4.2 |
| Microcrystalline Cellulose, NF (Avicel PH302) | 222.2 | 92.6 | 213.2 | 88.8 |
| Croscarmellose Sodium, NF (Ac-Di-Sol) | 12.0 | 5.0 | 12.0 | 5.0 |
| Sodium Lauryl Sulfate, NF | 2.4 | 1.0 | 2.4 | 1.0 |
| Magnesium Stearate, NF | 2.4 | 1.0 | 2.4 | 1.0 |
| Total[a] | 240.0 | 100.0 | 240.0 | 100.0 |
| Blue Size 1 Hard Gelatin Capsule Shell | 1 | | 1 | |

***In vivo* Activity in Humans**

Example 96

Administration of the capsules described in example 95A in Human Cancer Patients

Human cancer patients were administered a single dose of the 1 mg or 10 mg capsule composition described above in example 95A. For a 2mg dose, patients were given 2 x 1mg capsules; for a 4mg dose, patients were given 4 x 1mg capsules; for a 6mg dose, patients were given 6 x 1mg capsules; for a 10mg dose, patients were given 1 x 10mg capsule; for a 20mg dose, patients were given 2 x 10mg capsules.

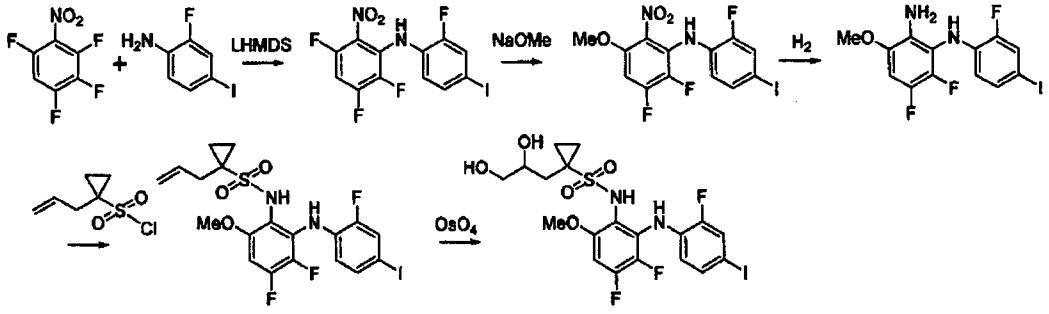
The concentration-time profiles were monitored and are shown in Fig. 4 and in the table below:

| Dose (mg) | Day | $T_{max}$ (hr) | $C_{max}$ (ng/mL) | $C_{12hr}$ (ng/mL) | $AUC_{0-12hr}$ (ng·hr/mL) | AUCτ (ng·hr/mL) |
|---|---|---|---|---|---|---|
| 2 | 1 | 2.0 | 0.111 | 0.0378 | 0.700 | NA |
| | 35 | 2.0 | 0.202 | 0.0756 | NA | 2.07 |
| 4 | 1 | 1.5 | 0.292 | 0.134 | 2.26 | NA |
| | 35 | 1.0 | 0.544 | 0.310 | NA | 5.12 |
| 10 | 35 | NA | 1.57 | 1.01 | NA | 14.3 |
| 20 | 35 | NA | 3.28 | 2.19 | NA | 29.5 |

**Crystalline Polymorph Forms**

Example 97: Preparation of N-(3.4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide

N-(3.4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)-1-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide was prepared according to previously described procedures (see published international patent application WO 2007/014011) and as outlined below.




*Step A*: 2-Fluoro-N-(2,3,5-trifluoro-6-nitrophenyl)-4-iodobenzenamine

A solution of 1.0 M lithium hexa methyl disilazide ($LiN(SiMe_3)_2$) "LHMDS" (15.37mL, 15.37mmol) was slowly added to a stirred solution of 2-fluoro-4-iodoaniline (3.64g, 15.37mmol) in dry THF (100 mL) under nitrogen at -78°C and stirring continued at -78°C for another hour. 2,3,4,6-Tetrafluoronitrobenzene was added, and the reaction mixture was allowed to warm to room temperature and stirring continued for another 16 hours. Ethyl acetate (200 mL) was added and the organic phase was washed with water, dried over sodium sulfate and further purified by column chromatography

to provide the product as a yellow solid (3.75g, 59.24%). M-H$^+$: 410.9. $^1$H NMR (DMSO, 300 MHz): 6.85 (t, 1H); 7.38 (d, 1H); 7.62 (m, 2H); 8.78 (s, 1H).

*Step B*: 2-Fluoro-N-(2,3-difluoro-5-methoxy-6-nitrophenyl)-4-iodobenzenamine

A stirred solution of (2-fluoro-4-iodo-phenyl)-(2,3,5-trifluoro-6-nitro-phenyl)-amine (1.23g, 3 mmol) in dry THF (25 ml) under nitrogen was cooled to -78°C and a solution of 25% sodium methoxide (0.68 ml, 0.3 mmol) was added slowly. The reaction mixture was allowed to warm to room temperature and stirring continued for another 16 hours. TLC indicated incomplete reaction. Ethyl acetate (100 mL) was added to the reaction mixture and the organic layer was washed with water, dried over sodium sulfate and further purified by column chromatography to provide the desired compound as a yellow solid (0.6g, 47.6%). *m/z* = 424 [M+H]$^+$.

*Step C*: 5,6-Difluoro-N$^1$-(2-fluoro-4-iodophenyl)-3-methoxybenzene-1,2-diamine

Ammonium chloride (1.18g, 20.16 mmol) and iron powder (1.15g, 21.44 mmol) were added to a stirred solution of (2,3-difluoro-5-methoxy-6-nitro-phenyl)-(2-fluoro-4-iodo-phenyl)-amine (0.57g, 1.34 mmol) in ethanol (20 mL). The mixture was stirred at reflux for 16 hours, cooled to room temperature, filtered over celite and the filtrate concentrated to dryness. The resulting residue was taken into ethyl acetate, washed with water, dried over sodium sulfate and further purified by crystallization from ethanol to provide the product as an off-white solid (0.47g, 90.3%). M-H$^+$: 393.2. $^1$H NMR (DMSO, 300 MHz): 3.76 (s, 3H); 6.1 (t, 1H); 6.8 - 7.0 (m, 1H); 7.2 (d, 1H); 7.35 (s, 1H); 7.42 (d, 1H).

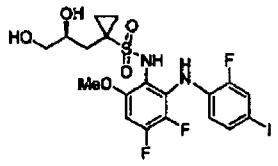
*Step D*: 1-Allyl-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl) cyclopropane-1-sulfonamide

To a stirred solution of 5,6-difluoro-N$^1$-(2-fluoro-4-iodophenyl)-3-methoxybenzene-1,2-diamine (1 eq) in anhydrous pyridine (5ml/mmole) was added 1-allyl-cyclopropanesulfonyl chloride (1 - 5 eq). The reaction mixture was stirred at 40°C for 48 hours. The reaction mixture was partitioned with water and ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica to obtain the title product. $^1$H NMR ($CDCl_3$, 300 MHz): δ 7.417 (dd, 1H), 7.309(s, 1H), 7.25 (m, 1H), 6.89 (m, 1H), 6.52(m, 1H), 6.427 (m, 1H), 6.03 (s, lH), 5.668 (m, 1H), 5.11 (t, 1H), 3.9 (s, 3H), 2.75 (d, 2H), 1.21 (m, 2H), 0.767 (m, 2H).

*Step E*: N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-l-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide

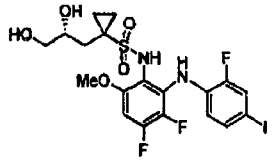
l-Allyl-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl) cyclopropane-l-sulfonamide (97mg, 0.18 mmol) and 4-methylmorpholine N-oxide (21mg, 0.18 mmol) were dissolved in THF (8 mL). Osmium tetroxide was added at room temperature (0.018 mmol, 0.13 mL, 4% in $H_2O$) and the reaction mixture was stirred at room temperature for 16 hours. Ethyl acetate was added, and the organic phase was washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified over silica gel chromatography (eluants: EtOAc/ MeOH) to obtain the titled product (0.80 g, 78 %). $^1$H NMR ($CDCl_3$, 300 MHz): δ 7.38 (dd, J = 1.7 & 10.3 Hz,1H), 7.26 (m, 1H), 7.14 (s, 1H), 6.87 (s, 1H), 6.53 (dd, J = 6.8 & 11.4 Hz, 1H), 6.43 (m, 1H), 4.06 (m, 1H), 3.89 (s, 3H), 3.63 (dd, J = 3.7 & 11.1 Hz, 1H), 3.49 (dd, J = 6.4 & 11.1 Hz, 1H), 2.3 (dd, J = 9.7 & 16.1 Hz, 1H), 1.77 (dd, J = 1.9 & 16.0 Hz, 1H), 1.37 (m, 1H), 1.25 (m, 1H), 1.21 (m, 2H), 0.86 (m, 2H); *m/z* = 571 [M-1]$^-$.

Example 98: Preparation of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-l-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide



The pure S isomer was obtained by chiral HPLC separation of the racemic mixture. $^1$H NMR ($CDCl_3$, 300 MHz): δ 7.38 (dd, J = 1.7 & 10.3 Hz,1H), 7.26 (m, 1H), 7.14 (s, 1H), 6.87 (s, 1H), 6.53 (dd, J = 6.8 & 11.4 Hz, 1H), 6.43 (m, 1H), 4.06 (m, 1H), 3.89 (s, 3H), 3.63 (dd, J = 3.7 & 11.1 Hz, 1H), 3.49 (dd, J = 6.4 & 11.1 Hz, 1H), 2.3 (dd, J = 9.7 & 16.1 Hz, 1H), 1.77 (dd, J = 1.9 & 16.0 Hz, 1H), 1.37 (m, 1H), 1.25 (m, 1H), 1.21 (m, 2H), 0.86 (m, 2H); *m/z* = 571 $[M-1]^-$.

Example 99: Preparation of N-(R)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-l-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide



The pure R isomer was obtained by chiral HPLC separation of the racemic mixture. $^1$H NMR ($CDCl_3$, 300 MHz): δ 7.38 (dd, J = 1.7 & 10.3 Hz,1H), 7.26 (m, 1H), 7.14 (s, 1H), 6.87 (s, 1H), 6.53 (dd, J = 6.8 & 11.4 Hz, 1H), 6.43 (m, 1H), 4.06 (m, 1H), 3.89 (s, 3H), 3.63 (dd, J = 3.7 & 11.1 Hz, 1H), 3.49 (dd, J = 6.4 & 11.1 Hz, 1H), 2.3 (dd, J = 9.7 & 16.1 Hz, 1H), 1.77 (dd, J = 1.9 & 16.0 Hz, 1H), 1.37 (m, 1H), 1.25 (m, 1H), 1.21 (m, 2H), 0.86 (m, 2H); *m/z* = 571 $[M-1]^-$.

Example 100: Preparation of crystalline polymorph Form A of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-l-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide

*Preparation i)* N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-l-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide (216.10g) was charged to a 4L Erlenmeyer flask equipped with a large magnetic stir bar and a magnetic stirrer/hot plate. Ethyl Acetate (ca. 600 mL, purchased from Fisher) was added. Heating and stirring were initiated to form a brown suspension. The mixture was brought to a low reflux and additional ethyl acetate (ca. 200 mL) was added to effect complete dissolution giving a dark brown solution. Heptane (purchased from Acros) was slowly added portionwise to the refluxing solution at a rate that all precipitates that formed on each addition were quickly dissolved and reflux maintained. Upon the addition of 2 L of heptanes to the solution the solids formed dissolved very slowly at reflux. Heating was stopped and the crystallization mixture allowed to equilibrate to room temperature with stirring over 16 h. A thick layer of crystalline material developed around the surface of the glass over the aging period. The resulting suspension was equilibrated in an ice/water bath with stirring. The suspension was filtered on a 25 cm Buchner funnel dressed with Whatman #1 filter media. The collected crystals were washed with heptanes (1 L) and allowed to air dry under vacuum. The crystals were further dried at 40°C/ <1 torr over 20 h to yield the product as a pink crystalline solid (160.99 g, 77.2%).

*Preparation ii)* N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-l-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide (13.2g) and ethyl acetate (30mL) were charged to an Erlenmeyer flask equipped with a large magnetic stir bar and a magnetic stirrer/hot plate. Stirring and heating to low reflux were initiated to effect complete dissolution giving a dark brown solution. Heptanes were slowly added portionwise to the refluxing solution at a rate that all precipitates that formed on each addition were quickly dissolved and reflux maintained, until the addition of heptanes to the solution caused the solids formed to dissolve very slowly at reflux (~90mL heptanes). Heating was stopped and the crystallization mixture allowed to equilibrate to room temperature with stirring over 16 h. A thick layer of crystalline

material developed around the surface of the glass over the aging period. The resulting suspension was equilibrated in an ice/water bath with stirring. The suspension was filtered on Buchner funnel dressed with Whatman #1 filter media. The collected crystals were washed with heptanes, and allowed to air dry under vacuum. The crystals were further dried at 40°C/ <1 torr over 20 h to yield the product as a pink crystalline solid.

*Preparation iii)* N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide (44.8g) and ethyl acetate (750mL) were charged to an Erlenmeyer flask equipped with a large magnetic stir bar and a magnetic stirrer/hot plate. Stirring and heating to low reflux were initiated to effect complete dissolution giving a dark brown solution. Hexanes were slowly added portionwise to the refluxing solution at a rate that all precipitates that formed on each addition were quickly dissolved and reflux maintained, until the addition of hexanes to the solution caused the solids formed to dissolve very slowly at reflux (~2L hexanes). Heating was stopped and the crystallization mixture allowed to equilibrate to room temperature with stirring over 16 h. A thick layer of crystalline material developed around the surface of the glass over the aging period. The resulting suspension was equilibrated in an ice/water bath with stirring. The suspension was filtered on Buchner funnel dressed with Whatman #1 filter media. The collected crystals were washed, and allowed to air dry under vacuum. The crystals were further dried at 40°C/ <1 torr over 20 h to yield the product as a pink crystalline solid.

Example 101: Preparation of crystalline polymorph of N-(R)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide

N-(R)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide (216.10g) is charged to a 4L Erlenmeyer flask equipped with a large magnetic stir bar and a magnetic stirrer/hot plate. Ethyl Acetate (ca. 600 mL) is added. Heating and stirring are initiated to form a brown suspension. The mixture is brought to a low reflux and additional ethyl acetate (ca. 200 mL) is added to effect complete dissolution giving a dark brown solution. Heptane is charged to the solution slowly portionwise to the refluxing solution at a rate that all precipitates that form on each addition are quickly dissolved and reflux is maintained. Upon the addition of 2 L of heptanes to the solution the solids formed dissolve very slowly at reflux. Heating is stopped and the crystallization mixture is allowed to equilibrate to room temperature with stirring over 16 h. A thick layer of crystalline material develops around the surface of the glass over the aging period. The resulting suspension is equilibrated in an ice/water bath with stirring. The suspension is filtered on a 25 cm Buchner funnel dressed with Whatman #1 filter media. The collected crystals are washed with heptanes (1 L) and allowed to air dry under vacuum. The crystals are further dried at 40°C/ <1 torr over 20 h.

Example 102: Generation of IC50 Data

Materials and preparation of reagents: Human GST-MEK1 and the constitutively active allele GST-MEK1$^{CA}$ (harboring the mutations Ser218Asp and Ser222Asp) were subcloned into the yeast expression vector pGEM4Z (Promega, Madison, WI) from the wild type human MEK1 cDNA. GST-MEK1$^{CA}$ was expressed in *Escherichia coli* and partially purified using Glutathione Sepharose 4B affinity resin (Amersham Pharmacia Biotech, Piscataway, NJ). The ERK2 allele was subcloned from MAPK2/Erk2 cDNA (wild type) in pUSEamp (Upstate Biotechnology, Inc., Waltham, MA) into the vector pET21a (Novagen, Madison, WI) resulting in an N-terminal histidine-tagged mouse ERK2 allele. ERK2 was expressed and purified to homogeneity [Zhang, 1993 #33]. Myelin basic protein (MBP) was purchased from Gibco BRL (Rockville, MD). EasyTides adenosine 5'-triphosphate (ATP) ([$\gamma$-$^{33}$P]) (NEN Perkin Elmer, Wellesley, MA) was the source of radiolabel for all kinase reactions. Activated Raf-1 (truncated) and activated MAPKinase 2/ERK2 were purchased from Upstate, Inc. (Lake Placid, NY). 4-20% Criterion Precast gels were purchased from Bio-Rad (Hercules, CA).

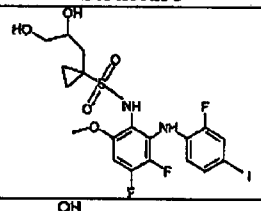
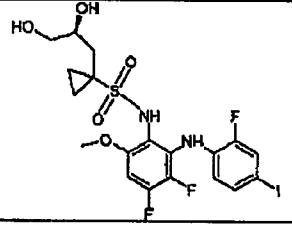
Determination of enzymatic activity: Compounds were diluted from dimethylsulfoxide (DMSO) stocks into 1xHMNDE (20 mM HEPES pH 7.2, 1 mM $MgCl_2$, 100 mM NaCl, 1.25 mM DTT, 0.2 mM EDTA). A typical 25-microliter assay contained 0.002 nanomoles $MEK1^{CA}$, 0.02 nanomoles ERK2, 0.25 nanomoles MBP, 0.25 nanomoles unlabeled ATP, and 0.1 μCi [$\gamma^{33}$P] ATP. The screening assay essentially comprised four additions. Five μl of diluted compound were dispensed to 96-well assay plates. Ten μl of 2.5x enzyme cocktail ($MEK1^{CA}$ and ERK2 only) were then added to each well followed by a pre-incubation for 30 minutes at ambient temperature. Ten μl of 2.5x substrate cocktail (labeled and unlabeled ATP plus MBP) were then added, followed by incubation for 60 minutes at ambient temperature. Finally, 100 μl of 10% trichloroacetic acid (TCA) were added and incubated for 30 minutes at room temperature to halt the reaction and precipitate radiolabeled protein products. Reaction products were harvested on glass fiber 96 well filter plates prewetted with water and 1% pyrophosphate. The filter plate was then washed 5 times with water. Water was displaced by absolute ethanol and the plate was allowed to air dry for 30 minutes at room temperature. A back seal was applied manually and 40 μl of scintillation cocktail were dispensed to each well. A top seal was applied and the plate was counted in the TopCount for two seconds per well. For certain experiments a truncated version of MEK that requires activation by Raf kinase were used.

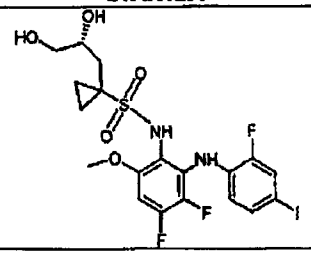
Example 103: Generation of EC50 Data

Effects of compounds in the cell were determined by Western blotting for phosphorylated ERK. MDA-MB-231 breast cancer cells were plated in a 48 well plate at 20,000 cells per well and grown in a 37° humidified $CO_2$ incubator. The following day, the growth media (DMEM + 10% fetal bovine serum) was removed and replaced with starve media (DMEM + 0.1% fetal bovine serum). Cells were incubated in the starve media for sixteen hours and then treated with a range of compound concentrations for thirty minutes. After incubation with compound, cells were stimulated with 100ng/ml EGF for five minutes. The cells were then lysed and analyzed by Western blot using a monoclonal antibody raised to phosphorylated ERK. The signal was amplified using a secondary antibody conjugated to a near -IR dye and detected on a Licor Odyssey scanner. The intensity of signal was quantitated and this data was used to generate dose response curves and EC50 calculations.

Example 104: Activity data of compounds

The compounds described in examples 1, 2 and 3 were tested in the assays described above. The results are summarized in the table below (A, $EC_{50}$ = < 2.0nM; B, $EC_{50}$ = 2.0-15nM):

| Compound Number | Structure | Activity |
|---|---|---|
| Eg. 97 (Racemic) |  | A |
| Eg. 98 (S isomer) |  | A |

| Compound Number | Structure | Activity |
|---|---|---|
| Eg. 99 (R isomer) |  | B |

Example 105: XRPD Data

XPRD was performed on a Inel XRG-3000 diffractometer, equipped with a curved position-sensitive detector with a 2θ range of 120°. Real time data was collected using Cu Kα radiation at a resolution of 0.03 °2θ. The tube voltage and amperage were set to 40kV and 30mA, respectively. Patterns are displayed from 2.5 to 40 °2θ to facilitate direct pattern comparisons. Samples of (S)-N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-l-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide (synthesized as described herein) were prepared for analysis by packing them into thin-walled glass capillaries. Each capillary was moved onto a goniometer head that is motorized to permit spinning of the capillary during data acquisition. The samples were analyzed for 5 minutes. Instrument calibration was preformed daily using a silicon reference standard. FIG. **5** is a graph of a powder x-ray diffraction (PXRD) pattern of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide Form A. FIG. **7** is a graph of the powder x-ray diffraction (PXRD) patterns of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide Form A (top) and Amorphous (bottom).

Example 106: Differential Scanning Calorimetry (DSC)

Analyses were carried out on a TA Instruments differential scanning calorimeter Q1000. The instrument was calibrated using indium as the reference material. The sample was placed into a standard aluminum DSC pan with a non-crimped lid configuration, and the weight accurately recorded. To determine the glass transition temperature ($T_g$) of amorphous material, the sample cell was cycled several times between -40°C and 140°C. The final temperature was ramped to 150°C. The $T_g$ is reported from the inflection point of the last cycle transition. FIG. **6** is a graph of a modulated DSC thermogram of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide (Form A). The graph plots the normalized heat flow in Watts/gram (W/g) versus the measured sample temperature in °C.

Example 107: Dynamic Vapor Sorption/Desorption (DVS)

Moisture sorption/desorption data were collected on a VTI SGA-100 Vapor Sorption Analyzer. Sorption and desorption data were collected over a range of 5% to 95% relative humidity (RH) at 10% RH intervals under a nitrogen purge. Samples were not dried prior to analysis. Equilibrium criteria used for analysis were less than 0.0100% weight change in 5 minutes, with a maximum equilibration time of 3 hours if the weight criterion was not met. Data were not corrected for the initial moisture content of the samples. Sodium chloride and polyvinypyrrolidine were used as calibration standards. FIG. **8** shows a DVS isotherm of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide (Form A). The material exhibits a negligible weight change during the experiment.

Example 108: Thermogravimetry (TG)

Analyses were carried out on a TA Instrument 2950 thermogravimetric analyzer. The calibration standards were nickel and Alumel™. Each sample was placed in an aluminum sample pan and inserted into the TG furnace. Samples were equilibrated at 25°C, and then heated under a stream of nitrogen at a heating rate of 10°C/min, up to a final temperature of 350°C. FIG. 9 shows a TG thermogram of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide (Form A) demonstrating negligible weight loss up to 140°C, indicating polymorph, form A is unsolvated.

Example 109: In Vitro Cancer Screen

The human tumor cell lines were grown in RPMI 1640 medium containing 5% fetal bovine serum and 2 mM L-glutamine. Cells are inoculated into 96 well microtiter plates in 100 µL at plating densities ranging from 5,000 to 40,000 cells/well depending on the doubling time of individual cell lines. After cell inoculation, the microtiter plates are incubated at 37° C, 5 % $CO_2$, 95 % air and 100 % relative humidity for 24 h prior to addition of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide.

After 24 h, two plates of each cell line were fixed in situ with TCA, to represent a measurement of the cell population for each cell line at the time of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide addition (Tz). N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide was solubilized in dimethyl sulfoxide at 400-fold the desired final maximum test concentration and stored frozen prior to use. At the time of addition, an aliquot of frozen concentrate is thawed and diluted to twice the desired final maximum test concentration with complete medium containing 50 µg/ml gentamicin. Additional four, 10-fold or ½ log serial dilutions are made to provide a total of five concentrations plus control. Aliquots of 100 µl of these different dilutions are added to the appropriate microtiter wells already containing 100 µl of medium, resulting in the required final concentrations.

Following addition of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide, the plates were incubated for an additional 48 h at 37°C, 5 % $CO_2$, 95 % air, and 100 % relative humidity. For adherent cells, the assay is terminated by the addition of cold TCA. Cells are fixed in situ by the gentle addition of 50 µl of cold 50 % (w/v) TCA (final concentration, 10 % TCA) and incubated for 60 minutes at 4°C. The supernatant is discarded, and the plates are washed five times with tap water and air dried. Sulforhodamine B (SRB) solution (100 µl) at 0.4 % (w/v) in 1 % acetic acid is added to each well, and plates are incubated for 10 minutes at room temperature. After staining, unbound dye is removed by washing five times with 1 % acetic acid and the plates are air dried. Bound stain is subsequently solubilized with 10 mM trizma base, and the absorbance is read on an automated plate reader at a wavelength of 515 nm. For suspension cells, the methodology is the same except that the assay is terminated by fixing settled cells at the bottom of the wells by gently adding 50 µl of 80 % TCA (final concentration, 16 % TCA). Using the seven absorbance measurements [time zero, (Tz), control growth, (C), and test growth in the presence of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide at the five concentration levels (Ti)], the percentage growth was calculated at each of the drug concentrations levels. Percentage growth inhibition is calculated as:

$$\text{Percentage growth inhibition (concentrations for which } Ti \geq Tz) = \frac{Ti - Tz}{C - Tz} \times 100$$

$$\text{Percentage growth inhibition (concentrations for which } Ti < Tz) = \frac{Ti - Tz}{Tz} \times 100$$

Three dose response parameters were calculated. Growth inhibition of 50 % (GI50) was calculated from [(Ti-Tz)/(C-Tz)] x 100 = 50, which is the concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation. The N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-

methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide concentration resulting in total growth inhibition (TGI) was calculated from Ti = Tz. The LC50 (concentration of drug resulting in a 50% reduction in the measured protein at the end of the drug treatment as compared to that at the beginning) indicating a net loss of cells following treatment is calculated from [(Ti-Tz)/Tz] x 100 = -50. Values were calculated for each of these three parameters if the level of activity was reached; however, if the effect was not reached or wasexceeded, the value for that parameter is expressed as greater or less than the maximum or minimum concentration tested.

Panels corresponding to Leukemia, Non-Small Cell Lung Cancer, Colon Cancer, CNS Cancer, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer, for the cell lines indicated were examined and the results are shown below.

| Panel | Cell Line | GI50 (μM) | LC50 (μM) | TGI (μM) |
|---|---|---|---|---|
| Leukemia | CCRF-CEM | 17.378 | 100.000 | 60.256 |
| Leukemia | HL-60(TB) | 0.010 | 100.000 | 100.000 |
| Leukemia | K-562 | 6.607 | 100.000 | 100.000 |
| Leukemia | MOLT-4 | 10.965 | 100.000 | 69.183 |
| Leukemia | RPMI-8226 | 26.915 | 100.000 | 100.000 |
| Leukemia | SR | 38.019 | 100.000 | 100.000 |
| Non-Small Cell Lung Cancer | A549/ATCC | 0.589 | 100.000 | 64.565 |
| Non-Small Cell Lung Cancer | EKVX | 0.214 | 61.660 | 13.804 |
| Non-Small Cell Lung Cancer | HOP-62 | 0.069 | 42.658 | 12.589 |
| Non-Small Cell Lung Cancer | HOP-92 | 0.047 | 58.884 | 0.324 |
| Non-Small Cell Lung Cancer | NCI-H226 | 3.311 | 74.131 | 24.547 |
| Non-Small Cell Lung Cancer | NCI-H23 | 0.056 | 74.131 | 2.884 |
| Non-Small Cell Lung Cancer | NCI-H322M | 0.162 | 46.774 | 15.488 |
| Non-Small Cell Lung Cancer | NCI-H460 | 3.631 | 52.481 | 19.498 |
| Non-Small Cell Lung Cancer | NCI-H522 | 5.248 | 100.000 | 29.512 |
| Colon Cancer | HCC-2998 | 0.010 | 0.457 | 0.035 |
| Colon Cancer | HCT-116 | 0.195 | 67.608 | 12.589 |
| Colon Cancer | HCT-15 | 0.603 | 60.256 | 16.982 |
| Colon Cancer | HT29 | 0.026 | 29.512 | 3.090 |
| Colon Cancer | KM12 | 0.229 | 48.978 | 13.490 |
| Colon Cancer | SW-620 | 0.039 | 66.069 | 12.589 |
| CNS Cancer | SF-268 | 2.570 | 100.000 | 25.704 |
| CNS Cancer | SF-295 | 9.333 | 53.703 | 23.442 |
| CNS Cancer | SF-539 | 1.514 | 60.256 | 20.417 |
| CNS Cancer | SNB-19 | 0.251 | 75.858 | 24.547 |
| CNS Cancer | SNB-75 | 0.302 | 34.674 | 4.467 |
| CNS Cancer | U251 | 0.891 | 44.668 | 17.378 |
| Melanoma | LOX IMVI | 0.195 | 38.905 | 10.715 |
| Melanoma | MALME-3M | 0.010 | 19.953 | 0.014 |
| Melanoma | M14 | 0.015 | 29.512 | 0.166 |
| Melanoma | SK-MEL-28 | 0.028 | 22.387 | 0.214 |
| Melanoma | SK-MEL-5 | 0.062 | 38.905 | 13.804 |
| Melanoma | UACC-257 | 0.020 | 66.069 | 10.233 |
| Melanoma | UACC-62 | 0.014 | 20.893 | 0.170 |

| Panel | Cell Line | GI50 (μM) | LC50 (μM) | TGI (μM) |
|---|---|---|---|---|
| Ovarian Cancer | IGROV1 | 0.018 | 19.055 | 0.295 |
| Ovarian Cancer | OVCAR-3 | 2.512 | 48.978 | 17.783 |
| Ovarian Cancer | OVCAR-4 | 0.562 | 72.444 | 16.218 |
| Ovarian Cancer | OVCAR-5 | 0.017 | 40.738 | 12.023 |
| Ovarian Cancer | SK-OV-3 | 12.882 | 100.000 | 41.687 |
| Renal Cancer | 786-0 | 5.129 | 63.096 | 23.442 |
| Renal Cancer | A498 | 0.191 | 44.668 | 4.169 |
| Renal Cancer | ACHN | 0.275 | 83.176 | 21.878 |
| Renal Cancer | CAKI-1 | 0.389 | 100.000 | 26.915 |
| Renal Cancer | SN12C | 0.851 | 47.863 | 18.621 |
| Renal Cancer | TK-10 | 0.224 | 100.000 | 23.442 |
| Renal Cancer | UO-31 | 0.158 | 40.738 | 11.482 |
| Prostate Cancer | PC-3 | 8.128 | 100.000 | 37.154 |
| Prostate Cancer | DU-145 | 2.138 | 95.499 | 22.387 |
| Breast Cancer | MCF7 | 10.965 | 85.114 | 30.903 |
| Breast Cancer | NCI/ADR-RES | 3.467 | 100.000 | 25.704 |
| Breast Cancer | MDA-MB-231 | 0.069 | 35.481 | 10.471 |
| Breast Cancer | HS 578T | 0.617 | 85.114 | 13.490 |
| Breast Cancer | MDA-MB-435 | 0.035 | 41.687 | 12.303 |
| Breast Cancer | BT-549 | 5.754 | 47.863 | 20.893 |
| Breast Cancer | T-47D | 4.898 | 100.000 | 38.019 |
| Breast Cancer | MDA-MB-468 | 0.019 | 54.954 | 10.233 |

Example 110: *In Vitro* Anti-Proliferative Activity

In the present example, the following effects of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide were examined: (1) activity ($GI_{50}$) against the growth of several tumor cell lines harboring different mutations; (2) activity ($GI_{50}$) against the growth of several B-Raf mutant cell lines; (3) effects on anchorage independent cell growth; (4) effects on the cell cycle; and (5) toxic effects on primary liver and kidney cells.

***Cell Culture/Growth Inhibition Assay***

Human melanoma A375 cells and human colon cancer Colo205 cells were obtained from ATCC (Manassas, VA). A375 cells were maintained in DMEM supplemented with 10% fetal bovine serum, glutamine (2 mM), penicillin (100 U/ml), and streptomycin (100 μg/ml). Cells were maintained at 37°C, 5% $CO_2$, and 100% humidity. Colo205 cells were maintained in RPMI supplemented with 10% fetal bovine serum, glutamine (2 mM), penicillin (100 U/ml), and streptomycin (100 μg/ml). For growth inhibition experiments, cells were plated in white 384-well microplates at 1000 cells/20 μl/well. After 24 hr, 5 μl of a 5X drug stock solution was added. All drugs were initially prepared as 200X stocks in DMSO, such that final DMSO concentration was 0.5%. Cells were incubated for 48 hr at 37°C and ATP levels were determined using CellTiterGlo (Promega, Madison, WI). Adenylate kinase (AK) release was determined using Toxilight (Cambrex, Walkersville, MD). Non-linear curve-fitting was performed using GraphPad Prism 4 (GraphPad Software, San Diego, CA). 4-Amino-8-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrido[2,3-d]pyrimidin-5(8H)-one (VRX-14686) is a cytotoxic agent used as a reference compound.

Growth inhibition (%) = (Vehicle Only control (RLU)- N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide RLU)/(Vehicle Only control RLU-1 μM N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide RLU); based on growth arrest induced by N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide where ATP levels are measured.

Cell Viability (%) = (N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide RLU-10 μM VRX-14686 RLU)/(Vehicle Only control RLU-10 μM Tamoxifen RLU); based on cell killing induced by VRX-14686 where ATP levels are measured.

Cell Killing (%) = (N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide RLU- Vehicle Only control RLU)/(10 μM Tamoxifen RLU - Vehicle Only control RLU); based on cell killing induced by Tamoxifen where AK release is measured.

RLU = Relative Luminescence Units

***Evaluation of Cell Cycle Arrest***

A375 cells were plated in 96-well microplates at 10,000 cells/200 μl/well. After 24 hr cells were approximately 50% confluent and 50 μl of a 5X drug stock solution was added. After another 24 hr, cells were trypsinized, fixed in 200 μl Prefer (Anatech, Battle Creek, MI), and stored at 4° C overnight. Cells were then rinsed in PBS, permeabilized and stained in 0.1% Triton X-100, 200 μg/ml DNase-free RNase, and 25 μg/ml propidium iodide (Molecular Probes, Sunnyvale, CA), and analyzed on the Guava PCA-96 (Guava Technologies, Foster City, CA). Data were analyzed using ModFit LT (version 3.0, Verity, Topsham, ME).

(1) Evaluation of anchorage independent cell growth inhibition

Wells of an "ultra low binding" plate (Corning, Acton MA) were filled with 60 μl of a 0.15% agarose solution in complete RPMI. Then, 60 μl complete RPMI containing 9000 Colo205 cells in 0.15% agarose was added per well. After 24 hr, 60 μl of a 3X drug solution in agarose free complete RPMI was added. After 7 days, 36 μl 6X MTS reagent (CellTiter 96 Aqueous, Promega, Madison, WI) was added per well. After 2 hr at 37° C, absorbance at 490 nm was determined on the M5 plate reader (Molecular Devices, Sunnyvale, CA). Non-linear curve-fitting was performed using GraphPad Prism 4.

(2) Growth Inhibition ($GI_{50}$) against MEK-dependent cancer cell growth

Log phase dividing B-Raf mutant cells A375 (human melanoma), A431 (melanoma), Colo205 (colon carcinoma), HT29 (colorectal adenocarcinoma), MDA-MB231 (breast adenocarcinoma), and BxPC3 (pancreatic adenocarcinoma) were exposed to N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide for 48 hr and analyzed for ATP content. 100% growth arrest was determined using 1 μM N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide.

The table below shows the mean $GI_{50}$ values from at least three experiments, for each cell line and show that N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide caused growth inhibition in three B-Raf mutant cell lines (A375, Colo205, and HT29), as well as one ras/raf/MEK/MAPK pathway wild-type cell line (A431) with a mean potency of 79 nM (±9 nM).

| Cell Line | Mean | StDev | C.V. |
|---|---|---|---|
| **A375** | 71nM | 12.1nM | 17% |
| **A431** | 86nM | 25.4nM | 30% |
| **Colo205** | 89nM | 40.1nM | 45% |

| | | | |
|---|---|---|---|
| **HT29** | 70nM | 12.2nM | 18% |
| **MDA** | >1uM | | |
| **BxPC3** | >1uM | | |

In a separate study, log phase dividing B-Raf mutant cells A375 (human melanoma), SK Mel28 (human melanoma), and Colo205 (human colon carcinoma) were exposed to N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide for 48 hr and analyzed for ATP content. The table below shows the $GI_{50}$ for each cell line indicating N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide caused growth inhibition with a potency approximating its $EC_{50}$ value for MEK inhibition.

| Cell Line | $GI_{50}$ (nM) |
|---|---|
| **A375** | 56 |
| **SK Mel 28** | 105 |
| **Colo205** | 27 |

**Figures 10A** and **10B** show growth arrest of Log phase dividing A375 cells exposed to increasing concentrations of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide.. Cells were analyzed for ATP content. 100% growth arrest was determined using 1μM N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide.

Cell supernatants were analyzed for cytotoxic lysis by measuring adenylate kinase (AK) release. Log phase dividing A375 cells were exposed to N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide and PD-325901 for 48 hr. (100% cell killing was determined using 20 μM tamoxifen.) The results are shown in **Figure 11.** This data indicates that N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide causes a non-toxic growth arrest in several susceptible human cancer cell lines, demonstrated by i) growth arrest measurements (ATP quantitation); and ii) lack of cytotoxic cell lysis (AK release). The lack of AK release was confirmed for all cell lines tested.

***Anchorage Independent Growth Inhibition***

Anchorage independent growth of Colo205, A375, and MDA-MB231 cells exposed to N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide for 7 days, was quantitatively assessed in a 96-well microplate format. Viability was determined by MTS assay. $GI_{50}$ values are shown below:

| Cell Line | Mean | StDev | C.V. |
|---|---|---|---|
| **Colo205** | 40nM | 8.1nM | 20% |
| **A375** | 84nM | 17.2nM | 21% |
| **MDA-MB231** | 81nM | 55.6nM | 69% |

**Figures 12A-12C** show N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide growth inhibition of (A) human colorectal carcinoma Colo205 cells ($GI_{50}$ = 11 nM); (B) A375 cells ($GI_{50}$ = 22 nM) and (C) inhibition of MDA-MB231 cells which do not show N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide - induced growth arrest in 2-dimensional anchorage dependent assays.

Log phase dividing A375 cells were exposed to N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide (1uM) for 48 hr and the cell supernatants analyzed for growth inhibition (ATP content) and cytotoxic lysis (AK release). 100% viability (ATP assay) was determined in

vehicle only control wells. The table below shows the results indicating N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide causes non-toxic growth arrest in B-Raf mutant human melanoma A375 cells.

| | % Control |
|---|---|
| ATP, Cell viability | 27% |
| AK, Cell killing | 4% |

***Anchorage Independent Growth Inhibition***

Anchorage independent growth was quantitatively assessed in a 96-well microplate format. **Figure 13A** shows inhibition of growth of human colorectal carcinoma Colo205 cells, with $GI_{50}$ values at 6 nM and 11 nM respectively. **Figure 13B** shows inhibition of growth of A375 cells with $GI_{50}$ values at 5 nM and 22 nM.

***Cell Cycle Analysis of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide Induced Growth Arrest***

MEK inhibition has been shown to induce G1/S phase cell cycle arrest in A375 cells.

Log phase dividing A375 cells were exposed to N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide for 24 hr and the percentages of cells which stained for phase dependent amounts of intracellular DNA were determined using flow cytometry.

The table below shows percentage distribution of cells in respective growth phases in N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide and control (vehicle only) treated cells.

| | | Phase % | | |
|---|---|---|---|---|
| | | G1 | S | G2 |
| Control | | 61.8 | 27.1 | 11.1 |
| N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide | 111 nM | 84.7 | 11.8 | 3.5 |
| | 37 nM | 74.3 | 18.7 | 7.0 |

**Figure 14A** and **Figure 14B** show the effect of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide on cell cycle progression, demonstrating that exposure of A375 cells to N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide causes arrest in the G1 phase of the cell cycle, indicated by the depletion of cells in both the G2 and S phases.

***Evaluation of Primary Hepatocyte and Renal Cell Toxicity***

Cryopreserved rat hepatocytes were obtained from CellzDirect (Austin, TX) and plated on collagen coated 96-well plates according to manufacturer's instructions. Drug was added 4 hr after plating (final DMSO concentration 0.5%).

Plated human hepatocytes were obtained from CellzDirect and processed according to manufacturer's instructions.

Cryopreserved human renal proximal tubule epithelial cells (RPTEC) were obtained from Cambrex and were processed according to manufacturer's instructions. Cells were expanded for 4 days and then plated in 96-well plates at 50,000 cells/well for drug exposure.

After 48 hr, supernatant AK levels were determined using Toxilight, and cellular ATP levels were determined using CellTiterGlo. Full kill values were determined using 15 μM VRX-14686.

The results are shown in below. Very little cell lysis was observed. Minimal toxicity (81% survival) was seen at 30 μM N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-

sulfonamide in freshly plated primary human hepatocytes. RPTEC cells showed a dose dependent ATP depletion and evident cell lysis at 30 μM.

| | ATP (% Cell Survival) | | | AK release (% Cell Survival) | | |
|---|---|---|---|---|---|---|
| | Hepatocytes | | RPTEC | Hepatocytes | | RPTEC |
| Compound A | Rat | Human | Human | Rat | Human | Human |
| 30.0 | 57% | 81% | 34% | 91% | 109% | 41% |
| 10.0 | 72% | 107% | 85% | 93% | 112% | 99% |
| 3.3 | 87% | 104% | 91% | 97% | 102% | 95% |
| 1.1 | 114% | 108% | 94% | 96% | 92% | 96% |

The above data illustrates that (1) N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide inhibits cell growth and division in select human cancer cells with $GI_{50}$ values ranging from 70-89 nM in anchorage dependent proliferation assays without causing toxicity as determined by cell lysis assay; (2) N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide inhibits cell growth and division in select human cancer cells with $GI_{50}$ values of 51 nM and 22 nM in anchorage dependent and independent proliferation assays respectively; (3) N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide causes G1 arrest and inhibits anchorage independent growth in A375 cells, providing evidence of anticancer activity in a physiologically relevant *in vitro* model; and (4) N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide shows little cytotoxicity against primary normal human hepatocytes, human renal proximal tubule epithelial cells and rat hepatocytes.

Example 111: Pharmacokinetics of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide in Cancer Patients following Multiple Doses

| Dose (mg) | N | $T_{max}$ (hr) | $C_{max}$ (μg/mL) | $C_{24hr}$ (μg/mL) | $AUC_\tau$ (μg·hr/mL) | $t_{1/2}$* (hr) | $R_{ac}$ $C_{max}$ | $R_{ac}$ $AUC_\tau$ |
|---|---|---|---|---|---|---|---|---|
| 2 | 3 | 1.33 (21.7) | 0.0504 (49.2) | 0.00938 (82.8) | 0.517 (61.2) | 11.4 (38.8) | 1.76 (35.6) | 1.90 (23.9) |
| 4 | 3 | 1.50 (33.3) | 0.105 (41.0) | 0.0313 (41.1) | 1.39 (42.7) | 14.9 (0.992) | 1.49 (21.6) | 1.91 (36.1) |
| 6 | 3 | 1.50 (33.3) | 0.205 (16.6) | 0.0489 (12.2) | 2.22 (5.79) | 15.6 (23.8) | 1.58 (38.5) | 2.07 (23.5) |

$R_{ac}$: accumulation index

* Inaccurate estimate due to limited sampling time

Following multiple dosing of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide at 2, 4, or 6 mg/subject, N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide was readily absorbed with mean $T_{max}$ ranging between 1.33 to 1.50 hr. Mean $C_{max}$, $C_\tau$, and AUC values increased with dose in a dose-proportional manner. Accumulation indices range between 1.49 to 1.76 for $C_{max}$ and 1.90 to 2.07 for AUC, respectively, indicating moderate accumulation. Although the half-life cannot be accurately measured due to limited sampling time following multiple doses, the hale-life was expected to be longer than 22 hr following multiple doses based on the accumulation indices. These half-life values are significantly longer than observed in the mouse efficacy model which a typical range of 2 – 3 hr was seen. In addition, encouraging peak-to-trough ratios were seen in all doses.

Example 112: Pharmacokinetics of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide in Healthy Volunteers following Multiple Doses

| Dose (mg) | N | $T_{max}$ (hr) | $C_{max}$ (μg/mL) | $C_{24hr}$ (μg/mL) | $AUC_\tau$ (μg·hr/mL) | $t_{1/2}$ (hr) | $R_{ac}$ $C_{max}$ | $R_{ac}$ $AUC_\tau$ |
|---|---|---|---|---|---|---|---|---|
| 10 | 6 | 2.00 (61.2) | 0.182 (35.5) | 0.0318 (53.0) | 1.02 (1.80) (43.7) (39.7) | 14.6 (15.2) | 1.14 (19.0) | 1.29 (13.4) |
| 20 | 6 | 2.25 (39.1) | 0.313 (17.6) | 0.0350 (36.5) | 2.60 (22.0) | 13.4 (21.9) | 1.23 (24.1) | 1.24 (6.51) |

$R_{ac}$: accumulation index

* Inaccurate estimate due to limited sampling time

Following multiple dosing of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide at 10 or 20 mg/subject, N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide was readily absorbed with mean $T_{max}$ ranging between 2.00 to 2.25 hr. Mean $C_{max}$, $C_\tau$, and AUC values increased with dose. Accumulation indices range between 1.14 to 1.23 for $C_{max}$ and 1.24 to 1.29 for AUC, respectively, indicating insignificant accumulation. Half-lives were similar for two dose regimens ranging between 13 and 15 hr. These half-life values are shorter than observed in the cancer patients.

Example 113: *In Vitro* Anti-Proliferative Activity

The effect of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide on inhibition of cell proliferation was examined in a cell line derived from a human gastric carcinoma ("stomach cancer") in a cell proliferation assay.

***Cell culture/ Growth Inhibition Assay***: Human gastric carcinoma Hs746t cells were obtained from ATCC (Manassas, VA). Hs746t cells were maintained in DMEM supplemented with 10% fetal bovine serum, penicillin (100 U/ml), and streptomycin (100 μg/ml). Cells were maintained at 37°C, 5% $CO_2$, and 100% humidity. For cell proliferation experiments, cells were plated in white 96-well plates with clear bases at 3000 cells/100 μl/well. After 24 hr, cell media was removed and replaced with media containing N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide at various doses. Following incubation for 48 hours at 37°C, ATP levels were determined using CellTiterGlo (Promega, Madison, WI) and reading luminescence values using a LJL Biosystems Analyst HT (Sunnyvale, CA). The ATP level for each dose was determined in triplicate using independent wells.

Relative cell number =(mean RLU (N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide treated))/(mean RLU Vehicle Only control).

**Figure 19** shows a graph of cell number (relative to vehicle) vs concentration of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide and demonstrates that N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide inhibits the proliferation of human gastric carcinoma Hs746t cells after 48 hours treatment

Example 114: *In Vitro* Anti-Proliferative Activity

The effect of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide on inhibition of cell proliferation was examined in a cell line derived from a human gastric adenocarcinoma ("stomach cancer") in a cell proliferation assay.

*Cell culture/ Growth Inhibition Assay*

Human gastric adenocarcinoma AGS cells were obtained from ATCC (Manassas, VA). AGS cells were maintained in DMEM/F12 supplemented with 10% fetal bovine serum, penicillin (100 U/ml), and streptomycin (100

μg/ml). Cells were maintained at 37°C, 5% $CO_2$, and 100% humidity. For cell proliferation experiments, cells were plated in white 96-well plates with clear bases at 3000 cells/100 μl/well. After 24 hr, cell media was removed and replaced with media containing N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide at various doses. Following incubation for 3 days at 37°C, ATP levels were determined using CellTiterGlo (Promega, Madison, WI) and reading luminescence values using a LJL Biosystems Analyst HT (Sunnyvale, CA). The ATP level for each dose was determined in triplicate using independent wells. In another experiment, 1000 cells/100ul/well were plated and the cells were treated for 6 days and assayed as before.

Relative cell number=(mean RLU (N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide treated))/(mean RLU Vehicle Only control).

**Figure 15A** and **Figure 15B** shows a graphical plot of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide concentration vs cell number (relative to vehicle) after (A) 3 days and (B) 6 days exposure to N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide, demonstrating that N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide inhibits the proliferation of the human gastric adenocarcinoma AGS cell line.

Example 115: Growth Response of Orthotopic Human Hep3B Tumors in Nude Mice treated with different amounts of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide

The dose response efficacy of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide ("Compound A"), in inhibiting the development of orthotopic Hep3B2.1-7 human hepatic carcinoma was assessed in BALB/c *nu/nu* mice, in comparison with an optimal dose of 5-Fluorouracil (75mg/kg).

***Animals***: Female BALB/c *nu/nu* mice (University of Adelaide, Waite Campus, SA, Australia), aged 10-14 weeks, with a body weight range: of 19.1-29.94g (mean 22.95g) were used for the study. The mice were divided into 6 Study groups (4 treatment groups and 2 control groups) as follows:

Number of Mice per Group: 10 in Groups 1 to 5 inclusive
15 in 'Take-Rate' Control Group (Group 6)

The mice were kept in a controlled environment (targeted ranges: temperature 21±3°C, humidity 30-70%, 10-15 air changes per hour) under barrier (quarantine) conditions with a 12hour light/12hour dark cycle. Temperature and relative humidity were monitored continuously. A commercial rodent diet (Rat and Mouse Cubes, Speciality Feeds Pty Ltd, Glen Forrest, Western Australia) and tap water were provided to the animals *ad libitum*. Both food and water supplies were sterilized by autoclaving.

***Tumor Inoculation***: Hep3B human hepatic carcinoma cells (Passage 2 from working stock VP-Stock 353) were cultured in RPMI1640 cell culture medium, which was supplemented with 10% FBS and penicillin-streptomycin (50IU/mL final concentration). The cells were harvested by trypsinisation, washed twice in HBSS and counted. The cells were then resuspended in HBSS:Matrigel (1:1, v/v) and adjusted to a final volume containing $1x10^8$ cells/mL. Prior to inoculation, the incision site was liberally swabbed with alcohol and an incision made through the abdominal wall to expose the liver. The needle was introduced through the surface of the liver where 10μL of cells ($1x10^6$ cells) were discharged. The needle was held in this position for approximately 30 seconds to allow the Matrigel® to polymerize in order to avoid leakage of tumor cells into the abdominal cavity.

Treatment commenced 14 days post-inoculation. On Day 7 of the study (21 days post-inoculation), all mice from the 'Take-Rate' control group were culled and the livers visually assessed for the presence of tumors.

***Materials***: The following were obtained from the respective suppliers.

Sterile saline solution (0.9% NaCl(aq)) was obtained from Baxter Healthcare Australia, Old Toongabbie, NSW, Australia. CremophorEL was obtained from Sigma-Aldrich Pty Ltd, Castle Hill, NSW, Australia. 5-Fluorouracil, clinical formulation, clear, colorless liquid was obtained from Mayne Pharma Pty Ltd. RPMI1640 cell culture medium, FBS and HBSS were obtained from Invitrogen Australia Pty Ltd, Mt Waverley, VIC, Australia. Penicillin-streptomycin and Trypan Blue were obtained from Sigma-Aldrich, Castle Hill, NSW, Australia. Hep3B2.1-7 human hepatic carcinoma cells were sourced from American Type Culture Collection (ATCC), Rockville, MD, USA. Matrigel® was obtained from BD Biosciences, North Ryde, NSW, Australia.

The use of Matrigel® in the inoculation suspension improves the take rate of the tumor and decrease tumor size variability, and the growth of the Hep3B2.1-7 human hepatic carcinoma is more stable when inoculated in the presence of this extracellular matrix.

***Compound Preparation and Administration***: CremophorEL:Saline (1:9, v/v; vehicle control), N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide ("Compound A") or 5-Fluorouracil (compound control) were administered according to the schedule below:

| *Group* | *Compound* | *Dose (mg/kg)* | *Scheduled Treatment* | *Treatment Administered* |
|---|---|---|---|---|
| 1 | Vehicle Control | 10mL/kg | Once daily for 21 Days (Day 0 to 20) | Once daily for 19 Days (Day 0 to 18) |
| 2 | Compound A | 0.2mL @ 10mL/kg=2mg/kg | Once daily for 21 Days (Day 0 to 20) | Once daily for 19 Days (Day 0 to 18) |
| 3 | Compound A | 1.0mL @ 10mL/kg=10mg/kg | Once daily for 21 Days (Day 0 to 20) | Once daily for 19 Days (Day 0 to 18) |
| 4 | Compound A | 5.0mL @ 10mL/kg=50mg/kg | Once daily for 21 Days (Day 0 to 20) | Once daily for 19 Days (Day 0 to 18) |
| 5 | 5-Fluorouracil | 7.5mL @ 10mL/kg=75mg/kg | Once weekly for 21 Days (Day 0,7 and 14) | Once weekly for three weeks (Day 0, 7 and 14) |
| 6 | 'Take-Rate' Control | No treatment | - | - |

The Vehicle Control, CremophorEL:Saline (1:9, v/v), was administered p.o. in a dosing volume of 10mL/kg, once daily for 21 consecutive days (Day 0 to 20).

N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide, was formulated in CremophorEL:Saline (1:9, v/v). A stock solution was prepared weekly and stored at 4°C. Dosing solutions were prepared on each day of administration. N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide was administered p.o. in a dosing volume of 10mL/kg, once daily for 21 days (Day 0 to 20). The compound was administered at doses of 2, 10 and 50mg/kg.

5-Fluorouracil clinical formulation was diluted in sterile saline and administered i.v. via the tail vein at a concentration of 75mg/kg, in a dosing volume of 10mL/kg, once per week for three weeks (on Day 0, 7 and 14).

No treatment was administered to the mice in Group 6 ('Take-Rate' Control). On Day 7 of the study (21 days post-inoculation), the mice were culled and the liver exposed to determine the 'Take-Rate' and the size of the tumors in the liver wall.

Each animal's body weight was measured immediately prior to dosing. The volume administered to each mouse was calculated and adjusted based on the body weight.

***Tumor Measurements***: Liver and tumor wet weight were measured when each were excised post-mortem on the termination day of the study. At the termination of the study, livers were excised from all mice in each study group and weighed. The number of visible tumors, if present, was counted. These tumors were removed from the liver and weighed.

***Data Measurement and Sample Collection Schedule***

| ***Data Measurement*** | ***Schedule*** |
|---|---|
| Body weight | Day 0, then three times per week (Monday, Wednesday and Friday), and on the termination day of the study for Groups 1 to 5 inclusive. |
| Liver weight and tumor weight | Wet weight of excised liver and tumor all mice in Groups 1 to 5 inclusive, post-mortem on the termination day of the study, and from one mouse in Group 5 which died on the final treatment day. |
| ***Sample Collection*** | |
| Livers and tumors | From all mice in Group 6 ('Take-Rate' Control) on Day 7 of the study. |
| Livers and tumors | From all mice in Groups 1 to 5 inclusive, post-mortem on the termination day of the study, and from one mouse in Group 5 which died on the final treatment day. |
| Liver | From all mice in Groups 1 to 5 inclusive, post-mortem on the termination day of the study, and from one mouse in Group 5 which died on the final treatment day. |

***Data Acquisition and Calculation:*** Each animal's transponder (Bar Code Data Systems Pty Ltd, Botany Bay, NSW) was scanned using a barcode reader (LabMax I, DataMars, Switzerland) immediately prior to acquisition of data. All measurements were acquired with the same handheld calipers (Absolute Digimatic Model CD-6" CS, Mitutoyo Corporation, Japan). The data was synchronized with *vivo*Pharm's secure relational database using Pendragon Forms 4.0 (Pendragon® Software Corporation, Libertyville, IL, U.S.A.) as transfer software. AIDAM v2.4 was used for data reports and data calculation.

***Statistical and Calculations***: All statistical calculations were performed using SigmaStat 3.0. (SPSS Australasia Pty Ltd, North Sydney, NSW, Australia).

A two-sample t-test was used to determine the significance in body weight change within a treatment group between Day 0 and the termination day of the study. Where the data failed the Normality test or the Equal Variance Test, a Mann-Whitney Rank Sum Test was performed.

A One-Way Analysis of Variance (ANOVA) (All Pairwise Multiple Comparison Procedure and Multiple Comparison versus Control Group) was performed on liver weight and tumor weight data at the end of the study. Where this test did not pass the Equal Variance test, the Kruskal-Wallis One-Way Analysis of Variance (ANOVA) on ranks was performed. The same statistical analyses were performed on the data for the tumor-bearing mice in the study.

A p value of less than 0.05 was considered significant.

***Liver Weight and Tumor Weight Data for Tumor-Bearing Mice and Average Weight of Liver and Tumors per Mouse per Group for Tumor-Bearing Mice***

| Group | Treatment | Average Liver Weight (g) | SEM | Average Tumor Weight (g) | SEM | No. of Mice with Tumors (out of 10) |
|---|---|---|---|---|---|---|
| 1 | Vehicle Control | 4.560 | 0.673 | 3.382 | 0.979 | 4 |
| 2 | Compound A @ 2 mg/kg | 2.775 | 0.475 | 1.776 | 0.576 | 6 |
| 3 | Compound A | 2.551 | 0.446 | 1.407 | 0.465 | 7 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | @ 10 mg/kg | | | | | |
| 4 | Compound A @ 50 mg/kg | 1.677 | 0.161 | 0.624 | 0.257 | 4 |
| 5 | 5FU™ @ 75 mg/kg | 1.217 | 0.051 | 0.143 | 0.078 | 4 |

Samples were not collected from the mouse in Group 5 (5-Fluorouracil at 75mg/kg) which was culled during the study period. Due to the presence of large tumors in some of the mice, as indicated by a swollen appearance of the abdomen, the study was terminated 18 days post-initial treatment.

A dose-dependent trend in the decrease in liver and tumor weight is evident in the N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide-treated groups. When considering only the tumor-bearing mice, the average weight of the liver in the groups treated with N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide at the highest dose (Group 4 at 50mg/kg) and 5-Fluorouracil (Group 5 at 75mg/kg) was found to be significantly different to the Vehicle Control group (Group 1; $p < 0.05$). Also, the average weight of the tumors in the groups treated with N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide (Groups 3 and 4 at 10 mg/kg and 50mg/kg respectively) and 5-Fluorouracil (Group 5 at 75mg/kg) was found to be significantly different to the Vehicle Control group.

These results are presented graphically in **Figure 16** (Mean Liver weight – tumor-bearing mice only) and **Figure 17** (liver tumor weights – tumor bearing mice only)

Example 116: Growth Response of Orthotopic Human HT-29 Colon Tumors in Nude Mice treated with different amounts of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide

The dose response efficacy of N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide ("Compound A"), in inhibiting the development of the orthotopic HT-29 human colorectal adenocarcinoma was assessed in BALB/c *nu/nu* mice, in comparison with an optimal dose of 5-Fluorouracil (75mg/kg).

***Animals***: Female BALB/c *nu/nu* mice (University of Adelaide, Waite Campus, SA, Australia), aged 7-12 weeks, with a body weight range: of 16.58-25.39g (mean 21.52g) were used for the study. The mice were divided into 6 Study groups (4 treatment groups and 2 control groups) as follows:

Number of Mice per Group: 10 in Groups 1 to 5 inclusive
9 in 'Take-Rate' Control Group (Group 6)

The mice were kept in a controlled environment (targeted ranges: temperature 21±3°C, humidity 30-70%, 10-15 air changes per hour) under barrier (quarantine) conditions with a 12hour light/12hour dark cycle. Temperature and relative humidity were monitored continuously. A commercial rodent diet (Rat and Mouse Cubes, Speciality Feeds Pty Ltd, Glen Forrest, Western Australia) and tap water were provided to the animals *ad libitum*. Both food and water supplies were sterilized by autoclaving.

***Tumor Inoculation***: HT-29 human colorectal adenocarcinoma cells (Passage 4 from working stock VP-Stock 325) were cultured in RPMI1640 cell culture medium, which was supplemented with 10% FBS and penicillin-streptomycin (50IU/mL final concentration). The cells were harvested by trypsinisation, washed twice in HBSS and counted. The cells were then resuspended in HBSS and adjusted to a final volume containing $2x10^8$ cells/mL. Prior to inoculation, the incision site was liberally swabbed with alcohol and an incision made through the abdominal wall to expose the caecum

wall. The needle was introduced through the surface of the caecum wall where 5µL of cells ($1x10^6$ cells) were discharged.

***Materials***: The following were obtained from the respective suppliers.

Sterile saline solution (0.9% NaCl(aq)) was obtained from Baxter Healthcare Australia, Old Toongabbie, NSW, Australia. CremophorEL was obtained from Sigma-Aldrich Pty Ltd, Castle Hill, NSW, Australia. 5-Fluorouracil, clinical formulation, clear, colorless liquid was obtained from Mayne Pharma Pty Ltd. RPMI1640 cell culture medium, FBS and HBSS were obtained from Invitrogen Australia Pty Ltd, Mt Waverley, VIC, Australia. Penicillin-streptomycin and Trypan Blue were obtained from Sigma-Aldrich, Castle Hill, NSW, Australia. HT-29 human colorectal adenocarcinoma cells were sourced from American Type Culture Collection (ATCC), Rockville, MD, USA.

***Compound Preparation and Administration***: CremophorEL:Saline (1:9, v/v; vehicle control), N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide or 5-Fluorouracil (compound control) were administered according to the schedule below:

| *Group* | *Compound* | *Dose (mg/kg)* | *Scheduled Treatment* | *Treatments Administered* |
|---|---|---|---|---|
| 1 | Vehicle Control | 10mL/kg | Once daily for 21 Days (Day 0 to 20) | Once daily for 21 Days (Day 0 to 20) |
| 2 | Compound A | 0.2mL @ 10mL/kg=2mg/kg | Once daily for 21 Days (Day 0 to 20) | Once daily for 10 Days (Day 0 to 9) |
| 3 | Compound A | 1.0mL @ 10mL/kg=10mg/kg | Once daily for 21 Days (Day 0 to 20) | Once daily for 21 Days (Day 0 to 20) |
| 4 | Compound A | 5.0mL @ 10mL/kg=50mg/kg | Once daily for 21 Days (Day 0 to 20) | Once daily for 8 Days (Day 0 to 7) |
| 5 | 5-Fluorouracil | 7.5mL @ 10mL/kg=75mg/kg | Once weekly for three weeks (Day 0,7 and 14) | Once weekly for 3 weeks (Day 0, 7 and 14) |
| 6 | 'Take-Rate' Control | No treatment | - | - |

The Vehicle Control, CremophoreEL:Saline (1:9, v/v), was administered p.o. in a dosing volume of 10mL/kg, once daily for 21 consecutive days (Day 0 to 20).

N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide was formulated in CremophorEL:Saline (1:9, v/v). A stock solution was prepared weekly and stored at 4°C. Dosing solutions were prepared on each day of administration. N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide was administered p.o. at doses of 2, 10 and 50mg/kg, in a dosing volume of 10mL/kg, once daily for 21 days (Day 0 to 20).

5-Fluorouracil clinical formulation was diluted in sterile saline and administered i.v. via the tail vein at a concentration of 75mg/kg, in a dosing volume of 10mL/kg, once per week for three weeks (on Day 0, 7 and 14).

No treatment was administered to the mice in Group 6 ('Take-Rate' Control). On Day 7 of the study (21 days post-inoculation), the mice were culled and the colon exposed to determine the take-rate and size of the tumors in the caecum wall.

Each animal's body weight was measured immediately prior to dosing. The volume administered to each mouse was calculated and adjusted based on the body weight.

***Tumor Measurements***: Caecum and tumor wet weight were measured when each were excised post-mortem on the termination day of the study. At the termination of the study, the caecum was excised from all mice in each study group and weighed with the tumors intact. The tumors were then excised from the caecum and weighed.

The livers was also excised from all mice in each group at the termination of the study and fixed in 10% buffered formalin. Five liver samples from the Vehicle Control group were embedded in paraffin, sectioned and stained with haematoxylin and eosin (H&E) for histological assessment for morphological changes.

**Data Measurement and Sample Collection Schedule**

| ***Data Measurement*** | ***Schedule*** |
|---|---|
| Body weight | Day 0, then three times per week (Monday, Wednesday and Friday), and on the termination day of the study for Groups 1 to 5 inclusive. |
| Caecum weight and tumor weight | Excised caecum and tumor from each mouse at termination in Groups 1 to 5 inclusive |
| ***Sample Collection*** | |
| Caecum and tumors | From all mice in Group 6 ('Take-Rate' Control) post-mortem, on Day 7 of the study. |
| Caecum and tumors | From all mice in Groups 1 to 5 inclusive post-mortem, on the termination day of the study, and from mice which died during the study period. |
| Liver | From all mice in Groups 1 to 5 inclusive post-mortem, on the termination day of the study and from mice which died during the study period. |

***Data Acquisition and Calculation***: Each animal's transponder (Bar Code Data Systems Pty Ltd, Botany Bay, NSW) was scanned using a barcode reader (LabMax I, DataMars, Switzerland) immediately prior to acquisition of data. All measurements were acquired with the same handheld calipers (Absolute Digimatic Model CD-6" CS, Mitutoyo Corporation, Japan). The data was synchronized with vivoPharm's secure relational database using Pendragon Forms 4.0 (Pendragon® Software Corporation, Libertyville, IL, U.S.A.) as transfer software. AIDAM v2.4 was used for data reports and data calculations.

***Statistical and Calculations***: All statistical calculations were performed using SigmaStat 3.0. (SPSS Australasia Pty Ltd, North Sydney, NSW, Australia).

A two-sample t-test was used to determine the significance in body weight change within a treatment group between Day 0 and the termination day of the study. In the groups treated with N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide at 2 and 50 mg/kg, treatment was discontinued early due to excessive body weight loss. In these groups, a two-sample t-test was used to determine the significance in body weight change within a treatment group between Day 0 and the final treatment day of the study, and between the last treatment day and the termination day of the study. Where the data did not pass the Normality test or the Equal Variance Test, a Mann-Whitney Rank Sum Test was performed.

A One-Way Analysis of Variance (ANOVA) (All Pairwise Multiple Comparison Procedure and Multiple Comparison versus Control Group) was performed on the caecum weight and tumor weight data at the end of the study. Where the data did not pass the Normality test the values were converted to the natural logarithm prior to performing the procedure.

A p value of less than 0.05 was considered significant.

***Observations***: Average body weight loss was measured in all study groups, including the Vehicle Control group. Diarrhoea and signs of dehydration (loss of skin elasticity) were observed in all of the study groups, including the Vehicle Control. Severe body weight loss early during the study period led to the cessation of treatment in the groups receiving N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide at the lowest (2mg/kg) and highest dose (50mg/kg) on Day 9 and Day 7 of the study, respectively. As body weight loss was less severe in the group receiving N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide at 10mg/kg, all treatments for this group were

administered as scheduled. The average body weight losses at the end of the study for this group and the 5-Fluorouracil treatment group were significant.

Although the take rate of the HT-29 tumors in the 'Take -Rate' group 21 days after inoculation was 100%, the size of these tumors was much lower than anticipated. This may have contributed to there being no significant difference in average caecum and tumor weights between N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide – treated Groups and the Vehicle Control Group. There was also no effect of 5-Fluorouracil on the weight of the caecum and HT-29 tumors.

***Body Weight Measurements (± SEM) (Final Treatment Days and Study End Date)***

| Grp | Compound | Dose (mg/kg), Route, Schedule | | | Host Response | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Delta Body Weight (g) (± SEM) Final Treatment Day | % Delta Body Weight Final Treatment Day | Delta Body Weight (g) (± SEM) Final Study Day | % Delta Body Weight Final Study Day | Survival Number (No. Alive/ Total) |
| 1 | Vehicle Control | - | p.o. | Once daily for 21 days (Day 0 to 20) | - | - | -0.8 ± 0.4 | -3.6 | 8/10 |
| 2 | Compound A | 2 | p.o. | Once daily for ten Days (Day 0 to 9) | -2.4 ± 1.4 (Day 9) | -11.1 | 0.1 ± 0.9 | 0.4 | 4/10 |
| 3 | Compound A | 10 | p.o. | Once daily for 21 days (Day 0 to 20) | - | - | -1.5 ± 0.3 | -6.9 | 7/10 |
| 4 | Compound A | 50 | p.o. | Once daily for eight Days (Day 0 to 7) | -3.8 ± 0.5 (Day 7) | -17.8 | -1.3 ± 0.9 | -5.9 | 7/10 |
| 5 | 5-Fluorouracil | 75 | i.v. | Once weekly for three weeks (Day 0, 7 and 14) | - | - | -3.3 ± 0.4 | -15.2 | 8/10 |

Body weight data was not collected for Group 6 ('Take-Rate' Control). The group was culled on Day 7 of the study (Day 21 post-inoculation) to assess visually whether the tumors were growing adequately for the purpose of the study.

Treatment was discontinued in Group 2 (N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide at 2 mg/kg) on Day 9 of the study and in Group 4 (N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide at 50mg/kg) on Day 7 of the study, as the mice were losing excessive body weight. The remaining groups all received all of the scheduled treatments during the study period.

The average tumor weight in each group is shown in **Figure 18**. The average weight of tumor for each group includes only those which survived until the final day of the study. Values for mice which died during the study period are not included in the calculated average values.

***Caecum Weight and Tumor Weight Data***

| Group | Treatment | Animal ID | Caecum Weight (g) | Tumour Weight (g) | Average Caecum Weight (g) | SEM | Average Tumour Weight (g) | SEM |
|---|---|---|---|---|---|---|---|---|
| 1 | Vehicle Control | 173811 | 0.290 | 0.070 | 0.413 | 0.081 | 0.149 | 0.080 |
| | (CremophorEL:Sali | 170774 | 0.331 | 0.160 | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | ne) | 170729 | 0.267 | 0.017 | | | | |
| | | 173673 | 0.307 | 0.005 | | | | |
| | | 171429 | 0.311 | 0.326 | | | | |
| | | 175732 | 0.946 | 0.627 | | | | |
| | | 171539 | 0.286 | 0.038 | | | | |
| | | 173576 | 0.287 | 0.002 | | | | |
| | | 170836 | 0.397 | 0.000 | | | | |
| | | 172014 | 0.506 | 0.176 | | | | |
| 2 | Compound A @ 2 mg/kg | 175867 | 0.347 | 0.001 | 0.296 | 0.033 | 0.033 | 0.030 |
| | | 170936 | 0.170 | 0.001 | | | | |
| | | 172003 | 0.150 | 0.000 | | | | |
| | | 176472 | 0.205 | 0.005 | | | | |
| | | 171338 | 0.377 | 0.001 | | | | |
| | | 170825 | 0.233 | 0.122 | | | | |
| | | 174466 | 0.251 | 0.005 | | | | |
| | | 171587 | 0.322 | 0.003 | | | | |
| 3 | Compound A @ 10mg/kg | 173623 | 0.287 | 0.000 | 0.244 | 0.025 | 0.078 | 0.059 |
| | | 170793 | 0.198 | 0.000 | | | | |
| | | 172304 | 0.258 | 0.257 | | | | |
| | | 175676 | 0.111 | 0.008 | | | | |
| | | 171003 | 0.263 | 0.422 | | | | |
| | | 171466 | 0.237 | 0.001 | | | | |
| | | 176386 | 0.234 | 0.014 | | | | |
| | | 170858 | 0.289 | 0.004 | | | | |
| | | 175862 | 0.320 | 0.100 | | | | |
| | | 171364 | 0.251 | 0.000 | | | | |
| 4 | Compound A @ 50mg/kg | 175697 | 0.230 | 0.002 | 0.290 | 0.038 | 0.122 | 0.092 |
| | | 171349 | 0.254 | 0.002 | | | | |
| | | 174272 | 0.238 | 0.000 | | | | |
| | | 176335 | 0.201 | 0.004 | | | | |
| | | 171041 | 0.337 | 0.166 | | | | |
| | | 174536 | 0.169 | 0.655 | | | | |
| | | 175656 | 0.328 | 0.001 | | | | |
| | | 173626 | 0.217 | 0.001 | | | | |
| | | 171437 | 0.312 | 0.001 | | | | |
| | | 174501 | 0.463 | 0.026 | | | | |
| 5 | 5FU™ at 75 mg/kg | 171322 | 0.355 | 0.245 | 0.391 | 0.050 | 0.069 | 0.041 |
| | | 175559 | 0.199 | 0.001 | | | | |
| | | 176302 | 0.360 | 0.000 | | | | |
| | | 176241 | 0.284 | 0.000 | | | | |
| | | 175857 | 0.421 | 0.010 | | | | |
| | | 176242 | 0.706 | 0.329 | | | | |
| | | 174165 | 0.415 | 0.130 | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 176417 | 0.327 | 0.079 | | | | |
| | | 170592 | 0.237 | 0.000 | | | | |
| | | 171501 | 0.377 | 0.003 | | | | |

The shaded boxes indicate samples collected from mice which died during the study period. Calculated average values for caecum weight and tumor weight exclude these values. Trends indicate a reduction in HT-29 tumor and caecum weight data after treatment with 10 mg/kg N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide.

Example 117: Tumor growth delay in nude mice bearing human A375 melanoma xenografts

Six groups (n=9) of tumored mice were used. Control groups included one receiving the 10% Cremophor EL/saline vehicle by oral gavage (po), once-daily for 14 days (qd x14), and a second given paclitaxel as a reference agent at 30 mg/kg by tail vein injection (iv), every other day for five doses (qod x5). The four experimental groups received oral N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide ("Compound A") at 25 mg/kg or 50 mg/kg, qd x14, or at 12.5 or 25 mg/kg, bid x14. Treatment outcome was assessed by TGD, defined as the difference in median time to endpoint tumor volume in a treatment group compared to the control group. Toxicity was assessed by body weight measurements and clinical observations.

***Animals***: Female athymic nude mice (*nu/nu*, Harlan) were 10 to 11 weeks old and had a body weight (BW) range of 19.3 to 25.5 grams on Day 1 of the study. The animals were fed *ad libitum* water (reverse osmosis, 1 ppm Cl) and NIH 31 Modified and Irradiated Lab Diet® consisting of 18.0% crude protein, 5.0% crude fat, and 5.0% crude fiber. The mice were housed on irradiated ALPHA-Dri® bed-o'cobs® Laboratory Animal Bedding in static microisolators on a 12-hour light cycle at 21–22 °C (70–72 °F) and 40–60% humidity. The recommendations of the *Guide for Care and Use of Laboratory Animals* with respect to restraint, husbandry, surgical procedures, feed and fluid regulation, and veterinary care were adhered to.

***Tumor Implantation***: Xenografts were initiated from A375 human melanoma tumors by serial transplantation in athymic nude mice. An A375 tumor fragment (~ 1 $mm^3$) was implanted subcutaneously into the right flank of each test mouse, and tumor growth was monitored as the average size approached 100 - 150 $mm^3$. Thirteen days later, designated as Day 1 of the study, animals were placed into six groups each consisting of nine mice (reduced from ten) with individual tumor volumes ranging from 63 to 221 $mm^3$ and group mean tumor volumes of 125.3 to 125.9 $mm^3$. Tumor volume was calculated using the formula: $\text{Tumor Volume}\,(mm^3) = \frac{w^2 \times l}{2}$, where $w$ = width and $l$ = length in mm of an A375 tumor.

***Materials***: N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide was dissolved at 5 mg/mL in 10% Cremophor EL in saline with sonication, shaking, and heating to 35°C to assist in dissolution. The 5 mg/mL solution served as the dosing solution for treatment at 50 mg/kg, and dosing solutions for 25 mg/kg and 12.5 mg/kg treatment were prepared by serial dilution. Dosing solutions were stored for up to one week at room temperature protected from light.

Paclitaxel (NPI) dosing solutions were prepared from a 30 mg/mL stock for each day's use by diluting to 3 mg/mL in 5% ethanol, 5% Cremophor EL in 5% dextrose in water (D5W). Paclitaxel dosing was at 30 mg/kg.

***Treatment***: The table below shows the treatment regimen.

| | | Treatment Regimen | | | |
|---|---|---|---|---|---|
| **Group** | **n** | **Agent** | **mg/kg** | **Route** | **Schedule** |

| | | | | | |
|---|---|---|---|---|---|
| 1 | 9 | Vehicle | - | po | qd x 14 |
| 2 | 9 | Paclitaxel | 30 | iv | qod x 14 |
| 3 | 9 | Compound A | 50 | po | qd x 14 |
| 4 | 9 | Compound A | 25 | po | bid x 14 first day 1 dose |
| 5 | 9 | Compound A | 25 | po | qd x 14 |
| 6 | 9 | Compound A | 12.5 | po | bid x 14 first day 1 dose |

Mice in Group 1 received vehicle consisting of 10% Cremophor EL in saline by oral gavage (po) daily for fourteen doses (qd x14), and served as a control for tumor progression. Group 2 animals were administered intravenous (iv) paclitaxel as a reference agent at 30 mg/kg, once every other day for five doses (qod x5). Group 3 – 6 mice received oral N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide at the following respective schedules: 50 mg/kg, qd x14; 25 mg/kg, twice-daily for 14 days with a single dose given on the first and last days (bid x14); 25 mg/kg, qd x14; and 12.5 mg/kg, bid x14. All doses were given in volumes of 0.2 mL per 20 g of body weight, and were scaled to the body weight of the animal.

***Endpoint***: Tumors in all groups were measured twice weekly using calipers. Each animal was euthanized when its tumor reached the endpoint size of 2000 $mm^3$ or on the final day of the study (Day 60), whichever came first. The time to endpoint (TTE) for each mouse was calculated from the following equation:

$$\text{TTE (days)} = \frac{\log_{10}(\text{endpoint volume, } mm^3) - b}{m}$$, where b is the intercept and m is the slope of the line obtained by linear regression of a log-transformed tumor growth data set.

The data set was comprised of the first observation that exceeded the study endpoint volume and the three consecutive observations that immediately preceded the attainment of the endpoint volume. Animals that do not reach the endpoint are assigned a TTE value equal to the last day of the study. Animals classified as NTR (non-treatment-related) deaths due to accident (NTRa) or due to unknown causes (NTRu) are excluded from TTE calculations (and all further analyses). Animals classified as TR (treatment-related) deaths or NTRm (non-treatment-related due to metastasis) are assigned a TTE value equal to the day of death.

Treatment outcome was determined from tumor growth delay (TGD), defined as the increase in the median time to endpoint (TTE) in a treatment group compared to the control group: TGD = T – C, expressed in days, or as a percentage of the median TTE of the control group: $\%TGD = \frac{T-C}{C} \times 100$, where: T = median TTE for a treatment group, C = median TTE for the control group (Group 1).

Treatment may cause partial regression (PR) or complete regression (CR) of the tumor in an animal. In a PR response, the tumor volume is 50% or less of its Day 1 volume for three consecutive measurements during the course of the study, and equal to or greater than 13.5 $mm^3$ for one or more of these three measurements. In a CR response, the tumor volume is less than 13.5 $mm^3$ for three consecutive measurements during the course of the study. An animal with a CR response at the termination of a study is additionally classified as a tumor-free survivor (TFS). Tumor regressions were monitored and recorded.

***Side Effects***: Animals were weighed daily for the first five days of the study and then twice weekly. The mice were observed frequently for overt signs of any adverse, treatment-related side effects, and clinical signs were recorded when observed. Acceptable tolerability is defined as a group mean body-weight loss of less than 20% during the test and not more than one treatment-related death in a group of animals. Any dosing regimen that does not meet these criteria is considered above the maximum tolerated dose (MTD). A death is classified as TR if attributable to treatment side effects

as evidenced by clinical signs and/or necropsy, or may be classified as TR if due to unknown causes during the dosing period or within 10 days of the last dose. A death is classified as NTR if there is no evidence that death was related to treatment side effects.

***Statistical and Graphical Analyses***: The logrank test was used to analyze the significance of the differences between the TTE values of treated and control groups. Two-tailed statistical analyses were conducted at significance level $P = 0.05$.

Median tumor growth curves show group median tumor volumes as a function of time. When an animal exited the study due to tumor size or TR death, the final tumor volume recorded for the animal was included with the data used to calculate the group median tumor volume at subsequent time points. Curves were truncated after 50% of the animals in a group had exited the study due to tumor progression. Kaplan-Meier plots were constructed to show the percentage of animals remaining in the study as a function of time, and used the same data set as the logrank test. Prism (GraphPad) for Windows 3.03 was used for all graphic presentations and statistical analyses.

***Treatment Response Summary***

| Group | Median TTE | T-C | %TGD | Statistical Significance | MTV (n) Day 60 | Regressions | | | Mean BW Nadir |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | PR | CR | TFS | |
| 1 | 22.8 | - | - | - | - | 0 | 0 | 0 | - |
| 2 | 28.8 | 6.0 | 26 | ** | - | 0 | 0 | 0 | -5.3% Day 15 |
| 3 | 27.5 | 4.7 | 21 | ** | - | 1 | 0 | 0 | - |
| 4 | 59.9 | 37.1 | 163 | *** | 0 (4) | 4 | 5 | 4 | -0.6% Day 15 |
| 5 | 25.6 | 2.8 | 12 | Ns | - | 0 | 0 | 0 | - |
| 6 | 27.5 | 4.7 | 21 | * | - | 1 | 0 | 0 | - |

***Growth of A375 Tumors in Control Mice (Group 1)***: Animals in Group 1 received the 10% Cremophor EL/saline vehicle, po, qd x14. Tumors in the control mice grew progressively to the 2000 $mm^3$ endpoint volume with a median TTE of 22.8 days, establishing a maximum possible T-C in the study of 37.1 days, or 163% TGD.

***Effect of Treatment with Paclitaxel (Group 2)***: Group 2 animals were administered paclitaxel as a reference agent, 30 mg/kg, iv, qod x5. All nine of the animals achieved the tumor volume endpoint. Tumor growth paralleled and was slightly right-shifted compared with the control group. The median TTE value was 28.8 days, corresponding to 26% TGD, a significant result by Logrank analysis (Table 2, $P = 0.0088$ G1 vs. G2). No tumor regressions were associated with paclitaxel treatment.

***Effect of Treatment with N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide (Groups 3 - 6)***: Groups 3 – 6 received oral dosing with N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide as monotherapy. Group 3 animals were administered 50 mg/kg on a qd x14 schedule. The nine tumors in the group achieved the volume endpoint. Median tumor volume for the group underwent little net change for the first ~ 10 days, then increased for the duration of the study. A single animal experienced tumor PR. The median TTE value was 27.5 days, or 21% TGD, a significant result (P = 0.0054 G1 vs. G).

Animals in Group 4 received 25 mg/kg N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide on a bid x14 schedule. Four of the nine animals in the group remained on Day 60, all TFS. An additional 2/9 animals had tumors reaching the volume endpoint on the day before study's end. The group had 4/9 PR, 5/9 CR and 4/9 TFS. Median tumor volume dropped beginning in the first few days

of the study and continued for about 30 days. Tumor regrowth in 5/9 animals accounted for a resurgence of median tumor growth beginning on about Day 32 and continuing to the end of the study. The group median TTE value was 59.9 days, representing the maximum possible 163% TGD ($P < 0.0001$, Table A1).

Mice in Group 5 also received 25 mg/kg N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide, but on a less intense qd x14 schedule. All nine animals in Group 5 reached the tumor volume endpoint, with no tumor regressions. Tumor growth tracked closely with that of the control group. The median TTE was 25.6 days, or 12% TGD, a non-significant result ($P = 0.0662$ G1 vs. G5).

Group 6 animals were administered 12.5 mg/kg N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide on a bid x14 schedule. All tumors in the group achieved the volume endpoint. As with Group 4, median tumor volume in Group 6 dropped early in the study, but this reduction was sustained for only about nine days and was associated with a single PR response. Tumor volume increased from Day 10 to study end. The median TTE for the group was 27.5 days, corresponding to a significant 21% TGD ($P = 0.0424$ G1 vs. G6).

In summary, N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide displayed dose-related antitumor activity against human A375 melanoma xenografts with both once-daily and twice-daily oral dosing. Twice-daily dosing was superior to once-daily in the magnitude of TGD produced and in the numbers of objective responses. Thus, N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide antitumor activity is both dose- and schedule-dependent.

Example 118: Activity **Against Subcutaneous COLO 205 Human Colon Carcinoma Xenografts**

***Animals***: Female athymic nude mice (*nu/nu*, Harlan) were 12 to 13 weeks old and had a body weight (BW) range of 18.3 to 27.3 grams on Day 1 of the study. The animals were fed *ad libitum* water (reverse osmosis, 1 ppm Cl) and NIH 31 Modified and Irradiated Lab Diet® consisting of 18.0% crude protein, 5.0% crude fat, and 5.0% crude fiber. The mice were housed on irradiated ALPHA-Dri® bed-o'cobs® Laboratory Animal Bedding in static microisolators on a 12-hour light cycle at 21–22 °C (70–72 °F) and 40–60% humidity. The recommendations of the *Guide for Care and Use of Laboratory Animals* with respect to restraint, husbandry, surgical procedures, feed and fluid regulation, and veterinary care were adhered to.

***Tumor Implantation***: Xenografts were initiated from COLO 205 human colon carcinoma cells. Tumor cells were cultured 10% heat-inactivated fetal bovine serum, 100 units/mL penicillin G sodium, 100 µg/mL streptomycin sulfate, 0.25 µg/mL amphotericin B, and 25 µg/mL gentamicin, 2 mM glutamine, 1 mM sodium pyruvate, 10 mM HEPES and 0.075% sodium bicarbonate. Cell cultures were maintained in tissue culture flasks in a humidified incubator at 37°C, in an atmosphere of 5% $CO_2$ and 95% air. On the day of tumor cell implant, Colo 205 cells were harvested during logarithmic growth and resuspended in 50% Matrigel matrix (BD Biosciences) in PBS at a concentration of 5 x $10^6$ cells/mL. Each test mouse received 1 x $10^6$ Colo 205 cells implanted subcutaneously in the right flank, and the growth of tumors was monitored as the average size approached 80 - 120 $mm^3$. Fourteen days later, designated as Day 1 of the study, animals were placed into eight groups (n = 9) with individual tumor volumes ranging from 63 to 196 $mm^3$ and group mean tumor volumes of 118-119 $mm^3$. Tumor volume was calculated using the formula:

$\text{Tumor Volume}(mm^3) = \frac{w^2 \times l}{2}$, where $w$ = width and $l$ = length in mm of a COLO 205 tumor. Tumor weight may be estimated with the assumption that 1 mg is equivalent to 1 $mm^3$ of tumor volume.

***Materials***: Dosing solutions of Compound A were prepared fresh daily by dissolving the required amount of compound in 100% Cremophor EL, and then diluting ten-fold with normal saline. Final dosing solution concentrations were 2.5, 5, 10, or 20 mg/mL, in order to provide respective doses of 25, 50, 100 or 200 mg/kg in a dosing volume of 10 mL/kg. Paclitaxel (Natural Pharmaceuticals, Inc.) was prepared fresh on each day of dosing in a vehicle consisting of 5% ethanol and 5% Cremophor EL in 90% D5W (5% EC vehicle).

***Treatment***: The table below shows the treatment regimen.

| | | Treatment Regimen | | | |
|---|---|---|---|---|---|
| **Group** | **n** | **Agent** | **mg/kg** | **Route** | **Schedule** |
| 1 | 9 | Vehicle | - | po | qd x 14 |
| 2 | 9 | Paclitaxel | 30 | iv | qod x 14 |
| 3 | 9 | Compound A | 50 | po | qd x 14 |
| 4 | 9 | Compound A | 25 | po | bid x 14 first day 1 dose |
| 5 | 9 | Compound A | 25 | po | qd x 14 |
| 6 | 9 | Compound A | 12.5 | po | bid x 14 first day 1 dose |

Group 1 received the formulation vehicle (10% Cremophor EL in saline), and served as the tumor growth control group. Group 2 received the reference drug paclitaxel administered on its optimal schedule in nude mice (30 mg/kg i.v. qod x5). Groups 3 – 6 received 25, 50, 100 and 200 mg/kg doses, respectively, of Compound A administered p.o. qd x14, with dosing in Group 6 (200 mg/kg) discontinued after six days due to toxicity. All doses were scaled to the weight of the animal (0.2 mL per 20 grams body weight).

***Endpoint***: Tumors were measured twice each week using calipers. Each animal was euthanized when its tumor reached the pre-determined endpoint size of 2000 $mm^3$ or on the final day of the study (Day 74), whichever came first. However, control tumors did not exhibit logarithmic growth characteristics after attaining a size of approximately 800 $mm^3$. Therefore endpoint tumor size of 800 $mm^3$ was used for analysis of tumor growth delay (TGD). The time to endpoint (TTE) for each mouse was calculated from the following equation:

$$\text{TTE (days)} = \frac{\log_{10}(\text{endpoint volume}, mm^3) - b}{m}$$

, where b is the intercept and m is the slope of the line obtained by linear regression of a log-transformed tumor growth data set. The data set was comprised of the first observation that exceeded the study endpoint volume and the three consecutive observations that immediately preceded the attainment of the endpoint volume. Animals that do not reach the endpoint are assigned a TTE value equal to the last day of the study. Animals classified as NTR (non-treatment-related) deaths due to accident (NTRa) or due unknown causes (NTRu) are excluded from TTE calculations (and all further analyses). Animals classified as TR (treatment-related) deaths or NTRm (non-treatment-related death due to metastasis) are assigned a TTE value equal to the day of death.

Treatment outcome was evaluated by tumor growth delay (TGD), which is defined as the increase in the median time to endpoint (TTE) in a treatment group compared to the control group: TGD = T – C, expressed in days, or as a percentage of the median TTE of the control group: $\%TGD = \frac{T-C}{C} \times 100$, where: T = median TTE for a treatment group, C = median TTE for the control group.

The control group was specified as Group 1 mice.

Treatment may cause partial regression (PR) or complete regression (CR) of the tumor in an animal. In a PR response, the tumor volume is 50% or less of its Day 1 volume for three consecutive measurements during the course of the study, and equal to or greater than 13.5 $mm^3$ for one or more of these three measurements. In a CR response, the

tumor volume is less than 13.5 $mm^3$ for three consecutive measurements during the course of the study. Regression responses were monitored and recorded.

***Side Effects***: Animals were weighed daily for the first five days of the study and then twice weekly. The mice were observed frequently for overt signs of any adverse, treatment-related side effects, and clinical signs of toxicity were recorded when observed. Acceptable toxicity is defined as a group mean body-weight loss of less than 20% during the study and not more than one treatment-related (TR) death among ten treated animals, and any dosing regimen that results in greater toxicity is considered above the maximum tolerated dose (MTD). A death is classified as TR if attributable to treatment side effects as evidenced by clinical signs and/or necropsy, or may be assessed as TR if due to unknown causes during the dosing period or within 10 days of the last dose. A death is classified as an NTR if there is no evidence that death was related to treatment side effects. Animals were monitored for side effects by frequent observation and BW measurements. BW changes were unremarkable, and all treatments were acceptably tolerated, except Group 6. Six once daily p.o. doses of 200 mg/kg Compound Aresulted in one TR death assessed on Day 7 and two additional TR deaths on Day 8. All mice in Group 6 exhibited clinical symptoms of toxicity including hunched postures, hypoactivity, and loose stools.

***Statistical and Graphical Analyses***: The logrank test was used to analyze the significance of the differences between the TTE values of treated and control groups. Two-tailed statistical analyses were conducted at significance level $P = 0.05$.

Median tumor growth curves show group median tumor volumes plotted on a log scale as a function of time. When an animal exited the study due to tumor size or TR death, the final tumor volume recorded for the animal was included with the data used to calculate the group median tumor volume at subsequent time points. Curves were truncated after 50% of the animals in a group had exited the study due to tumor progression or after the second TR death in a group. Kaplan-Meier plots were constructed to show the percentage of animals remaining in the study as a function of time, and used the same data set as the logrank test. Prism (GraphPad) for Windows 3.03 was used for all graphic presentations and statistical analyses.

***Treatment Response Summary***

| Grp | Median | T-C | %TGD | SS | MTV (n) Day 74 | No of | | | | | MeanBW |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | PR | CR | TFS | TR | NTR | |
| 1 | 41.0 | - | - | - | 322 (2) | 0 | 0 | 0 | 0 | 0 | - |
| 2 | 60.0 | 19.0 | 46% | ns | 0 (3) | 1 | 0 | 0 | 2 | 2 | - |
| 3 | 47.9 | 6.9 | 17% | ns | 0 (3) | 1 | 0 | 0 | 2 | 2 | - |
| 4 | 59.1 | 18.1 | 44% | ns | 195 (1) | 4 | 0 | 0 | 0 | 0 | - |
| 5 | 74.0 | 33.0 | 80% | ns | 320 (5) | 4 | 0 | 0 | 1 | 0 | - |
| 6 | 57.8 | 16.8 | 41% | ne | 0 (3) | 1 | 3 | 0 | 2 | 2 | 0.1% Day 22 |

***Growth of COLO 205 Tumors in Control Mice (Group 1)***

Group 1 tumors exhibited slow, heterogeneous growth. The tumors of 7/9 vehicle-treated Group 1 control mice attained the 800 $mm^3$ tumor volume endpoint and two mice remained at study's end. The Group 1 median TTE was 41.0 days, and therefore the maximum TGD possible in this 74-day study was 33.0 days (80%).

***Effect of Treatment with Paclitaxel (Group 2)***

Eight Group 2 mice (n = 9) that received treatment with paclitaxel remained in the study on Day 74 with an MTV of 143 $mm^3$. This corresponds to the maximum possible TGD (33.0 days or 80%) and statistically significant activity ($P = 0.002$). Five PR responses were documented. The median tumor growth curve shows a decrease in MTV through Day 19, followed by little change until Day 47 when tumor growth resumed.

***Effect of Treatment with Compound A (Groups 3–6)***

Groups 3, 4, 5 produced median TTEs of 47.9, 59.1 and 74.0 days, respectively. Groups 3 and 4 had non-significant logrank results, and the Group 5 logrank test attained borderline significance ($P = 0.058$). These treatments produced dose-dependent numbers of regressions, however, the type of regression response (PR vs. CR) and the numbers of 74-day survivors per group did not correlate with dose. The median tumor growth curves indicate similar activities for the three dose levels early in the study (through Day 29), followed by dose-dependent delays in tumor re-growth. Group 6 produced three TR deaths, and dosing was stopped after Day 6. The 200 mg/kg treatment was therefore deemed above the MTD and not evaluable for TGD.

Compound A demonstrated dose-dependent activity against COLO 205 colon carcinoma xenografts. When administered at 25 mg/kg, Compound A exhibited a TGD of 3%. At 50 mg/kg, Compound A produced a TGD of 46%. The 100 mg/kg treatment was acceptably tolerated and, like the paclitaxel treatment, resulted in the maximum TGD possible in the experiment with a similar number of regression responses. The 200 mg/kg treatment produced 3/9 TR deaths and was above the MTD. A more pronounced initial decrease in tumor burden for Compound A compared to paclitaxel was observed; however, the duration of the effect was shorter. Tumor re-growth in the 25 and 50 mg/kg groups initially proceeded at a more rapid pace compared to controls, and by the end of study, MTVs approached those of controls. The 100 mg/kg treatment did not exhibit this rapid re-growth, but did show faster tumor growth compared to that of paclitaxel.

Example 119: ***Human Clinical Trial***

A randomized, Double-blind, open label, historical control, single group assignment, safety/efficacy human phase I clinical trial with compound A vs placebo in Patients with chemo-naive advanced or metastatic pancreatic cancer will be performed.

The primary purpose of the study is to evaluate the safety and tolerability of compound A. A secondary outcome will be to evaluate the response rate, clinical benefit, and tumor shrinkage after treatment with compound A. Further, the study will be designed to evaluate time to disease progeression and overall survival of patients with the pancreatic cancer. In addition, pharmacodynamic changes in tumor vascular parameters will be evaluated (including, e.g. blood flow, blood volume, time to peak ROC-receiver operator characteristics curve) by DCE-MRI.

Moreover, the biologic markers such as MEK1 and MEK2 genetic plymorphisms and serum proteomics will be used to correlate outcomes. This will also permit the resectability rates of tumors after treatment to be determined, as well as the MTD for compound A to be evaluated.

During the study, compound A will be administered in varying does of about about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 3.5 mg, about 4.0 mg, about 4.5 mg, about 5 mg, about 5.5 mg, about 6 mg, about 6.5 mg, about 7 mg, about 7.5 mg, about 8 mg, about 8.5 mg, about 9 mg, about 9.5 mg, about 10 mg, about 10.5 mg, about 11 mg, about 11.5 mg, about 12 mg, about 12.5 mg, about 13 mg, about 13.5 mg, about 14 mg, about 14.5, or about 15 mg.

Inclusion criteria for the study will be based on the follwoing factors:

- Histologically/pathologically confirmed locally advanced unresectable or borderline unresectable pancreatic cancer, and no evidence of metastatic disease.

- Diagnosis of locally advanced unresectable pancreatic cancer based on assessment by dual-phase CT scan and/or endoscopic ultrasound (EUS) (EUS described in Appendix F).

- Measurable disease according to RECIST and obtained by dual-phase CT scan within 14 days prior to being registered for protocol therapy.

- Tumor size greater than or equal to 2 cm on dual-phase computed tomography scan.

- Adequate organ function documented within 14 days of registration as evidenced by:absolute neutrophil count > 1500/mm3; platelet count;100,000/mm3; hemoglobin $^3$ 9 gm/dL without transfusion requirement in the prior 4 weeks; total bilirubin ≤ 1.5 times upper limit of normal (ULN); transaminases (AST and/or ALT) ≤ 2.5 x ULN; PT (or INR) ≤ 1.5 x ULN and aPTT within normal limits (patients who receive anticoagulation treatment with an agent such as warfarin or heparin will be allowed to participate; for patients on warfarin, close monitoring of at least weekly evaluations will be performed until INR is stable based on a measurement at predose, as defined by the local standard of care; Creatinine clearance of > 60 ml/ min calculated using the Cockcroft-Gault formula.

Exclusion Criteria will include: prior treatment with compound A within 6 months prior to registration; clinical evidence of duodenal mucosal invasion by tumor (as documented by endoscopy or endoscopic ultrasound); minor surgical procedure (e.g fine needle aspiration or needle biopsy) within 14 days of study registration; major surgical procedure, significant traumatic injury, or serious non-healing wound, ulcer or bone fracture within 21 days of study registration; any of the following within 6 months prior to study drug administration: severe/unstable angina (anginal symptoms at rest), new onset angina (began within the last 3 months) or myocardial infarction, congestive heart failure, cardiac ventricular arrhythmias requiring anti-arrhythmic therapy; history of thrombotic or embolic events such as cerebrovascular accident or transient ischemic attack within the past 6 months; history of aneurysm or arteriovenous malformation; known human immunodeficiency virus (HIV) infection or chronic Hepatitis B or C; active clinically serious infection greater than CTCAE grade 2; receipt of any investigational agent within 4 weeks of study registration; uncontrolled hypertension defined as systolic blood pressure greater than 150 mmHg or diastolic pressure greater than 90 mmHg, despite optimal medical management; pulmonary hemorrhage/bleeding event greater than CTCAE Grade 2 within 4 weeks of study registration; any other hemorrhage/bleeding event greater than CTCAE Grade 3 within 4 weeks of study registration; evidence or history of bleeding diathesis or coagulopathy; chronic, daily treatment with aspirin or other nonsteroidal anti-inflammatory medications; use of St. John's Wort, rifampin (rifampicin), ketoconazole, itraconazole, ritonavir, or grapefruit juice; known or suspected allergy to compound A; any condition that impairs patient's ability to swallow whole pill; any malabsorption problem; other severe, acute or chronic medical or psychiatric condition, or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and in the judgment of the investigator would make the patient inappropriate for entry into this study; history of collagen vascular disease; any contraindication to undergo magnetic resonance imaging.

Example 120: ***Human Clinical Trial***

A randomized, Double-blind, open label, historical control, single group assignment, safety/efficacy human phase I clinical trial with compound A in Patients with chemo-naive advanced or metastatic stomach cancer will be performed in the same manner as that prescribed in Example 117, except the enrolled patients with be diagnosed either lymphoma, gastric stromal tumors, or carcinoid tumors of the stomach.

Example 121: ***Carrageenan-Induced Paw Edema (CPE) in Rats***

Compound A (6, 20 & 60 mg/kg) or indomethacin (3 mg/kg) were administered orally 2 hr prior to injection of 1% suspension of carrageenan into the right hind foot pad of male Sprague-Dawley rats (N=6 per treatment group). The hind paw edema was measured 3 hr later by assessing paw volume by plethysmography. Reduction of hind paw edema by 30% or greater indicates significant acute anti-inflammatory activity. Indomethacin (Indo) was used as a positive control drug. Shown in figure 22are the increases in paw volume in each of the treatment groups demonstrating that oral administration of Compound A resulted in significant anti-inflammatory activity in the rat carrageenan paw edema model in all dose groups.

Example 122: ***Rat Adjuvant Arthritis Inflammation Assay***

In the rat adjuvant induced arthritis model, Complete Freund's Adjuvant (CFA) is injected into the right hind paw of rats to induce pathologies similar to rheumatoid arthritis in humans. Compound A was administered orally for 5 consecutive days at 2, 6, and 20 mg/kg. Dexamethasone at 5 mg/kg was also administered orally for 5 days. Enbrel at 10 mg/kg was administered by subcutaneous injection on days 1 and 4. CFA was injected into the right hind paw one hour after the first dose on day 1. The percent inhibition of right hind paw swelling relative to vehicle treated controls on days 1 and 5 were determined for the acute phase while the percent inhibition of left hind paw swelling relative to vehicle treated controls on days 14 and 18 were determined for the delayed phase. Polyarthritis was scored as the presence of swelling in front paws, tail, nose or ear.

Shown in **Figure 23A** and **Figure 23B** are the percent inhibition of swelling relative to control for the different treatment groups. Compound A at 20 mg/kg showed significant reduction in swelling in both the acute and delayed phases. For the polyarthritis scoring, all 6 animals in the vehicle treated group had swelling in the front paws and tail. For the 20 mg/kg Compound A group, 2 of 6 did not have front paw swelling and 4 of 6 did not have swelling in the tail. For the enbrel group, no animals were protected from front paw swelling and 3 of 6 animals did not have swelling in the tail.

Example 123: ***Inhibition of Collagen-Antibody Induced-Arthritis (CAIA) in Mice***

Male Balb/c mice (N=8 per treatment group) were injected intravenously (tail vein) with 2 mg of collagen antibody cocktail (Chondrex) on day 0. RDEA119 (1, 3 & 10 mg/kg QD) or dexamethasone (1 mg/kg QD) were administered orally from days 0-4, while Enbrel was injected subcutaneously on days 1 and 3. An intraperitoneal injection of LPS (50 μg) was given on day 3 to all mice except naïve animals. The determination of the arthritic scores on all limbs were determined and are shown in **Figure 24** (maximum score 16). Significant anti-inflammatory activity was noted for all test articles and reference drugs. Enbrel and dexamethasone were used as positive controls.

Example 124: ***In Vivo Cell Proliferation Assay***

A method for determining cell proliferation counts in cancerous cells treated with a MEK protein kinase inhibitor, is understood in the art and is described in Kenny, L.M. et al., Positron Emission Tomography (PET) Imaging of Cell Proliferation in Oncology, Clinical Oncology, 16:176-185 (2004), which is hereby incorporated by reference in its entirety. A MEK protein kinase inhibitor (e.g. Compound A) is examined in vivo to determine their effect on proliferation of cancerous cells. 50 patients are voluntarily enrolled in the study, all of which are suffering from pancreatic cancer at a similar stage of cancerous development. 25 patients are administered a combination of compound A. The final 25 patients are administered placebo. Each patient is administered a daily dose for 14 days with a radio labeled tracer, e.g. labeled fluoro-2-deoxy-DF-glucose (FDG).

After 14 days of treatment, a trained physician using a non-invasive positron emission tomography (PET) imaging apparatus detects tumor cell proliferation. Moreover, the trained physician will determine cell proliferation counts of both tumor and normal cell tissue for patients treated with Compound A and placebo. The results will indicate a decrease in cell proliferation counts between the MEK protein kinase inhibitor (e.g. Compound A) and placebo. This

assay for the determining cell proliferation counts using labeled tracers and PET imaging is referred to herein as an "in vivo cell proliferation method." Other *in vivo* cell proliferation methods are known in the art.

Similar analysis can be used to determine decrease in tumor size.

Example 125: ***In Vivo Apoptosis Assay***

MEK inhibitor, e.g., Compound A is examined in vivo to determine its effect on apoptosis of cancer cells. 40 patients are voluntarily enrolled in the study, all of which are suffering from pancreatic cancer at a similar stage of cancerous development. 20 patients are administered compound A and 20 patients are administered placebo. Each patient is adminsitered a daily dose for 14 days.

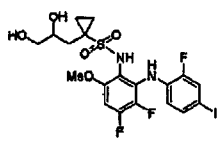
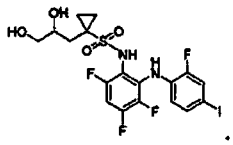
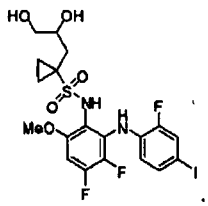
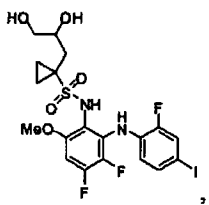
After 14 days, each patient will consume a detectable lipopolysaccharide binding protein (LBP) reagent coupled to a label. In accordance wth WO/2006/054068, which is hereby incorporated by reference in its entirety, each patient is then placed in the field of a scanning apparatus whereby the scaning apparatus detects the consumed reagent bound to dead cells. The number of dead cells can be correlated to a level apoptosis of each patient. The apoptosis levels in patients administered the combinations and those administered the single entity agents can be compared against each others, as well as with respect to the cohort group administered placebo. This assay for the detection of apoptosis levels using a lipopolysaccharide binding protein and scanning apparatus is referred to as the herein as an "in vivo apoptosis method."

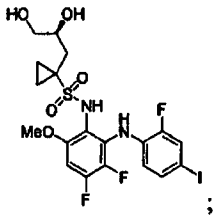
Example 126: Dissolution Studies

Capsules containing Compound A were prepared as described in the above examples. The following dissolution data was obtained using the USP<711> method for dissolution.

| | 1mg from | 10mg form |
|---|---|---|
| Time (min) | % Release (%RSD) | % Release (%RSD) |
| 15 | 78 (8.3) | 80 (7.3) |
| 30 | 82 (7.1) | 87 (9.2) |
| 45 | 82 (6.7) | 92 (9.6) |
| 60 | 88 (6.3) | 92 (7.2) |
| 70 | 86 (5.7) | 95 (5.4) |

**WHAT IS CLAIMED IS:**

1. A composition comprising a compound selected from:  and  .
2. The composition of claim 1, wherein the 2-OH carbon on the compound is in the R configuration.
3. The composition of claim 1, wherein the 2-OH carbon on the compound is in the S configuration.
4. The composition of claim 1, wherein the composition is substantially free of the S- isomer of the compound.
5. The composition of claim 1, wherein the composition is substantially free of the R- isomer of the compound.
6. The composition of claim 1, wherein the compound contains less than 10% of the S- isomer of the compound.
7. The composition of claim 1, wherein the compound contains less than 10% of the R- isomer of the compound.
8. The composition of claim 1, wherein the compound contains less than 5% of the S- isomer of the compound.
9. The composition of claim 1, wherein the compound contains less than 5% of the R- isomer of the compound.
10. The composition of claim 1, wherein the compound contains less than 1% of the S- isomer of the compound.
11. The composition of claim 1, wherein the compound contains less than 1% of the R- isomer of the compound.
12. The composition of any of the preceding claims comprising about 1-100 mg of a compound having the following structure:  .
13. The composition of claim 12, wherein the composition allows for modified release of the compound.
14. The composition of claim 12, wherein the composition allows for sustained release of the compound.
15. The composition of claim 12, wherein the composition allows for delayed release of the compound.
16. The composition of claim 12, wherein the compound is present in an amount of about 1-50 mgs.
17. The composition of claim 12, wherein the compound is present in an amount of about 1-10 mgs.
18. The composition of claim 12, wherein the compound is present in an amount of about 10-20 mgs.
19. The composition of claim 12, wherein the compound is present in an amount of about 20-40 mgs.
20. The composition of claim 12, wherein the compound is present in an amount of about 40-50 mgs.
21. The composition of any of claims 1-15 comprising: about 1-50 mg of a compound having the following structure  , wherein the composition allows for modified release of the drug.
22. The composition of any of claims 1-21 further comprising microcrystalline cellulose.
23. The composition of any of claims 1-22 further comprising croscarmellose sodium.
24. The composition of any of claims 1-23 further comprising sodium lauryl sulfate.
25. The composition of any of claims 1-24 further comprising magnesium stearate.
26. The composition of any of claims 1-15 comprising



about 1mg of a compound of structure: ;

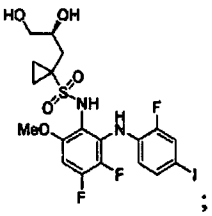
about 222.2mg of microcrystalline cellulose;

about 12.0mg of croscarmellose sodium;

about 2.4mg of sodium lauryl sulfate; and

about 2.4mg of magnesium stearate.

27. The composition of any of claims 1-15 comprising:



about 10mg of a compound of structure ;

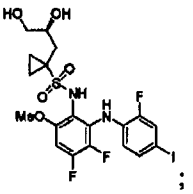
about 213.2mg of microcrystalline cellulose;

about 12.0mg of croscarmellose sodium;

about 2.4mg of sodium lauryl sulfate; and

about 2.4mg of magnesium stearate.

28. The composition of any of claims 1-15 comprising:



about 20mg of a compound of structure ;

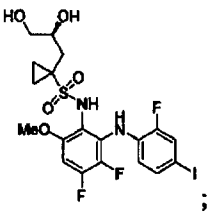
about 203.2mg of microcrystalline cellulose;

about 12.0mg of croscarmellose sodium;

about 2.4mg of sodium lauryl sulfate; and

about 2.4mg of magnesium stearate.

29. The composition of any of claims 1-15 comprising:



about 40mg of a compound of structure ;

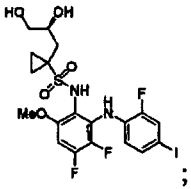
about 183.2mg of microcrystalline cellulose;

about 12.0mg of croscarmellose sodium;

about 2.4mg of sodium lauryl sulfate; and

about 2.4mg of magnesium stearate.

30. The composition of any of claims 1-15 comprising: about 0.4% by weight of a compound of structure



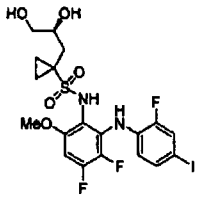
; and about 99.6% by weight of a pharmaceutically acceptable carrier or vehicle.

31. The composition of claim 30, wherein the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose.

32. The composition of claim 31, wherein the microcrystalline cellulose is about 92.6% by weight of the composition.

33. The composition of claim 32, further comprising: about 5% by weight croscarmellose sodium; about 1% by weight sodium lauryl sulfate; and about 1% by weight magnesium stearate.

34. The composition of any of claims 1-15 comprising: about 4.2% by weight of a compound of structure

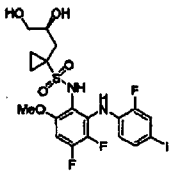


; and about 95.8 % by weight of a pharmaceutically acceptable carrier or vehicle.

35. The composition of claim 34, wherein the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose.

36. The composition of claim 35, wherein the microcrystalline cellulose is about 88.8% by weight of the composition.

37. The composition of claim 36, further comprising: about 5% by weight croscarmellose sodium; about 1% by weight sodium lauryl sulfate; and about 1% by weight magnesium stearate.

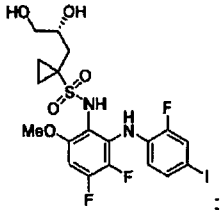
38. The composition of any of claims 1-15 comprising: from about 2% to about 10% by weight of a compound of structure  ; and from about 98% to about 90% by weight of a pharmaceutically acceptable carrier or vehicle.

39. The composition of claim 38, wherein the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose.

40. The composition of claim 39, wherein the microcrystalline cellulose is from about 85% to about 95% by weight of the composition.

41. The composition of claim 40, further comprising: from about 1% to about 6% by weight croscarmellose sodium; from about 0.1% to about 2% by weight sodium lauryl sulfate; and from about 0.25% to about 1.5% by weight magnesium stearate.

42. The composition of any of claims 1-15 comprising:

about 1mg of a compound of structure:  ;

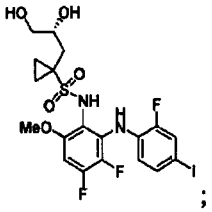
about 222.2mg of microcrystalline cellulose;

about 12.0mg of croscarmellose sodium;

about 2.4mg of sodium lauryl sulfate; and

about 2.4mg of magnesium stearate.

43. The composition of any of claims 1-15 comprising:



about 10mg of a compound of structure: ;

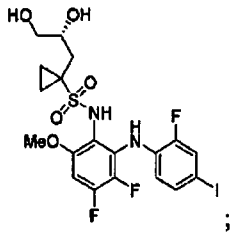
about 213.2mg of microcrystalline cellulose

about 12.0mg of croscarmellose sodium;

about 2.4mg of sodium lauryl sulfate; and

about 2.4mg of magnesium stearate.

44. The composition of any of claims 1-15 comprising:



about 20mg of a compound of structure: ;

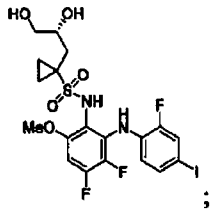
about 203.2mg of microcrystalline cellulose;

about 12.0mg of croscarmellose sodium;

about 2.4mg of sodium lauryl sulfate; and

about 2.4mg of magnesium stearate.

45. The composition of any of claims 1-15 comprising:



about 40mg of a compound of structure: ;

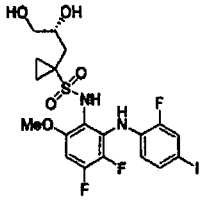
about 183.2mg of microcrystalline cellulose;

about 12.0mg of croscarmellose sodium;

about 2.4mg of sodium lauryl sulfate; and

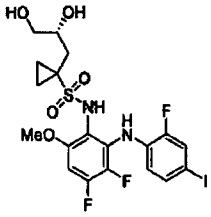
about 2.4mg of magnesium stearate.

46. The composition of any of claims 1-15 comprising: about 0.4% by weight of a compound of structure:

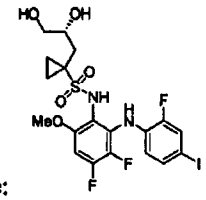


; and about 99.6% by weight of a pharmaceutically acceptable carrier or vehicle.

47. The composition of claim 46 wherein the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose.
48. The composition of claim 47, wherein the microcrystalline cellulose is about 92.6% by weight of the composition.
49. The composition of claim 48, further comprising: about 5% by weight croscarmellose sodium; about 1% by weight sodium lauryl sulfate; and about 1% by weight magnesium stearate.
50. The composition of any of claims 1-15 comprising: about 4.2% by weight of a compound of structure:

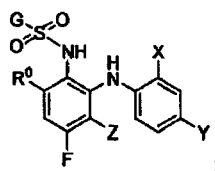


and about 95.8 % by weight of a pharmaceutically acceptable carrier or vehicle.
51. The composition of claim 50, wherein the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose.
52. The composition of claim 51, wherein the microcrystalline cellulose is about 88.8% by weight of the composition.
53. The composition of claim 52, further comprising: about 5% by weight croscarmellose sodium; about 1% by weight sodium lauryl sulfate; and about 1% by weight magnesium stearate.
54. The composition of any of claims 1-15 comprising: from about 2% to about 10% by weight of a compound of structure:



; and from about 98% to about 90% by weight of a pharmaceutically acceptable carrier or vehicle.
55. The composition of claim 54, wherein the pharmaceutically acceptable carrier or vehicle comprises microcrystalline cellulose.
56. The composition of claim 55, wherein the microcrystalline cellulose is from about 85% to about 95% by weight of the composition.
57. The composition of claim 56, further comprising: from about 1% to about 6% by weight croscarmellose sodium; from about 0.1% to about 2% by weight sodium lauryl sulfate; and from about 0.25% to about 1.5% by weight magnesium stearate.
58. The composition of any of the preceding claims, further comprising at least one pharmaceutically acceptable carrier.
59. A crystalline polymorph Form A of N-(-)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide that exhibits a powder x-ray diffraction pattern comprising at least 50% of the peaks identified in the powder x-ray diffraction pattern shown in FIG. 5.
60. The crystalline polymorph Form A of claim 59, wherein the powder x-ray diffraction pattern comprises at least 70% of the peaks identified in the powder x-ray diffraction pattern shown in FIG. 5.
61. The crystalline polymorph Form A of claim 59, wherein the powder x-ray diffraction pattern comprises at least 90% of the peaks identified in the powder x-ray diffraction pattern shown in FIG. 5.
62. The crystalline polymorph Form A of claim 59, wherein the powder x-ray diffraction pattern substantially the same as the powder x-ray diffraction pattern shown in FIG. 5.

63. The crystalline polymorph of any of claims 59-62, wherein the crystalline polymorph has a melting point onset as determined by differential scanning calorimetry at about 143°C.
64. The crystalline polymorph of any of claims 59-62, wherein the crystalline polymorph is substantially free of water.
65. The crystalline polymorph of any of claims 59-62, wherein the crystalline polymorph is substantially free of solvent.
66. A pharmaceutical composition comprising an effective amount of the crystalline polymorph of any of claims 59-62 and at least one excipient or carrier.
67. A crystalline polymorph Form A of N-(-)-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide that exhibits a differential scanning calorimetry pattern substantially the same as the differential scanning calorimetry pattern shown in FIG. 6.
68. The crystalline polymorph of claim 67, wherein the crystalline polymorph has a melting point onset as determined by differential scanning calorimetry at about 143°C.
69. The crystalline polymorph of claim 67 or 68, wherein the crystalline polymorph is substantially free of water.
70. The crystalline polymorph of any of claims 67-69, wherein the crystalline polymorph is substantially free of solvent.
71. A pharmaceutical composition comprising an effective amount of the crystalline polymorph of any of claims 67-70 and at least one excipient or carrier.
72. A polymorphic form of N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide made by a method comprising the step of crystallizing amorphous N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl) cyclopropane-1-sulfonamide.
73. The polymorphic form of claim 72, wherein the crystallization step comprises crystallizing from a mixture of of ethyl acetate and heptane.
74. The polymorphic form of claim 73, wherein the mixture of ethyl acetate and heptane is in a ratio of from about 1-4 parts ethyl acetate to about 2-10 parts heptane.
75. The polymorphic form of claim 73, wherein the mixture of ethyl acetate and heptane is in a ratio of from about 2 parts ethyl acetate to about 5 parts heptane.
76. A method for inhibiting MEK enzymes comprising contacting said MEK enzyme with a compound or composition according to any of claims 1-75, wherein the compound is present in an amount sufficient to inhibit said enzyme by at least 25%.
77. The method of claim 76, wherein said MEK enzyme is MEK kinase.
78. The method of claim 76, wherein said contacting occurs within a cell.
79. A method of treatment of a MEK mediated disorder in an individual suffering from said disorder, comprising administering to said individual an effective amount of a compound or composition according to any of claims 1-75.
80. The method of claim 79, in combination with an additional therapy.
81. The method of claim 80, wherein said additional therapy is radiation therapy, non-MEK kinase inhibitor therapy, chemotherapy, surgery, Glucocorticoid, methotrexate, biological response modifiers, or any combination thereof.
82. The method of claim 79, wherein said MEK mediated disorder is selected from the group consisting of inflammatory diseases, infections, autoimmune disorders, stroke, ischemia, cardiac disorder, neurological disorders, fibrogenetic disorders, proliferative disorders, hyperproliferative disorders, tumors, leukemias, neoplasms, cancers, carcinomas, metabolic diseases and malignant diseases.
83. The method of claim 79 wherein said MEK mediated disorder is a hyperproliferative disease.
84. The method of claim 79 wherein said MEK mediated disorder is cancer, tumors, leukemias, neoplasms, or carcinomas.

85. The method of claim 79 wherein said MEK mediated disorder is an inflammatory disease.
86. The method of claim 85 wherein said inflammatory disease is rheumatoid arthritis or multiple sclerosis.
87. A method for the treatment or prophylaxis of a proliferative disease in an individual comprising administering to said individual an effective amount of a compound or composition according to any of claims 1-75.
88. The method of claim 87 wherein said proliferative disease is cancer, psoriasis, restenosis, disease, or atherosclerosis.
89. The method of claim 87, wherein said proliferative disease is cancer.
90. The method of claim 89, wherein said cancer is brain cancer, breast cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, colorectal cancer, leukemia, myeloid leukemia, glioblastoma, follicular lymphona, pre-B acute leukemia, chronic lymphocytic B-leukemia, stomach cancer, mesothelioma or small cell lung cancer.
91. The method of any of claims 87-90, further comprising administering at least one therapeutic agent.
92. The method of any of claims 87-90, further comprising administering at least one additional cancer therapy.
93. The method of claim 92, wherein said additional therapy is radiation therapy, non-MEK kinase inhibitor therapy, chemotherapy, surgery, Glucocorticoid, methotrexate, biological response modifiers, or any combination thereof.
94. A method for the treatment or prophylaxis of an inflammatory disease in an individual comprising administering to said individual an effective amount of a composition comprising a compound of any of claims 1-75.
95. The method of claim 94, wherein said inflammatory disease is rheumatoid arthritis or multiple sclerosis.
96. A method for degrading, inhibiting the growth of or killing cancer cells comprising contacting the cells with an amount of the compound or composition of any of claims 1-75 effective to degrade, inhibit the growth of or kill cancer cells.
97. The method of claim 96, wherein said cancer cells comprise brain, breast, lung, ovarian, pancreatic, prostate, renal, liver, stomach or colorectal cancer cells.
98. A method of inhibiting tumor size increase, reducing the size of a tumor, reducing tumor proliferation or preventing tumor proliferation in an individual comprising administering to said individual an effective amount of the compound or composition of any of claims 1-75 to inhibit tumor size increase, reduce the size of a tumor, reduce tumor proliferation or prevent tumor proliferation.
99. The method of claim 98, for inhibiting tumor size increase or reducing the size of a tumor wherein said tumor occurs in the brain, breast, lung, ovaries, pancreas, prostate, kidney, liver, stomach, colon or rectum.
100. The method of claim 98, for inhibiting tumor size increase or reducing the size of a tumor wherein said individual is a mammal.
101. A method for treating or preventing ankylosing spondylitis, gout, tendonitis, bursitis or sciatica, comprising administering to a subject in need thereof an effective amount of a compound of formula (I) or a pharmaceutical salt thereof:  ; wherein:

Z is H or F;

X is F, Cl, $CH_3$, $CH_2OH$, $CH_2F$, $CHF_2$, or $CF_3$;

Y is I, Br, Cl, $CF_3$, $C_1$-$C_3$ alkyl, $C_2$-$C_3$ alkenyl, $C_2$-$C_3$ alkynyl, cyclopropyl, OMe, OEt, SMe, phenyl or Het, where Het is a 5- to 10- membered mono- or bicyclic heterocyclic group, which group is saturated, olefinic, or aromatic, containing 1-5 ring heteroatoms selected independently from N, 0, and S; where

all said phenyl or Het groups are optionally substituted with F, Cl, Br, I, acetyl, methyl, CN, $NO_2$, $CO_2H$, $C_1$-$C_3$ alkyl, $C_1$-$C_3$ alkoxy, $C_1$-$C_3$ alkyl-C(=O)-, $C_1$-$C_3$ alkyl-C(=S)-, $C_1$-$C_3$ alkoxy-C(=S)-, $C_1$-$C_3$ alkyl-C(=O)O-, $C_1$-$C_3$ alkyl-0-(C=O)-, $C_1$-$C_3$ alkyl-C(=O)NH-, $C_1$-$C_3$ alkyl-C(=NH)NH-, $C_1$-$C_3$ alkyl-NH-(C=O)-, di-$C_1$-$C_3$ alkyl-N-(C=O)-, $C_1$-$C_3$ alkyl-C(=O)N($C_1$-$C_3$ alkyl)-, $C_1$-$C_3$ alkyl-S(=O)$_2$NH- or trifluoromethyl;

all said methyl, ethyl, $C_1$-$C_3$ alkyl, and cyclopropyl groups are optionally substituted with OH;

all said methyl groups are optionally substituted with one, two, or three F atoms;

$R^0$ is H, F, Cl, Br, I, $CH_3NH$-, $(CH_3)_2N$-, $C_1$-$C_6$ alkyl, $C_1$-$C_4$ alkoxy, $C_3$-$C_6$ cycloalkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, phenyl, monosubstituted phenyl, O($C_1$-$C_4$ alkyl), O-C(=O)($C_1$-$C_4$ alkyl) or C(=O)O($C_1$-$C_4$ alkyl); where

said alkyl, alkoxy, cycloalkyl, alkenyl, alkynyl and phenyl groups are optionally substituted with 1-3 substituents selected independently from F, Cl, Br, I, OH, CN, cyanomethyl, nitro, phenyl and trifluoromethyl;

said $C_1$-$C_6$ alkyl and $C_1$-$C_4$ alkoxy groups also optionally substituted with $OCH_3$or $OCH_2CH_3$;

G is $G_1$, $G_2$, $R_{1a}$, $R_{1b}$, $R_{1c}$, $R_{1d}$, $R_{1e}$, $Ar_1$, $Ar_2$ or $Ar_3$; where

$G_1$ is $C_1$-$C_6$ alkyl optionally substituted with one amino, $C_1$-$C_3$ alkylamino, or dialkylamino group, said dialkylamino group comprising two $C_1$-$C_4$ alkyl groups which may be identical or non-identical; or

$G_1$ is a $C_3$-$C_8$ diamino alkyl group;

$G_2$ is a 5- or 6- membered ring, which is saturated, unsaturated, or aromatic, containing 1-3 ring heteroatoms selected independently from N, 0, and S, optionally substituted with 1-3 substituents selected independently from F, Cl, OH, O($C_1$-$C_3$ alkyl), $OCH_3$, $OCH_2CH_3$, $CH_3C(=O)NH$, $CH_3C(=O)O$, CN, $CF_3$, and a 5-membered aromatic heterocyclic group containing 1-4 ring heteroatoms selected independently from N, O , and S;

$R_{1a}$ is methyl, optionally substituted with 1-3 fluorine atoms or 1-3 chlorine atoms, or with OH, cyclopropoxy, or $C_1$- $C_3$ alkoxy, where said cyclopropoxy group or the $C_1$- $C_3$ alkyl moieties of said $C_1$- $C_3$ alkoxy groups are optionally substituted with one hydroxy or methoxy group, and where all $C_3$- alkyl groups within said $C_1$- $C_4$ alkoxy are optionally further substituted with a second OH group;

$R_{1b}$ is $CH(CH_3)$-$C_{1-3}$ alkyl or $C_3$-$C_6$ cycloalkyl, said alkyl and cycloalkyl groups optionally substituted with 1-3 substituents selected independently from F, Cl, Br, I, OH, $OCH_3$, and CN;

$R_{1c}$ is $(CH_2)_nO_mR'$; where

m is 0 or 1; and where

when m is 0, n is 1 or 2;

when m is 1, n is 2 or 3;

R' is $C_1$-$C_6$ alkyl, optionally substituted with 1-3 substituents selected independently from F, Cl, OH, $OCH_3$, $OCH_2CH_3$, and $C_3$-$C_6$ cycloalkyl;

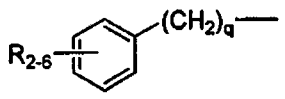
$R_{1d}$ is C(A)(A')(B)-; where

B is H or $C_{1-4}$ alkyl, optionally substituted with one or two OH groups;

A and A' are independently H or $C_{1-4}$ alkyl, optionally substituted with one or two OH groups; or

A and A', together with the carbon atom to which they are attached, form a 3- to 6- member saturated ring;

$R_{1e}$ is



$R_{1e}$

where

q is 1 or 2;

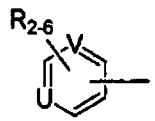
$R_2$ and $R_3$ are each independently, H, F, Cl, Br, $CH_3$, $CH_2F$, $CHF_2$, $CF_3$ $OCH_3$, $OCH_2F$, $OCHF_2$, $OCF_3$, ethyl, *n*-propyl, isopropyl, cyclopropyl, isobutyl, *sec*-butyl, *tert*-butyl or methylsulfonyl;

$R_4$ is H, F, Cl, Br, $CH_3$, $CH_2F$, $CHF_2$, $CF_3$ $OCH_3$, $OCH_2F$, $OCHF_2$, $OCF_3$, ethyl, *n*-propyl, isopropyl, cyclopropyl, isobutyl, *sec*-butyl, *tert*-butyl, methylsulfonyl, nitro, acetamido, amidinyl, cyano, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, l,3,4-oxadiazol-2-yl, 5-methyl-l,3,4- oxadiazol, 1,3,4-thiadiazol, 5-methyl-l,3,4-thiadiazol lH-tetrazolyl, N-morpholyl carbonyl amino, N-morpholylsulfonyl and N-pyrrolidinylcarbonylamino;

$R_5$ is H, F, Cl or methyl;

$R_6$ is H, F, Cl or methyl;

$Ar_1$ is




$Ar_1$

where

U and V are, independently, N, $CR_2$ or $CR_3$;

$R_2$, $R_3$ and $R_4$ are, independently, H, F, Cl, Br, $CH_3$, $CH_2F$, $CHF_2$, $CF_3$ $OCH_3$, $OCH_2F$, $OCHF_2$, $OCF_3$, ethyl, *n*-propyl, isopropyl, cyclopropyl, isobutyl, *sec*-butyl, *tert*-butyl, acetamido, amidinyl, cyano, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, l,3,4-oxadiazol-2-yl, 5-methyl-l,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, 5-methyl-l,3,4-thiadiazolyl, lH-tetrazolyl, N-morpholylcarbonylamino, N-morpholylsulfonyl, N-pyrrolidinylcarbonylamino, and methylsulfonyl;

$R_5$ and $R_6$ are, independently, H, F, Cl or methyl;

$Ar_2$ is




$Ar_2$

where

the dashed line represents alternative formal locations for the second ring double bond;

U is -S-, -O- or -N =, and where

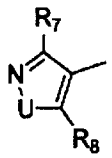
when U is -O- or -S-, V is -CH=, -CCl= or -N =;

when U is -N =, V is -CH=, -CCl=, or -N=;

$R_7$ is H or methyl;

$R_8$ is H, acetamido, methyl, F or Cl;

$Ar_3$ is



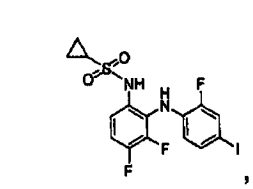
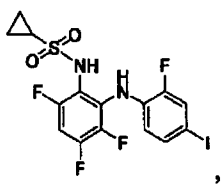
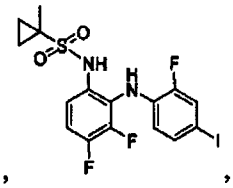
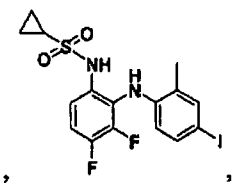
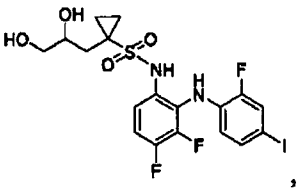
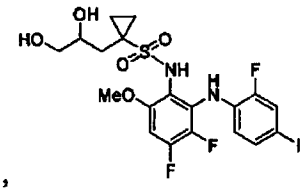
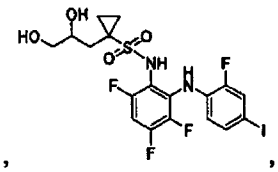
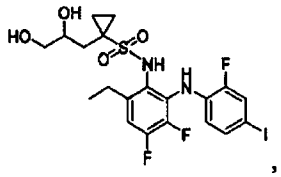
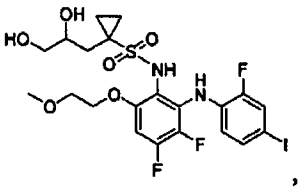
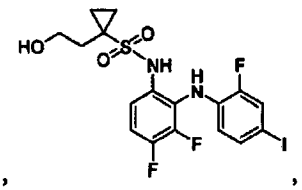
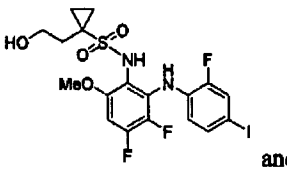
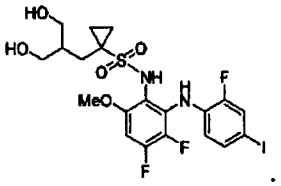
$Ar_3$

where

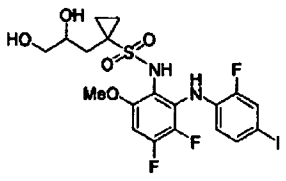
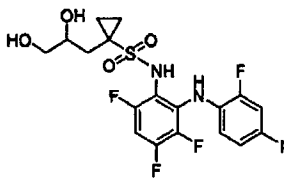
U is -NH-, $-NCH_3-$ or -O-;

$R_7$ and $R_8$ are, independently, H, F, Cl, or methyl.

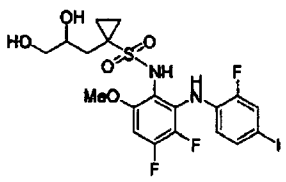
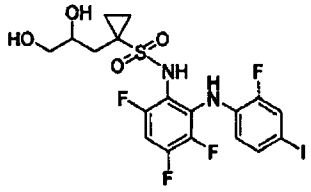
102. The method of claim 101 wherein the compound of formula (I), or a pharmaceutical salt thereof, is selected from:


,

,

,

,

,

,

,

,

,

,

and

.

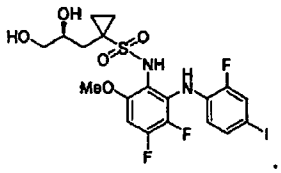
103. The method of claim 101 wherein the compound of formula (I), or a pharmaceutical salt thereof, is selected from


and

; where the 2-OH carbon is in the R configuration.

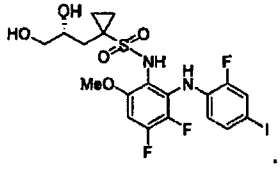
104. The method of claim 101 wherein the compound of formula (I), or a pharmaceutical salt thereof, is selected from


and

; where the 2-OH carbon is in the S configuration.

105. The method of claim 167 wherein the compound of formula (I), or a pharmaceutical salt thereof, is


.

106. The method of claim 167 wherein the compound of formula (I), or a pharmaceutical salt thereof, is


.

107. A method for treating stomach cancer by administering a therapeutically effective amount of a compound or composition according to any of claims 1-75.

108. A method for treating leukemiam melanoma, or hepatoma by administering a therapeutically effective amount of a compound or composition according to any of claims 1-75.

109. A method for treating non-small cell lung cancer by administering a therapeutically effective amount of a compound or composition according to any of claims 1-75.

110. A method for treating colon cancer by administering a therapeutically effective amount of a compound or composition according to any of claims 1-75.

111. A method for treating CNS cancer by administering a therapeutically effective amount of a compound or composition according to any of claims 1-75.

112. A method for treating ovarian cancer by administering a therapeutically effective amount of a compound or composition according to any of claims 1-75.

113. A method for treating renal cancer by administering a therapeutically effective amount of a compound or composition according to any of claims 1-75.

114. A method for treating prostate cancer by administering a therapeutically effective amount of a compound or composition according to any of claims 1-75.

115. A method for treating breast cancer by administering a therapeutically effective amount of a compound or composition according to any of claims 1-75.

116. The method of any of claims 107-115, further comprising administering at least one therapeutic agent.

117. The method of any of claims 107-115, further comprising administering at least one additional cancer therapy.

118. The method of claim 117, wherein said additional cancer therapy is radiation therapy, chemotherapy, surgery, or any combination thereof.

119. The method of any of claims 76-118, wherein the compound or composition is administered orally.

120. The method of any of claims 76-118, wherein the compound or composition is administered once a day or twice a day.

121. The method of any of claims 76-118, wherein the compound or composition is administered once a day for at least one week.

122. A method for treating or preventing psoriasis by administering a therapeutically effective amount of a compound or composition according to any of claims 1-75 in a topical dosage form.

123. The method of any of claims 76-121, wherein $T_{max}$ of the compound is achieved between 1 hour and 3 hours after administration of the composition to a fasted subject.

124. The compound, composition or method of any of the preceding claims, wherein upon administration to a subject, the compound reaches a $C_{max}$ between about 0.01 μg/ml to about 1.0 μg/ml on day 1.

125. The compound, composition or method of claim 124, wherein upon administration to a subject, the compound reaches a $C_{max}$ between about 0.01 μg/ml to about 0.8 μg/ml on day 1.

126. The compound, composition or method of claim 124, wherein upon administration to a subject, the compound reaches a $C_{max}$ between about 0.03 μg/ml to about 0.5 μg/ml on day 1.

127. The compound, composition or method of any of the preceding claims, wherein upon administration to a group of 10 subjects, the compound reaches a mean $C_{max}$ between about 0.01 μg/ml to about 1.0 μg/ml on day 1.

128. The compound, composition or method of claim 127, wherein upon administration to a group of 10 subjects, the compound reaches a mean $C_{max}$ between about 0.01 μg/ml to about 0.8 μg/ml on day 1.

129. The compound, composition or method of claim 127, wherein upon administration to a group of 10 subjects, the compound reaches a mean $C_{max}$ between about 0.03 μg/ml to about 0.5 μg/ml on day 1.

130. The compound, composition or method of any of claims 124-126, wherein the compound has an AUC between about 0.1 μg hr/mL to about 5.0 μg hr/mL from 0-12 hours.

131. The compound, composition or method of claim 130, wherein the compound has an AUC between about 0.1 μg hr/mL to about 4.0 μg hr/mL.

132. The compound, composition or method of claim 130, wherein the compound has an AUC between about 0.5 μg hr/mL to about 3.0 μg hr/mL.

133. The compound, composition or method of any of claims 127-129, wherein the compound has a mean AUC between about 0.1 μg hr/mL to about 5.0 μg hr/mL.

134. The compound, composition or method of claim 134, wherein the compound has a mean AUC between about 0.1 μg hr/mL to about 4.0 μg hr/mL.

135. The compound, composition or method of claim 134, wherein the compound has a mean AUC between about 0.5 μg hr/mL to about 3.0 μg hr/mL.

136. The compound, composition or method of any of claims 124-126 and 130-132, wherein the compound has a $T_{max}$ between 0.5 and 5.0 hours.

137. The compound, composition or method of claim 133, wherein the compound has a $T_{max}$ between 1.0 and 3.0 hours.

138. The compound, composition or method of claim 133, wherein the compound has a $T_{max}$ between 1.0 and 2.5 hours.

139. The compound, composition or method of any of claims 127-129 and 133-135, wherein the compound has a mean $T_{max}$ between 0.5 and 5.0 hours.

140. The compound, composition or method of claim 139, wherein the compound has a mean $T_{max}$ between 1.0 and 3.0 hours.

141. The compound, composition or method of claim 139, wherein the compound has a mean $T_{max}$ between 1.0 and 2.5 hours.

142. The compound, composition or method of any of claims 124-126, 130-132 and 136-138, wherein the compound has a plasma concentration greater than about 0.01 mg/mL after 5 hours after a single dose.

143. The compound, composition or method of any of claims 124-126, 130-132 and 136-138, wherein the compound has a plasma concentration greater than about 0.01 mg/mL after 10 hours after a single dose.

80 144. The compound, composition or method of any of claims 124-126, 130-132 and 136-138, wherein the compound has a plasma concentration greater than about 0.01 mg/mL after 15 hours after a single dose.

145. The method of any of claims 76-141, wherein after daily administration of the drug for 5 days, the tumor decreases in volume by at least about 25%.

146. The method of any of claims 76-141, wherein after daily administration of the drug for 5 days, the tumor decreases in volume by at least about 50%.

147. The method of any of claims 76-141, wherein after daily administration of the drug for 5 days, the tumor decreases in volume by at least about 20-70%.

148. The method of any of claims 76-141, wherein after daily administration of the drug for 15 days, the tumor decreases in volume by at least about 25%.

149. The method of any of claims 76-141, wherein after daily administration of the drug for 15 days, the tumor decreases in volume by at least about 50%.

150. The method of any of claims 76-141, wherein after daily administration of the drug for 15 days, the tumor decreases in volume by at least about 20-70%.

151. The method of any of claims 76-141, wherein after daily administration of the drug for 30 days, the tumor decreases in volume by at least about 25%.

152. The method of any of claims 76-141, wherein after daily administration of the drug for 30 days, the tumor decreases in volume by at least about 50%.

153. The method of any of claims 76-141, wherein after daily administration of the drug for 30 days, the tumor decreases in volume by at least about 20-70%.

154. The method of any of claims 76-141, wherein after administration of the drug, the tumor growth is inhibited by at least about 20%.

155. The method of any of claims 76-141, wherein after administration of the drug, the tumor growth is inhibited by at least about 40%.

156. The method of any of claims 76-141, wherein after administration of the drug, the tumor growth is inhibited by at least about 60%.

157. The method of any of claims 76-141, wherein after administration of the drug, the tumor growth is inhibited by at least about 80%.

158. The method of any of claims 76-141, wherein after administration of the drug, the tumor growth is inhibited by between about 20% to about 100%.

159. The method of any of claims 76-141, wherein after administration of the drug, the tumor growth is substantially inhibited.

160. The method of any of claims 145-159, wherein the drug is administered twice a day.

161. The method of any of claims 145-159, wherein the drug is administered once a day.

162. The method of any of claims 76-157, wherein the MEK inhibitor does not interfere with the coadministration of a second tumor suprressing agent.

163. The compound, composition or method of any of the previous claims, wherein the composition is in the form of a tablet, a capsule, a gel cap, a caplet, a pellet, or a bead.

164. The compound, composition or method of claim 163, wherein the composition is in the form of a capsule or tablet dosage form has a total weight of about 50 mg to about 1000 mg.

165. The compound, composition or method of claim 163, wherein the composition is in the form of a capsule or tablet has a total weight selected from the group consisting of 50 mg, 75mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, and 500 mg.

166. The compound, composition or method of claim 163, wherein the composition is in the form of a capsule or tablet has a total weight of about 240 mg.

167. The composition or method of any of claims 1-58, 66, 71 or 76-166, wherein the composition further comprises at least one filler selected from microcrystalline cellulose, silicified microcrystalline cellulose, lactose, a compressible sugar, xylitol, sorbitol, mannitol, pregelatinized starch, maltodextrin, calcium phosphate, calcium carbonate, starch and a calcium silicate.

168. The composition or method of any of claims 1-58, 66, 71 or 76-166, wherein the composition further comprises at least one disintegrant selected from croscarmellose sodium, sodium starch glycolate, crospovidone, methylcellulose, alginic acid, sodium alginate, starch derivatives, betonite and veegum.

169. The composition or method of any of claims 1-58, 66, 71 or 76-166, wherein the composition further comprises at least one lubricant selected from magnesium stearate, metallic stearates, talc, sodium stearyl fumarate and stearic acid.

170. The composition or method of any of claims 1-58, 66, 71 or 76-166, wherein the composition further comprises at least one wetting agent or surfactant selected from sodium lauryl sulfate, glycerol, sorbitan oleates, sorbitan stearates, polyoxyethylenated sorbitan laurate, palmitate, stearate, oleate or hexaolate, polyoxyethylene stearyl alcohol and sorbitan monolaurate.

171. The composition or method of any of claims 1-58, 66, 71 or 76-170 wherein the composition is in the formulation fo a capsule or tablet and the capsule or tablet releases at least 60 percent of the drug within 30 minutes using *U.S. Pharmacopeia* (USP) Apparatus II at 50 rpm with 1% sodium lauryl sulfate in water as the dissolution medium.

172. The compound, composition or method of claim 171, wherein the composition is in the formulation fo a capsule or tablet and the capsule or tablet releases about 60-100 percent of the drug within 30 minutes using *U.S. Pharmacopeia* (USP) Apparatus II at 50 rpm with 1% sodium lauryl sulfate in water as the dissolution medium.

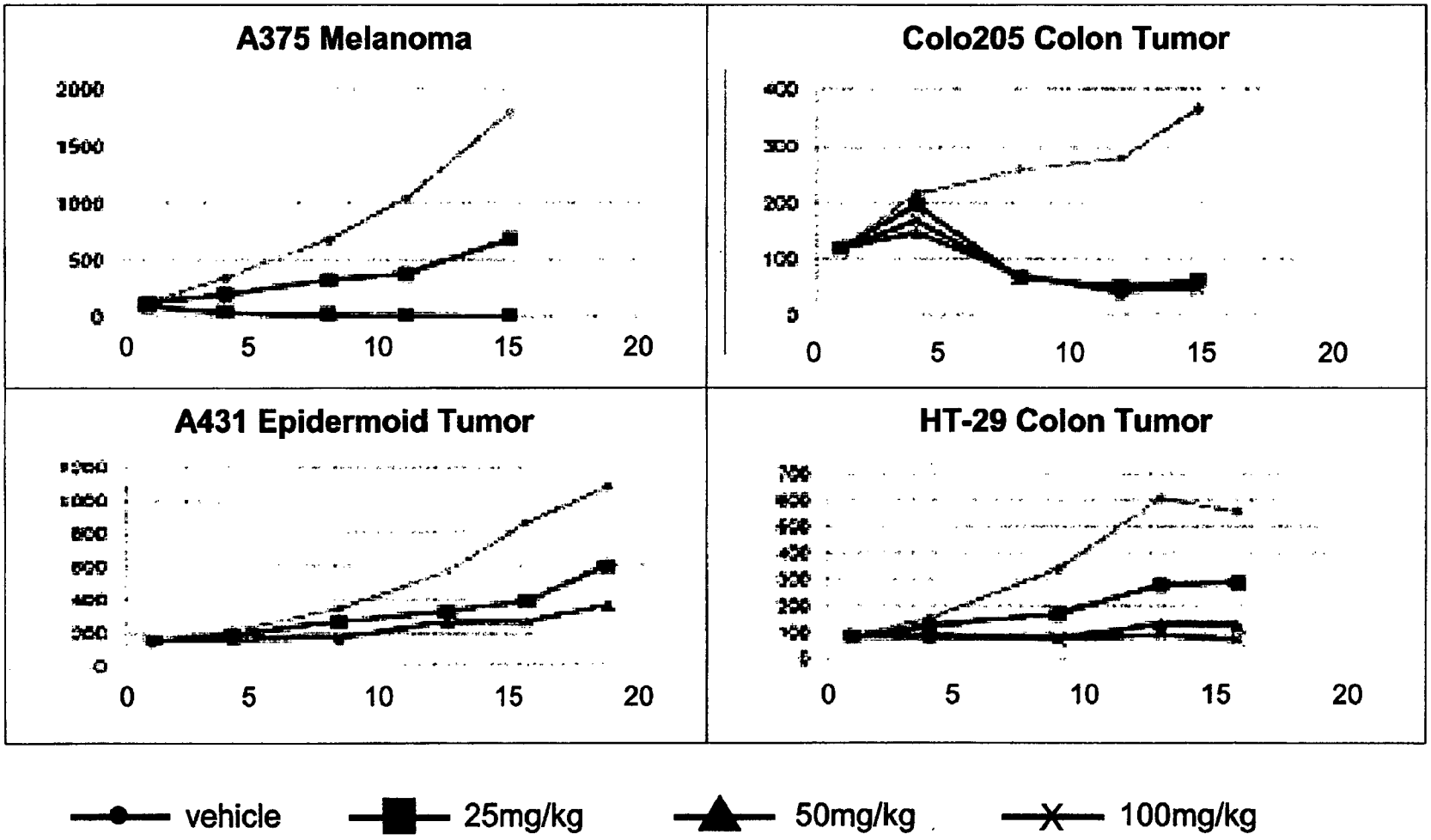
173. The compound, composition or method of claim 171, wherein the composition is in the formulation fo a capsule or tablet and the capsule or tablet releases about 60-90 percent of the drug within 30 minutes using *U.S. Pharmacopeia* (USP) Apparatus II at 50 rpm with 1% sodium lauryl sulfate in water as the dissolution medium.

174. The compound, composition or method of claim 171, wherein the composition is in the formulation fo a capsule or tablet and the capsule or tablet releases about 60-80 percent of the drug within 30 minutes using *U.S. Pharmacopeia* (USP) Apparatus II at 50 rpm with 1% sodium lauryl sulfate in water as the dissolution medium.

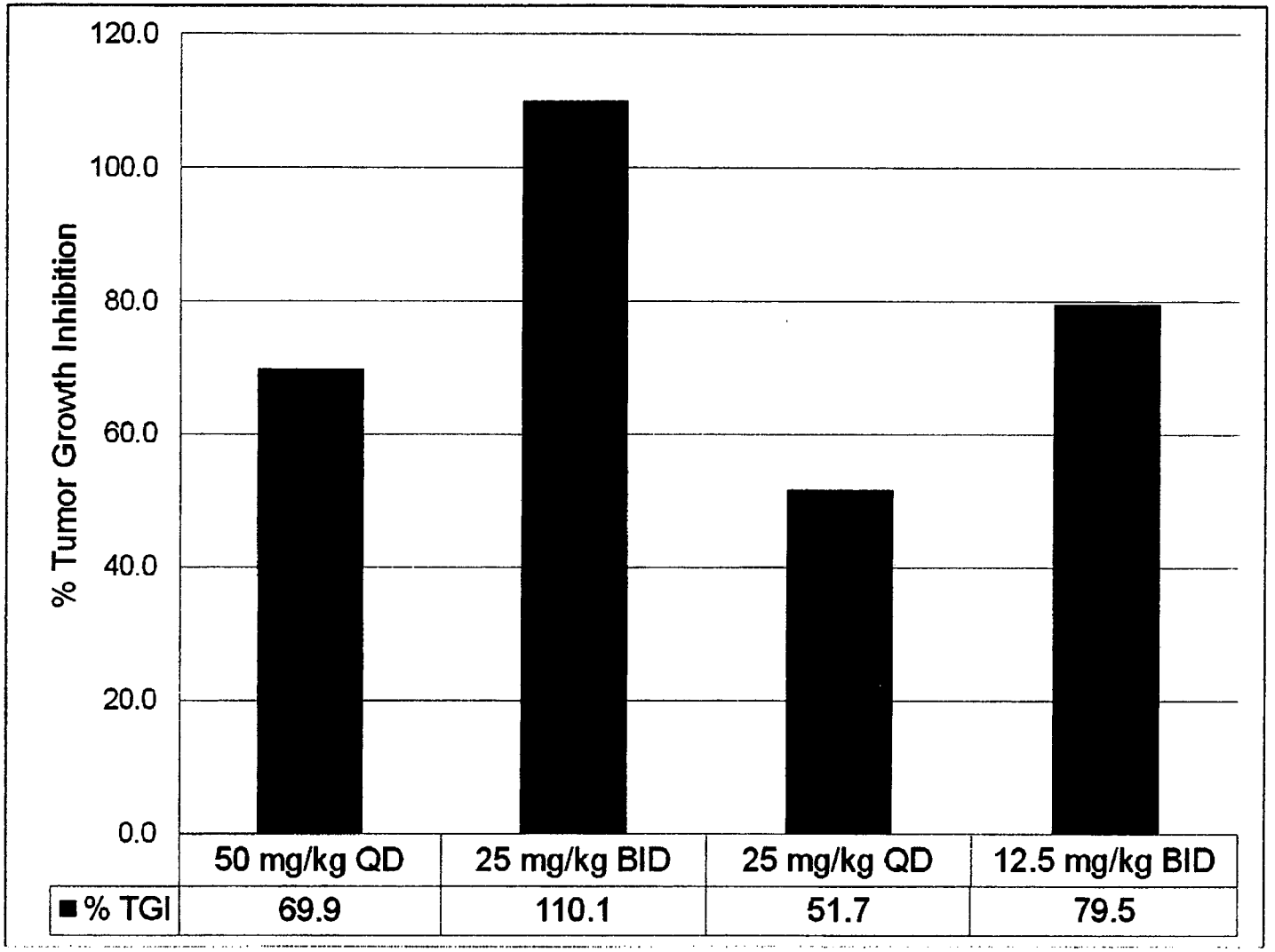
175. A batch of capsules or tablets, each comprising from about 1 to about 50 mg of a compound of any of claims 1-75, having a USP acceptance value for content uniformity of less than about 15.

176. A method for treating liver cancer by administering a therapeutically effective amount of a compound or composition according to any of claims 1-75.

# FIGURE 1


A375 Melanoma
2000
1500
1000
500
0
0
5
10
15
20
Colo205 Colon Tumor
400
300
200
100
0
5
10
15
20
A431 Epidermoid Tumor
800
600
400
200
0
0
5
10
15
20
HT-29 Colon Tumor
0
5
10
15
20
vehicle
25mg/kg
50mg/kg
100mg/kg

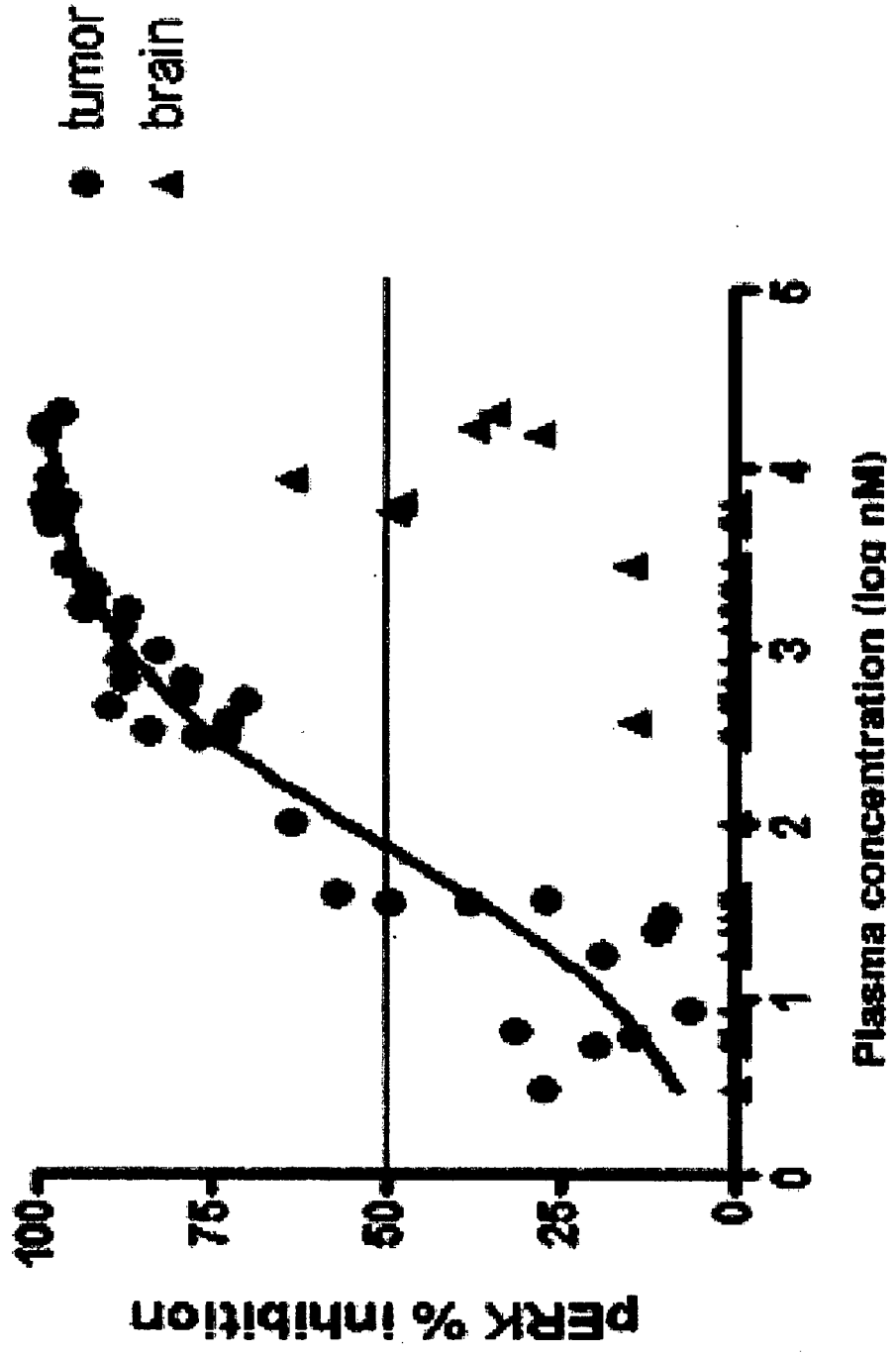
# FIGURE 2


120.0
100.0
80.0
60.0
40.0
20.0
0.0
% Tumor Growth Inhibition
50 mg/kg QD
25 mg/kg BID
25 mg/kg QD
12.5 mg/kg BID
% TGI
69.9
110.1
51.7
79.5



263

FIGURE 3


tumor
brain
PERK % inhibition
100
75
50
25
0
0
1
2
3
4
5
Plasma concentration (log nM)

# FIGURE 4

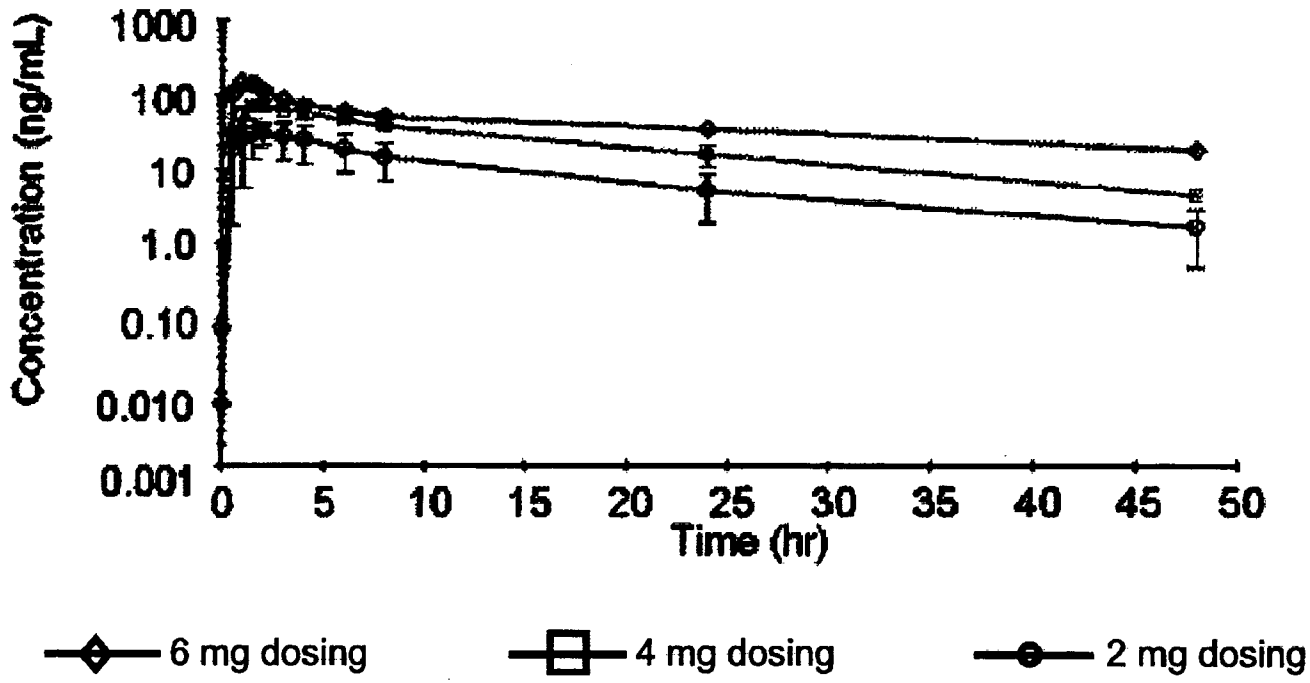
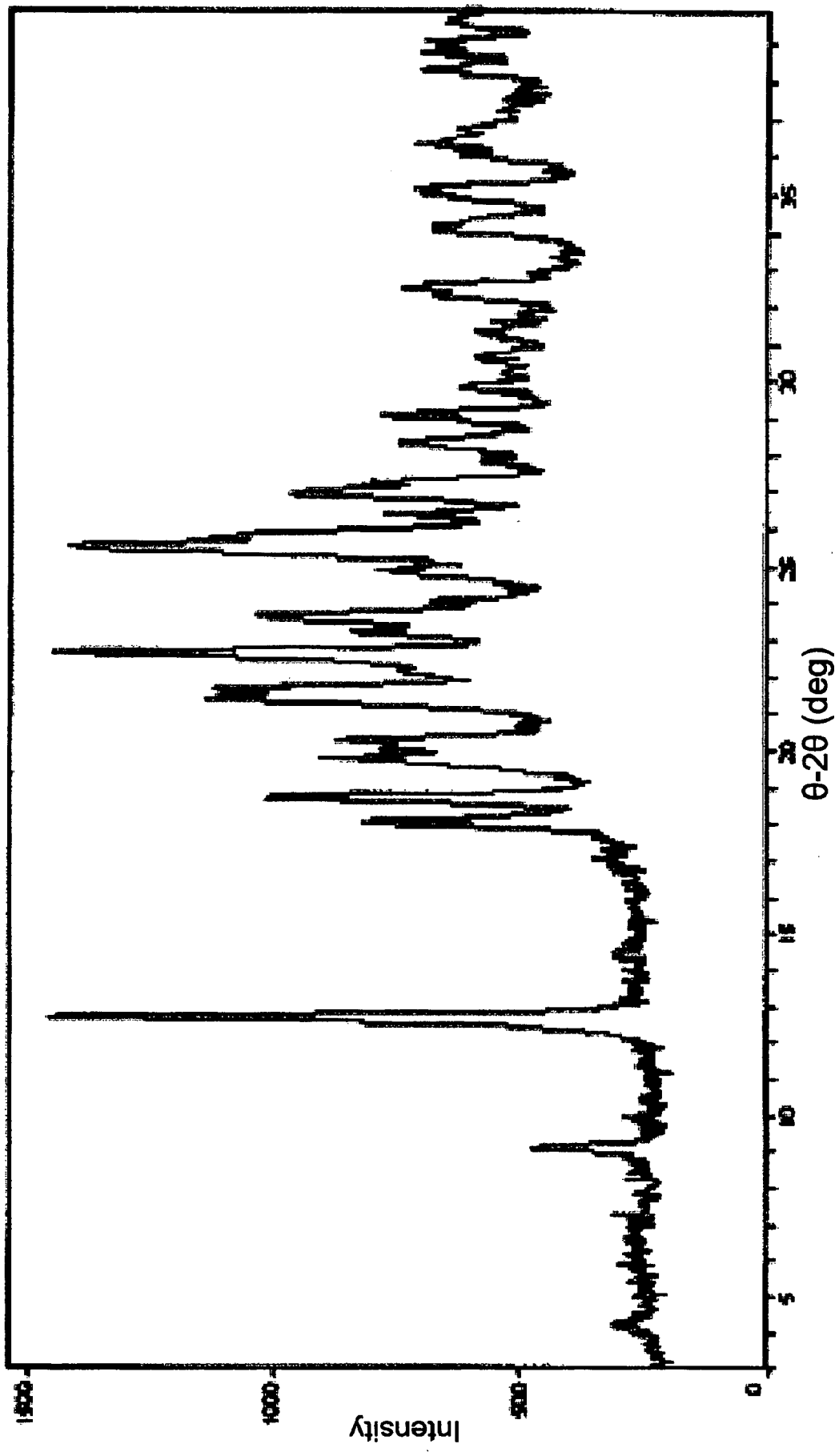
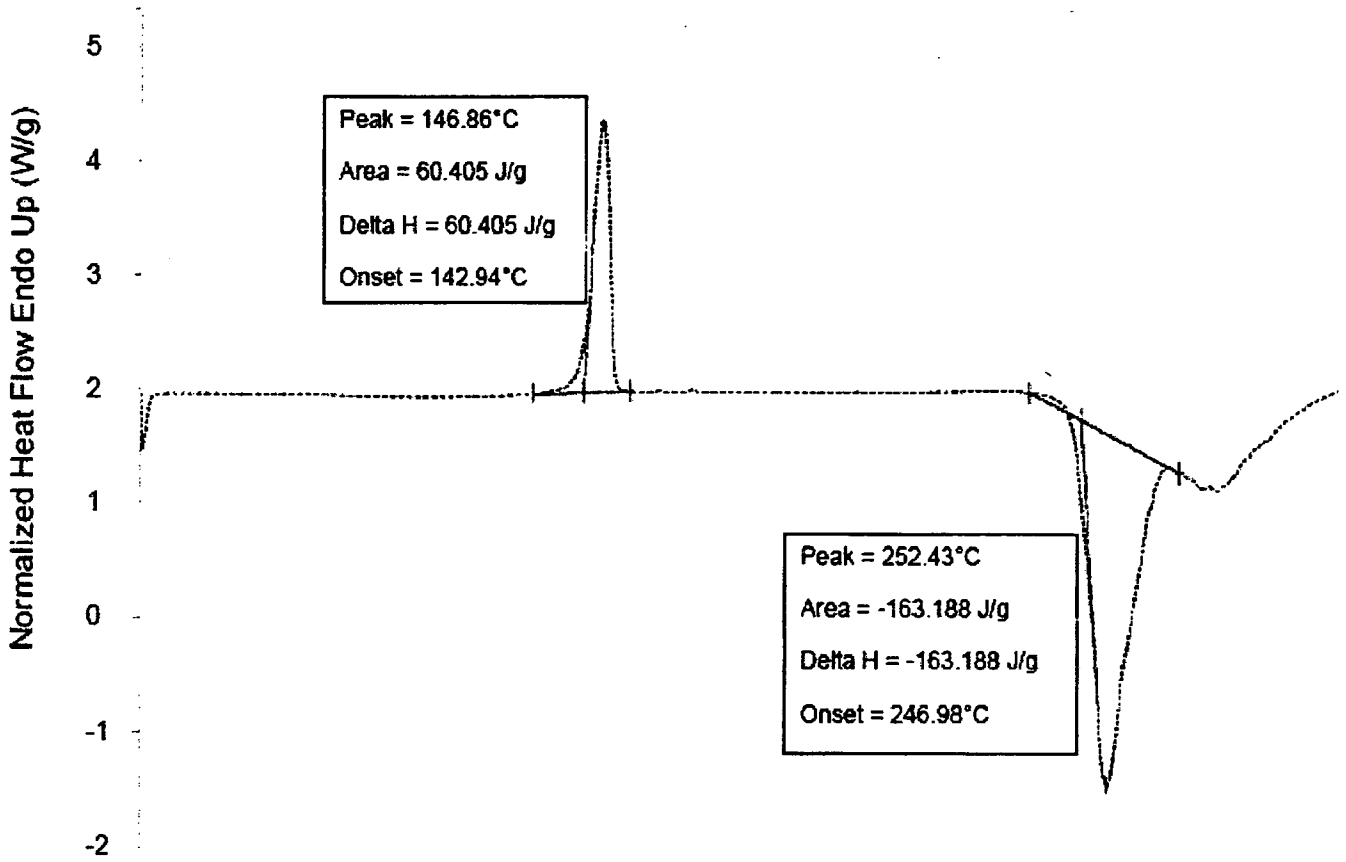

Concentration (ng/mL)
1000
100
10
1.0
0.10
0.010
0.001
0
5
10
15
20
25
30
35
40
45
50
Time (hr)
6 mg dosing
4 mg dosing
2 mg dosing

FIGURE 5

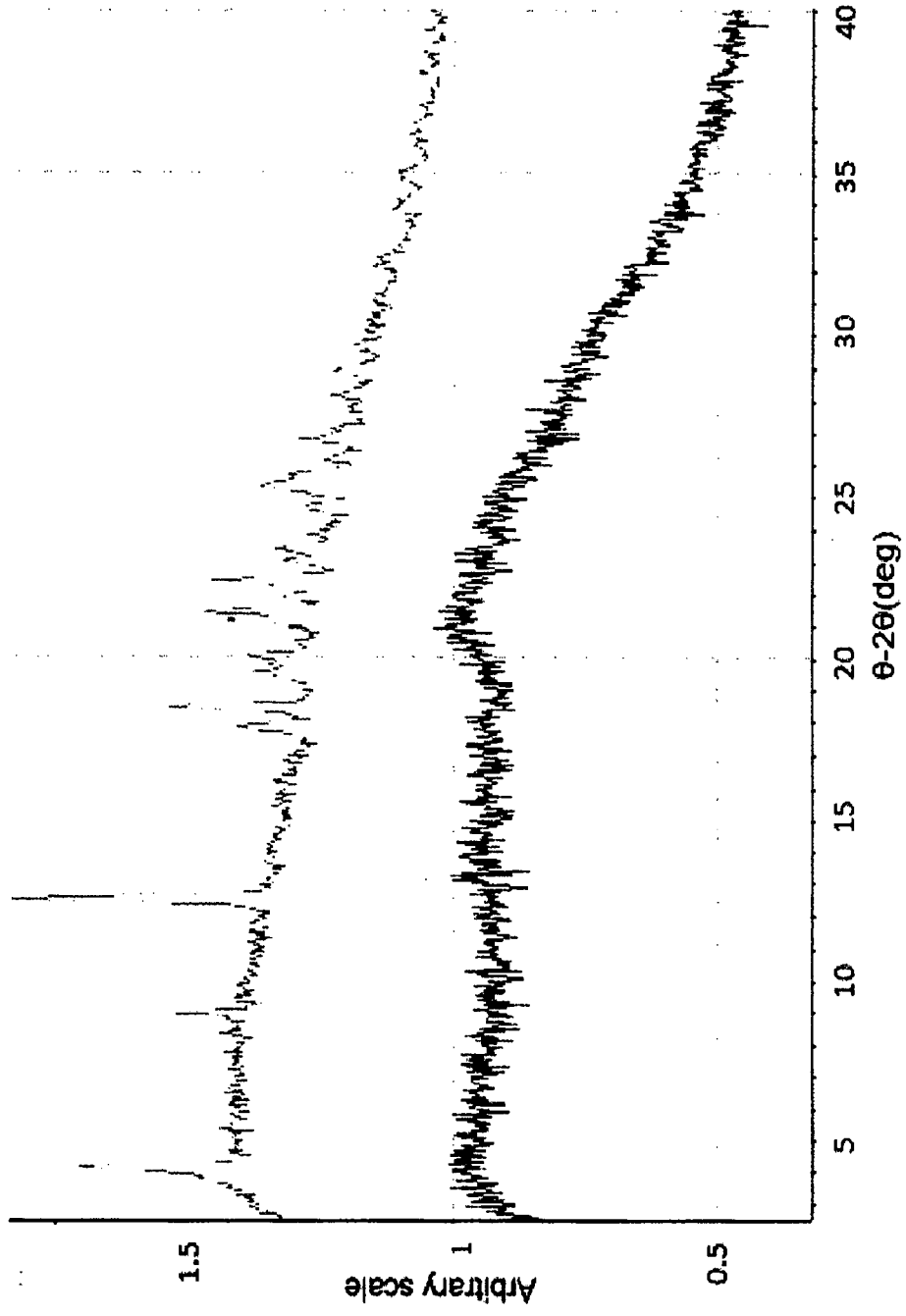


# FIGURE 6

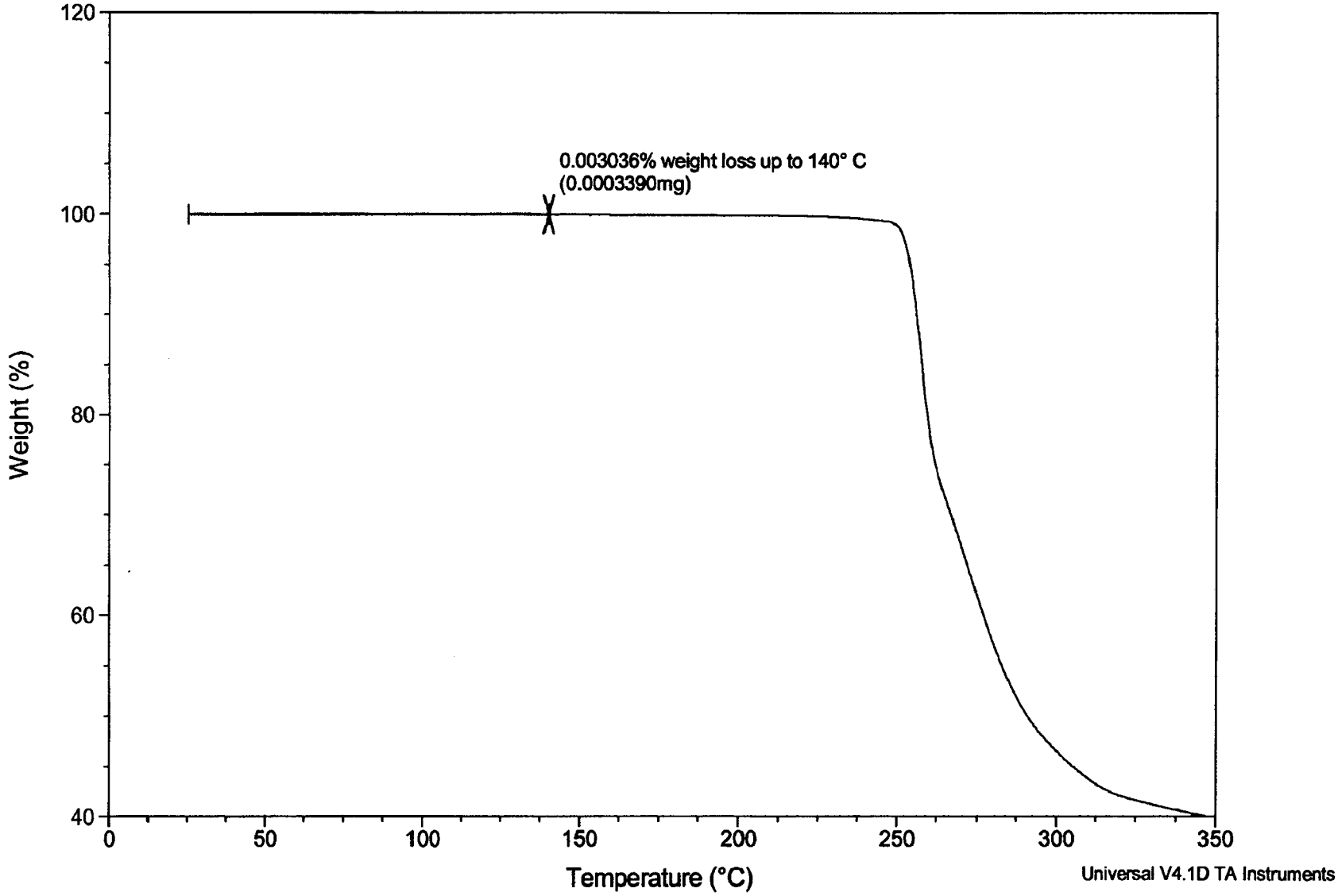

Normalized Heat Flow Endo Up (W/g)
5
4
3
2
1
0
-1
-2
Peak = 146.86°C
Area = 60.405 J/g
Delta H = 60.405 J/g
Onset = 142.94°C
Peak = 252.43°C
Area = -163.188 J/g
Delta H = -163.188 J/g
Onset = 246.98°C

268

FIGURE 7

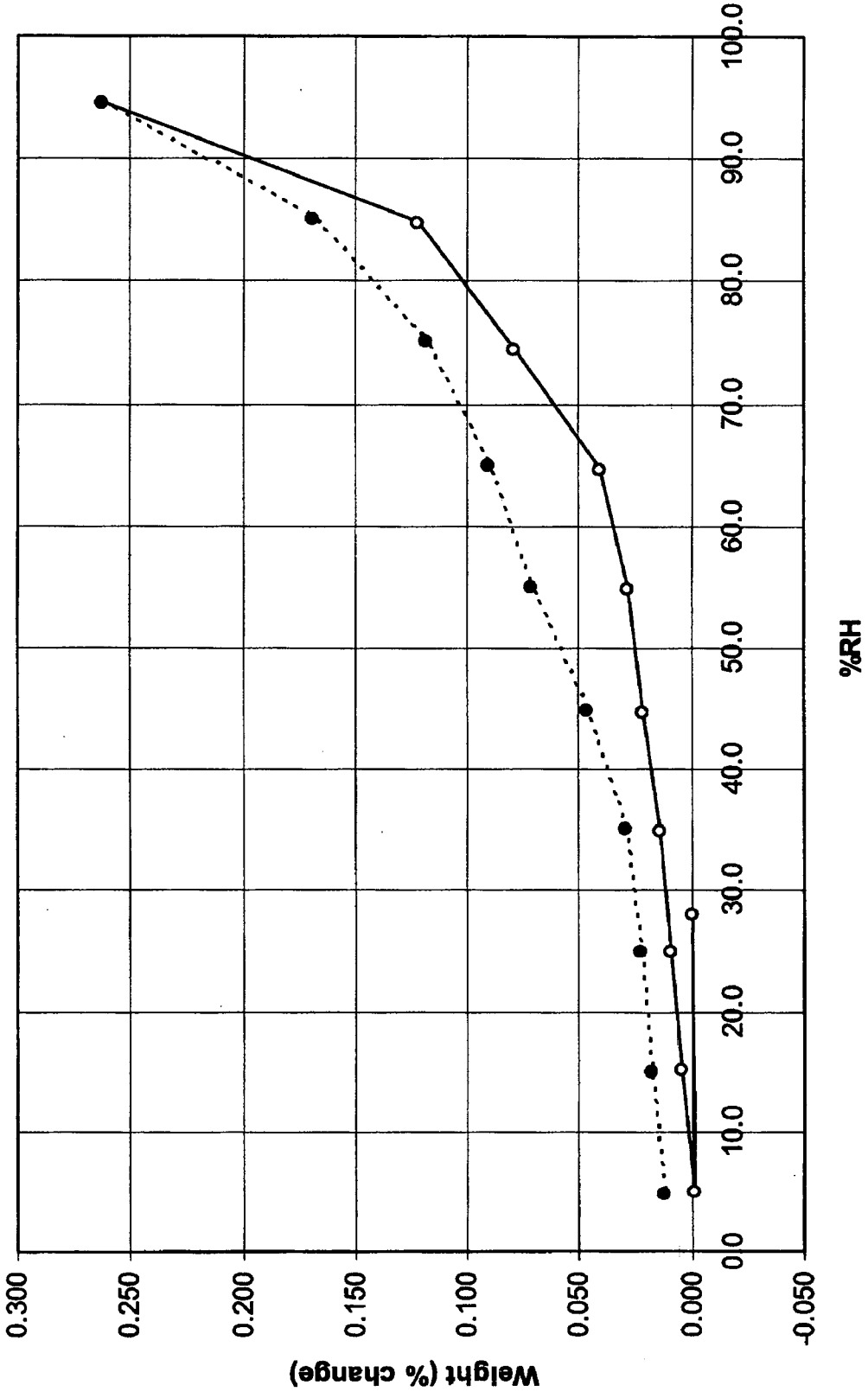


# FIGURE 8


120
100
80
60
40
Weight (%)
0.003036% weight loss up to 140° C
(0.0003390mg)
0
50
100
150
200
250
300
350
Temperature (°C)
Universal V4.1D TA Instruments

270

FIGURE 9


Adsorption
Desorption
Weight (% change)
0.300
0.250
0.200
0.150
0.100
0.050
0.000
-0.050
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
%RH

# FIGURE 10

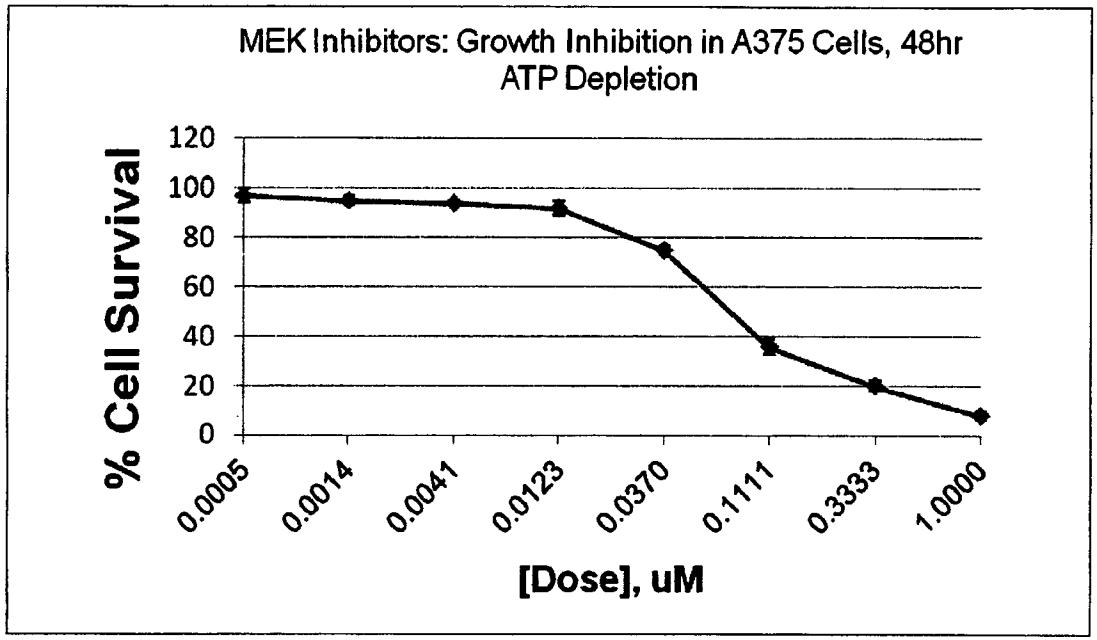



Fig 10(A)

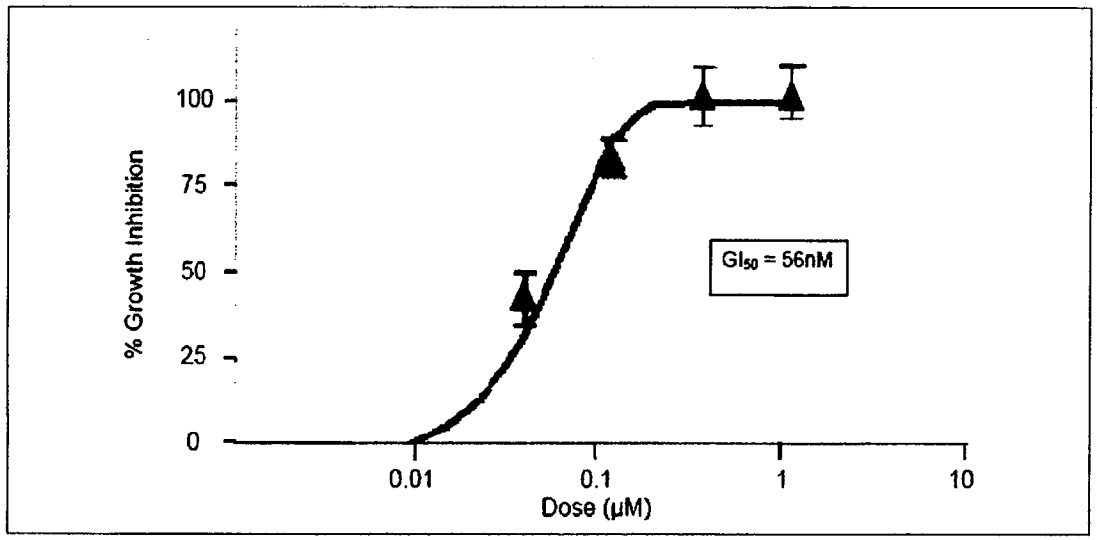
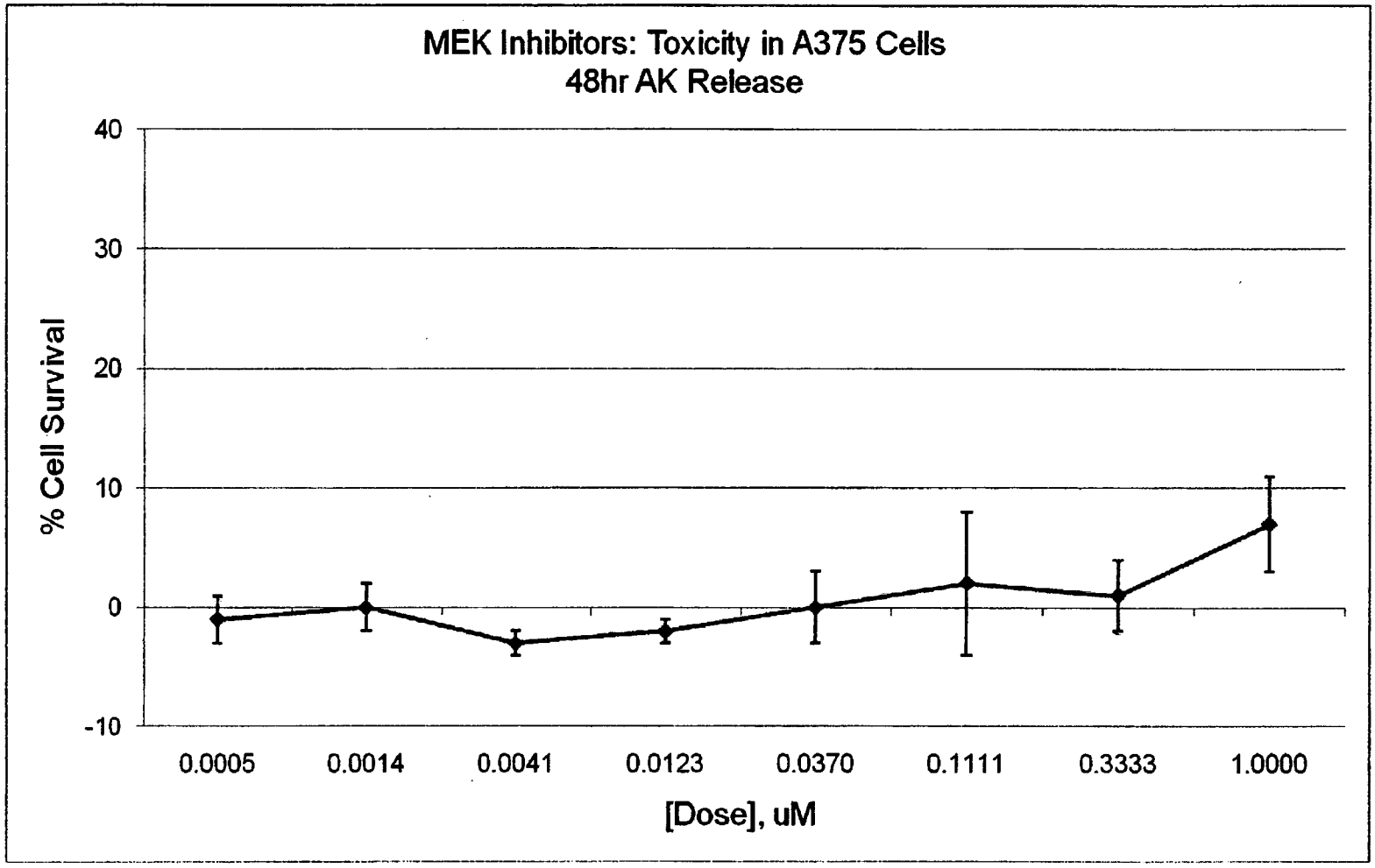



Fig 10(B)

# FIGURE 11


MEK Inhibitors: Toxicity in A375 Cells
48hr AK Release
% Cell Survival
40
30
20
10
0
-10
0.0005
0.0014
0.0041
0.0123
0.0370
0.1111
0.3333
1.0000
[Dose], uM

# FIGURE 12

7 day, MTS Assay: 3 Day Growth Inhibition

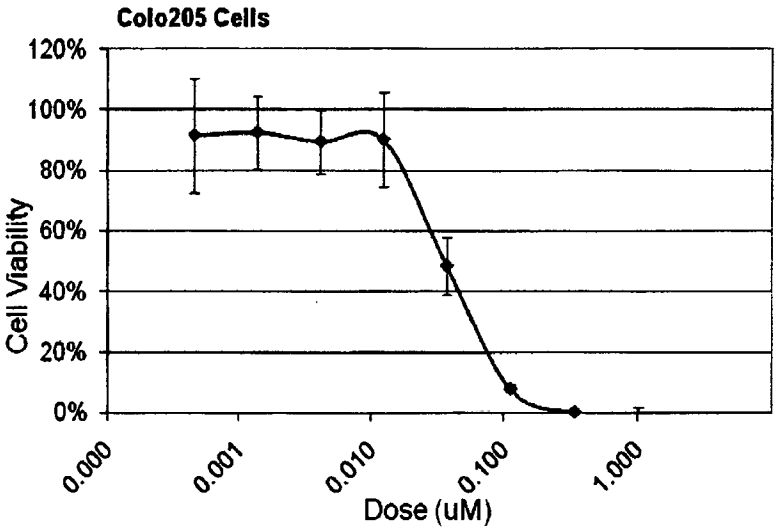



Fig 12 (A)

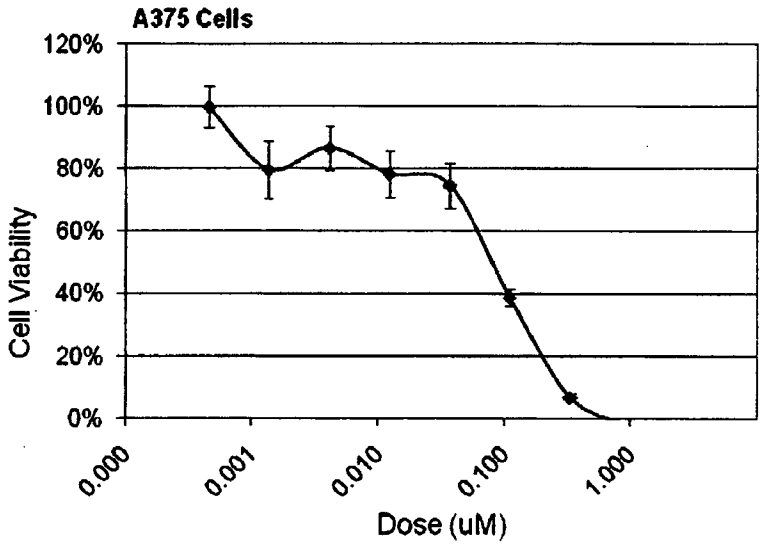



Fig 12 (B)

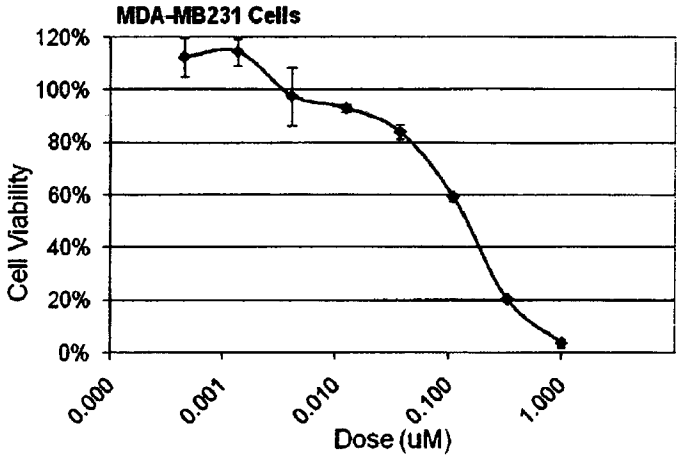



Fig 12 (C)



273

274

FIGURE 13

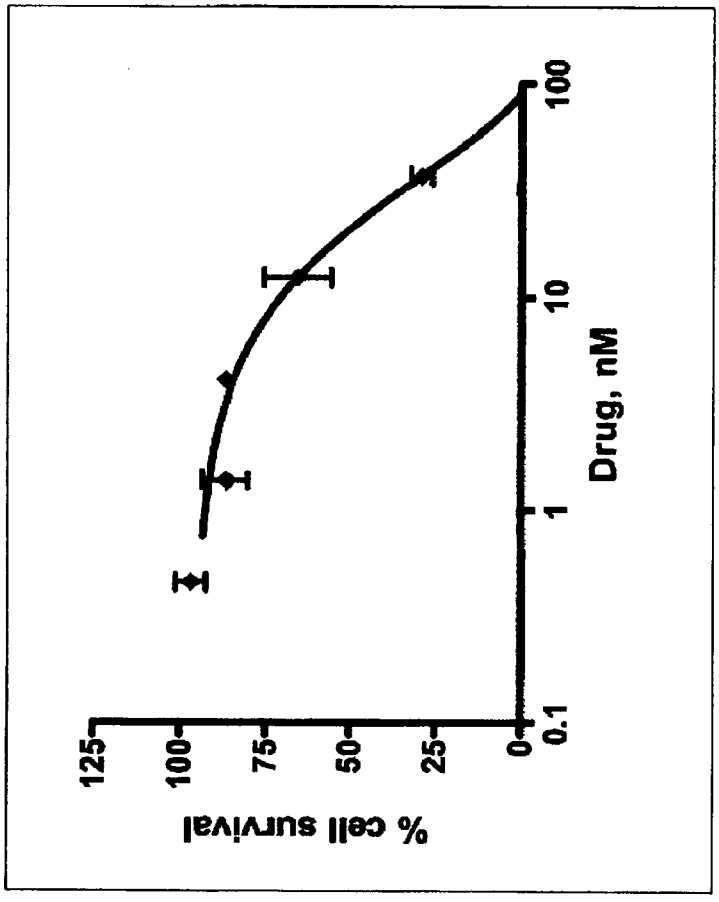



Fig 13(B)

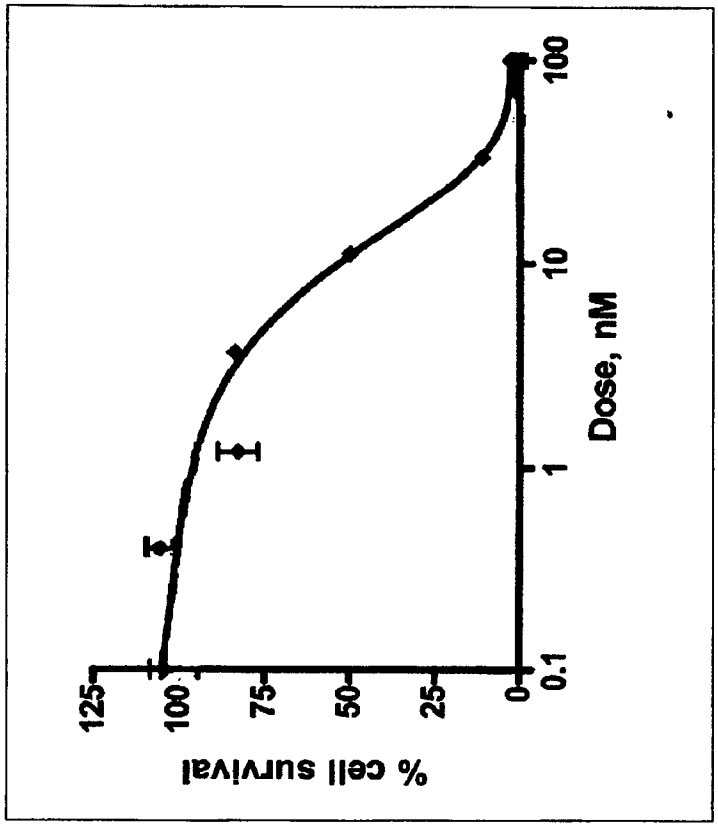



Fig 13(A)

# FIGURE 14

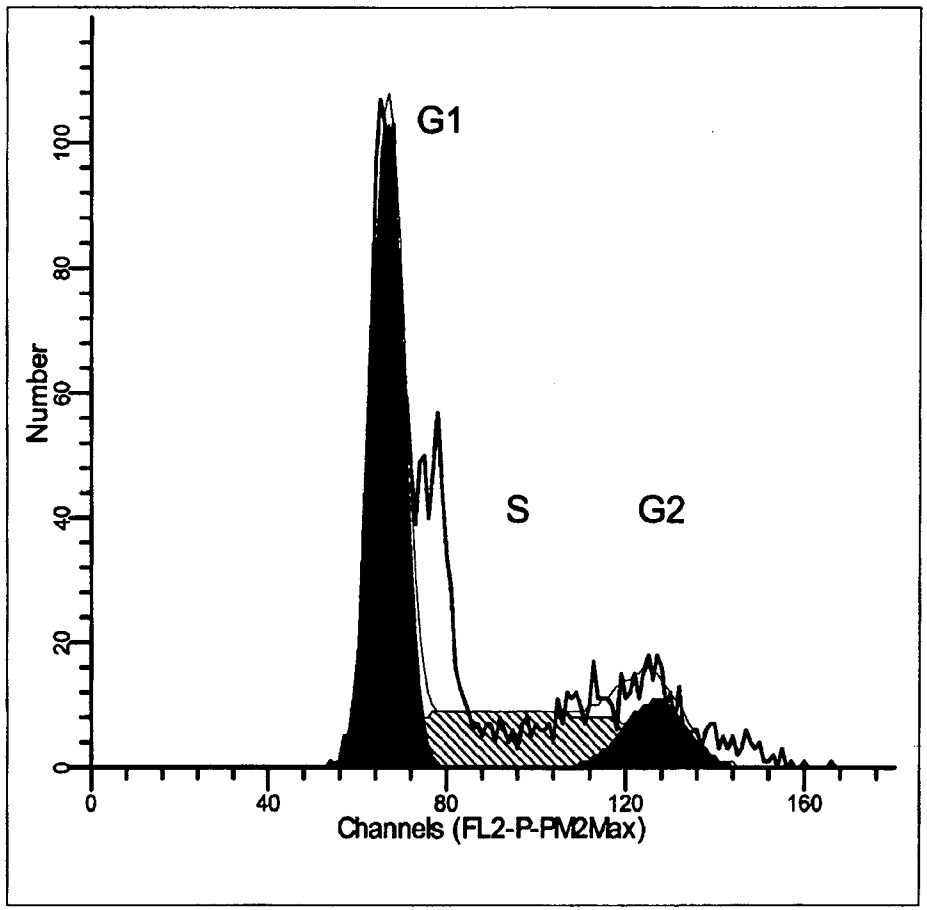



Fig 14(A)

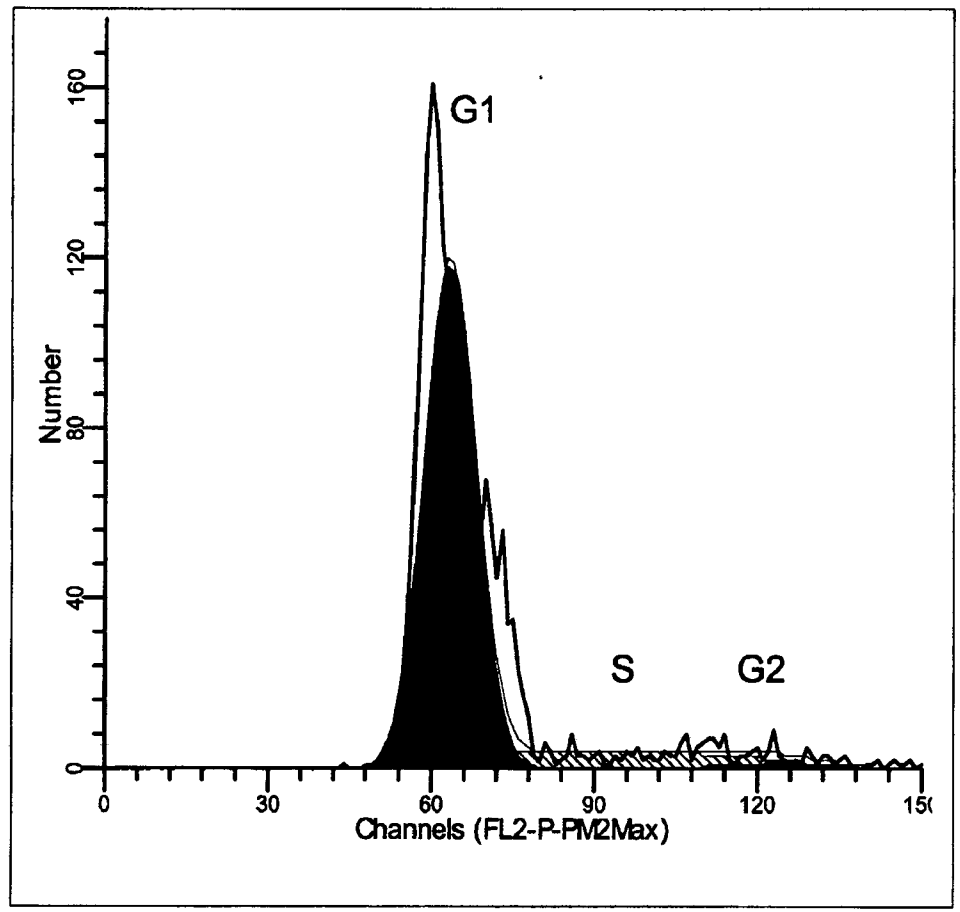



Fig 14(B)

# FIGURE 15

Inhibition of AGS cell proliferation

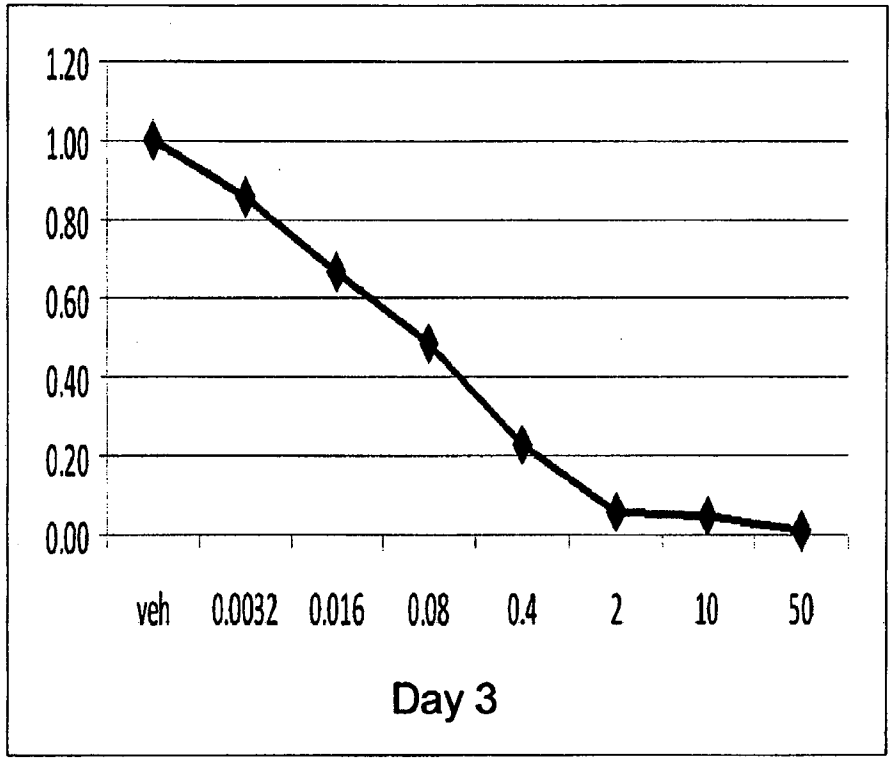



Fig 15(A)

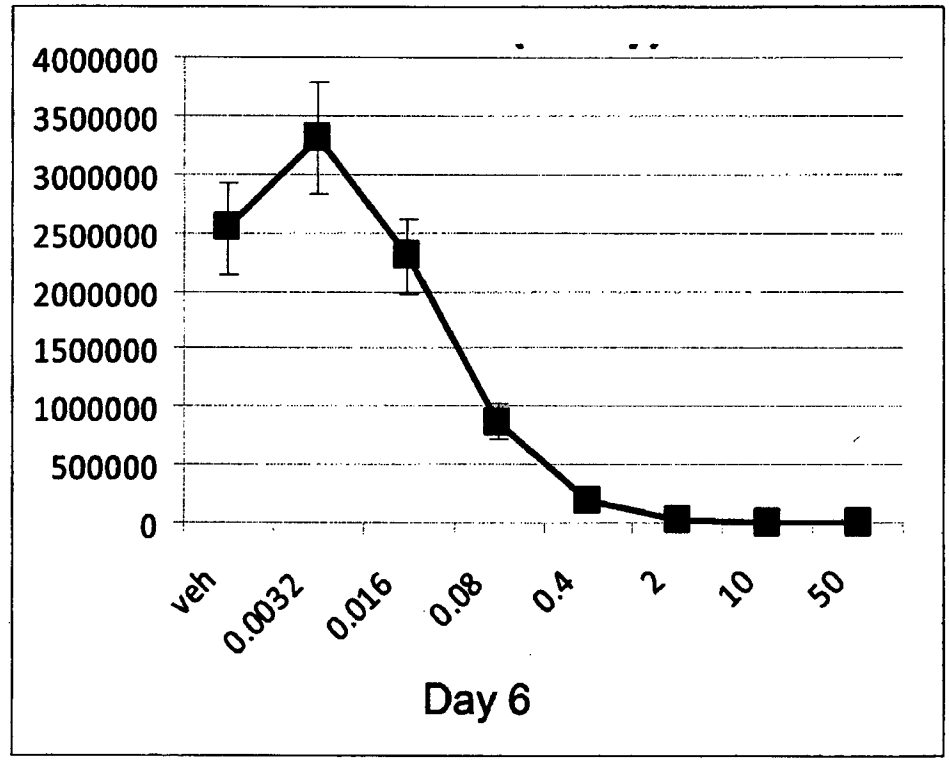


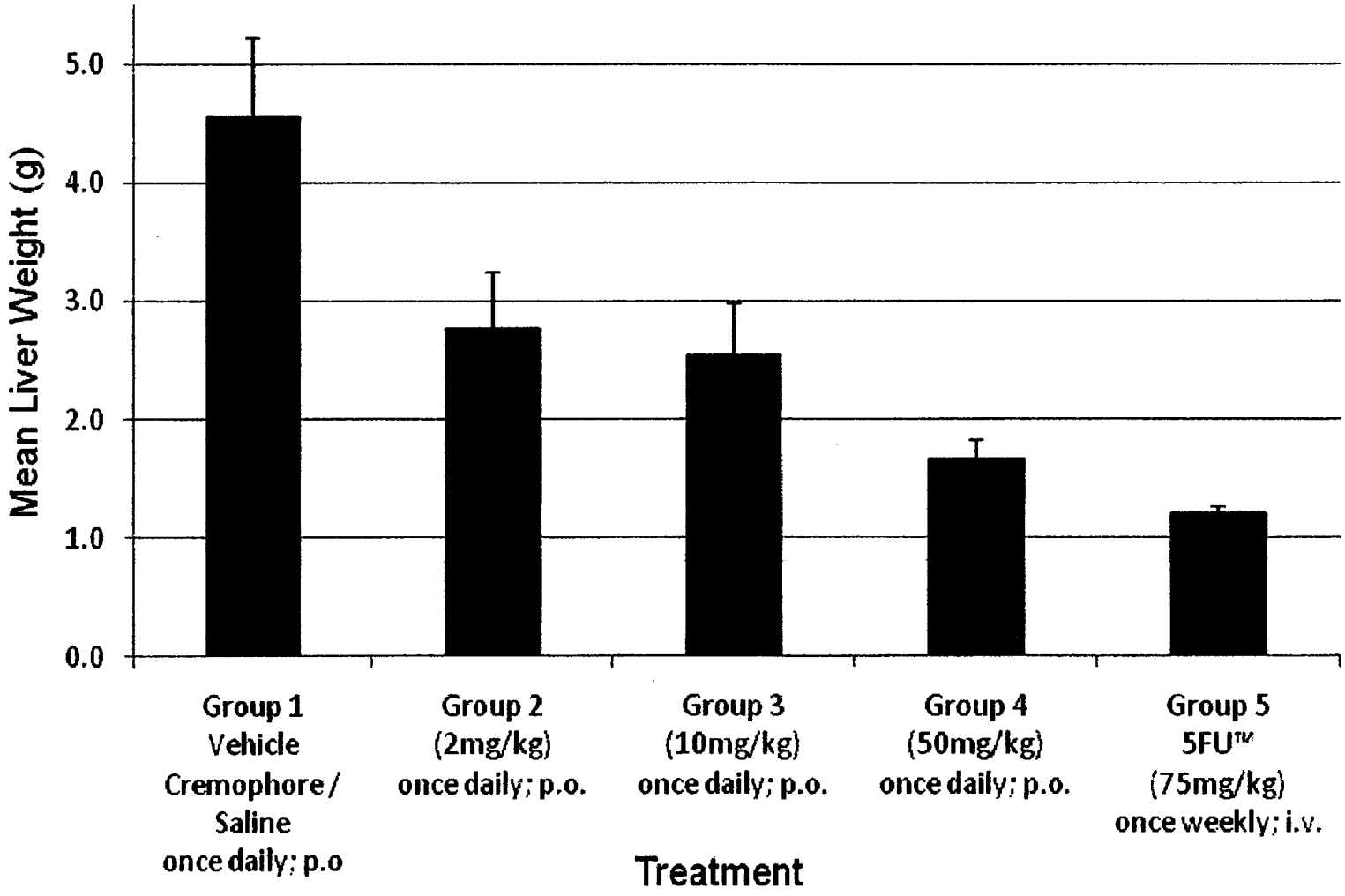

Fig 15(B)



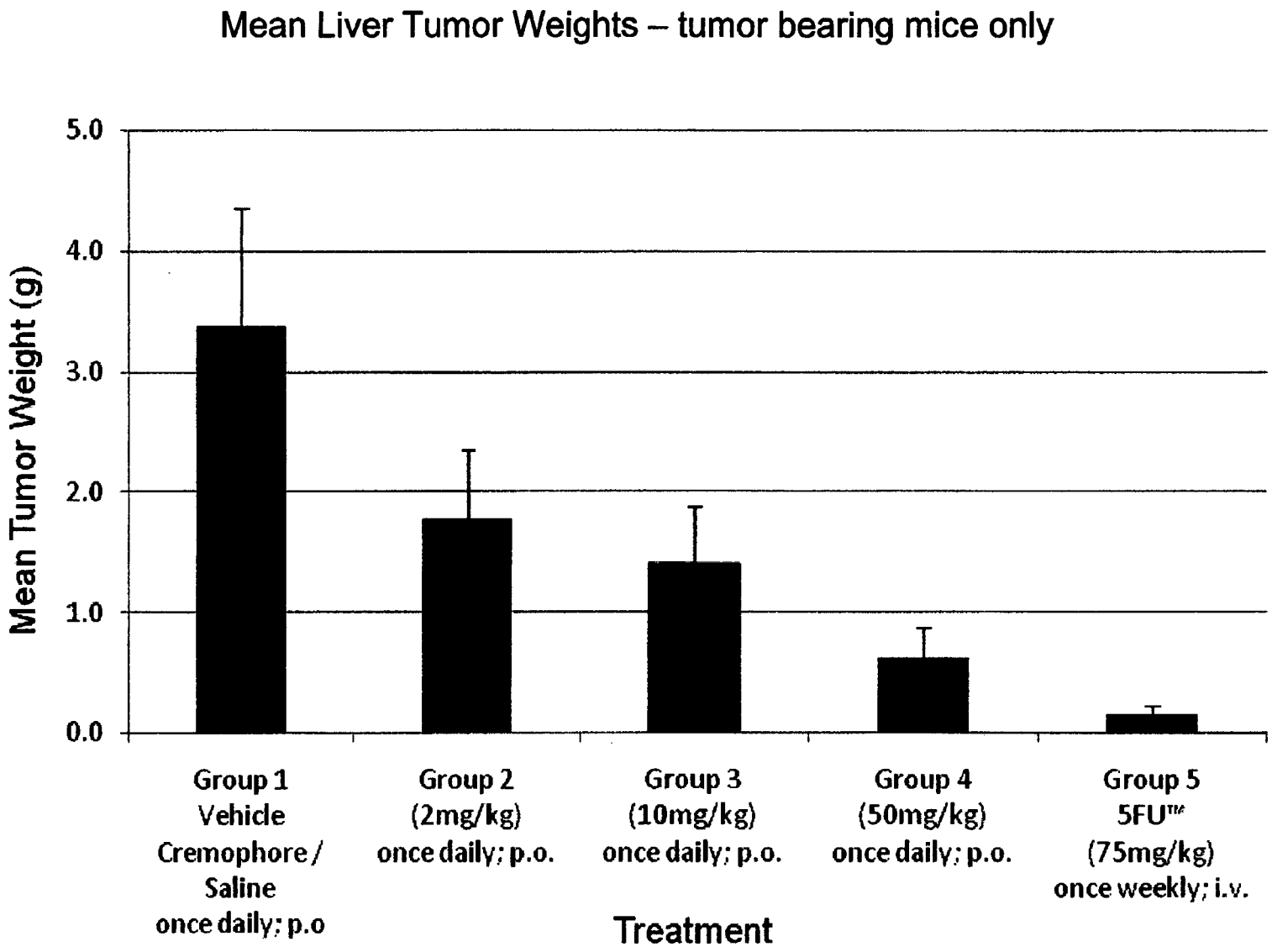
276

# FIGURE 16

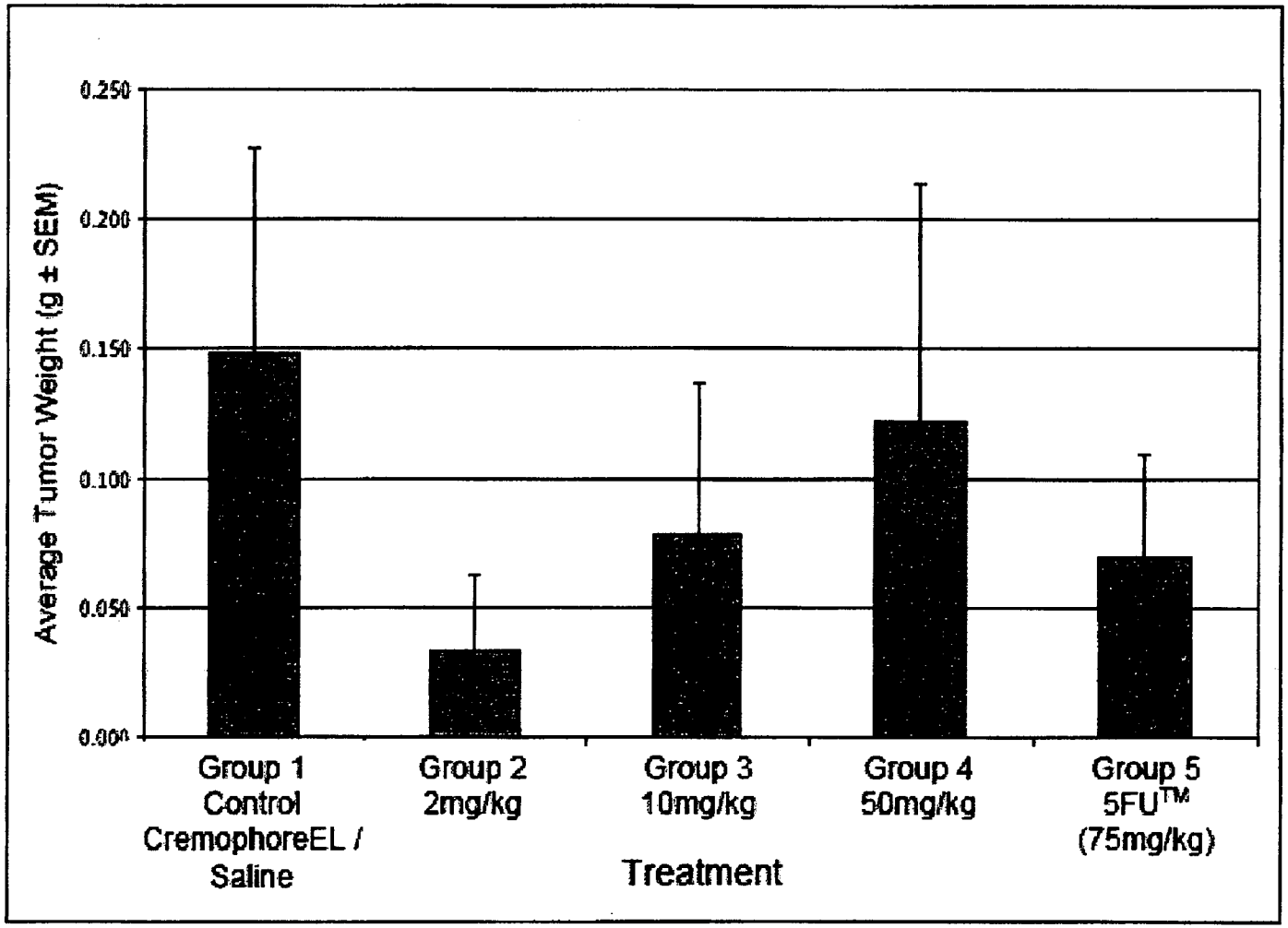
Mean Liver Weights - tumor bearing mice only



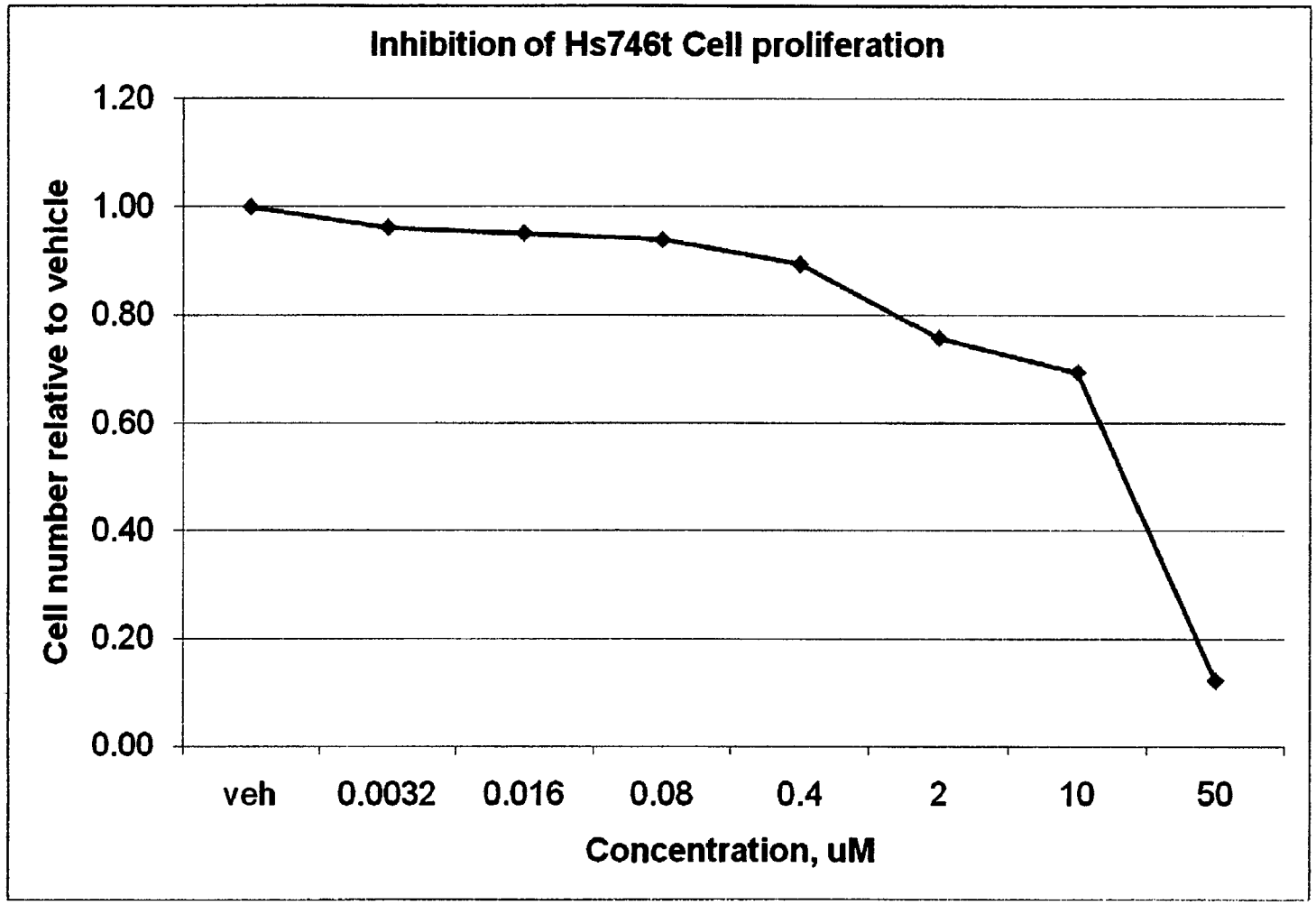
# FIGURE 17


Mean Liver Tumor Weights – tumor bearing mice only
Mean Tumor Weight (g)
5.0
4.0
3.0
2.0
1.0
0.0
Group 1 Vehicle Cremophore / Saline once daily; p.o
Group 2 (2mg/kg) once daily; p.o.
Group 3 (10mg/kg) once daily; p.o.
Group 4 (50mg/kg) once daily; p.o.
Group 5 5FU™ (75mg/kg) once weekly; i.v.
Treatment

# FIGURE 18


Average Tumor Weight (g ± SEM)
0.250
0.200
0.150
0.100
0.050
0.000
Group 1 Control CremophoreEL / Saline
Group 2 2mg/kg
Group 3 10mg/kg
Group 4 50mg/kg
Group 5 5FU™ (75mg/kg)
Treatment

# FIGURE 19


Inhibition of Hs746t Cell proliferation
Cell number relative to vehicle
1.20
1.00
0.80
0.60
0.40
0.20
0.00
veh
0.0032
0.016
0.08
0.4
2
10
50
Concentration, uM

# FIGURE 20

All figures: horizontal axis = conc (uM); vertical axis = % cell death

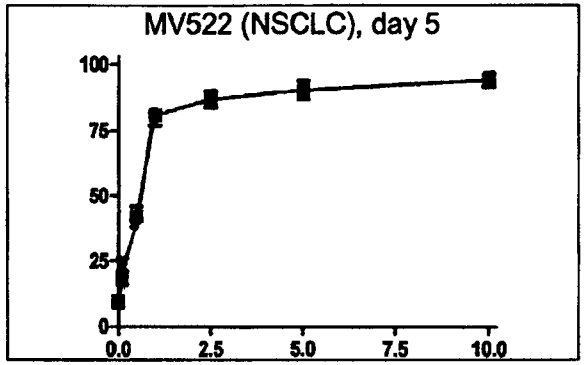



Fig 20(A)

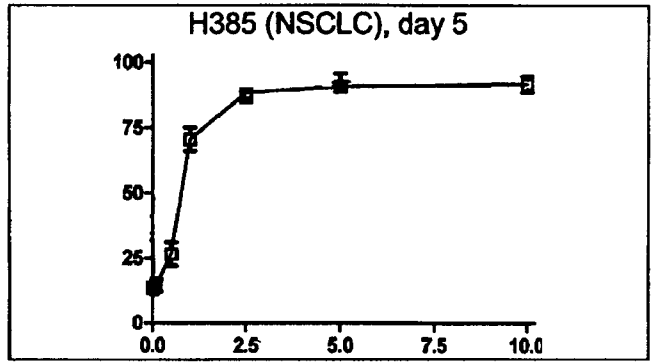



Fig 20(B)

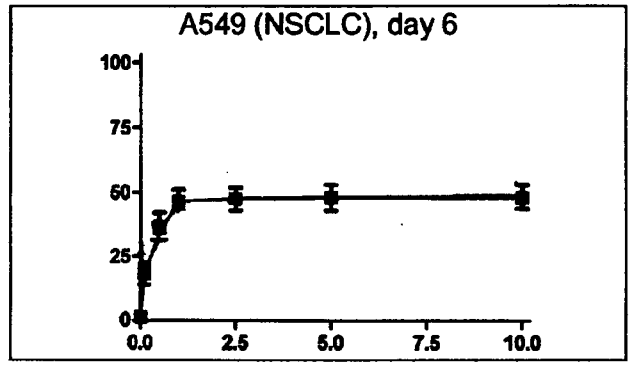



Fig 20(C)

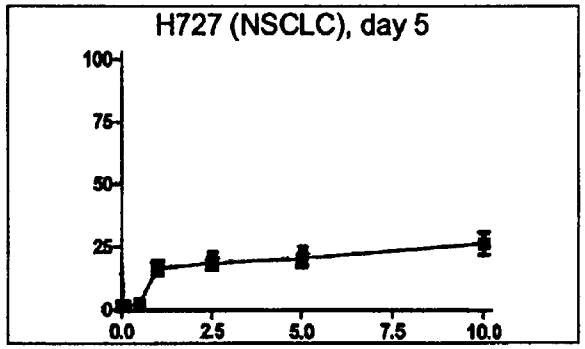



Fig 20(D)

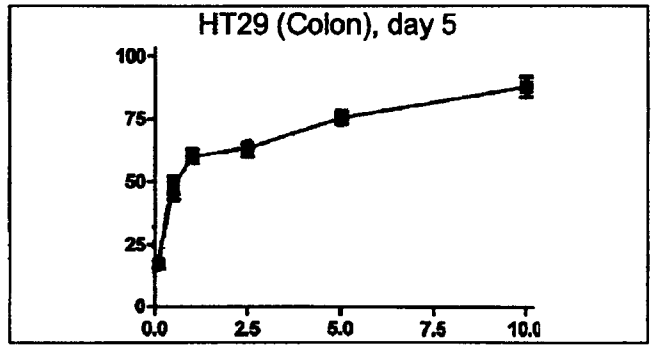



Fig 20(E)

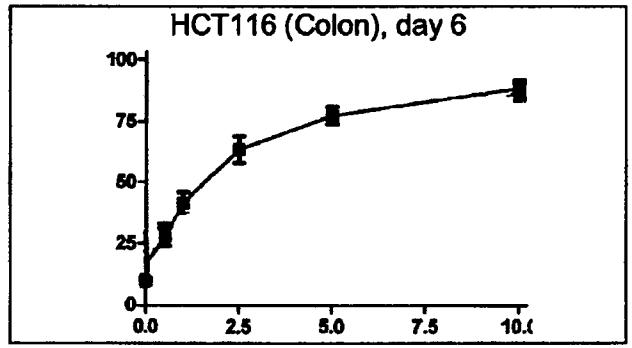



Fig 20(F)

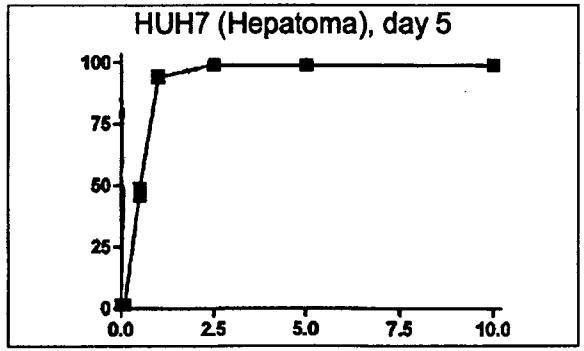



Fig 20(G)

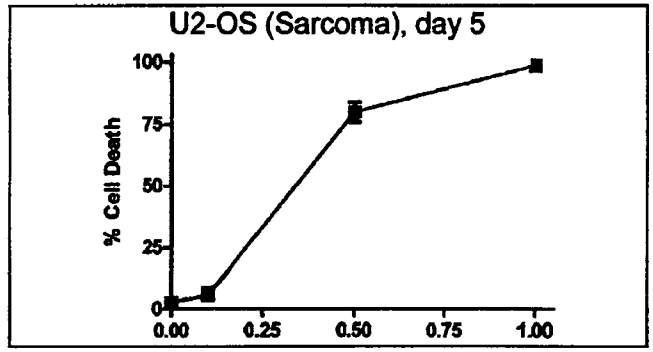



Fig 20(H)

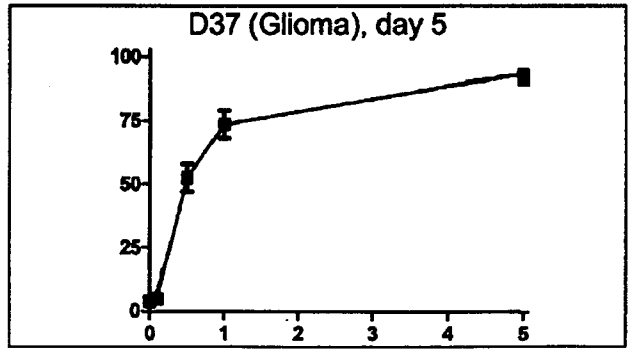



Fig 20(I)

(12) Publicación de la solicitud internacional bajo PCT
(19) Organización Mundial de Propiedad Intelectual
Oficina Internacional
(43) Fecha de publicación internacional : 05 de febrero de 2009 (05.02.2009)
(10) Número de publicación internacional: WO 2009/018233 A1

(51) Clasificación internacional de patentes:
A01N 41/06 (2006.01) A61K 31/18 (2006.01)
(21) Número de solicitud internacional: PCT/US2008/071392
(22) Fecha de presentación internacional: 28 de julio de 2008 (28.07.2008)
(25) Idioma de la presentación: inglés
(26) Idioma de la publicación: inglés
(30) Fecha de prioridad:
11/830,733 del 30 de julio de 2007 (30.07.2007) US
61/034,466 del 06 de marzo de 2008 (06.03.2008) US
61/034,464 del 06 de marzo de 2008 (06.03.2008) US
61/044,886 del 14 de abril de 2008 (14.04.2008) US
(71) Solicitante (para todos los estados designados con excepción de US): ARDEA BIOSCIENCES, INC. [US/US]; 4939 Directors Place, San Diego, CA 92121 (US).
(72) Inventores; y
(75) Inventor/Solicitante *(solamente para US):* VERNIER, Jean-Michel [FR/US]; 24831 Cutter, Laguna Niguel, CA 92677 (US). ROWLINGS, Colin, Edward [US/US]; 1908 Paxton Way, Encinitas, CA 92024 (US). GIRARDET, Jean-Luc [FR/US]; 17 Open View Lane, Aliso Viejo, CA 92656 (US). DIMOCK, Stuart [US/US]; 24144 Graystone Drive, Lake Forest, CA 92630 (US). QUART, Barry [US/US]; 3273 Violet Ridge, Encinitas, CA 92024 (US). MINER, Jeffrey, N. [US/US]; 4572 Pauling Ave., San Diego, CA 92122 (US).
(74) Agente: HADDACH Aubrey, A. et.al.; Wilson Sonsini Goodrich & Rosati, 650 Page Mill Road, Palo Alto, CA 94304-1050 (US).
(81) Estados designados (en la medida en que no se indique lo contrario, para cada tipo de protección nacional disponible): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
(84) Estados designados (en la medida en que no se indique lo contrario, para cada tipo de protección regional disponible): Patente ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Patente euroasiatica (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Patente europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE,

IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Publicado:
- con el informe de búsqueda internacional

Véanse las explicaciones („Guidance Notes on Codes an Abbreviations") al comienzo de cada edicion regular de la Gaceta-PCT para la explicación del código de dos dígitos y de las otras abreviaturas

---

(54) Título: DERIVADOS DE N-(ARILAMINO) SULFONAMIDAS QUE INCLUYEN POLIMORFOS COMO INHIBIDORES DE MEK ASÍ COMO COMPOSICIONES, MÉTODOS DE USO Y DE PREPARACIÓN DE LOS MISMOS

(57) Resumen:

Esta invención se relaciona con compuestos N-(2-arilamino) aril sulfonamida que son inhibidores de MEK incluyendo formas polimórficas cristalinas que exhiben un perfil de difracción de rayos X en polvo específico y/o un perfil de calorimetría diferencial de barrido específico. Esta invención también se relaciona con composiciones farmacéuticas que comprenden los compuestos descritos y métodos de uso de los compuestos y composiciones descritos , incluyendo el uso en el tratamiento y/o prevención de cáncer, enfermedades hiperproliferativas y condiciones inflamatorias. La invención también se relaciona con métodos para obtener los compuestos y composiciones que se describen.

# DERIVADOS DE N-(ARILAMINO) SULFONAMIDAS QUE INCLUYEN POLIMORFOS COMO INHIBIDORES DE MEK ASÍ COMO COMPOSICIONES, MÉTODOS DE USO Y DE PREPARACIÓN DE LOS MISMOS

## REFERENCIA A SOLICITUDES RELACIONADAS

Esta solicitud invoca prioridad de las Solicitudes Provisionales de Patentes de los EE.UU. N° Acta: 61/044.886, presentada el 14 de abril, 2008, 61/034.466, presentada el 6 de marzo, 2008, y 61/034.464, presentada el 6 de marzo, 2008, cada una de las cuales se incorpora por completo en la presente a modo de referencia. Esta solicitud también invoca prioridad de la Solicitud Provisional de Patente de los EE.UU. N° Acta: 11/830,733, presentada el 30 de julio, 2007, que invoca beneficio de la Solicitud Provisional de Patente de los EE.UU. N° Acta: 60/833.886, presentada el 28 de julio, 2006 y de la Solicitud de Patente Internacional N° Acta: PCT/US2006/028326, presentada el 21 de julio, 2006 como una continuación en parte de la solicitud, cada una de las cuales se incorpora por completo en la presente a modo de referencia. La Solicitud de Patente Internacional N° Acta: PCT/US2006/028326 también invoca prioridad de las Solicitudes Provisionales de Patentes de los EE.UU. N° Acta: 60/701.814, presentada el 21 de julio, 2005; 60/706.719,

presentada el 8 de agosto, 2005, y 60/731.633, presentada el 28 de octubre, 2005, cada una de las cuales se incorpora por completo en la presente a modo de referencia.

CAMPO DE LA INVENCIÓN

Esta invención se refiere a compuestos de N-(2-arilamino)arilsulfonamida que son inhibidores de MEK, incluyendo las formas cristalinas polimórficas que exhiben un perfil específico de difracción de rayos X de polvo y/o un perfil específico de calorimetría de barrido diferencial. Esta invención también se refiere a composiciones farmacéuticas que comprenden los compuestos que se describen en la presente y a métodos de uso de los compuestos y las composiciones que se describen en la presente, incluyendo el uso en el tratamiento y/o la prevención de cáncer, enfermedades hiperproliferativas y condiciones inflamatorias. La invención también se refiere a métodos para elaborar los compuestos y las composiciones que se describen en la presente.

ANTECEDENTES DE LA INVENCIÓN

Los oncogenes -- genes que contribuyen en la producción de distintos tipos de cáncer - son en general formas mutadas de determinados genes celulares normales ("proto-oncogenes"). Los oncogenes a menudo codifican versiones anormales de los componentes de una vía de señales, tales como las tirosina quinasas de receptores, serina-treonina

quinasas o moléculas de señalización descendentes en la vía. Las moléculas de señalización centrales descendentes en la vía son las proteínas Ras, que están ancladas sobre las superficies internas de las membranas citoplasmáticas, y que hidrolizan el guanosina trifosfato (GTP) en guanosina difosfato (GDP) unido. Cuando son activados por un factor de crecimiento, los receptores de factores de crecimiento inician una cadena de reacciones que conduce a la activación de una actividad de intercambio del nucleótido guanina sobre Ras. Ras alterna entre un estado activo "on" con un GTP unido (de aquí en adelante "Ras.GTP") y un estado inactivo "off" con un GDP unido. El estado activo "on", Ras.GTP, se une y activa a las proteínas que controlan el crecimiento y la diferenciación de las células.

Por ejemplo, en la "cascada de la proteína quinasa activada por mitógeno (MAP quinasa)", Ras.GTP conduce a la activación de una cascada de serina/treonina quinasas. Uno de los distintos grupos de quinasas conocidos por requerir Ras.GTP para su propia activación constituye la familia Raf. Las proteínas Raf activan a "MEK1" y "MEK2", abreviaturas para quinasas activadoras de ERK activadas por mitógeno (donde ERK es la proteína quinasa regulada por señales extracelulares, otra denominación para MAPK). MEK1 y MEK2 son serina/treonina y tirosina proteína quinasas de función doble y también se conocen como MAP quinasa quinasas.

Entonces, Ras.GTP activa a Raf, que activa a MEK1 y MEK2, que a su vez activa a la MAP quinasa (MAPK). La activación de la MAP quinasa por mitógenos parece ser esencial para la proliferación, y la activación constitutiva de esta quinasa es suficiente para inducir la transformación celular. El bloqueo de la señalización descendente de Ras, como mediante el uso de una proteína Raf-1 dominante negativa, puede inhibir por completo la mitogénesis, ya sea inducida por receptores de la superficie celular o por mutantes Ras oncogénicos.

La interacción de Raf y Ras es un paso regulador clave en el control de la proliferación celular. Hasta la fecha, no se han identificado otro sustrato de MEK distinto de MAPK; sin embargo, informes recientes indican que MEK también puede ser activada por otras proteínas de señales ascendentes en la vía, tal como MEK quinasa o MEKK1 y PKC. La MAPK activada es traslocada y se acumula en el núcleo, donde puede fosforilar y activar factores de transcripción, tales como Elk-1 y Sapla, lo cual conduce a una expresión mejorada de genes, tal como de c-fos.

Una vez activada, Raf y otras quinasas fosforilan MEK en dos residuos de serina vecinos, $S^{218}$ y $S^{222}$ en el caso de MEK1. Estas fosforilaciones son necesarias para la activación de MEK como una quinasa. A su vez, MEK fosforila la MAP quinasa en dos residuos separados por un solo

aminoácido: una tirosina, $Y^{185}$ y una treonina, $T^{183}$. MEK parece asociarse fuertemente con la MAP quinasa antes de fosforilarla, lo cual sugiere que la fosforilación de la MAP quinasa por MEK puede requerir una fuerte interacción anterior entre las dos proteínas. Hay dos factores — la especificidad poco común de MEK y su requerimiento de una fuerte interacción con la MAP quinasa antes de la fosforilación - que sugieren que el mecanismo de acción de MEK puede diferir suficientemente de los mecanismos de otras proteína quinasas como para que puedan actuar como inhibidores selectivos de MEK. Posiblemente, dichos inhibidores funcionarían por medio de mecanismos alostéricos en lugar del mecanismo más común que comprende bloqueo de un sitio de unión a ATP.

Por consiguiente, MEK1 y MEK2 son blancos validados y aceptados para las terapias anti-proliferativas, aún cuando la mutación oncogénica no afecte la estructura o expresión de MEK. Véanse, por ejemplo, las publicaciones de Patente de los EE.UU. N°: 2003/0149015 de Barrett *et al.*, y 2004/0029898 de Boyle *et al.*

Se han descrito diversos ejemplos de inhibidores de arilo-(fenilamino-2(*p*-sustituido)-1-sustituido de MEK. En las Patentes de los EE.UU. N°: 6.440.966 y 6.750.217 y la correspondiente publicación WO 00/42003 se describen ésteres de ácido carboxílico e hidroxámico y derivados de amidas N-

sustituidas de ésteres de ácido 2(4-iodofenilamino)-benzoico sustituido con sulfonamidas y benzamidas N-sustituidas que funcionan como inhibidores de MEK. La sulfonamida también puede estar N-sustituida.

En la Patente de los EE.UU. N°: 6.545.030 y la correspondiente publicación WO 00/42029 se describen inhibidores de MEK que son 1-heterociclil-2(4-iodofenilamino)-benceno, donde el heterociclo es un anillo que contiene nitrógeno de cinco miembros, tal como pirazol, triazol, oxazol, isoxazol e isoxazolinona. En la publicación más reciente de Patente de los EE.UU. N°: 2005/004186 se describen compuestos relacionados en los cuales el sustituyente 4-iodo de la patente '030 es reemplazado por un género muy amplio de grupos incluyendo alquilo, alcoxi, aciloxi, alquenilo, carbamoílo, carbamoilalquilo, carboxilo, carboxilalquilo, N-acilsulfonamida y otros.

La Patente de los EE.UU. N°: 6.469.004 y la correspondiente publicación WO 00/42022 describe ésteres del ácido carboxílico e hidroxámico de un grupo de compuestos de fenileno de heterociclos condensados, es decir, benzimidazoles, benzoxazoles, benzotiazoles, benzotiadiazoles, quinazolinas, *etc.* Los heterociclos son ésteres del ácido 7-F-6-(4-iodo-fenilamino)-5-carboxílico, amidas de ácido carboxílico o ésteres de ácido hidroxámico.

La publicación más reciente de Patente de los EE.UU. N°: 2005/0026970 describe compuestos similares en los cuales el sustituyente 4-iodo se reemplazó por un género muy amplio de estructuras. Se describen compuestos relacionados en las publicaciones de patente WO 03/077855, WO 03/77914 y US 2005/0554701. Otros ejemplos de ésteres de ácido 2-(4-iodofenilamino)-fenilhidroxámico considerados de utilidad como inhibidores de MEK se pueden consultar en WO 2005/028426.

En la publicación de patente WO 02/06213 y la correspondiente Solicitud de Patente de los EE.UU. N° Acta: 10/333.399 (U.S. 2004/0054172) se describen ésteres de ácidos hidroxi-sustituidos de ácido 1-oxámico-2(4-halofenilamino)-3,4-difluorobenceno. En la Patente de los EE.UU. N°: 6.891.066 y la correspondiente publicación WO 03/62191 se describen compuestos similares en donde el sustituyente 4-halo es reemplazado por un género muy amplio de estructuras. Entre los sustituyentes en la posición 4 había metilo, etilo, etinilo y 2-hidroxietilo. Los compuestos específicos relacionados se describen en la Patente de los EE.UU. N°: 6.770.778.

La publicación de Patente WO 04/083167, publicada el 30 de septiembre, 2004, (en japonés) divulga más de dos mil - pero solamente provee los datos de RMN para 400 - sulfonilurea 1(N-sustituido)-2(2,4-dihalofenilamino)-3,4-

difluorobencenos y asevera que son de utilidad como inhibidores de MEK. Se presentaron datos indicativos de inhibición de MEK para un subgrupo de tan solo doce compuestos. Además de una amina secundaria o terciaria, estos doce compuestos contenían todos uno de los siguientes grupos: una sulfonilurea N,N-disustituida, N-piperazinsulfonamida, N-piperidinsulfonamida o N-pirrolidinsulfonamida.

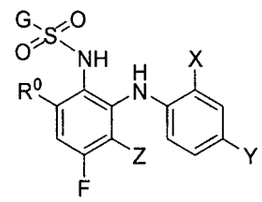
La cascada de MEK también se ha relacionado con enfermedades y trastornos inflamatorios. Publicación de la Solicitud de Patente de los EE.UU. N°: 2006/0030610 de Koch *et al.*, publicación de la Solicitud de Patente de los EE.UU. N°: 2006/0140872 de Furue *et al.* Esto incluye trastornos de inflamación aguda y crónica. Los ejemplos de tales trastornos son dermatitis de contacto alérgica, artritis reumatoide, osteoartritis, enfermedades de intestino inflamatorio, trastorno pulmonar obstructivo crónico, psoriasis, esclerosis múltiple, asma, enfermedades y trastornos relacionados con las complicaciones diabéticas y complicaciones inflamatorias del sistema cardiovascular, tal como el síndrome coronario agudo. Las enfermedades de intestino inflamatorio incluyen enfermedad de Crohn y colitis ulcerosa.

MEK1 y MEK2 son blancos validados y aceptados para las terapias anti-proliferativas, aún cuando la mutación

oncogénica no afecte la estructura o expresión de MEK. Véanse, por ejemplo, las publicaciones de Patente de los EE.UU. N°: 2003/0149015 de Barrett *et al.*, y 2004/0029898 de Boyle *et al.*

**RESUMEN DE LA INVENCIÓN**

Se proveen aquí compuestos de fórmula I, o sales aceptables farmacéuticamente, solvatos, polimorfos, ésteres, tautómeros o prodrogas de los mismos:




fórmula I

donde

Z es H o F;

X es F, Cl, $CH_3$, $CH_2OH$, $CH_2F$, $CHF_2$, o $CF_3$;

Y es I, Br, Cl, $CF_3$, $C_1$-$C_3$ alquilo, $C_2$-$C_3$ alquenilo, $C_2$-$C_3$ alquinilo, ciclopropilo, OMe, OEt, SMe, fenilo o Het, donde Het es un grupo heterocíclico mono o bicíclico de 5 a 10 miembros, el cual es saturado, olefínico o aromático, que contiene 1-5 heteroátomos en el anillo seleccionados en forma independiente entre N, O, y S; donde

todos dichos grupos fenilo o Het están opcionalmente sustituidos con F, Cl, Br, I, acetilo, metilo, CN, $NO_2$, $CO_2H$, $C_1$-$C_3$ alquilo, $C_1$-$C_3$ alcoxi, $C_1$-$C_3$

alquil-C(=O)-, $C_1$-$C_3$ alquil-C(=S)-, $C_1$-$C_3$ alcoxi-C(=S)-, $C_1$-$C_3$ alquil-C(=O)O-, $C_1$-$C_3$ alquil-O-(C=O)-, $C_1$-$C_3$ alquil-C(=O)NH-, $C_1$-$C_3$ alquil-C(=NH)NH-, $C_1$-$C_3$ alquil-NH-(C=O)-, di-$C_1$-$C_3$ alquil-N-(C=O)-, $C_1$-$C_3$ alquil-C(=O)N($C_1$-$C_3$ alquil)-, $C_1$-$C_3$ alquil-S(=O)$_2$NH- o trifluorometilo;

todos dichos grupos metilo, etilo, $C_1$-$C_3$ alquilo, y ciclopropilo están opcionalmente sustituidos con OH;

todos dichos grupos metilo están opcionalmente sustituidos con uno, dos o tres átomos de F;

$R^0$ es H, F, Cl, Br, I, $CH_3NH$-, $(CH_3)_2N$-, $C_1$-$C_6$ alquilo, $C_1$-$C_4$ alcoxi, $C_3$-$C_6$ cicloalquilo, $C_2$-$C_6$ alquenilo, $C_2$-$C_6$ alquinilo, fenilo, fenilo monosustituido, O($C_1$-$C_4$ alquilo), O-C(=O)($C_1$-$C_4$ alquilo) o C(=O)O($C_1$-$C_4$ alquil); donde

dichos grupos alquilo, alcoxi, cicloalquilo, alquenilo, alquinilo y fenilo están opcionalmente sustituidos con 1-3 sustituyentes seleccionados en forma independiente entre F, Cl, Br, I, OH, CN, cianometilo, nitro, fenilo y trifluorometilo;

dichos grupos $C_1$-$C_6$ alquilo y $C_1$-$C_4$ alcoxi también están opcionalmente sustituidos con $OCH_3$ o $OCH_2CH_3$;

G es $G_1$, $G_2$, $R_{1a}$, $R_{1b}$, $R_{1c}$, $R_{1d}$, $R_{1e}$, $Ar_1$, $Ar_2$ o $Ar_3$; donde

$G_1$ es $C_1$-$C_6$ alquilo opcionalmente sustituido con un grupo amino, $C_1$-$C_3$ alquilamino, o dialquilamino, dicho

grupo dialquilamino comprende dos grupos $C_1$-$C_4$ alquilo los cuales pueden ser idénticos o no idénticos; o

$G_1$ es un grupo $C_3$-$C_8$ diaminoalquilo;

$G_2$ es un anillo de 5 o 6 miembros, el cual es saturado, no saturado o aromático, que contiene 1-3 heteroátomos en el anillo seleccionados en forma independiente entre N, O, y S, opcionalmente sustituidos con 1-3 sustituyentes seleccionados en forma independiente entre F, Cl, OH, O($C_1$-$C_3$ alquilo), $OCH_3$, $OCH_2CH_3$, $CH_3C(=O)NH$, $CH_3C(=O)O$, CN, $CF_3$, y un grupo heterocíclico aromático de 5 miembros que contiene 1-4 heteroátomos en el anillo seleccionados en forma independiente entre N, O , y S;

$R_{1a}$ es metilo, opcionalmente sustituido con 1-3 átomos de flúor o 1-3 átomos de cloro, o con OH, ciclopropoxi, o $C_1$- $C_3$ alcoxi, donde dicho grupo ciclopropoxi o las unidades $C_1$-$C_3$ alquilo de dichos grupos $C_1$-$C_3$ alcoxi están opcionalmente sustituidas con un grupo hidroxi o metoxi, y donde todos los grupos $C_3$-alquilo dentro de dicho $C_1$- $C_4$ alcoxi están opcionalmente sustituidos adicionalmente con un segundo grupo OH;

$R_{1b}$ es $CH(CH_3)$-$C_{1-3}$ alquilo o $C_3$-$C_6$ cicloalquilo, dichos grupos alquilo y cicloalquilo están opcionalmente sustituidos con 1-3 sustituyentes

seleccionados en forma independiente entre F, Cl, Br, I, OH, $OCH_3$, y CN;

$R_{1c}$ es $(CH_2)_nO_mR'$; donde

m es 0 o 1; y donde

cuando m es 0, n es 1 o 2;

cuando m es 1, n es 2 o 3;

R' es $C_1$-$C_6$ alquilo, opcionalmente sustituido con 1-3 sustituyentes seleccionados en forma independiente entre F, Cl, OH, $OCH_3$, $OCH_2CH_3$, y $C_3$-$C_6$ cicloalquilo;

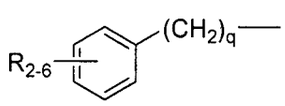
$R_{1d}$ es C(A)(A')(B)-; donde

B es H o $C_{1-4}$ alquilo, opcionalmente sustituido con uno o dos grupos OH;

A y A' son en forma independiente H o $C_{1-4}$ alquilo, opcionalmente sustituido con uno o dos grupos OH; o

A y A', junto con el átomo de carbono al cual se encuentran unidos, forman un anillo saturado de 3 a 6 miembros;

$R_{1e}$ es




**$R_{1e}$**

donde

q es 1 o 2;

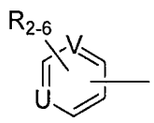
$R_2$ y $R_3$ son en forma independiente entre sí, H, F, Cl, Br, $CH_3$, $CH_2F$, $CHF_2$, $CF_3$ $OCH_3$, $OCH_2F$, $OCHF_2$, $OCF_3$, etilo, *n*-propilo, isopropilo, ciclopropilo, isobutilo, *sec*-butilo, *tert*-butilo o metilsulfonilo;

$R_4$ es H, F, Cl, Br, $CH_3$, $CH_2F$, $CHF_2$, $CF_3$ $OCH_3$, $OCH_2F$, $OCHF_2$, $OCF_3$, etilo, *n*-propilo, isopropilo, ciclopropilo, isobutilo, *sec*-butilo, *tert*-butilo, metilsulfonilo, nitro, acetamido, amidinilo, ciano, carbamoilo, metilcarbamoilo, dimetilcarbamoilo, 1,3,4-oxadiazol-2-ilo, 5-metil-1,3,4- oxadiazol, 1,3,4-tiadiazol, 5-metil-1,3,4-tiadiazol 1H-tetrazolilo, N-morfolilo carbonilo amino, N-morfolilsulfonilo y N-pirrolidinilcarbonilamino;

$R_5$ es H, F, Cl o metilo;

$R_6$ es H, F, Cl o metilo;

$Ar_1$ es




**$Ar_1$**

donde

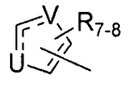
U y V son, en forma independiente, N, $CR_2$ o $CR_3$;

$R_2$, $R_3$ y $R_4$ son, en forma independiente, H, F, Cl, Br, $CH_3$, $CH_2F$, $CHF_2$, $CF_3$ $OCH_3$, $OCH_2F$, $OCHF_2$, $OCF_3$, etilo, *n*-propilo, isopropilo, ciclopropilo, isobutilo, *sec*-butilo, *tert*-butilo, acetamido,

amidinilo, ciano, carbamoilo, metilcarbamoilo, dimetilcarbamoilo, 1,3,4-oxadiazol-2-ilo, 5-metil-1,3,4-oxadiazolilo, 1,3,4-tiadiazolilo, 5-metil-1,3,4-tiadiazolilo, 1H-tetrazolilo, N-morfolilcarbonilamino, N-morfolilsulfonilo, N-pirrolidinilcarbonilamino, y metilsulfonilo;

$R_5$ y $R_6$ son, en forma independiente, H, F, Cl o metilo;

$Ar_2$ es




**$Ar_2$**

donde

la línea de guiones representa ubicaciones formales alternativas para la unión doble del segundo anillo;

U es -S-, -O- o -N =, y donde

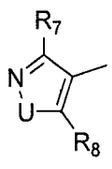
cuando U es -O- o -S-, V es -CH=, -CCl= o -N =;

cuando U es -N =, V es -CH=, -CCl=, o -N=;

$R_7$ es H o metilo;

$R_8$ es H, acetamido, metilo, F o Cl;

$Ar_3$ es

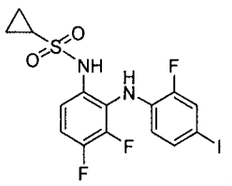
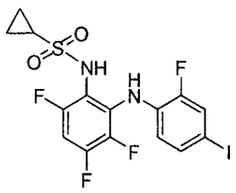
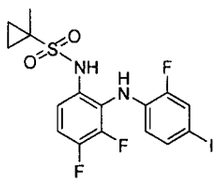
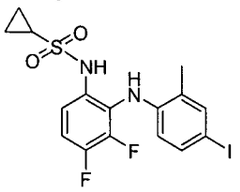
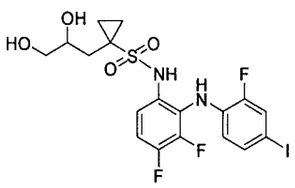
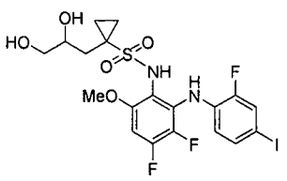
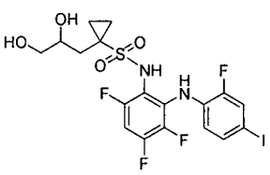
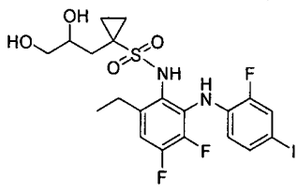
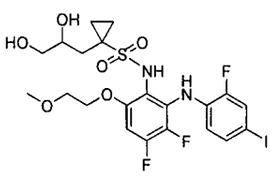
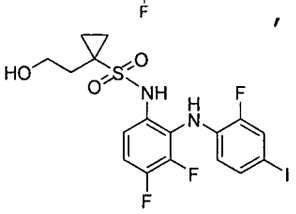
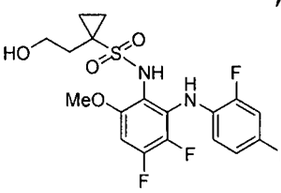
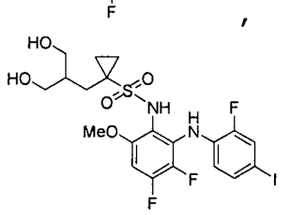
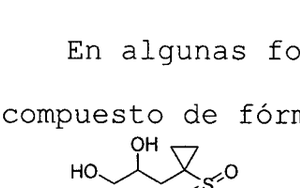
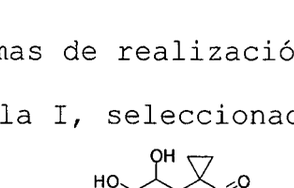
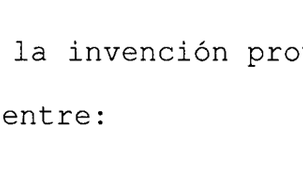


**$Ar_3$**

donde

U es -NH-, $-NCH_3-$ o -O-;

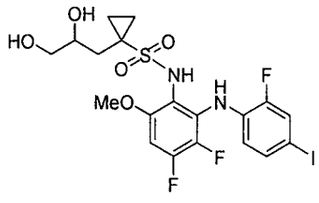
$R_7$ y $R_8$ son, en forma independiente, H, F, Cl, o metilo.

En algunas formas de realización, la invención provee un compuesto de fórmula I, seleccionado entre los siguientes compuestos:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , y  .

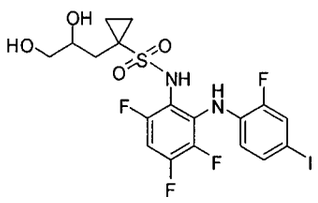
En algunas formas de realización, la invención provee un compuesto de fórmula I, seleccionado entre:  y , donde el carbono

2-OH es de configuración R.

En algunas formas de realización, la invención provee un compuesto de fórmula I, seleccionado entre:

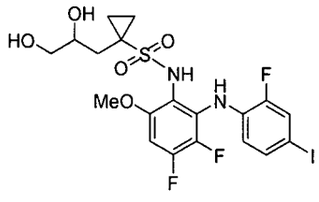



y

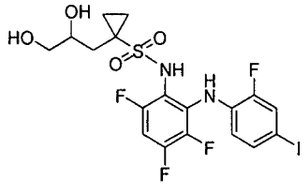



, donde el carbono 2-OH es de configuración S.

En algunas formas de realización, la invención provee una composición que comprende un compuesto de fórmula I, seleccionado entre aquellos que se muestran a continuación, donde el carbono 2-OH es de configuración R, sustancialmente libre del isómero S.

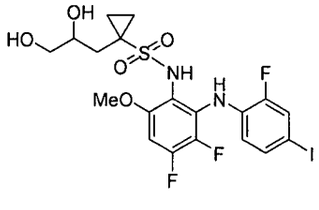



,

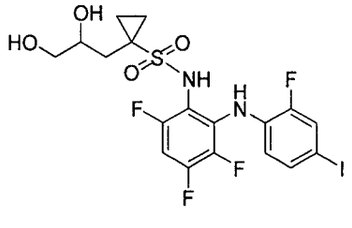



.

En algunas formas de realización, la invención provee una composición que comprende un compuesto de fórmula I, seleccionado entre aquellos que se muestran a continuación, donde el carbono 2-OH es de configuración S, sustancialmente libre del isómero R.




,




.

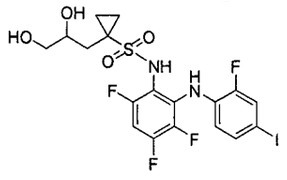
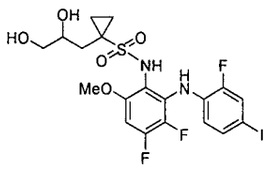
En algunas formas de realización, esta invención provee

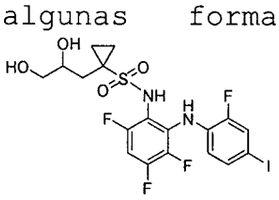
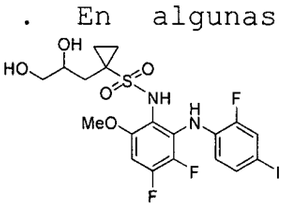
un compuesto de fórmula I, donde Y es fenilo, piridilo, o pirazolilo. En otra forma de realización subgenérica, esta invención provee un compuesto de fórmula I, donde Y es fenilo, piridilo, o pirazolilo sustituido. En aún otra forma de realización subgenérica, esta invención provee un compuesto de fórmula I, donde Y es Br o I. En una realización subgenérica, esta invención provee un compuesto de fórmula I, donde G es 1-piperidilo, 2-piperidilo, 3-piperidilo, o 4-piperidilo. En otra forma de realización subgenérica, esta invención provee un compuesto de fórmula I, donde G es 1-piperazilo o 2-piperazilo. En otra forma de realización subgenérica, esta invención provee un compuesto de fórmula I, donde G es morfolilo. En otra forma de realización subgenérica, esta invención provee un compuesto de fórmula I, donde G es N-metil-2-aminoetilo. En una realización subgenérica, esta invención provee un compuesto de fórmula I, donde G es N-metil-3-amino-n-propilo. En otra forma de realización subgenérica, esta invención provee un compuesto de fórmula I, donde G es $(CH_3)_2N-CH_2CH_2-NH-(CH_2)_n-$, donde n es 1, 2, o 3. En otra forma de realización subgenérica, esta invención provee un compuesto de fórmula I, donde G es $(CH_3CH_2)_2N-CH_2CH_2-NH-(CH_2)_n-$, donde n es 1 o 2. En una realización subgenérica más específica, esta invención provee un compuesto de fórmula I, donde G es 1-piperidilo, 2-piperidilo, 3-piperidilo, o 4-piperidilo; R°

es H, halo, o metoxi; X es F; e Y es I. En otra forma de realización subgenérica más específica, esta invención provee un compuesto de fórmula I, donde G es 1-piperazilo o 2-piperazilo; $R^o$ es H, halo, o metoxi; X es F; e Y es I. En otra forma de realización subgenérica más específica, esta invención provee un compuesto de fórmula I, donde G es morfolilo; $R^o$ es H, halo, o metoxi; X es F; e Y es I. En otra forma de realización subgenérica más específica, esta invención provee un compuesto de fórmula I, donde G es N-metil-2-aminoetilo; $R^o$ es H, halo, o metoxi; X es F; e Y es I En otra forma de realización subgenérica más específica, esta invención provee un compuesto de fórmula I, donde G es N-metil-3-amino-n-propilo; $R^o$ es H, halo, o metoxi; X es F; e Y es I. En otra forma de realización subgenérica más específica, esta invención provee un compuesto de fórmula I, donde G es $(CH_3)_2N-CH_2CH_2-NH-(CH_2)_n-$, donde n es 1, 2, o 3; $R^o$ es H, halo, o metoxi; X es F; e Y es I. En otra forma de realización subgenérica más específica, esta invención provee un compuesto de fórmula I, donde G es $(CH_3CH_2)_2N-CH_2CH_2-NH-(CH_2)_n-$, donde n es 1 o 2; $R^o$ es H, halo, o metoxi; X es F; e Y es I.

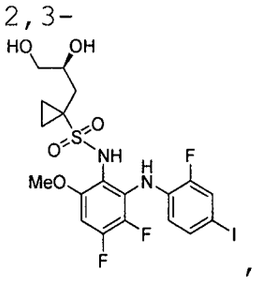
En algunas formas de realización, la invención provee una composición farmacéutica que comprende un compuesto de fórmula I o una sal, solvato, polimorfo, éster, tautómero o prodroga farmacéuticamente aceptable del mismo. En algunas

formas de realización la composición farmacéutica comprende además al menos un vehículo farmacéuticamente aceptable.

En algunas formas de realización, la invención provee una composición farmacéutica que comprende un compuesto seleccionado entre:  y  , o una sal, solvato, polimorfo, éster, tautómero o prodroga farmacéuticamente aceptable del mismo. En algunas formas de realización, la composición farmacéutica comprende además al menos un vehículo farmacéuticamente aceptable. En algunas formas de realización, el compuesto es de configuración R. En algunas formas de realización, el compuesto es de configuración R, sustancialmente libre del isómero S. En algunas formas de realización, el compuesto es de configuración S.

En algunas formas de realización, el compuesto es de configuración S, sustancialmente libre del isómero R. En algunas formas de realización, el compuesto es:  . En algunas formas de realización, el compuesto es:  .

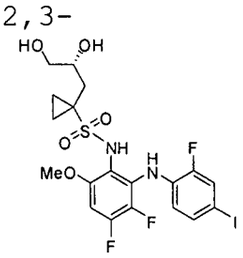
La invención también se relaciona con un polimorfo cristalino de forma A de N-(S)-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida (también mencionado aquí como "Compuesto A" y "N-(-)-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida"):



, que exhibe un patrón de difracción de rayos X en polvo específico. En algunas formas de realización, el patrón de difracción de rayos X en polvo contiene al menos 50% de los picos que se muestran en **FIG. 5**. En algunas formas de realización, el patrón de difracción de rayos X en polvo contiene al menos 70% de los picos que se muestran en **FIG. 5**. En algunas formas de realización, el patrón de difracción de rayos X en polvo contiene al menos 90% de los picos que se muestran en **FIG. 5**. En algunas formas de realización, el patrón de difracción de rayos X en polvo es sustancialmente el mismo que el patrón de difracción de rayos X en polvo que se muestra en **FIG. 5**. El Compuesto A se caracterizó como el isómero "S" realizando los ésteres R y S del MTPA sobre el alcohol secundario y comparando la diferencia en el desplazamiento químico del protón. *Véase, por ejemplo,* Dale,

J.A.; Mosher, H.S., *J. Am. Chem. Soc.*, 1973, 95, 512 y Ohtani *et al.*, *J. Am. Chem. Soc.*, 1991, 113, 4092.

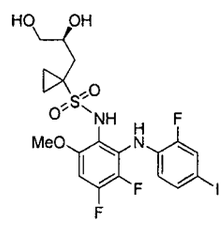
La invención también se relaciona con N-(R)-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida (también mencionado aquí como "Compuesto B" y "N-(+)-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida"):



.

El Compuesto B se caracterizó como el isómero "R" realizando los ésteres R y S del MTPA sobre el alcohol secundario y comparando la diferencia en el desplazamiento químico del protón. *Véase, por ejemplo,* Dale, J.A.; Mosher, H.S., *J. Am. Chem. Soc.*, 1973, 95, 512 y Ohtani *et al.*, *J. Am. Chem. Soc.*, 1991, 113, 4092.

La invención también se relaciona con un polimorfo cristalino de forma A de N-(S)-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida:



que exhibe un patrón de calorimetría diferencial de barrido específico. En algunas formas de realización, el patrón de

calorimetría diferencial de barrido es sustancialmente el mismo que el patrón de calorimetría diferencial de barrido que se muestra en **FIG. 6.**

La invención también se relaciona con composiciones farmacéuticas que comprenden una cantidad efectiva de polimorfo cristalino de forma A de N-(S)-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida y un vehículo farmacéuticamente aceptable.

En algunas formas de realización, el polimorfo cristalino de forma A de N-(S)-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida es útil para el tratamiento o prevención de cáncer o una enfermedad inflamatoria. La invención además se relaciona con métodos para el tratamiento o la prevención de cáncer o una enfermedad inflamatoria, que comprende administrar una cantidad efectiva de un polimorfo cristalino de forma A de N-(S)-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida a un sujeto en necesidad del mismo.

En otros aspectos, la presente invención se dirige a composiciones farmacéuticas que comprenden cantidades efectivas de un compuesto de fórmula I o una sal, solvato, polimorfo, éster, tautómero o prodroga farmacéuticamente

aceptable del mismo. En algunas formas de realización, las composiciones farmacéuticas además comprenden un vehículo farmacéuticamente aceptable. Tales composiciones pueden contener adyuvantes, excipientes, y conservantes, agentes para retrasar la absorción, rellenos, aglutinantes, adsorbentes, amortiguadores, agentes desintegradores, agentes solubilizantes, otros vehículos, y otros ingredientes inertes. Los métodos para la formulación de tales composiciones son bien conocidos en el arte.

En otros aspectos, la presente invención se dirige a una composición farmacéutica que comprende un compuesto de fórmula I o una sal, solvato, polimorfo, éster, tautómero o prodroga farmacéuticamente aceptable del mismo. En algunas formas de realización, la composición farmacéutica se presenta en una forma adecuada para su administración oral. En formas de realización adicionales, la composición farmacéutica se presenta en forma de una tableta, cápsula, píldora, polvo, formulación de liberación sostenida, solución, suspensión, para inyección parenteral como una solución, suspensión o emulsión estéril, para administración tópica como un ungüento o crema o para administración rectal como un supositorio. En formas de realización adicionales, la composición farmacéutica se presenta en formas unitarias de dosificación adecuadas para la administración de dosis precisas. En formas de realización adicionales la cantidad

de compuesto de fórmula I se encuentra en el rango de aproximadamente 0,001 a aproximadamente 1000 mg/kg de peso corporal/día. En formas de realización adicionales la cantidad de compuesto de fórmula I se encuentra en el rango de aproximadamente 0,5 a aproximadamente 50 mg/kg/día. En formas de realización adicionales la cantidad de compuesto de fórmula I es de aproximadamente 0,001 a aproximadamente 7 g/día. En formas de realización adicionales la cantidad de compuesto de fórmula I es de aproximadamente 0,002 a aproximadamente 6 g/día. En formas de realización adicionales la cantidad de compuesto de fórmula I es de aproximadamente 0,005 a aproximadamente 5 g/día. En formas de realización adicionales la cantidad de compuesto de fórmula I es de aproximadamente 0,01 a aproximadamente 5 g/día. En formas de realización adicionales la cantidad de compuesto de fórmula I es de aproximadamente 0,02 a aproximadamente 5 g/día. En formas de realización adicionales la cantidad de compuesto de fórmula I es de aproximadamente 0,05 a aproximadamente 2,5 g/día. En formas de realización adicionales la cantidad de compuesto de fórmula I es de aproximadamente 0,1 a aproximadamente 1 g/día.

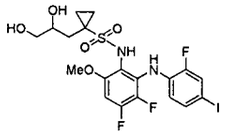
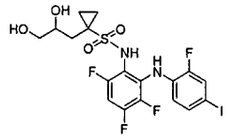
En formas de realización adicionales, los niveles de dosificación inferiores al límite inferior del rango previamente mencionado pueden ser más que adecuados. En

formas de realización adicionales, se pueden requerir niveles de dosificación por encima del límite superior del rango previamente mencionado. En formas de realización adicionales el compuesto de fórmula I se administra en una única dosis, una vez al día. En formas de realización adicionales el compuesto de fórmula I se administra en múltiples dosis, más de una vez al día. En formas de realización adicionales el compuesto de fórmula I se administra dos veces al día. En formas de realización adicionales el compuesto de fórmula I se administra tres veces al día. En formas de realización adicionales el compuesto de fórmula I se administra cuatro veces al día. En formas de realización adicionales el compuesto de fórmula I se administra más de cuatro veces al día.

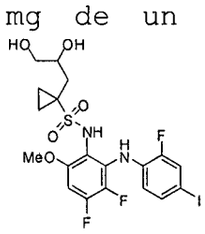
En algunas formas de realización, la composición farmacéutica es para su administración a un mamífero. En formas de realización adicionales, el mamífero es un ser humano.

En formas de realización adicionales, la composición farmacéutica comprende además un vehículo, excipiente y/o adyuvante farmacéuticamente aceptable. En formas de realización adicionales, la composición farmacéutica comprende además al menos un agente terapéutico. En formas de realización adicionales, el agente terapéutico se selecciona entre el grupo de agentes citotóxicos, agentes

antiangiogénicos y agentes antineoplásticos. En formas de realización adicionales, el agente antineoplástico se selecciona entre el grupo que consiste en agentes de la alquilación, antimetabolitos, epidofilotoxinas; enzimas antineoplásticas, inhibidores de la topoisomerasa, procarbazinas, mitoxantronas, complejos de coordinación de platino, modificadores de la respuesta biológica y inhibidores del crecimiento, agentes terapéuticos hormonales/antihormonales, y factores de crecimiento hematopoyéticos. En formas de realización adicionales, el agente terapéutico es taxol, bortezomib o ambos. En formas de realización adicionales, la composición farmacéutica se administra en combinación con una terapia adicional. En formas de realización adicionales, la terapia adicional es terapia de radiación, quimioterapia, cirugía o cualquier combinación de los mismos. En formas de realización adicionales, la composición farmacéutica comprende una sal farmacéuticamente aceptable de un compuesto de fórmula I.

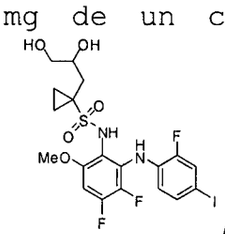
Se proveen aquí composiciones y métodos para usar una composición que comprende un compuesto seleccionado entre:  y  . En algunas formas de realización, el carbono 2-OH sobre el compuesto es de configuración R. En algunas formas de realización, el carbono 2-OH sobre el compuesto es de configuración S. En

algunas formas de realización, la composición se encuentra sustancialmente libre del isómero S del compuesto. En algunas formas de realización, la composición se encuentra sustancialmente libre del isómero R del compuesto. En algunas formas de realización, el compuesto contiene menos de 10% del isómero S del compuesto. En algunas formas de realización, el compuesto contiene menos de 10% del isómero R del compuesto. En algunas formas de realización, el compuesto contiene menos de 5% del isómero S del compuesto. En algunas formas de realización, el compuesto contiene menos de 5% del isómero R del compuesto. En algunas formas de realización, el compuesto contiene menos de 1% del isómero S del compuesto. En algunas formas de realización, el compuesto contiene menos de 1% del isómero R del compuesto.

También se proveen aquí composiciones y métodos para el tratamiento de cáncer o inflamación con composiciones que comprenden aproximadamente 1-100 mg de un compuesto que tiene la siguiente estructura: 

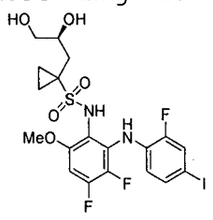
. En algunas formas de realización, la composición tiene en cuenta la liberación modificada del compuesto. En algunas formas de realización, la composición tiene en cuenta la liberación sostenida del compuesto. En algunas formas de realización,

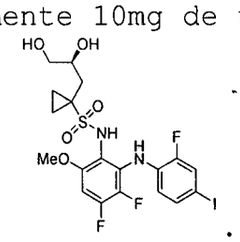
la composición tiene en cuenta la liberación retardada del compuesto. En algunas formas de realización, el compuesto se encuentra presente en una cantidad de aproximadamente 1-50 mgs. En algunas formas de realización, el compuesto se encuentra presente en una cantidad de aproximadamente 1-10 mgs. En algunas formas de realización, el compuesto se encuentra presente en una cantidad de aproximadamente 10-20 mgs. En algunas formas de realización, el compuesto se encuentra presente en una cantidad de aproximadamente 20-40 mgs. En algunas formas de realización, el compuesto se encuentra presente en una cantidad de aproximadamente 40-50 mgs.

También se proveen aquí composiciones y métodos para el tratamiento de cáncer o inflamación con composiciones que comprenden: aproximadamente 1-50 mg de un compuesto que tiene la siguiente estructura 

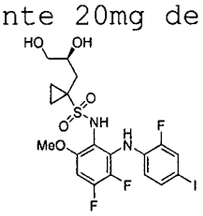
, donde la composición tiene en cuenta la liberación modificada de la droga. En algunas formas de realización, la composición comprende además celulosa microcristalina. En algunas formas de realización, la composición comprende además croscarmelosa de sodio. En algunas formas de realización, la composición comprende además lauril sulfato de sodio. En algunas formas de realización, la composición comprende

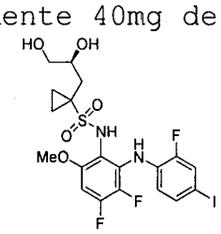
además estearato de magnesio.

También se proveen aquí composiciones que comprenden aproximadamente 1mg de un compuesto que tiene la siguiente estructura:  . En algunas formas de realización, la composición comprende además aproximadamente 222,2mg de celulosa microcristalina. En algunas formas de realización, la composición comprende además aproximadamente 12,0mg de croscarmelosa de sodio. En algunas formas de realización, la composición comprende además aproximadamente 2,4mg de lauril sulfato de sodio. En algunas formas de realización, la composición comprende además aproximadamente 2,4mg de estearato de magnesio.

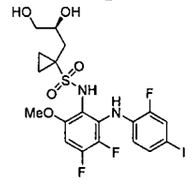
También se proveen aquí composiciones y métodos para el tratamiento de cáncer o inflamación con composiciones que comprenden aproximadamente 10mg de un compuesto que tiene la siguiente estructura  . En algunas formas de realización, la composición comprende además aproximadamente 213,2mg de celulosa microcristalina. En algunas formas de realización, la composición comprende además aproximadamente 12,0mg de croscarmelosa de sodio. En algunas formas de

realización, la composición comprende además aproximadamente 2,4mg de lauril sulfato de sodio. En algunas formas de realización, la composición comprende además aproximadamente 2,4mg de estearato de magnesio.

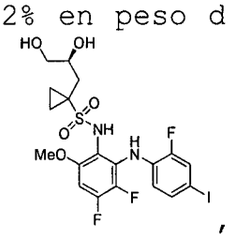
También se proveen aquí composiciones y métodos para el tratamiento de cáncer o inflamación con composiciones que comprenden aproximadamente 20mg de un compuesto que tiene la siguiente estructura:  . En algunas formas de realización, la composición comprende además aproximadamente 203,2mg de celulosa microcristalina. En algunas formas de realización, la composición comprende además aproximadamente 12,0mg de croscarmelosa de sodio. En algunas formas de realización, la composición comprende además aproximadamente 2,4mg de lauril sulfato de sodio. En algunas formas de realización, la composición comprende además aproximadamente 2,4mg de estearato de magnesio.

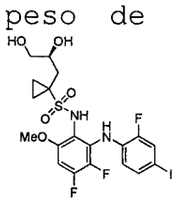
También se proveen aquí composiciones y métodos para el tratamiento de cáncer o inflamación con composiciones que comprenden aproximadamente 40mg de un compuesto que tiene la siguiente estructura  . En algunas formas de realización, la composición comprende además aproximadamente

183,2mg de celulosa microcristalina. En algunas formas de realización, la composición comprende además aproximadamente 12,0mg de croscarmelosa de sodio. En algunas formas de realización, la composición comprende además aproximadamente 2,4mg de lauril sulfato de sodio. En algunas formas de realización, la composición comprende además aproximadamente 2,4mg de estearato de magnesio.

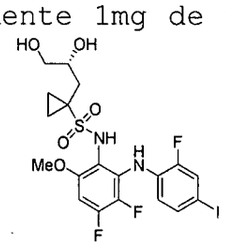
También se proveen aquí composiciones y métodos para el tratamiento de cáncer o inflamación con composiciones que comprenden: aproximadamente 0,4% en peso de un compuesto que tiene la siguiente estructura 

, y aproximadamente 99,6% en peso de un vehículo farmacéuticamente aceptable. En algunas formas de realización, el vehículo farmacéuticamente aceptable comprende celulosa microcristalina. En algunas formas de realización, la celulosa microcristalina es de aproximadamente 92,6% en peso de la composición. En algunas formas de realización, la composición comprende además aproximadamente 5% en peso de croscarmelosa de sodio. En algunas formas de realización, la composición comprende además aproximadamente 1% en peso de lauril sulfato de sodio. En algunas formas de realización, la composición comprende además aproximadamente 1% en peso de estearato de magnesio.

También se proveen aquí composiciones y métodos para el tratamiento de cáncer o inflamación con composiciones que comprenden aproximadamente 4,2% en peso de un compuesto que tiene la siguiente estructura  , y aproximadamente 95,8 % en peso de un vehículo farmacéuticamente aceptable. En algunas formas de realización, el vehículo farmacéuticamente aceptable comprende celulosa microcristalina. En algunas formas de realización, la celulosa microcristalina es de aproximadamente 88,8% en peso de la composición. En algunas formas de realización, la composición comprende además aproximadamente 5% en peso de croscarmelosa de sodio. En algunas formas de realización, la composición comprende además aproximadamente 1% en peso de lauril sulfato de sodio. En algunas formas de realización, la composición comprende además aproximadamente 1% en peso de estearato de magnesio.

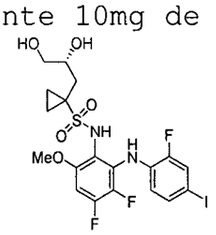
También se proveen aquí composiciones y métodos para el tratamiento de cáncer o inflamación con composiciones que comprenden entre aproximadamente 2% y aproximadamente 10% en peso de un compuesto que tiene la siguiente estructura  , y entre aproximadamente 98% y aproximadamente

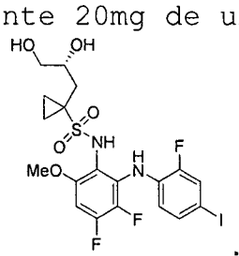
90% en peso de un vehículo farmacéuticamente aceptable. En algunas formas de realización, el vehículo farmacéuticamente aceptable comprende además celulosa microcristalina. En algunas formas de realización, la celulosa microcristalina es entre aproximadamente 85% y aproximadamente 95% en peso de la composición. En algunas formas de realización, la composición comprende además entre aproximadamente 1% y aproximadamente 6% en peso de croscarmelosa de sodio. En algunas formas de realización, la composición comprende además entre aproximadamente 0,1% y aproximadamente 2% en peso de lauril sulfato de sodio. En algunas formas de realización, la composición comprende además entre aproximadamente 0,25% y aproximadamente 1,5% en peso de estearato de magnesio.

También se proveen aquí composiciones y métodos para el tratamiento de cáncer o inflamación con composiciones que comprenden aproximadamente 1mg de un compuesto que tiene la siguiente estructura 

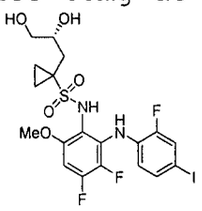
. En algunas formas de realización, la composición comprende además aproximadamente 222,2mg de celulosa microcristalina. En algunas formas de realización, la composición comprende además aproximadamente 12,0mg de croscarmelosa de sodio. En algunas formas de

realización, la composición comprende además aproximadamente 2,4mg de lauril sulfato de sodio. En algunas formas de realización, la composición comprende además aproximadamente 2,4mg de estearato de magnesio.

También se proveen aquí composiciones y métodos para el tratamiento de cáncer o inflamación con composiciones que comprenden aproximadamente 10mg de un compuesto que tiene la siguiente estructura:  . En algunas formas de realización, la composición comprende además aproximadamente 213,2mg de celulosa microcristalina. En algunas formas de realización, la composición comprende además aproximadamente 12,0mg de croscarmelosa de sodio. En algunas formas de realización, la composición comprende además aproximadamente 2,4mg de lauril sulfato de sodio. En algunas formas de realización, la composición comprende además aproximadamente 2,4mg de estearato de magnesio.

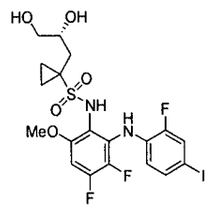
También se proveen aquí composiciones y métodos para el tratamiento de cáncer o inflamación con composiciones que comprenden aproximadamente 20mg de un compuesto que tiene la siguiente estructura:  . En algunas formas de

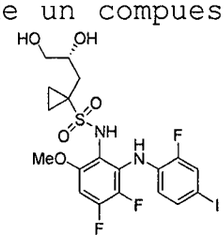
realización, la composición comprende además aproximadamente 203,2mg de celulosa microcristalina. En algunas formas de realización, la composición comprende además aproximadamente 12,0mg de croscarmelosa de sodio. En algunas formas de realización, la composición comprende además aproximadamente 2,4mg de lauril sulfato de sodio. En algunas formas de realización, la composición comprende además aproximadamente 2,4mg de estearato de magnesio.

También se proveen aquí composiciones y métodos para el tratamiento de cáncer o inflamación con composiciones que comprenden aproximadamente 40mg de un compuesto que tiene la siguiente estructura: 

. En algunas formas de realización, la composición comprende además aproximadamente 183,2mg de celulosa microcristalina. En algunas formas de realización, la composición comprende además aproximadamente 12,0mg de croscarmelosa de sodio. En algunas formas de realización, la composición comprende además aproximadamente 2,4mg de lauril sulfato de sodio. En algunas formas de realización, la composición comprende además aproximadamente 2,4mg de estearato de magnesio.

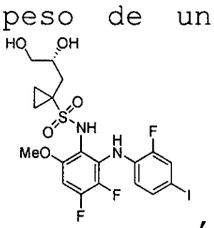
También se proveen aquí composiciones y métodos para el tratamiento de cáncer o inflamación con composiciones que comprenden aproximadamente 0,4% en peso de un compuesto que

tiene la siguiente estructura  , y aproximadamente 99,6% en peso de un vehículo farmacéuticamente aceptable. En algunas formas de realización, el vehículo farmacéuticamente aceptable comprende celulosa microcristalina. En algunas formas de realización, la celulosa microcristalina es de aproximadamente 92,6% en peso de la composición. En algunas formas de realización, la composición comprende además aproximadamente 5% en peso de croscarmelosa de sodio. En algunas formas de realización, la composición comprende además aproximadamente 1% en peso de lauril sulfato de sodio. En algunas formas de realización, la composición comprende además aproximadamente 1% en peso de estearato de magnesio.

También se proveen aquí composiciones y métodos para el tratamiento de cáncer o inflamación con composiciones que comprenden aproximadamente 4,2% en peso de un compuesto que tiene la siguiente estructura  , y aproximadamente 95,8 % en peso de un vehículo farmacéuticamente aceptable. En algunas formas de realización, el vehículo farmacéuticamente aceptable

comprende celulosa microcristalina. En algunas formas de realización, la celulosa microcristalina es de aproximadamente 88,8% en peso de la composición. En algunas formas de realización, la composición comprende además aproximadamente 5% en peso de croscarmelosa de sodio. En algunas formas de realización, la composición comprende además aproximadamente 1% en peso de lauril sulfato de sodio. En algunas formas de realización, la composición comprende además aproximadamente 1% en peso de estearato de magnesio.

También se proveen aquí composiciones y métodos para el tratamiento de cáncer o inflamación con composiciones que comprenden entre aproximadamente 2% y aproximadamente 10% en peso de un compuesto que tiene la siguiente estructura




, y entre aproximadamente 98% y aproximadamente 90% en peso de un vehículo farmacéuticamente aceptable. En algunas formas de realización, el vehículo farmacéuticamente aceptable comprende celulosa microcristalina. En algunas formas de realización, la celulosa microcristalina es entre aproximadamente 85% y aproximadamente 95% en peso de la composición. En algunas formas de realización, la composición comprende además entre aproximadamente 1% y aproximadamente 6% en peso de croscarmelosa de sodio. En

algunas formas de realización, la composición comprende además entre aproximadamente 0,1% y aproximadamente 2% en peso de lauril sulfato de sodio. En algunas formas de realización, la composición comprende además entre aproximadamente 0,25% y aproximadamente 1,5% en peso de estearato de magnesio.

También se provee aquí un polimorfo cristalino de forma A de N-(-)-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida que exhibe un patrón de difracción de rayos X en polvo que comprende al menos 50% de los picos identificados en el patrón de difracción de rayos X en polvo que se muestra en FIG. **5** y composiciones que comprenden este compuesto. En algunas formas de realización, el polimorfo cristalino de forma A, donde el patrón de difracción de rayos X en polvo comprende al menos 70% de los picos identificados en el patrón de difracción de rayos X en polvo que se muestra en FIG. **5**. En algunas formas de realización, el patrón de difracción de rayos X en polvo comprende al menos 90% de los picos identificados en el patrón de difracción de rayos X en polvo que se muestra en FIG. **5**. En algunas formas de realización, el patrón de difracción de rayos X en polvo es sustancialmente el mismo que el patrón de difracción de rayos X en polvo que se muestra en FIG. **5**. En algunas formas de realización, el polimorfo cristalino

tiene una temperatura del comienzo de la fusión según se determinó mediante calorimetría diferencial de barrido en aproximadamente 143°C. En algunas formas de realización, el polimorfo cristalino se encuentra sustancialmente libre de agua. En algunas formas de realización, el polimorfo cristalino se encuentra sustancialmente libre de solvente.

También se provee aquí un polimorfo cristalino de forma A de N-(-)-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida que exhibe un patrón de calorimetría diferencial de barrido sustancialmente igual al patrón de calorimetría diferencial de barrido que se muestra en FIG. **6** y composiciones que comprenden este compuesto. En algunas formas de realización, el polimorfo cristalino tiene una temperatura del comienzo de la fusión según se determinó mediante calorimetría diferencial de barrido en aproximadamente 143°C. En algunas formas de realización, el polimorfo cristalino de la reivindicación 67 o 68, donde el polimorfo cristalino se encuentra sustancialmente libre de agua. En algunas formas de realización, el polimorfo cristalino es de cualquiera de las reivindicaciones 67-69, donde el polimorfo cristalino se encuentra sustancialmente libre de solvente.

También se provee aquí una forma polimórfica de N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-

(2,3-dihidroxipropil)ciclopropan-1-sulfonamida realizada mediante un método que comprende el paso de cristalizar N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida amorfa y composiciones que comprenden este compuesto. En algunas formas de realización, el paso de cristalización comprende cristalizar a partir de una mezcla de acetato de etilo y heptano. En algunas formas de realización, la mezcla de acetato de etilo y heptano es en una relación de entre aproximadamente 1-4 partes acetato de etilo y aproximadamente 2-10 partes heptano. En algunas formas de realización, la mezcla de acetato de etilo y heptano es en una relación de entre aproximadamente 2 partes acetato de etilo y aproximadamente 5 partes heptano.

También se proveen en la presente métodos para inhibir enzimas MEK que comprenden poner dicha enzima MEK en contacto con un compuesto o una composición que se describe en la presente, en donde el compuesto está presente en una cantidad suficiente como para inhibir dicha enzima en al menos un 25%. En algunas formas de realización, la enzima MEK es MEK quinasa. En algunas formas de realización, dicho contacto tiene lugar dentro de una célula.

También se proveen en la presente métodos para tratar un trastorno mediado por MEK en un individuo que sufre de dicho trastorno, que comprenden administrarle a dicho

individuo una cantidad eficaz de un compuesto o una composición descrita en la presente. En algunas formas de realización, el inhibidor de MEK se administra en combinación con una terapia adicional. En algunas formas de realización, la terapia adicional es una terapia por radiación, una terapia con inhibidor que no es de MEK quinasa, quimioterapia, cirugía, glucocorticoides, metotrexato, modificadores de la respuesta biológica o cualquier combinación de los mismos. En algunas formas de realización, el trastorno mediado por MEK se selecciona del grupo que consiste de enfermedades inflamatorias, infecciones, trastornos autoinmunes, accidente cerebrovascular, isquemia, trastornos cardíacos, trastornos neurológicos, trastornos fibrogenéticos, trastornos proliferativos, trastornos hiperproliferativos, tumores, leucemias, neoplasmas, distintos tipos de cáncer, carcinomas, enfermedades metabólicas y enfermedades malignas. En algunas formas de realización, el trastorno mediado por MEK es una enfermedad hiperproliferativa. En algunas formas de realización, el trastorno mediado por MEK es cáncer, tumores, leucemias, neoplasmas o carcinomas. En algunas formas de realización, el trastorno mediado por MEK es una enfermedad inflamatoria. En algunas formas de realización, dicha enfermedad inflamatoria es artritis reumatoide o esclerosis múltiple.

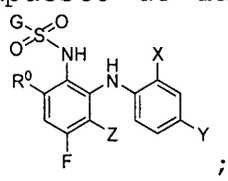
También se proveen en la presente métodos para el tratamiento o la profilaxis de una enfermedad proliferativa en un individuo que comprende administrarle a dicho individuo una cantidad eficaz de un compuesto o una composición que se describe en la presente. En algunas formas de realización, la enfermedad proliferativa es cáncer, psoriasis, restenosis, enfermedad autoinmune o aterosclerosis. En algunas formas de realización, la enfermedad proliferativa es cáncer. En algunas formas de realización, el cáncer es cáncer de cerebro, cáncer de mama, cáncer de pulmón, cáncer de ovario, cáncer pancreático, cáncer de próstata, cáncer renal, cáncer colorrectal, leucemia, leucemia mieloide, glioblastoma, linfoma folicular, leucemia aguda pre-B, leucemia linfocítica B crónica, cáncer de estómago, mesotelioma o cáncer de pulmón de células pequeñas. En algunas formas de realización, el método comprende además la administración de al menos un agente terapéutico. En algunas formas de realización, este paso comprende la administración de al menos una terapia contra cáncer adicional. En algunas formas de realización, la terapia adicional es una terapia por radiación, una terapia con inhibidor que no es de MEK quinasa, quimioterapia, cirugía, glucocorticoides, metotrexato, modificadores de la respuesta biológica o cualquier combinación de los mismos.

También se proveen en la presente métodos para el tratamiento o la profilaxis de una enfermedad inflamatoria en un individuo que comprende administrarle a dicho individuo una cantidad eficaz de una composición que comprende un compuesto que se describe en la presente. En algunas formas de realización, la enfermedad inflamatoria es artritis reumatoide o esclerosis múltiple.

También se proveen en la presente métodos para degradar, inhibir el crecimiento o matar células cancerosas que comprende poner las células en contacto con una cantidad del compuesto o de la composición que se describe en la presente que sea eficaz para degradar, inhibir el crecimiento o matar células cancerosas. En algunas formas de realización, las células cancerosas comprenden células de cáncer de cerebro, de mama, de pulmón, de ovario, pancreático, de próstata, renal, de estómago o colorrectal.

También se proveen en la presente métodos para inhibir un incremento del tamaño tumoral, para reducir el tamaño de un tumor, para reducir la proliferación de un tumor o para prevenir la proliferación de un tumor en un individuo, que comprenden administrarle a dicho individuo una cantidad eficaz del compuesto o de la composición que se describe en la presente para inhibir un incremento del tamaño tumoral, reducir el tamaño de un tumor, reducir la proliferación de un tumor o prevenir la proliferación de un tumor. En algunas

formas de realización, el tumor aparece en el cerebro, la mama, el pulmón, los ovarios, el páncreas, la próstata, el riñón, el estómago, el colon o el recto.

También se proveen en la presente métodos para tratar o prevenir espondilitis anquilosante, gota, tendonitis, bursitis o ciática, que comprenden administrarle a un sujeto que lo necesita una cantidad eficaz de un compuesto de la fórmula (I) o una sal farmacéutica del mismo: 

;

en donde:

Z es H o F;

X es F, Cl, $CH_3$, $CH_2OH$, $CH_2F$, $CHF_2$, o $CF_3$;

Y es I, Br, Cl, $CF_3$, $C_1$-$C_3$ alquilo, $C_2$-$C_3$ alquenilo, $C_2$-$C_3$ alquinilo, ciclopropilo, OMe, OEt, SMe, fenilo o Het, donde Het es un grupo heterocíclico mono o bicíclico de 5 a 10 miembros, el cual es saturado, olefínico o aromático, que contiene 1-5 heteroátomos en el anillo seleccionados en forma independiente entre N, O, y S; donde

todos dichos grupos fenilo o Het están opcionalmente sustituidos con F, Cl, Br, I, acetilo, metilo, CN, $NO_2$, $CO_2H$, $C_1$-$C_3$ alquilo, $C_1$-$C_3$ alcoxi, $C_1$-$C_3$ alquil-C(=O)-, $C_1$-$C_3$ alquil-C(=S)-, $C_1$-$C_3$ alcoxi-C(=S)-, $C_1$-$C_3$ alquil-C(=O)O-, $C_1$-$C_3$ alquil-O-(C=O)-, $C_1$-$C_3$

alquil-C(=O)NH-, $C_1$-$C_3$ alquil-C(=NH)NH-, $C_1$-$C_3$ alquil-NH-(C=O)-, di-$C_1$-$C_3$ alquil-N-(C=O)-, $C_1$-$C_3$ alquil-C(=O)N($C_1$-$C_3$ alquil)-, $C_1$-$C_3$ alquil-S(=O)$_2$NH- o trifluorometilo;

todos dichos grupos metilo, etilo, $C_1$-$C_3$ alquilo, y ciclopropilo están opcionalmente sustituidos con OH;

todos dichos grupos metilo están opcionalmente sustituidos con uno, dos o tres átomos de F;

$R^0$ es H, F, Cl, Br, I, $CH_3NH$-, $(CH_3)_2N$-, $C_1$-$C_6$ alquilo, $C_1$-$C_4$ alcoxi, $C_3$-$C_6$ cicloalquilo, $C_2$-$C_6$ alquenilo, $C_2$-$C_6$ alquinilo, fenilo, fenilo monosustituido, O($C_1$-$C_4$ alquilo), O-C(=O)($C_1$-$C_4$ alquilo) o C(=O)O($C_1$-$C_4$ alquil); donde

dichos grupos alquilo, alcoxi, cicloalquilo, alquenilo, alquinilo y fenilo están opcionalmente sustituidos con 1-3 sustituyentes seleccionados en forma independiente entre F, Cl, Br, I, OH, CN, cianometilo, nitro, fenilo y trifluorometilo;

dichos grupos $C_1$-$C_6$ alquilo y $C_1$-$C_4$ alcoxi también están opcionalmente sustituidos con $OCH_3$ o $OCH_2CH_3$;

G es $G_1$, $G_2$, $R_{1a}$, $R_{1b}$, $R_{1c}$, $R_{1d}$, $R_{1e}$, $Ar_1$, $Ar_2$ o $Ar_3$; donde

$G_1$ es $C_1$-$C_6$ alquilo opcionalmente sustituido con un grupo amino, $C_1$-$C_3$ alquilamino, o dialquilamino, dicho grupo dialquilamino comprende dos grupos $C_1$-$C_4$ alquilo los cuales pueden ser idénticos o no idénticos; o

$G_1$ es un grupo $C_3$-$C_8$ diaminoalquilo;

$G_2$ es un anillo de 5 o 6 miembros, el cual es saturado, no saturado o aromático, que contiene 1-3 heteroátomos en el anillo seleccionados en forma independiente entre N, O, y S, opcionalmente sustituidos con 1-3 sustituyentes seleccionados en forma independiente entre F, Cl, OH, O($C_1$-$C_3$ alquilo), $OCH_3$, $OCH_2CH_3$, $CH_3C(=O)NH$, $CH_3C(=O)O$, CN, $CF_3$, y un grupo heterocíclico aromático de 5 miembros que contiene 1-4 heteroátomos en el anillo seleccionados en forma independiente entre N, O , y S;

$R_{1a}$ es metilo, opcionalmente sustituido con 1-3 átomos de flúor o 1-3 átomos de cloro, o con OH, ciclopropoxi, o $C_1$- $C_3$ alcoxi, donde dicho grupo ciclopropoxi o las unidades $C_1$-$C_3$ alquilo de dichos grupos $C_1$-$C_3$ alcoxi están opcionalmente sustituidos con un grupo hidroxi o metoxi, y donde todos los grupos $C_3$-alquilo dentro de dicho $C_1$- $C_4$ alcoxi están opcionalmente sustituidos adicionalmente con un segundo grupo OH;

$R_{1b}$ es $CH(CH_3)$-$C_{1-3}$ alquilo o $C_3$-$C_6$ cicloalquilo, dichos grupos alquilo y cicloalquilo opcionalmente sustituido con 1-3 sustituyentes seleccionados en forma independiente entre F, Cl, Br, I, OH, $OCH_3$, y CN;

$R_{1c}$ es $(CH_2)_nO_mR'$; donde

m es 0 o 1; y donde

cuando m es 0, n es 1 o 2;

cuando m es 1, n es 2 o 3;

R' es $C_1$-$C_6$ alquilo, opcionalmente sustituido con 1-3 sustituyentes seleccionados en forma independiente entre F, Cl, OH, $OCH_3$, $OCH_2CH_3$, y $C_3$-$C_6$ cicloalquilo;

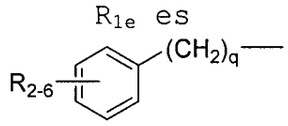
$R_{1d}$ es C(A)(A')(B)-; donde

B es H o $C_{1-4}$ alquilo, opcionalmente sustituido con uno o dos grupos OH;

A y A' son en forma independiente H o $C_{1-4}$ alquilo, opcionalmente sustituido con uno o dos grupos OH; o

A y A', junto con el átomo de carbono al cual se encuentran unidos, forman un anillo saturado de 3 a 6 miembros;

$R_{1e}$ es




**$R_{1e}$**

donde

q es 1 o 2;

$R_2$ y $R_3$ son en forma independiente entre sí, H, F, Cl, Br, $CH_3$, $CH_2F$, $CHF_2$, $CF_3$ $OCH_3$, $OCH_2F$, $OCHF_2$, $OCF_3$, etilo, *n*-propilo, isopropilo, ciclopropilo,

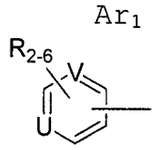
isobutilo, *sec*-butilo, *tert*-butilo o metilsulfonilo;

$R_4$ es H, F, Cl, Br, $CH_3$, $CH_2F$, $CHF_2$, $CF_3$ $OCH_3$, $OCH_2F$, $OCHF_2$, $OCF_3$, etilo, *n*-propilo, isopropilo, ciclopropilo, isobutilo, *sec*-butilo, *tert*-butilo, metilsulfonilo, nitro, acetamido, amidinilo, ciano, carbamoilo, metilcarbamoilo, dimetilcarbamoilo, 1,3,4-oxadiazol-2-ilo, 5-metil-1,3,4- oxadiazol, 1,3,4-tiadiazol, 5-metil-1,3,4-tiadiazol 1H-tetrazolilo, N-morfolilo carbonilo amino, N-morfolilsulfonilo y N-pirrolidinilcarbonilamino;

$R_5$ es H, F, Cl o metilo;

$R_6$ es H, F, Cl o metilo;

$Ar_1$ es




**$Ar_1$**

donde

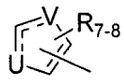
U y V son, en forma independiente, N, $CR_2$ o $CR_3$;

$R_2$, $R_3$ y $R_4$ son, en forma independiente, H, F, Cl, Br, $CH_3$, $CH_2F$, $CHF_2$, $CF_3$ $OCH_3$, $OCH_2F$, $OCHF_2$, $OCF_3$, etilo, *n*-propilo, isopropilo, ciclopropilo, isobutilo, *sec*-butilo, *tert*-butilo, acetamido, amidinilo, ciano, carbamoilo, metilcarbamoilo, dimetilcarbamoilo, 1,3,4-oxadiazol-2-ilo, 5-metil-1,3,4-oxadiazolilo, 1,3,4-tiadiazolilo, 5-metil-

1,3,4-tiadiazolilo, 1H-tetrazolilo, N-morfolilcarbonilamino, N-morfolilsulfonilo, N-pirrolidinilcarbonilamino, y metilsulfonilo;

$R_5$ y $R_6$ son, en forma independiente, H, F, Cl o metilo;

$Ar_2$ es




**$Ar_2$**

donde

la línea de guiones representa ubicaciones formales alternativas para la unión doble del segundo anillo;

U es -S-, -O- o -N =, y donde

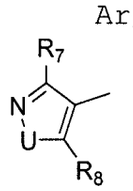
cuando U es -O- o -S-, V es -CH=, -CCl= o -N =;

cuando U es -N =, V es -CH=, -CCl=, o -N=;

$R_7$ es H o metilo;

$R_8$ es H, acetamido, metilo, F o Cl;

$Ar_3$ es

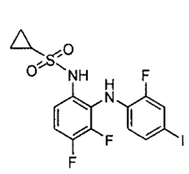
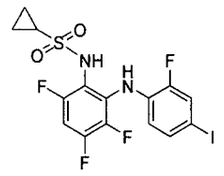
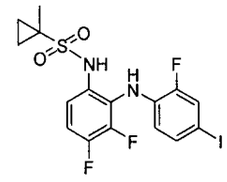
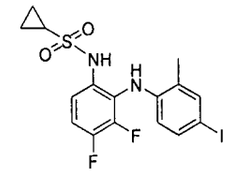
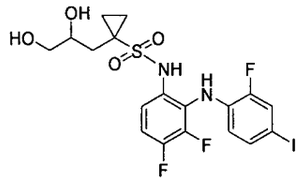
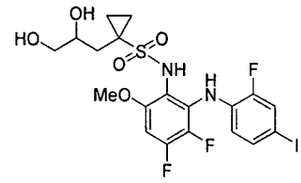
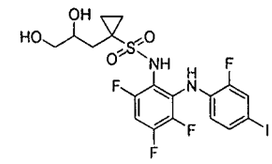
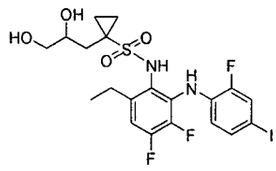
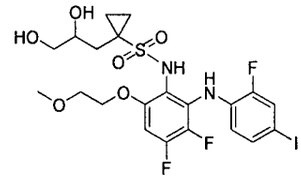
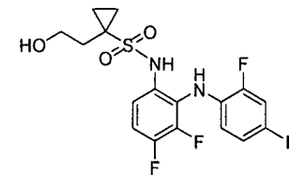
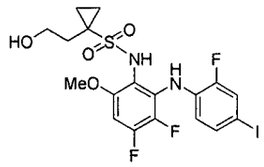
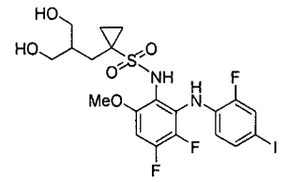
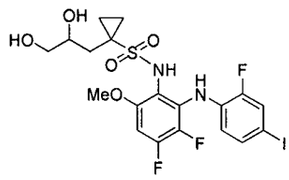
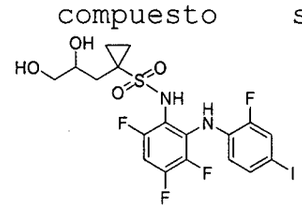
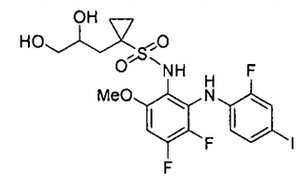


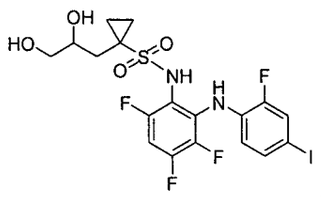

**$Ar_3$**

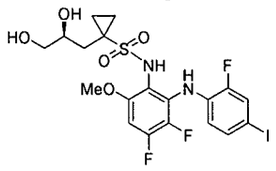
donde

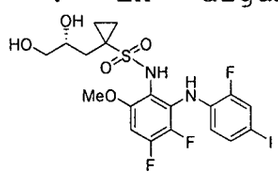
U es -NH-, $-NCH_3-$ o -O-;

$R_7$ y $R_8$ son, en forma independiente, H, F, Cl, o metilo. En algunas formas de realización, el compuesto se selecciona entre:


,

,

,

,

,

,

,

,

,

,

y

. En algunas formas de realización, el compuesto se selecciona entre

y

; donde el carbono 2-OH es de configuración R. En algunas formas de realización, el compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, se selecciona entre

y




; donde el carbono 2-OH es de configuración S. En algunas formas de realización, el compuesto es 

. En algunas formas de realización, el compuesto es 

.

También se proveen aquí métodos para el tratamiento de cáncer de estómago que comprenden administrar una cantidad terapéuticamente eficaz de un compuesto o composición descrito aquí. También se proveen aquí métodos para tratar leucemia, melanoma, o hepatoma administrando una cantidad terapéuticamente eficaz de un compuesto o composición descrito aquí.

También se proveen aquí métodos para tratar cáncer pulmonar de célula no pequeña mediante la administración de una cantidad terapéuticamente eficaz de un compuesto o composición descrito aquí. También se proveen aquí métodos para tratar cáncer de colon mediante la administración de una cantidad terapéuticamente eficaz de un compuesto o composición descrito aquí. También se proveen aquí métodos para tratar cáncer del sistema nervioso central mediante la

administración de una cantidad terapéuticamente eficaz de un compuesto o composición descrito aquí. También se proveen aquí métodos para tratar cáncer de ovario mediante la administración de una cantidad terapéuticamente eficaz de un compuesto o composición descrito aquí. También se proveen aquí métodos para tratar cáncer de riñón mediante la administración de una cantidad terapéuticamente eficaz de un compuesto o composición descrito aquí. También se proveen aquí métodos para tratar cáncer de próstata mediante la administración de una cantidad terapéuticamente eficaz de un compuesto o composición descrito aquí. También se proveen aquí métodos para tratar cáncer de mama mediante la administración de una cantidad terapéuticamente eficaz de un compuesto o composición descrito aquí. En varias realizaciones, estos métodos además comprenden administrar al menos un agente terapéutico adicional. En algunas formas de realización, se realiza al menos una terapia de cáncer adicional. En algunas formas de realización, la terapia de cáncer adicional es terapia de radiación, quimioterapia, cirugía, o cualquier combinación de los mismos.

También se proveen aquí métodos para tratar o prevenir psoriasis mediante la administración de una cantidad terapéuticamente eficaz de un compuesto o composición descrito aquí en forma de dosificación tópica.

En varias realizaciones, las composiciones se

administran oralmente. En algunas formas de realización, la composición se administra una vez al día o dos veces al día. En algunas formas de realización, la composición se administra una vez al día por al menos una semana.

En algunas formas de realización, luego de la administración oral de la composición, se logra $T_{max}$ del compuesto entre 1 hora y 3 horas luego de la administración de la composición a un sujeto en ayunas. En algunas formas de realización, luego de la administración a un sujeto, el compuesto alcanza una $C_{max}$ entre aproximadamente 0,01 µg/ml y aproximadamente 1,0 µg/ml en el día 1. En algunas formas de realización, luego de la administración a un sujeto, el compuesto alcanza una $C_{max}$ entre aproximadamente 0,01 µg/ml y aproximadamente 0,8 µg/ml en el día 1. En algunas formas de realización, luego de la administración a un sujeto, el compuesto alcanza una $C_{max}$ entre aproximadamente 0,03 µg/ml y aproximadamente 0,5 µg/ml en el día 1. En algunas formas de realización, el compuesto tiene un AUC entre aproximadamente 0,1 µg hr/ml y aproximadamente 5,0 µg hr/ml entre 0-12 horas. En algunas formas de realización, el compuesto tiene un AUC entre aproximadamente 0,1 µg hr/ml y aproximadamente 4,0 µg hr/ml. En algunas formas de realización, el compuesto tiene un AUC entre aproximadamente 0,5 µg hr/ml y aproximadamente 3,0 µg hr/ml. En algunas formas de realización, el compuesto tiene un $T_{max}$ de entre 0,5 y 5,0

horas. En algunas formas de realización, el compuesto tiene un $T_{max}$ de entre 1,0 y 3,0 horas. En algunas formas de realización, el compuesto tiene un $T_{max}$ de entre 1,0 y 2,5 horas. En algunas formas de realización, el compuesto tiene una concentración en el plasma mayor a aproximadamente 0,01 mg/ml luego de 5 horas luego de una única dosis. En algunas formas de realización, el compuesto tiene una concentración en el plasma mayor a aproximadamente 0,01 mg/ml luego de 10 horas luego de una única dosis. En algunas formas de realización, el compuesto tiene una concentración en el plasma mayor a aproximadamente 0,01 mg/ml luego de 15 horas luego de una única dosis.

En algunas formas de realización, luego de la administración a un grupo de 10 sujetos, el compuesto alcanza una $C_{max}$ media entre aproximadamente 0,01 µg/ml y aproximadamente 1,0 µg/ml en el día 1. En algunas formas de realización, luego de la administración a un grupo de 10 sujetos, el compuesto alcanza una $C_{max}$ media entre aproximadamente 0,01 µg/ml y aproximadamente 0,8 µg/ml en el día 1. En algunas formas de realización, luego de la administración a un grupo de 10 sujetos, el compuesto alcanza una $C_{max}$ media entre aproximadamente 0,03 µg/ml y aproximadamente 0,5 µg/ml en el día 1. En algunas formas de realización, el compuesto tiene un AUC medio entre aproximadamente 0,1 µg hr/ml y aproximadamente 5,0 µg hr/ml.

En algunas formas de realización, el compuesto tiene un AUC medio entre aproximadamente 0,1 μg hr/ml y aproximadamente 4,0 μg hr/ml. En algunas formas de realización, el compuesto tiene un AUC medio entre aproximadamente 0,5 μg hr/ml y aproximadamente 3,0 μg hr/ml. En algunas formas de realización, el compuesto has a mean $T_{max}$ entre 0,5 y 5,0 horas. En algunas formas de realización, el compuesto has a mean $T_{max}$ entre 1,0 y 3,0 horas. En algunas formas de realización, el compuesto tiene un $T_{max}$ medio entre 1,0 y 2,5 horas.

También se proveen aquí métodos para disminuir el volumen de un tumor mediante la administración de los compuestos y composiciones descritos aquí. En algunas formas de realización, luego de la administración diaria de la droga por 5 días, el tumor disminuye en volumen en al menos aproximadamente 25%. En algunas formas de realización, luego de la administración diaria de la droga por 5 días, el tumor disminuye en volumen en al menos aproximadamente 50%. En algunas formas de realización, luego de la administración diaria de la droga por 5 días, el tumor disminuye en volumen en al menos aproximadamente 20-70%. En algunas formas de realización, luego de la administración diaria de la droga por 15 días, el tumor disminuye en volumen en al menos aproximadamente 25%. En algunas formas de realización, luego de la administración diaria de la droga por 15 días, el

tumor disminuye en volumen en al menos aproximadamente 50%. En algunas formas de realización, luego de la administración diaria de la droga por 15 días, el tumor disminuye en volumen en al menos aproximadamente 20-70%. En algunas formas de realización, luego de la administración diaria de la droga por 30 días, el tumor disminuye en volumen en al menos aproximadamente 25%. En algunas formas de realización, luego de la administración diaria de la droga por 30 días, el tumor disminuye en volumen en al menos aproximadamente 50%. En algunas formas de realización, luego de la administración diaria de la droga por 30 días, el tumor disminuye en volumen en al menos aproximadamente 20-70%.

También se proveen aquí métodos para inhibir el crecimiento de un tumor mediante la administración de los compuestos descritos aquí. En algunas formas de realización, luego de la administración de la droga, el crecimiento del tumor de inhibe en al menos aproximadamente 20%. En algunas formas de realización, luego de la administración de la droga, el crecimiento del tumor de inhibe en al menos aproximadamente 40%. En algunas formas de realización, luego de la administración de la droga, el crecimiento del tumor de inhibe en al menos aproximadamente 60%. En algunas formas de realización, luego de la administración de la droga, el crecimiento del tumor de inhibe en al menos aproximadamente 80%. En algunas formas de realización, luego de la

administración de la droga, el crecimiento del tumor de inhibe en entre aproximadamente 20% y aproximadamente 100%. En algunas formas de realización, luego de la administración de la droga, el crecimiento del tumor se inhibe sustancialmente.

En algunas formas de realización, la composición se administra dos veces al día. En algunas formas de realización, la composición se administra una vez al día.

En algunas formas de realización, el inhibidor de MEK no interfiere con la coadministración de un segundo agente supresor de tumores.

En algunas formas de realización, la composición se presenta en forma de una tableta, a cápsula, una cápsula de gelatina, un comprimido oblongo, un pelet o una esfera. En algunas formas de realización, la composición se presenta en forma de dosificación de cápsula o de tableta con un peso total de aproximadamente 50 mg y aproximadamente 1000 mg. En algunas formas de realización, la composición se presenta en forma de cápsula o tableta con un peso total seleccionado entre el grupo que consiste en 50 mg, 75mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, y 500 mg. En algunas formas de realización, la composición se presenta en forma de cápsula o tableta con un peso total de aproximadamente 240 mg.

En algunas formas de realización, la composición

comprende además al menos un relleno seleccionado entre celulosa microcristalina, celulosa microcristalina silicificada, lactosa, un azúcar compresible, xilitol, sorbitol, mannitol, almidón pregelatinizado, maltodextrina, fosfato de calcio, carbonato de calcio, almidón y un silicato de calcio.

En algunas formas de realización, la composición comprende además al menos un desintegrante seleccionado entre croscarmelosa de sodio, glicolato sódico de almidón, crospovidona, metilcelulosa, ácido algínico, alginato de sodio, derivados de almidón, betonita y veegum.

En algunas formas de realización, la composición comprende además al menos un lubricante seleccionado entre estearato de magnesio, estearatos metálicos, talco, estearil fumarato de sodio y ácido esteárico.

En algunas formas de realización, la composición comprende además al menos un agente humectante o tensioactivo seleccionado entre lauril sulfato de sodio, glicerol, oleatos de sorbitan, estearatos de sorbitan, laurato de sorbitan polioxietilenado, palmitato, estearato, oleato o hexaolato, alcohol estearílico polioxietileno y monolaurato de sorbitan.

Se proveen aquí composiciones en forma de una cápsula o tableta y la cápsula o tableta libera al menos 60 por ciento de la droga al cabo de 30 minutos usando el Aparato II de

*U.S. Pharmacopeia* (USP) a 50 rpm con lauril sulfato de sodio al 1% en agua como medio de disolución. En algunas formas de realización, la composición se presenta en forma de cápsula o tableta y la cápsula o tableta libera aproximadamente 60-100 por ciento de la droga al cabo de 30 minutos usando el Aparato II de *U.S. Pharmacopeia* (USP) a 50 rpm con lauril sulfato de sodio al 1% en agua como medio de disolución. En algunas formas de realización, la composición se presenta en forma de cápsula o tableta y la cápsula o tableta libera aproximadamente 60-90 por ciento de la droga al cabo de 30 minutos usando el Aparato II de *U.S. Pharmacopeia* (USP) a 50 rpm con lauril sulfato de sodio al 1% en agua como medio de disolución. En algunas formas de realización, la composición se presenta en forma de cápsula o tableta y la cápsula o tableta libera aproximadamente 60-80 por ciento de la droga al cabo de 30 minutos usando el Aparato II de *U.S. Pharmacopeia* (USP) a 50 rpm con lauril sulfato de sodio al 1% en agua como medio de disolución.

También se proveen aquí lotes de cápsulas o tabletas, cada uno comprende entre aproximadamente 1 y aproximadamente 50 mg de un compuesto descrito aquí y con un valor de aceptación USP para la uniformidad del contenido inferior a aproximadamente 15.

***Métodos de Tratamiento***

La invención se relaciona con métodos para tratar o

prevenir cáncer, que comprende administrar a un sujeto en necesidad una cantidad efectiva de una composición farmacéutica que comprende un compuesto de fórmula (I), como se describe aquí. En varias realizaciones, los compuestos y composiciones útiles en estos métodos son como se describe mediante el género de fórmula (I) o cualquier subgénero o especie ejemplificado por medio de la presente solicitud abarcado por la fórmula (I).

La invención se relaciona con métodos para tratar o prevenir una enfermedad inflamatoria, que comprende administrar a un sujeto en necesidad una cantidad efectiva de una composición farmacéutica que comprende un compuesto de fórmula (I), como se describe aquí. En varias realizaciones, los compuestos y composiciones útiles en estos métodos son como se describe mediante el género de fórmula (I) o cualquier subgénero o especie ejemplificado por medio de la presente solicitud abarcado por la fórmula (I).

En algunas formas de realización, la invención se relaciona con métodos para tratar o prevenir espondilitis anquilosante, gota, tendinitis, bursitis o ciática, que comprende administrar a un sujeto en necesidad del mismo una cantidad efectiva de una composición farmacéutica que comprende un compuesto de fórmula (I), como se describe aquí. En varias realizaciones, los compuestos y

composiciones útiles en estos métodos son como se describe mediante el género de fórmula (I) o cualquier subgénero o especie ejemplificado por medio de la presente solicitud abarcado por la fórmula (I).

En algunos aspectos, la presente invención también se dirige a un método de tratamiento de una enfermedad en un individuo que sufre de dicha enfermedad que comprende administrar a dicho individuo una cantidad efectiva de una composición que comprende un compuesto de fórmula I o una sal, solvato, polimorfo, éster, tautómero o prodroga farmacéuticamente aceptable del mismo.

En otros aspectos, la presente invención se dirige a un método de tratamiento de un trastorno en un mamífero, que comprende administrar a dicho mamífero una cantidad terapéuticamente eficaz del compuesto de fórmula I o una sal, solvato, polimorfo, éster, tautómero o prodroga farmacéuticamente aceptable del mismo

En otros aspectos, la presente invención se dirige a un método de tratamiento de un trastorno en un humano, que comprende administrar a dicho humano una cantidad terapéuticamente eficaz del compuesto de fórmula I o una sal, solvato, polimorfo, éster, tautómero o prodroga farmacéuticamente aceptable del mismo

En otros aspectos, la presente invención se dirige a un método para el tratamiento de un trastorno

hiperproliferativo en un mamífero, incluyendo un humano, que comprende administrar a dicho mamífero una cantidad terapéuticamente eficaz del compuesto de fórmula I o una sal, solvato, polimorfo, éster, tautómero o prodroga farmacéuticamente aceptable del mismo

En otros aspectos, la presente invención se dirige a un método para el tratamiento de una enfermedad, condición o trastorno inflamatorio en un mamífero, incluyendo un humano, que comprende administrar a dicho mamífero una cantidad terapéuticamente eficaz del compuesto de fórmula I, o una sal farmacéuticamente aceptable, éster, prodroga, solvato, hidrato o derivado del mismo.

En otros aspectos, la presente invención se dirige a un método para el tratamiento de un trastorno o condición el cual se modula mediante la cascada de MEK en un mamífero, incluyendo un humano, que comprende administrar a dicho mamífero una cantidad del compuesto de fórmula I, o una sal farmacéuticamente aceptable, éster, prodroga, solvato, hidrato o derivado del mismo, efectiva para modular dicha cascada. La dosificación apropiada para un paciente en particular se puede determinar, de acuerdo a métodos conocidos, por aquellos versados en el arte.

Inhibición de la Enzima MEK

En otros aspectos, la presente invención se dirige a un método para inhibir una enzima MEK. En algunas formas de

realización, el método comprende poner en contacto dicha enzima MEK con una cantidad de una composición que comprende un compuesto de fórmula I o una sal, solvato, polimorfo, éster, tautómero o prodroga farmacéuticamente aceptable del mismo, suficiente para inhibir dicha enzima, donde dicha enzima se inhibe. En formas de realización adicionales la enzima se inhibe al menos en aproximadamente 1%. En formas de realización adicionales la enzima se inhibe al menos en aproximadamente 2%. En formas de realización adicionales la enzima se inhibe al menos en aproximadamente 3%. En formas de realización adicionales la enzima se inhibe al menos en aproximadamente 4%. En formas de realización adicionales la enzima se inhibe al menos en aproximadamente 5%. En formas de realización adicionales la enzima se inhibe al menos en aproximadamente 10%. En formas de realización adicionales la enzima se inhibe al menos en aproximadamente 20%. En formas de realización adicionales la enzima se inhibe al menos en aproximadamente 25%. En formas de realización adicionales la enzima se inhibe al menos en aproximadamente 30%. En formas de realización adicionales la enzima se inhibe al menos en aproximadamente 40%. En formas de realización adicionales la enzima se inhibe al menos en aproximadamente 50%. En formas de realización adicionales la enzima se inhibe al menos en aproximadamente 60%. En formas de realización adicionales la enzima se inhibe al menos en aproximadamente 70%. En formas

de realización adicionales la enzima se inhibe al menos en aproximadamente 75%. En formas de realización adicionales la enzima se inhibe al menos en aproximadamente 80%. En formas de realización adicionales la enzima se inhibe al menos en aproximadamente 90%. En formas de realización adicionales la enzima se inhibe esencialmente en forma completa. En formas de realización adicionales la enzima MEK es MEK quinasa. En formas de realización adicionales la enzima MEK es MEK1. En formas de realización adicionales la enzima MEK es MEK2. En formas de realización adicionales el contacto ocurre dentro de una célula. En formas de realización adicionales la célula es una célula de un mamífero. En formas de realización adicionales la célula de mamífero es una célula humana. En formas de realización adicionales, la enzima MEK se inhibe con una composición que comprende una sal farmacéuticamente aceptable de un compuesto de fórmula I.

Desorden mediado por MEK

En otros aspectos, la presente invención se dirige a un método de tratamiento de un trastorno mediado por MEK en un individuo que sufre de dicho trastorno que comprende administrar a dicho individuo una cantidad efectiva de una composición que comprende un compuesto de fórmula I o una sal, solvato, polimorfo, éster, tautómero o prodroga farmacéuticamente aceptable del mismo. En algunas formas de realización, la composición que comprende un compuesto de

fórmula I se administra oralmente, intraduodenalmente, parenteralmente (incluyendo intravenoso, subcutáneo, intramuscular, intravascular o mediante infusión), tópicamente o rectalmente. En algunas formas de realización, la composición farmacéutica se presenta en una forma adecuada para su administración oral. En formas de realización adicionales, la composición farmacéutica se presenta en forma de una tableta, cápsula, píldora, polvo, formulación de liberación sostenidas, solución, suspensión, para inyección parenteral como una solución, suspensión o emulsión estéril, para administración tópica como un ungüento o crema o para administración rectal como un supositorio. En formas de realización adicionales, la composición farmacéutica se presenta en formas unitarias de dosificación adecuadas para la administración de dosis precisas. En formas de realización adicionales, la composición farmacéutica comprende además un vehículo, excipiente y/o adyuvante farmacéuticamente aceptable.

En formas de realización adicionales la cantidad de compuesto de fórmula I se encuentra en el rango de aproximadamente 0,001 y aproximadamente 1000 mg/kg de peso corporal/día. En formas de realización adicionales la cantidad de compuesto de fórmula I se encuentra en el rango de aproximadamente 0,5 y aproximadamente 50 mg/kg/día. En formas de realización adicionales la cantidad de compuesto

de fórmula I es de aproximadamente 0,001 y aproximadamente 7 g/día. En formas de realización adicionales la cantidad de compuesto de fórmula I es de aproximadamente 0,01 y aproximadamente 7 g/día. En formas de realización adicionales la cantidad de compuesto de fórmula I es de aproximadamente 0,02 y aproximadamente 5 g/día. En formas de realización adicionales la cantidad de compuesto de fórmula I es de aproximadamente 0,05 y aproximadamente 2,5 g/día. En formas de realización adicionales la cantidad de compuesto de fórmula I es de aproximadamente 0,1 y aproximadamente 1 g/día. En formas de realización adicionales, los niveles de dosificación inferiores al límite inferior del rango previamente mencionado pueden ser más que adecuados. En formas de realización adicionales, pueden requerirse niveles de dosificación por encima del límite superior del rango previamente mencionado.

En formas de realización adicionales el compuesto de fórmula I se administra en una única dosis, una vez al día. En formas de realización adicionales el compuesto de fórmula I se administra en múltiples dosis, más de una vez al día. En formas de realización adicionales el compuesto de fórmula I se administra dos veces al día. En formas de realización adicionales el compuesto de fórmula I se administra tres veces al día. En formas de realización adicionales el compuesto de fórmula I se administra cuatro veces al día. En

formas de realización adicionales el compuesto de fórmula I se administra más de cuatro veces al día. En algunas formas de realización, el individuo que sufre del trastorno mediado por MEK es un mamífero. En formas de realización adicionales, el individuo es un humano.

En algunas formas de realización, la composición que comprende un compuesto de fórmula I se administra en combinación con una terapia adicional. En formas de realización adicionales, la terapia adicional es terapia de radiación, quimioterapia, cirugía o cualquier combinación de los mismos. En formas de realización adicionales, la composición que comprende un compuesto de fórmula I se administra en combinación con al menos un agente terapéutico. En formas de realización adicionales, el agente terapéutico se selecciona entre el grupo de agentes citotóxicos, agentes antiangiogénicos y agentes antineoplásticos. En formas de realización adicionales, el agente antineoplástico se selecciona entre el grupo que consiste en agentes de la alquilación, antimetabolitos, epidofilotoxinas; enzimas antineoplásticas, inhibidores de la topoisomerasa, procarbazinas, mitoxantronas, complejos de coordinación de platino, modificadores de la respuesta biológica y inhibidores del crecimiento, agentes terapéuticos hormonales/antihormonales, y factores de crecimiento hematopoyéticos. En formas de realización

adicionales, el agente terapéutico se selecciona entre taxol, bortezomib o ambos.

En algunas formas de realización, el trastorno mediado por MEK se selecciona entre el grupo que consiste en enfermedades inflamatorias, infecciones, trastornos autoinmunes, accidente cerebrovascular, isquemia, trastorno cardíaco, trastornos neurológicos, trastornos fibrogenéticos, trastornos proliferativos, trastornos hiperproliferativos, trastornos hiperproliferativos no relacionados con cáncer, tumores, leucemias, neoplasmas, cánceres, carcicomas, enfermedades metabólicas, enfermedad maligna, restenosis vascular, psoriasis, ateroesclerosis, artritis reumatoide, osteoartritis, falla cardíaca, dolor crónico, dolor neuropático, ojo seco, glaucoma de ángulo cerrado y glaucoma de ángulo abierto. En formas de realización adicionales, el trastorno mediado por MEK es una enfermedad inflamatoria. En formas de realización adicionales, el trastorno mediado por MEK es una enfermedad hiperproliferativa. En formas de realización adicionales, el trastorno mediado por MEK se selecciona entre el grupo que consiste en tumores, leucemias, neoplasmas, cánceres, carcicomas y enfermedad maligna. En formas de realización adicionales, el cáncer es cáncer de cerebro, cáncer de mama, cáncer de pulmón, cáncer de ovario, cáncer de páncreas, cáncer de próstata, cáncer de estómago, cáncer de riñón,

cáncer colorrectal o leucemia. En formas de realización adicionales, el trastorno fibrogenético es esclerodermia, polimiositis, lupus sistémico, artritis reumatoide, cirrosis de hígado, formación de queloide, nefritis intersticial o fibrosis pulmonar. En formas de realización adicionales, se administra una cantidad efectiva de una composición que comprende una sal farmacéuticamente aceptable de un compuesto de fórmula I.

Lograr efectos

En otros aspectos, la presente invención se dirige a un método para lograr un efecto en un paciente que comprende la administración de una cantidad efectiva de una composición que comprende un compuesto de fórmula I o una sal, solvato, polimorfo, éster, tautómero o prodroga farmacéuticamente aceptable del mismo, a un paciente, donde el efecto se selecciona entre el grupo que consiste en inhibición de varios cánceres, enfermedades inmunológicas, y enfermedades inflamatorias. En algunas formas de realización, el efecto es inhibición de varios cánceres. En formas de realización adicionales, el efecto es inhibición de enfermedades inmunológicas. En formas de realización adicionales, el efecto es inhibición enfermedades inflamatorias.

En algunas formas de realización, la composición que comprende un compuesto de fórmula I se administra en combinación con una terapia adicional. En formas de

realización adicionales, la terapia adicional es terapia de radiación, quimioterapia, cirugía o cualquier combinación de los mismos. En formas de realización adicionales, la composición que comprende un compuesto de fórmula I se administra en combinación con al menos un agente terapéutico.

En algunas formas de realización, la composición se administra oralmente, intraduodenalmente, parenteralmente (incluyendo intravenoso, subcutáneo, intramuscular, intravascular o mediante infusión), tópicamente o rectalmente. En formas de realización adicionales la cantidad de compuesto de fórmula I se encuentra en el rango de aproximadamente 0,001 y aproximadamente 1000 mg/kg de peso corporal/día. En formas de realización adicionales la cantidad de compuesto de fórmula I se encuentra en el rango de aproximadamente 0,5 y aproximadamente 50 mg/kg/día. En formas de realización adicionales la cantidad de compuesto de fórmula I es de aproximadamente 0,001 y aproximadamente 7 g/día. En formas de realización adicionales la cantidad de compuesto de fórmula I es de aproximadamente 0,01 y aproximadamente 7 g/día. En formas de realización adicionales la cantidad de compuesto de fórmula I es de aproximadamente 0,02 y aproximadamente 5 g/día. En formas de realización adicionales la cantidad de compuesto de fórmula I es de aproximadamente 0,05 y aproximadamente 2,5 g/día. En

formas de realización adicionales la cantidad de compuesto de fórmula I es de aproximadamente 0,1 y aproximadamente 1 g/día. En formas de realización adicionales, los niveles de dosificación inferiores al límite inferior del rango previamente mencionado puede ser más que adecuado. En formas de realización adicionales, se pueden requerir niveles de dosificación por encima del límite superior del rango previamente mencionado.

En formas de realización adicionales el compuesto de fórmula I se administra en una única dosis, una vez al día. En formas de realización adicionales el compuesto de fórmula I se administra en múltiples dosis, más de una vez al día. En formas de realización adicionales el compuesto de fórmula I se administra dos veces al día. En formas de realización adicionales el compuesto de fórmula I se administra tres veces al día. En formas de realización adicionales el compuesto de fórmula I se administra cuatro veces al día. En formas de realización adicionales el compuesto de fórmula I se administra más de cuatro veces al día. En algunas formas de realización, el individuo que sufre de cáncer es un mamífero. En formas de realización adicionales, el individuo es un humano. En formas de realización adicionales, una cantidad efectiva de una composición que comprende una sal farmacéuticamente aceptable de un compuesto de fórmula I se administra.

En otros aspectos, la presente invención se dirige a un método para degradar, inhibir el crecimiento de o matar una célula cancerígena que comprende poner en contacto dicha célula con una cantidad de una composición efectiva para degradar, inhibir el crecimiento de o matar dicha célula, la composición que comprende un compuesto de fórmula I o una sal, solvato, polimorfo, éster, tautómero o prodroga farmacéuticamente aceptable del mismo. En algunas formas de realización, las células cancerígenas comprenden células de cáncer de cerebro, pulmón, ovario, páncreas, próstata, riñón, o colorrectal. En formas de realización adicionales, la composición se administra con al menos un agente terapéutico. En formas de realización adicionales, el agente terapéutico es taxol, bortezomib o ambos. En formas de realización adicionales, el agente terapéutico se selecciona entre el grupo que consiste en agentes citotóxicos, agentes antiangiogénicos y agentes antineoplásticos. En formas de realización adicionales, los agentes antineoplásticos se seleccionan entre el grupo que consiste en agentes de la alquilación, antimetabolitos, epidofilotoxinas; enzimas antineoplásticas, inhibidores de la topoisomerasa, procarbazinas, mitoxantronas, complejos de coordinación de platino, modificadores de la respuesta biológica y inhibidores del crecimiento, agentes terapéuticos hormonales/antihormonales, y factores de crecimiento

hematopoyéticos. En algunas formas de realización, las células cancerígenas se degradan. En formas de realización adicionales, 1% de las células cancerígenas se degradan. En formas de realización adicionales, 2% de las células cancerígenas se degradan. En formas de realización adicionales, 3% de las células cancerígenas se degradan. En formas de realización adicionales, 4% de las células cancerígenas se degradan. En formas de realización adicionales, 5% de las células cancerígenas se degradan. En formas de realización adicionales, 10% de las células cancerígenas se degradan. En formas de realización adicionales, 20% de las células cancerígenas se degradan. En formas de realización adicionales, 25% de las células cancerígenas se degradan. En formas de realización adicionales, 30% de las células cancerígenas se degradan. En formas de realización adicionales, 40% de las células cancerígenas se degradan. En formas de realización adicionales, 50% de las células cancerígenas se degradan. En formas de realización adicionales, 60% de las células cancerígenas se degradan. En formas de realización adicionales, 70% de las células cancerígenas se degradan. En formas de realización adicionales, 75% de las células cancerígenas se degradan. En formas de realización adicionales, 80% de las células cancerígenas se degradan. En formas de realización adicionales, 90% de las células

cancerígenas se degradan. En formas de realización adicionales, 100% de las células cancerígenas se degradan. En formas de realización adicionales, esencialmente todas las células cancerígenas se degradan. En varias realizaciones, la degradación previamente mencionada ocurre en un día, cinco días, diez días, un mes, dos meses, seis meses o un año.

En algunas formas de realización, las células cancerígenas se matan. En formas de realización adicionales, 1% de las células cancerígenas se matan. En formas de realización adicionales, 2% de las células cancerígenas se matan. En formas de realización adicionales, 3% de las células cancerígenas se matan. En formas de realización adicionales, 4% de las células cancerígenas se matan. En formas de realización adicionales, 5% de las células cancerígenas se matan. En formas de realización adicionales, 10% de las células cancerígenas se matan. En formas de realización adicionales, 20% de las células cancerígenas se matan. En formas de realización adicionales, 25% de las células cancerígenas se matan. En formas de realización adicionales, 30% de las células cancerígenas se matan. En formas de realización adicionales, 40% de las células cancerígenas se matan. En formas de realización adicionales, 50% de las células cancerígenas se matan. En formas de realización adicionales, 60% de las células cancerígenas se

matan. En formas de realización adicionales, 70% de las células cancerígenas se matan. En formas de realización adicionales, 75% de las células cancerígenas se matan. En formas de realización adicionales, 80% de las células cancerígenas se matan. En formas de realización adicionales, 90% de las células cancerígenas se matan. En formas de realización adicionales, 100% de las células cancerígenas se matan. En formas de realización adicionales, esencialmente todas las células cancerígenas se matan. En varias realizaciones, la muerte de las células cancerígenas previamente mencionada ocurre en un día, cinco días, diez días, un mes, dos meses, seis meses o un año.

En formas de realización adicionales, el crecimiento de las células cancerígenas se inhibe. En formas de realización adicionales, el crecimiento de las células cancerígenas se inhibe en aproximadamente 1%. En formas de realización adicionales, el crecimiento de las células cancerígenas se inhibe en aproximadamente 2%. En formas de realización adicionales, el crecimiento de las células cancerígenas se inhibe en aproximadamente 3%. En formas de realización adicionales, el crecimiento de las células cancerígenas se inhibe en aproximadamente 4%. En formas de realización adicionales, el crecimiento de las células cancerígenas se inhibe en aproximadamente 5%. En formas de realización adicionales, el crecimiento de las células cancerígenas se

inhibe en aproximadamente 10%. En formas de realización adicionales, el crecimiento de las células cancerígenas se inhibe en aproximadamente 20%. En formas de realización adicionales, el crecimiento de las células cancerígenas se inhibe en aproximadamente 25%. En formas de realización adicionales, el crecimiento de las células cancerígenas se inhibe en aproximadamente 30%. En formas de realización adicionales, el crecimiento de las células cancerígenas se inhibe en aproximadamente 40%. En formas de realización adicionales, el crecimiento de las células cancerígenas se inhibe en aproximadamente 50%. En formas de realización adicionales, el crecimiento de las células cancerígenas se inhibe en aproximadamente 60%. En formas de realización adicionales, el crecimiento de las células cancerígenas se inhibe en aproximadamente 70%. En formas de realización adicionales, el crecimiento de las células cancerígenas se inhibe en aproximadamente 75%. En formas de realización adicionales, el crecimiento de las células cancerígenas se inhibe en aproximadamente 80%. En formas de realización adicionales, el crecimiento de las células cancerígenas se inhibe en aproximadamente 90%. En formas de realización adicionales, el crecimiento de las células cancerígenas se inhibe en aproximadamente 100%. En varias realizaciones, la inhibición previamente mencionada ocurre en un día, cinco días, diez días, un mes, dos meses, seis meses o un año.

En otros aspectos, la presente invención se dirige a un método de reducir el tamaño de un tumor, inhibir el incremento de tamaño de un tumor, reducir la proliferación de un tumor o prevenir la proliferación de un tumor en un individuo, que comprende administrar a dicho individuo una cantidad efectiva de una composición que comprende un compuesto de fórmula I o una sal, solvato, polimorfo, éster, tautómero o prodroga farmacéuticamente aceptable del mismo. En algunas formas de realización, el tamaño de un tumor se reduce. En formas de realización adicionales, el tamaño de un tumor se reduce en al menos 1%. En formas de realización adicionales, el tamaño de un tumor se reduce en al menos 2%. En formas de realización adicionales, el tamaño de un tumor se reduce en al menos 3%. En formas de realización adicionales, el tamaño de un tumor se reduce en al menos 4%. En formas de realización adicionales, el tamaño de un tumor se reduce en al menos 5%. En formas de realización adicionales, el tamaño de un tumor se reduce en al menos 10%. En formas de realización adicionales, el tamaño de un tumor se reduce en al menos 20%. En formas de realización adicionales, el tamaño de un tumor se reduce en al menos 25%. En formas de realización adicionales, el tamaño de un tumor se reduce en al menos 30%. En formas de realización adicionales, el tamaño de un tumor se reduce en al menos 40%. En formas de realización adicionales, el tamaño de un

tumor se reduce en al menos 50%. En formas de realización adicionales, el tamaño de un tumor se reduce en al menos 60%. En formas de realización adicionales, el tamaño de un tumor se reduce en al menos 70%. En formas de realización adicionales, el tamaño de un tumor se reduce en al menos 75%. En formas de realización adicionales, el tamaño de un tumor se reduce en al menos 80%. En formas de realización adicionales, el tamaño de un tumor se reduce en al menos 85%. En formas de realización adicionales, el tamaño de un tumor se reduce en al menos 90%. En formas de realización adicionales, el tamaño de un tumor se reduce en al menos 95%. En formas de realización adicionales, el tumor es erradicado. En algunas formas de realización, el tamaño de un tumor no se incrementa. En varias realizaciones, lo efectos previamente mencionados sobre el tamaño del tumor ocurren en un día, cinco días, diez días, un mes, dos meses, seis meses o un año.

En algunas formas de realización, la proliferación del tumor se reduce. En algunas formas de realización, la proliferación del tumor se reduce en al menos 1 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos 2 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos 3 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos 4 %. En algunas formas de realización, la

proliferación del tumor se reduce en al menos 5 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos 10 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos 20 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos 25 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos 30 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos 40 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos 50 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos 60 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos 70 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos 75 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos 75 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos 80 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos 90 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos 95 %. En algunas formas de realización, la proliferación del tumor se previene. En varias realizaciones, los efectos previamente mencionados sobre la proliferación celular ocurren en un día, cinco días, diez días, un mes, dos meses, seis meses o un año.

En algunas formas de realización, la composición que comprende un compuesto de fórmula I se administra en combinación con una terapia adicional. En formas de realización adicionales, la terapia adicional es terapia de radiación, quimioterapia, cirugía o cualquier combinación de los mismos. En formas de realización adicionales, la composición que comprende un compuesto de fórmula I se administra en combinación con al menos un agente terapéutico. En formas de realización adicionales, el agente terapéutico se selecciona entre el grupo de agentes citotóxicos, agentes antiangiogénicos y agentes antineoplásticos. En formas de realización adicionales, el agente antineoplástico se selecciona entre el grupo que consiste en agentes de la alquilación, antimetabolitos, epidofilotoxinas; enzimas antineoplásticas, inhibidores de la topoisomerasa, procarbazinas, mitoxantronas, complejos de coordinación de platino, modificadores de la respuesta biológica y inhibidores del crecimiento, agentes terapéuticos hormonales/antihormonales, y factores de crecimiento hematopoyéticos. En formas de realización adicionales, el agente terapéutico se selecciona entre taxol, bortezomib o ambos.

En algunas formas de realización, la composición se administra oralmente, intraduodenalmente, parenteralmente (incluyendo intravenoso, subcutáneo, intramuscular,

intravascular o mediante infusión), tópicamente o rectalmente. En formas de realización adicionales la cantidad de compuesto de fórmula I se encuentra en el rango de aproximadamente 0,001 y aproximadamente 1000 mg/kg de peso corporal/día. En formas de realización adicionales la cantidad de compuesto de fórmula I se encuentra en el rango de aproximadamente 0,5 y aproximadamente 50 mg/kg/día. En formas de realización adicionales la cantidad de compuesto de fórmula I es de aproximadamente 0,001 y aproximadamente 7 g/día. En formas de realización adicionales la cantidad de compuesto de fórmula I es de aproximadamente 0,01 y aproximadamente 7 g/día. En formas de realización adicionales la cantidad de compuesto de fórmula I es de aproximadamente 0,02 y aproximadamente 5 g/día. En formas de realización adicionales la cantidad de compuesto de fórmula I es de aproximadamente 0,05 y aproximadamente 2,5 g/día. En formas de realización adicionales la cantidad de compuesto de fórmula I es de aproximadamente 0,1 y aproximadamente 1 g/día. En formas de realización adicionales, los niveles de dosificación inferiores al límite inferior del rango previamente mencionado pueden ser más que adecuados. En formas de realización adicionales, se pueden requerir niveles de dosificación por encima del límite superior del rango previamente mencionado.

En formas de realización adicionales el compuesto de

fórmula I se administra en una única dosis, una vez al día. En formas de realización adicionales el compuesto de fórmula I se administra en múltiples dosis, más de una vez al día. En formas de realización adicionales el compuesto de fórmula I se administra dos veces al día. En formas de realización adicionales el compuesto de fórmula I se administra tres veces al día. En formas de realización adicionales el compuesto de fórmula I se administra cuatro veces al día. En formas de realización adicionales el compuesto de fórmula I se administra más de cuatro veces al día. En algunas formas de realización, el individuo que sufre de cáncer es un mamífero. En formas de realización adicionales, el individuo es un humano. En formas de realización adicionales, se administra una cantidad efectiva de una composición que comprende una sal farmacéuticamente aceptable de un compuesto de fórmula I.

Enfermedades proliferativas

En otros aspectos, la presente invención está dirigida a un método para el tratamiento o la profilaxis de una enfermedad proliferativa en un individuo, que comprende administrarle a dicho individuo una cantidad eficaz de una composición que comprende un compuesto de la fórmula I o una sal, solvato, polimorfo, éster, tautómero o prodroga farmacéuticamente aceptable del mismo. En algunas formas de realización, la enfermedad proliferativa es cáncer,

psoriasis, restenosis, una enfermedad autoinmune o aterosclerosis. En otras formas de realización o adicionales, la enfermedad proliferativa es una enfermedad hiperproliferativa. En otras formas de realización o adicionales, la enfermedad proliferativa se selecciona del grupo que consiste de tumores, leucemias, neoplasmas, distintos tipos de cáncer, carcinomas y una enfermedad maligna. En otras formas de realización o adicionales, el cáncer es cáncer de cerebro, cáncer de mama, cáncer de pulmón, cáncer de ovario, cáncer pancreático, cáncer de próstata, cáncer renal, cáncer colorrectal, cáncer de estómago, cáncer de cabeza y cuello o leucemia. En otras formas de realización o adicionales, el trastorno fibrogenético es escleroderma, polimiositis, lupus sistémico, artritis reumatoide, cirrosis hepática, formación de queloides, nefritis intersticial o fibrosis pulmonar. En otras formas de realización o adicionales, es cáncer de estómago, cáncer de cerebro, cáncer de mama, cáncer de pulmón, cáncer de pulmón de células no pequeñas, cáncer de ovario, cáncer pancreático, cáncer de hígado, cáncer de próstata, cáncer renal, cáncer colorrectal o leucemia. En otras formas de realización o adicionales, el cáncer es cáncer de cerebro o carcinoma adrenocortical. En otras formas de realización o adicionales, el cáncer es cáncer de mama. En otras formas de realización o adicionales, el

cáncer es cáncer de ovario. En otras formas de realización o adicionales, el cáncer es cáncer pancreático. En otras formas de realización o adicionales, el cáncer es cáncer de próstata. En otras formas de realización o adicionales, el cáncer es cáncer renal. En otras formas de realización o adicionales, el cáncer es cáncer colorrectal. En otras formas de realización o adicionales, el cáncer es leucemia mieloide. En otras formas de realización o adicionales, el cáncer es un glioblastoma. En otras formas de realización o adicionales, el cáncer es linfoma folicular. En otras formas de realización o adicionales, el cáncer es leucemia aguda pre-B. En otras formas de realización o adicionales, el cáncer es leucemia linfocítica B crónica. En otras formas de realización o adicionales, el cáncer es mesotelioma. En otras formas de realización o adicionales, el cáncer es cáncer de pulmón de células pequeñas. En otras formas de realización, el cáncer es cáncer de estómago.

En algunas formas de realización, la composición que comprende un compuesto de la fórmula I se administra en combinación con una terapia adicional. En otras formas de realización o adicionales, la terapia adicional es una terapia por radiación, quimioterapia, cirugía o cualquier combinación de las mismas. En otras formas de realización o adicionales, la composición que comprende un compuesto de la fórmula I se administra en combinación con al menos un

agente terapéutico. En otras formas de realización o adicionales, el agente terapéutico se selecciona del grupo de agentes citotóxicos, agentes anti-angiogénesis y agentes anti-neoplásicos. En otras formas de realización o adicionales, el agente anti-neoplásico se selecciona del grupo que consiste de agentes alquilantes, anti-metabolitos, epidofilotoxinas; enzimas antineoplásicas, inhibidores de topoisomerasa, procarbazinas, mitoxantronas, complejos de coordinación de platino, modificadores de la respuesta biológica e inhibidores del crecimiento, agentes terapéuticos hormonales/anti-hormonales y factores de crecimiento hematopoyéticos.

En otras formas de realización o adicionales, el agente terapéutico se selecciona entre taxol, bortezomib o ambos. En algunas formas de realización, la composición se administra por vía oral, intraduodenal, parenteral (incluyendo intravenosa, subcutánea, intramuscular, intravascular o por infusión), tópica o rectal.

En otras formas de realización o adicionales, la cantidad del compuesto de la fórmula I se encuentra en el rango de entre aproximadamente 0,001 y aproximadamente 1000 mg/kg de peso corporal/día. En otras formas de realización o adicionales, la cantidad del compuesto de la fórmula I se encuentra en el rango de entre aproximadamente 0,5 y aproximadamente 50 mg/kg/día. En otras formas de realización

o adicionales, la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,001 y aproximadamente 7 g/día. En otras formas de realización o adicionales, la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,01 y aproximadamente 7 g/día. En otras formas de realización o adicionales, la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,02 y aproximadamente 5 g/día. En otras formas de realización o adicionales, la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,05 y aproximadamente 2,5 g/día. En otras formas de realización o adicionales, la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,1 y aproximadamente 1 g/día. En otras formas de realización o adicionales, serán más que adecuados los niveles de dosificación inferiores al límite inferior del rango mencionado previamente. En otras formas de realización o adicionales, pueden ser necesarios niveles de dosificación superiores al límite superior del rango mencionado previamente.

En otras formas de realización o adicionales, el compuesto de la fórmula I se administra en una sola dosis, una vez por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra en múltiples dosis, más de una vez por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra dos veces por día. En otras formas de realización

o adicionales, el compuesto de la fórmula I se administra tres veces por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra cuatro veces por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra más de cuatro veces por día. En algunas formas de realización, el individuo que sufre de la enfermedad proliferativa es un mamífero. En otras formas de realización o adicionales, el individuo es un ser humano. En otras formas de realización o adicionales, se administra una cantidad eficaz de una composición que comprende una sal farmacéuticamente aceptable de un compuesto de la fórmula I.

Enfermedades inflamatorias

En otros aspectos, la presente invención está dirigida a un método para el tratamiento o la profilaxis de una enfermedad inflamatoria en un individuo, que comprende administrarle a dicho individuo una cantidad eficaz de una composición que comprende un compuesto de la fórmula I o una sal, solvato, polimorfo, éster, tautómero o prodroga farmacéuticamente aceptable del mismo. En otras formas de realización o adicionales, la enfermedad inflamatoria se selecciona entre enfermedades inflamatorias crónicas, artritis reumatoide, artritis reumatoide, espondiloartropatías, artritis gotosa, osteoartritis, artritis juvenil, artritis reumática aguda, artritis

enteropática, artritis neuropática, artritis psoriática, artritis piogénica, aterosclerosis, lupus sistémica eritematosa, enfermedad de intestino inflamatorio, síndrome de intestino irritable, colitis ulcerosa, esofagitis por reflujo, enfermedad de Crohn, gastritis, asma, alergias, síndrome de dificultad respiratoria, pancreatitis, enfermedad pulmonar obstructiva crónica, fibrosis pulmonar, psoriasis, eczema o escleroderma.

En algunas formas de realización, la composición que comprende un compuesto de la fórmula I se administra en combinación con una terapia adicional. En otras formas de realización o adicionales, la composición que comprende un compuesto de la fórmula I se administra en combinación con al menos un agente terapéutico.

En algunas formas de realización, la composición se administra por vía oral, intraduodenal, parenteral (incluyendo intravenosa, subcutánea, intramuscular, intravascular o por infusión), tópica o rectal. En otras formas de realización o adicionales, la cantidad del compuesto de la fórmula I se encuentra en el rango de entre aproximadamente 0,001 y aproximadamente 1000 mg/kg de peso corporal/día. En otras formas de realización o adicionales, la cantidad del compuesto de la fórmula I se encuentra en el rango de entre aproximadamente 0,5 y aproximadamente 50 mg/kg/día. En otras formas de realización o adicionales la

cantidad de compuesto de la fórmula I es de entre aproximadamente 0,001 y aproximadamente 7 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,01 y aproximadamente 7 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,02 y aproximadamente 5 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,05 y aproximadamente 2,5 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,1 y aproximadamente 1 g/día. En otras formas de realización o adicionales, serán más que adecuados los niveles de dosificación inferiores al límite inferior del rango mencionado previamente. En otras formas de realización o adicionales, pueden ser necesarios niveles de dosificación superiores al límite superior del rango mencionado previamente.

En otras formas de realización o adicionales, el compuesto de la fórmula I se administra en una sola dosis, una vez por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra en múltiples dosis, más de una vez por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra dos veces por día. En otras formas de realización

o adicionales, el compuesto de la fórmula I se administra tres veces por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra cuatro veces por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra más de cuatro veces por día. En algunas formas de realización, el individuo que sufre de la enfermedad inflamatoria es un mamífero. En otras formas de realización o adicionales, el individuo es un ser humano. En otras formas de realización o adicionales, se administra una cantidad eficaz de una composición que comprende una sal farmacéuticamente aceptable de un compuesto de la fórmula I.

Cáncer

En otros aspectos, la presente invención está dirigida a un método para el tratamiento o la profilaxis de cáncer en un individuo, que comprende administrarle a dicho individuo una cantidad eficaz de una composición que comprende un compuesto de la fórmula I o una sal, solvato, polimorfo, éster, tautómero o prodroga farmacéuticamente aceptable del mismo. En otras formas de realización o adicionales, el cáncer es cáncer de cerebro, cáncer de mama, cáncer de estómago, cáncer de pulmón, cáncer de ovario, cáncer pancreático, cáncer de próstata, cáncer renal, cáncer colorrectal o leucemia. En otras formas de realización o adicionales, el trastorno fibrogenético es escleroderma,

polimiositis, lupus sistémica, artritis reumatoide, cirrosis hepática, formación de queloides, nefritis intersticial o fibrosis pulmonar. En otras formas de realización o adicionales, el cáncer es cáncer de cerebro, cáncer de mama, cáncer de pulmón, cáncer de ovario, cáncer pancreático, cáncer de próstata, cáncer renal, cáncer de estómago, cáncer colorrectal o leucemia. En otras formas de realización o adicionales, el cáncer es cáncer de cerebro o carcinoma adrenocortical. En otras formas de realización o adicionales, el cáncer es cáncer de mama. En otras formas de realización o adicionales, el cáncer es cáncer de ovario. En otras formas de realización o adicionales, el cáncer es cáncer pancreático. En otras formas de realización o adicionales, el cáncer es cáncer de próstata. En otras formas de realización o adicionales, el cáncer es cáncer renal. En otras formas de realización o adicionales, el cáncer es cáncer colorrectal. En otras formas de realización o adicionales, el cáncer es leucemia mieloide. En otras formas de realización o adicionales, el cáncer es glioblastoma. En otras formas de realización o adicionales, el cáncer es linfoma folicular. En otras formas de realización o adicionales, el cáncer es leucemia aguda pre-B. En otras formas de realización o adicionales, el cáncer es leucemia linfocítica B crónica. En otras formas de realización o adicionales, el cáncer es mesotelioma. En

otras formas de realización o adicionales, el cáncer es cáncer de pulmón de células pequeñas. En algunas formas de realización, el cáncer es cáncer de estómago.

En algunas formas de realización, la composición que comprende un compuesto de la fórmula I se administra en combinación con una terapia adicional. En otras formas de realización o adicionales, la terapia adicional es una terapia por radiación, quimioterapia, cirugía o cualquier combinación de las mismas. En otras formas de realización o adicionales, la composición que comprende un compuesto de la fórmula I se administra en combinación con al menos un agente terapéutico. En otras formas de realización o adicionales, el agente terapéutico se selecciona del grupo de agentes citotóxicos, agentes anti-angiogénesis y agentes anti-neoplásicos. En otras formas de realización o adicionales, el agente anti-neoplásico se selecciona del grupo que consiste de agentes alquilantes, anti-metabolitos, epidofilotoxinas; enzimas antineoplásicas, inhibidores de topoisomerasa, procarbazinas, mitoxantronas, complejos de coordinación de platino, modificadores de la respuesta biológica e inhibidores del crecimiento, agentes terapéuticos hormonales/anti-hormonales y factores de crecimiento hematopoyéticos. En otras formas de realización o adicionales, el agente terapéutico se selecciona entre taxol, bortezomib o ambos.

En algunas formas de realización, la composición se administra por vía oral, intraduodenal, parenteral (incluyendo intravenosa, subcutánea, intramuscular, intravascular o por infusión), tópica o rectal. En otras formas de realización o adicionales, la cantidad del compuesto de la fórmula I se encuentra en el rango de entre aproximadamente 0,001 y aproximadamente 1000 mg/kg de peso corporal/día. En otras formas de realización o adicionales, la cantidad del compuesto de la fórmula I se encuentra en el rango de entre aproximadamente 0,5 y aproximadamente 50 mg/kg/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,001 y aproximadamente 7 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,01 y aproximadamente 7 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,02 y aproximadamente 5 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,05 y aproximadamente 2,5 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,1 y aproximadamente 1 g/día. En otras formas de realización o adicionales, serán más que adecuados los niveles de dosificación inferiores al límite

inferior del rango mencionado previamente.

En otras formas de realización o adicionales, pueden ser necesarios niveles de dosificación superiores al límite superior del rango mencionado previamente. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra en una sola dosis, una vez por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra en múltiples dosis, más de una vez por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra dos veces por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra tres veces por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra cuatro veces por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra más de cuatro veces por día. En algunas formas de realización, el individuo que sufre de cáncer es un mamífero. En otras formas de realización o adicionales, el individuo es un ser humano. En otras formas de realización o adicionales, se administra una cantidad eficaz de una composición que comprende una sal farmacéuticamente aceptable de un compuesto de la fórmula I.

INCORPORACIÓN A MODO DE REFERENCIA

Todas las publicaciones y solicitudes de patente mencionadas en esta memoria descriptiva se incorporan en la

presente a modo de referencia como si cada publicación o solicitud de patente individual se incorporara específicamente e individualmente en la presente a modo de referencia.

DESCRIPCIÓN BREVE DE LAS FIGURAS

Las características novedosas de la invención se describen particularmente en las reivindicaciones adjuntas. Se podrá lograr una mejor comprensión de las características y ventajas de la presente invención con referencia a la siguiente descripción detallada que describe las formas de realización ilustrativas, en donde se utilizan los principios de la invención y las figuras adjuntas donde:

La Figura 1 muestra gráficos del volumen tumoral promedio en función del tiempo (días) en ratones que fueron implantados con células de melanoma A375, tumor de colon Colo205, tumor epidermoide A431 o tumor de colon HT-29. Los ratones recibieron dosis por vía oral (25 mg/kg, 50 mg/kg o 100 mg/kg), una vez por día, durante 14 días.

La Figura 2 muestra un gráfico del % de inhibición del crecimiento tumoral (%TGI) en ratones con xenoinjerto de A375, que recibieron dosis de 50 mg/kg QD, 25 mg/kg BID, 50 mg/kg QD y 12,5mg/kg BID.

La Figura 3 muestra un gráfico de concentración en plasma (log nM) versus % de inhibición de pERK en ratones nu/nu hembra que fueron implantados con células tumorales

Colo205. Los ratones recibieron una sola dosis de 2,5, 5, 10 ó 25 mg/kg.

La Figura 4 muestra un gráfico de concentración en plasma (ng/ml) en función del tiempo (horas) en humanos después de la administración de una sola dosis de 2 mg (2 cápsulas x 1 mg), 4 mg (4 x cápsulas 1 mg) o 6 mg (6 cápsulas x 1 mg).

La Figura 5 es un gráfico de un patrón de difracción de rayos X de polvo (PXRD) de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida, Forma A, generado usando un difractómetro Inel XRG-3000. El trazado del gráfico indica la intensidad de los picos definida por cuentas por segundo versus el ángulo de difracción 2θ en grados.

La Figura 6 es un gráfico de un termograma por calorimetría de barrido diferencial (DSC) modulado de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida, Forma A, generada usando un calorímetro de barrido diferencial Q1000 de TA Instruments. El trazado del gráfico indica el flujo de calor normalizado en unidades de Vatios/gramo (W/g) versus la temperatura de la muestra medida en °C.

La Figura 7 es un gráfico de los patrones de PXRD de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-

metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida, Forma A, (parte superior) y N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida, amorfa (parte inferior), generados usando un difractómetro Inel XRG-3000. El trazado del gráfico indica la intensidad de los picos definida por cuentas por segundo versus el ángulo de difracción 2θ en grados.

La Figura 8 muestra una isoterma de sorción/desorción dinámica de vapor (DVS) de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida, Forma A, generada usando un analizador de sorción de vapor VTI SGA-100.

La Figura 9 muestra un termograma por termogravimetría (TG) de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida, Forma A) generado usando un analizador termogravimétrico TA Instrument 2950.

La Figura 10(a) y la Figura 10(b) muestra un arresto del crecimiento de células A375 en división en fase log expuestas a concentraciones crecientes de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida. Se analizó el contenido de ATP en las células. El 100% de arresto del crecimiento se determinó usando N-(S)-(3,4-difluoro-2-(2-

fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida 1 µM.

La Figura 11 muestra un ensayo AK de 48 hs con células A375. Se expusieron células A375 en división en fase log a N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida y PD-325901 durante 48 hs y luego fueron analizadas por la liberación de AK.

Las Figuras 12A-12C muestran inhibición del crecimiento por N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida de (A) células de carcinoma colorrectal humano Colo205 ($GI_{50}$ = 11 nM); (B) células A375 ($GI_{50}$ = 22 nM) y (C) la inhibición de células MDA-MB231 que no muestran arresto del crecimiento inducido por N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida en ensayos dependientes del anclaje bidimensional.

La Figura 13A muestra la inhibición del crecimiento de células de carcinoma colorrectal humano Colo205, con valores de $GI_{50}$ a 6 nM y 11 nM, respectivamente.

La Figura 13B muestra la inhibición del crecimiento de células A375 con valores de $GI_{50}$ a 5 nM y 22 nM.

La Figura 14A y la Figura 14B muestran el efecto de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-

metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida sobre el avance del ciclo celular, demostrando que la exposición de células A375 a la N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida causa un arresto en la fase G1 del ciclo celular, indicado por la depleción de células en ambas fases G2 y S.

La Figura 15A y la Figura 15B muestran el efecto de la N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida sobre la línea celular AGS de cáncer de estómago (adenocarcinoma gástrico) después de 3 días (Figura 15A) y de 6 días (Figura 15B). El eje y es la cantidad de células con relación al vehículo y el eje x es la concentración uM de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida.

La Figura 16 muestra los pesos promedio de hígados en ratones portadores de tumores después del tratamiento con N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida (2 mg/kg, una vez por día, po; 10 mg/kg, una vez por día, po, y 50 mg/kg, una vez por día, po).

La Figura 17 muestra los pesos de tumores de hígado en ratones portadores de tumores después del tratamiento con N-

(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida (2 mg/kg, una vez por día, po; 10 mg/kg, una vez por día, po, y 50 mg/kg, una vez por día, po).

La Figura 18 muestra los pesos promedio de tumores después del tratamiento con N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida (2 mg/kg; 10 mg/kg; y 50 mg/kg).

La Figura 19 muestra la inhibición de la proliferación de células Hs746t en un gráfico de cantidad de células (con relación al vehículo) versus concentración de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida.

La Figura 20A representa un gráfico que compara los respectivos niveles de apoptosis a concentraciones crecientes de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida el día 5 de tratamiento de células MV522 de cáncer de pulmón de células no pequeñas (NSCLC).

La Figura 20B es un gráfico que demuestra los respectivos niveles de apoptosis a concentraciones crecientes de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-

dihidroxipropil)ciclopropan-1-sulfonamida el día 5 de tratamiento de células H358 de cáncer de pulmón de células no pequeñas (NSCLC).

La Figura 20C es un gráfico que demuestra los respectivos niveles de apoptosis a concentraciones crecientes de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida el día 6 de tratamiento de células A549 de cáncer de pulmón de células no pequeñas (NSCLC).

La Figura 20D es un gráfico que demuestra los respectivos niveles de apoptosis a concentraciones crecientes de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida el día 5 de tratamiento de células H727 de cáncer de pulmón de células no pequeñas (NSCLC).

La Figura 20E es un gráfico que demuestra los respectivos niveles de apoptosis a concentraciones crecientes de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida el día 5 de tratamiento de células HT29 de colon.

La Figura 20F es un gráfico que demuestra los respectivos niveles de apoptosis a concentraciones

crecientes de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida el día 6 de tratamiento de células HT116 de colon.

La Figura 20G es un gráfico que demuestra los respectivos niveles de apoptosis a concentraciones crecientes de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida el día 5 de tratamiento de células de hepatoma HUG7 de colon.

La Figura 20H es un gráfico que representa los respectivos niveles de apoptosis a concentraciones crecientes de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida el día 5 de tratamiento de células de sarcoma U2-OS.

La Figura 20I es un gráfico que demuestra los respectivos niveles de apoptosis a concentraciones crecientes de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida el día 5 de tratamiento de células de glioma D37.

La Figura 21 muestra la selectividad del compuesto A por MEK1 y MEK2 contra un panel de 205 enzimas a 10 □M. Las líneas celulares eran Colo205, A375, A431 y HT-29.

La Figura 22 es un gráfico que muestra los incrementos en el volumen de las patas en cada uno de los grupos de tratamiento y la reducción del edema con relación al control de vehículo, después de administrarles dosis a las ratas con 6, 20, 60 y 200 mg/kg de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida en el modelo de edema de patas con carragenina en rata.

La Figura 23A muestra la inhibición de la hinchazón en un modelo de artritis inducida por adyuvante, en fase aguda, de ratas tratadas con 2, 6 y 20 mg/kg de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida.

La Figura 23B muestra la inhibición de la hinchazón en un modelo de artritis inducida por adyuvante, en fase demorada, de ratas tratadas con 2, 6 y 20 mg/kg de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida.

La Figura 24 muestra los puntajes promedio de artritis en ratones con artritis inducida por anticuerpos de colágeno (CAIA) tratados con 1, 3 y 10 mg/kg QD de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Los encabezados de sección utilizados en la presente

solamente sirven a efectos de una mayor organización y no deben considerarse como limitativos del objeto descrito. Todos los documentos, o porciones de documento, citados en la solicitud incluyendo, en un sentido no limitativo, patentes, solicitudes de patente, artículos, libros, manuales y tratados se incorporan expresamente y por completo en este documento a modo de referencia.

***Terminología química***

A menos que se defina de otra manera, todos los términos técnicos y científicos utilizados en la presente tienen el mismo significado que el empleado comúnmente por los especialistas en el arte al cual pertenece el objeto reivindicado. Todas las patentes, solicitudes de patente, materiales publicados a los cuales se hace referencia en toda la divulgación de la presente, a menos que se indique de otra manera, se incorporan por completo a modo de referencia. En el caso que exista una pluralidad de definiciones para los términos utilizados aquí, prevalecerán los indicados en esta sección. Cuando se haga referencia a una URL u otro identificador o dirección semejante, se considera que dichos identificadores pueden cambiar y que la información particular en Internet puede variar, pero se puede hallar información equivalente mediante búsqueda en Internet u otra fuente de referencia apropiada. La referencia a las mismas evidencia la disponibilidad y

difusión pública de dicha información.

Se debe tener en cuenta que tanto la descripción general anterior como la siguiente descripción detallada solamente se ofrecen a modo de ejemplo y a efectos de una mayor explicación y no restringe el objeto reivindicado. En esta solicitud, el uso del singular incluye al plural a menos que específicamente se defina de otra manera. Se deberá tener en cuenta que, tal como se utilizan en la memoria descriptiva y en las reivindicaciones adjuntas, las formas en singular "un", "una", "la" y "el" incluyen los referentes al plural a menos que el contexto claramente indique lo contrario. También debería notarse que el uso de "o" significa "y/o" a menos que se defina de otra manera. Aún más, el uso del término "incluyendo" así como otras formas, tal como "incluyen", "que incluye" e "incluido", no se considera limitativo.

La definición de los términos químicos estándar se puede consultar en los trabajos de referencia, incluyendo Carey y Sundberg, "ADVANCED ORGANIC CHEMISTRY 4$^{A}$ ED.", Vols. A (2000) y B (2001), Plenum Press, Nueva York. A menos que se indique de otra manera, se emplean métodos convencionales de espectroscopía de masa, espectroscopía RMN, HPLC, IR y UV/Vis y farmacología, propios del conocimiento del arte. A menos que se proporcionen definiciones específicas, las nomenclaturas relativas empleadas y los procedimientos y

técnicas de laboratorio, química analítica, química orgánica de síntesis y química medicinal y farmacéutica descritos en la presente son conocidos en el arte. Se pueden emplear técnicas estándar para las síntesis químicas, los análisis químicos, las preparaciones, las formulaciones y la administración de productos farmacéuticos, y el tratamiento de pacientes. Las reacciones y las técnicas de purificación se pueden realizar por ejemplo, usando conjuntos de elementos de acuerdo con las especificaciones del proveedor o como es común en el arte o como se describe en la presente. Las técnicas y los procedimientos mencionados en general se pueden conducir de acuerdo con métodos convencionales bien conocidos en la técnica, y como se describe en diversas referencias generales y más específicas que se citan y se describen en toda la presente memoria descriptiva. En toda la memoria descriptiva, los grupos y los sustituyentes de los mismos pueden ser seleccionados por el especialista en este campo para proveer grupos y compuestos estables.

Cuando los grupos de sustituyentes son especificados por sus fórmulas químicas convencionales, escritas de izquierda a derecha, abarcan asimismo los sustituyentes químicamente idénticos que serían el resultado de escribir la estructura de derecha a izquierda. A modo de ejemplo no limitante, $-CH_2O-$ es equivalente a $-OCH_2-$.

A menos que se indique de otra manera, el uso de términos de química general tales como, aunque no en un sentido limitativo, "alquilo", "amina", "arilo", es equivalente a sus formas opcionalmente sustituidas. Por ejemplo, "alquilo", según se usa en la presente, incluye alquilo sustituido opcionalmente.

Los compuestos presentados en la presente pueden tener uno o más estereocentros y cada centro puede existir en la configuración R o S, o combinaciones de las mismas. Asimismo, los compuestos presentados en la presente pueden tener uno o más enlaces dobles y cada uno puede existir en la configuración E (*trans*) o Z (*cis*), o combinaciones de las mismas. La presentación de un estereoisómero, regioisómero, diastereómero, enantiómero o epímero particular incluirá todos los posibles estereoisómeros, regioisómeros, diastereómeros, enantiómeros o epímeros y mezclas de los mismos. Por consiguiente, los compuestos presentados en la presente incluyen todas las formas de configuración separadas estereoisoméricas, regioisoméricas, diastereoméricas, enantioméricas y epiméricas, así como las correspondientes mezclas de los mismos. La presentación de una estructura química o nombre químico particular para un compuesto que contiene uno o más centros quirales, pero que no indica una estereoquímica particular, incluirá todos los posibles estereoisómeros, incluyendo mezclas de todos los

posibles estereoisómeros, formas puras o formas sustancialmente puras de un estereoisómero particular y formas puras o formas sustancialmente puras del estereoisómero alternativo. Las técnicas para invertir o dejar sin cambios un estereocentro particular, y las empleadas para resolver las mezclas de estereoisómeros son bien conocidos en el arte y es propio de la capacidad de un especialista en el arte elegir el método apropiado para una situación particular. Véase, por ejemplo, Furniss *et al.*, (eds.), VOGEL'S ENCICLOPEDIA OF PRACTICAL ORGANIC CHEMISTRY 5ª ED., Longman Scientific and Technical Ltd., Essex, **1991**, 809-816; y Heller, *Acc. Chem. Res.* **1990**, *23*, 128.

Los términos "porción", "porción química", "grupo" y "grupo químico", según se usa en la presente se refiere a un segmento específico o grupo funcional de una molécula. Las unidades químicas a menudo son entidades químicas reconocidas embebidas en o unidas a una molécula.

El término "unión" o "unión simple" se refiere a una unión química entre dos átomos, o dos porciones cuando los átomos unidos por el enlace o la unión son consideradas como parte de una subestructura mayor.

El término "opcional" u "opcionalmente" significa que el evento o la circunstancia que se describe a continuación puede ocurrir o no, y que la descripción incluye instancias donde dicho evento o circunstancia tiene lugar e instancias

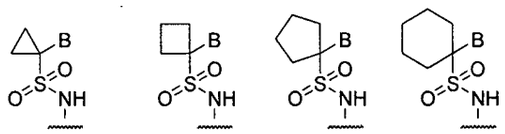
donde no tiene lugar. Por ejemplo, un "alquilo sustituido opcionalmente" abarca tanto un "alquilo" como un "alquilo sustituido" según se definirá más adelante. Además, un grupo sustituido opcionalmente puede no estar sustituido (por ejemplo, $-CH_2CH_3$), estar completamente sustituido (por ejemplo, $-CF_2CF_3$), monosustituido (por ejemplo, $-CH_2CH_2F$) o sustituido a un nivel que comprende cualquiera entre completamente sustituido y monosustituido (por ejemplo, $-CH_2CHF_2$, $-CH_2CF_3$, $-CF_2CH_3$, $-CFHCHF_2$, etc). Los especialistas en el arte comprenderán, con respecto a cualquier grupo que contiene uno o más sustituyentes, que dichos grupos no pretenden introducir cualquier substitución o patrón de sustituciones (por ejemplo, un alquilo sustituido incluye grupos cicloalquilo sustituidos opcionalmente, que a su vez se definen por incluir grupos alquilo sustituidos opcionalmente, potencialmente *ad infinitum*) que sea estéricamente imposible y/o que no sea factible sintetizar. Por ende, cualquier sustituyente descrito debería contener en general un peso molecular máximo de aproximadamente 1.000 daltons, y más típicamente, hasta y de 500 daltons aproximadamente (excepto en aquellos casos donde se consideren claramente sustituyentes macromoleculares, por ejemplo, polipéptidos, polisacáridos, polietilenglicoles, ADN, ARN y semejantes).

A menos que se indique de otra manera, cuando se usan

términos de química general tales como, aunque no en un sentido limitativo, "alquilo", "amina", "arilo", no están sustituidos.

Según se utiliza en la presente, $C_1$-$C_x$ incluye $C_{-1}$-$C_2$' $C_1$-$C_3$ . . . $C_1$-$C_x$. A modo de ejemplo solamente, un grupo designado como "$C_1$-$C_4$" indica que hay uno a cuatro átomos de carbono en el grupo, es decir grupos que contienen 1 átomo de carbono, 2 átomos de carbono, 3 átomos de carbono o 4 átomos de carbono, así como los rangos $C_1$-$C_2$ y $C_1$-$C_3$. Así, a modo de ejemplo solamente, "$C_1$-$C_4$ alquilo" indica que hay uno a cuatro átomos de carbono en el grupo alquilo, es decir, el grupo alquilo se selecciona entre metilo, etilo, propilo, *iso*-propilo, *n*-butilo, *iso*-butilo, *sec*-butilo y *t*-butilo. Siempre que se indique en la presente, un rango numérico tal como "1 a 10" se refiere a cada número entero en el rango indicado; por ejemplo, "1 a 10 átomos de carbono" significa que el grupo puede tener 1 átomo de carbono, 2 átomos de carbono, 3 átomos de carbono, 4 átomos de carbono, 5 átomos de carbono, 6 átomos de carbono, 7 átomos de carbono, 8 átomos de carbono, 9 átomos de carbono o 10 átomos de carbono.

El término " A y A', junto con el átomo de carbono al cual está unido, forma un anillo saturado de 3 a 6 miembros", según se usa en la presente, se refiere a las siguientes estructuras para los compuestos de la fórmula I:



Los términos "heteroátomo" o "hetero", según se usan en la presente, ya sea solos o en combinación, se refieren a un átomo distinto de carbono o hidrógeno. Los heteroátomos se pueden seleccionar de manera independiente entre oxígeno, nitrógeno, azufre, fósforo, silicona, selenio y estaño, pero no se limitan a estos átomos. En las realizaciones donde hay dos o más heteroátomos, dichos dos o más heteroátomos pueden ser iguales entre sí o parte o todos dichos dos o más heteroátomos pueden ser diferentes entre sí.

El término "alquilo", según se usa en la presente, ya sea solo o en combinación, se refiere a un monorradical hidrocarbonado saturado de cadena lineal o de cadena ramificada que tiene entre uno y aproximadamente diez átomos de carbono, o uno a seis átomos de carbono. Los ejemplos incluyen, pero en un sentido no limitativo, metilo, etilo, propilo, isopropilo, 2-metil-1-propilo, 2-metil-2-propilo, 2-metil-1-butilo, 3-metil-1-butilo, 2-metil-3-butilo, 2,2-dimetil-1-propilo, 2-metil-1-pentilo, 3-metil-1-pentilo, 4-metil-1-pentilo, 2-metil-2-pentilo, 3-metil-2-pentilo, 4-metil-2-pentilo, 2,2-dimetil-1-butilo, 3,3-dimetil-1-butilo, 2-etil-1-butilo, n-butilo, isobutilo, sec-butilo, t-butilo, n-pentilo, isopentilo, neopentilo, ter-amilo y hexilo, y grupos alquilo más largos, tales como heptilo, octilo y

semejantes. Cada vez que aparece en la presente, un rango numérico tal como "$C_1$-$C_6$ alquilo" o "$C_{1-6}$ alquilo", significa que el grupo alquilo puede consistir de 1 átomo de carbono, 2 átomos de carbono, 3 átomos de carbono, 4 átomos de carbono, 5 átomos de carbono o 6 átomos de carbono. En una forma de realización, el "alquilo" está sustituido. A menos que se indique de otra manera, el "alquilo" no está sustituido.

El término "alquenilo", según se usa en la presente, ya sea solo o en combinación, se refiere a un monorradical hidrocarbonado de cadena lineal o de cadena ramificada que contiene uno o más dobles enlaces carbono-carbono y entre dos y diez átomos de carbono aproximadamente, o entre dos y seis átomos de carbono aproximadamente. El grupo puede ser de conformación *cis* o *trans* alrededor de dichos uno o más enlaces dobles, y se considera que incluye ambos isómeros. Los ejemplos incluyen, pero en un sentido no limitativo, etenilo ($-CH=CH_2$), 1-propenilo ($-CH_2CH=CH_2$), isopropenilo [$-C(CH_3)=CH_2$], butenilo, 1,3-butadienilo y semejantes. Cada vez que aparece en la presente, un rango numérico tal como "$C_2$-$C_6$ alquenilo" o "$C_{2-6}$ alquenilo", significa que el grupo alquenilo puede consistir de 2 átomos de carbono, 3 átomos de carbono, 4 átomos de carbono, 5 átomos de carbono o 6 átomos de carbono. En una forma de realización, el "alquenilo" está sustituido. A menos que se indique de otra

manera, el "alquenilo" no está sustituido.

El término "alquinilo", según se usa en la presente, ya sea solo o en combinación, se refiere a un monoradical hidrocarbonado de cadena lineal o de cadena ramificada que contiene uno o más enlaces triples carbono-carbono y entre dos y diez átomos de carbono aproximadamente, o entre dos y seis átomos de carbono aproximadamente. Los ejemplos incluyen, pero en un sentido no limitativo, etinilo, 2-propinilo, 2-butinilo, 1,3-butadiinilo y semejantes. Cada vez que aparece en la presente, un rango numérico tal como "$C_2$-$C_6$ alquinilo" o "$C_{2-6}$ alquinilo", significa que el grupo alquinilo puede consistir de 2 átomos de carbono, 3 átomos de carbono, 4 átomos de carbono, 5 átomos de carbono o 6 átomos de carbono. En una forma de realización, el "alquinilo" está sustituido. A menos que se indique de otra manera, el "alquinilo" no está sustituido.

Los términos "heteroalquilo", "heteroalquenilo" y "heteroalquinilo", según se usan en la presente, ya sea solos o en combinación, se refieren a las estructuras alquilo, alquenilo y alquinilo, respectivamente, como se describió previamente, en las cuales uno o más de los átomos de carbono de la cadena del esqueleto (y cualquier átomo de hidrógeno asociado, según corresponda) es reemplazado de forma independiente por un heteroátomo (es decir un átomo distinto de carbono, tal como, aunque en un sentido no

limitativo, oxígeno, nitrógeno, azufre, silicona, fósforo, estaño o combinaciones de los mismos), o un grupo heteroatómico tal como, aunque en un sentido no limitativo, -O-O-, -S-S-, -O-S-, -S-O-, =N-N=, -N=N-, -N=N-NH-, $-P(O)_2-$, $-O-P(O)_2-$, $-P(O)_2-O-$, -S(O)-, $-S(O)_2-$, $-SnH_2-$ y semejantes.

Los términos "haloalquilo", "haloalquenilo" y "haloalquinilo", según se usan en la presente, ya sea solos o en combinación, se refieren a grupos alquilo, alquenilo y alquinilo, respectivamente, definidos precedentemente, en los cuales uno o más átomos de hidrógeno se reemplazan por átomos de flúor, cloro, bromo o iodo, o combinaciones de los mismos. En algunas formas de realización, se pueden reemplazar dos o más átomos de hidrógeno por átomos de halógeno que son iguales entre sí (por ejemplo difluorometilo); en otras formas de realización, se pueden reemplazar dos o más átomos de hidrógeno por átomos de halógeno que no son todos iguales entre sí (por ejemplo 1-cloro-1-fluoro-1-iodoetilo). Los ejemplos no limitativos de grupos haloalquilo comprenden fluorometilo, clorometilo y bromoetilo. Un ejemplo no limitativo de un grupo haloalquenilo es bromoetenilo. Un ejemplo no limitativo de un grupo haloalquinilo es cloroetinilo.

El término "cadena de carbono", según se usa en la presente, ya sea solo o en combinación, se refiere a cualquier grupo alquilo, alquenilo, alquinilo,

heteroalquilo, heteroalquenilo o heteroalquinilo, que sea lineal, cíclico o cualquier combinación de los mismos. Si la cadena es parte de un conector y dicho conector comprende uno o más anillos como parte del esqueleto central, a los fines de de calcular la longitud de la cadena, dicha "cadena" solamente incluye aquellos átomos de carbono que componen la parte inferior o la parte superior de un anillo dado y no ambos, y donde la parte superior e inferior de el o los anillos no es equivalente en cuanto a longitud, se usará la distancia más corta para determinar la longitud de la cadena. Si la cadena contiene heteroátomos como parte del esqueleto, dichos átomos no se calculan como parte de la longitud de la cadena de carbono.

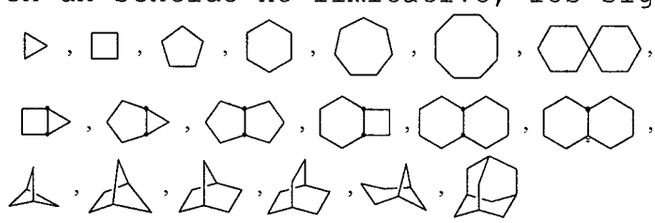
Los términos "ciclo", "cíclico", "anillo" y "anillo con miembros", según se usa en la presente, ya sea solos o en combinación, se refieren a cualquier estructura covalentemente cerrada, incluyendo sistemas de anillos fusionados o no fusionados alicíclicos, heterocíclicos, aromáticos, heteroaromáticos y policíclicos descritos en la presente. Los anillos pueden estar sustituidos opcionalmente. Los anillos pueden formar parte de un sistema de anillos. El término "con miembros" indica la cantidad de átomos del esqueleto que constituye el anillo. Por ende, a modo de ejemplo solamente, ciclohexano, piridina, pirano y pirimidina son anillos de seis miembros y ciclopentano,

pirrol, tetrahidrofurano y tiofeno son anillos de cinco miembros.

El término "fusionados", según se usa en la presente, ya sea solo o en combinación, se refiere a estructuras cíclicas en las cuales dos o más anillos comparten uno o más enlaces.

El término "cicloalquilo", según se usa en la presente, ya sea solo o en combinación, se refiere a un anillo de un monoradical hidrocarbonado, saturado, que contiene entre tres y quince átomos de carbono del anillo aproximadamente o entre tres y diez átomos de carbono del anillo aproximadamente, aunque pueden incluir átomos de carbono adicional, que no son del anillo como sustituyentes (por ejemplo, metilciclopropilo). Cada vez que aparece en la presente, un rango numérico tal como "$C_3$-$C_6$ cicloalquilo " o "$C_{3-6}$ cicloalquilo ", significa que el grupo cicloalquilo puede consistir de 3 átomos de carbono, 4 átomos de carbono, 5 átomos de carbono o 6 átomos de carbono, es decir, es ciclopropilo, ciclobutilo, ciclopentilo o cicloheptilo, aunque la presente definición también abarca la posibilidad del término " cicloalquilo " cuando no se designa un rango numérico. El término incluye radicales fusionados, no fusionados, con puentes y espiro. Un cicloalquilo fusionado puede contener entre dos y cuatro anillos fusionados cuando el anillo de unión es un anillo cicloalquilo, y el otro

anillo individual puede ser alicíclico, heterocíclico, aromático, heteroaromático o cualquier combinación de los mismos. Los ejemplos incluyen, pero en un sentido no limitativo, sistemas de anillos de ciclopropilo, ciclopentilo, ciclohexilo, decalinilo y biciclo [2.2.1] heptilo y adamantilo. Los ejemplos ilustrativos incluyen, pero en un sentido no limitativo, los siguientes grupos:



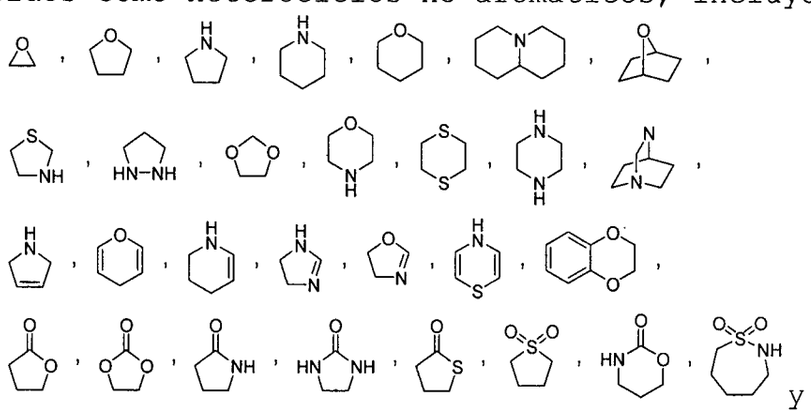
y semejantes.

En una forma de realización, el "cicloalquilo" está sustituido. A menos que se indique de otra manera, el "cicloalquilo" no está sustituido.

Los términos "heterociclilo no aromático" y "heteroaliciclilo", según se usan en la presente, ya sea solos o en combinación, se refieren a monoradicales en anillo no aromáticos saturados, parcialmente insaturados o completamente insaturados que contienen entre tres y veinte átomos del anillo aproximadamente, donde uno o más de los átomos del anillo son distintos de carbono, seleccionados de manera independiente entre oxígeno, nitrógeno, azufre, fósforo, silicona, selenio y estaño pero no se limitan a estos átomos. En las realizaciones donde hay dos o más heteroátomos en el anillo, dichos dos o más heteroátomos

pueden ser iguales entre sí o parte o todos dichos dos o más heteroátomos pueden ser diferentes entre sí. Los términos incluyen radicales fusionados, no fusionados, con puentes y espiro. Un radical heterocíclico no aromático fusionado puede contener entre dos y cuatro anillos fusionados, donde el anillo de unión es un heterociclo no aromático, y los otros anillos individuales pueden ser alicíclicos, heterocíclicos, aromáticos, heteroaromáticos o cualquier combinación de los mismos. Los sistemas de anillos fusionados se pueden fusionar a través de un enlace simple o de un enlace doble, así como mediante enlaces de carbono-carbono, carbono-heteroátomo o heteroátomo-heteroátomo. Los términos también incluyen radicales que tienen aproximadamente entre tres y doce átomos del esqueleto del anillo, así como a los que tienen entre aproximadamente tres y diez átomos del esqueleto del anillo. La unión de una subunidad heterocíclica no aromática con su molécula parental puede ser a través de un heteroátomo o un átomo de carbono. Asimismo, la sustitución adicional puede ser a través de un heteroátomo o de un átomo de carbono. A modo de ejemplo no limitante, un heterociclo no aromático de imidazolidina se puede unir a la molécula parental ya sea a través de sus N átomos (imidazolidin-1-ilo o imidazolidin-3-ilo) o cualquiera de sus átomos de carbono (imidazolidin-2-ilo, imidazolidin-4-ilo o imidazolidin-5-ilo). En

determinadas realizaciones, los heterociclos no aromáticos contienen uno o más grupos carbonilo o tiocarbonilo tal como, por ejemplo, grupos que contienen oxo y tio. Los ejemplos incluyen, pero en un sentido no limitativo, pirrolidinilo, tetrahidrofuranilo, dihidrofuranilo, tetrahidrotienilo, tetrahidropiranilo, dihidropiranilo, tetrahidrotiopiranilo, piperidino, morfolino, tiomorfolino, tioxanilo, piperazinilo, azetidinilo, oxetanilo, tietanilo, homopiperidinilo, oxepanilo, tiepanilo, oxazepinilo, diazepinilo, tiazepinilo, 1,2,3,6-tetrahidropiridinilo, 2-pirrolinilo, 3-pirrolinilo, indolinilo, 2H-piranilo, 4H-piranilo, dioxanilo, 1,3-dioxolanilo, pirazolinilo, ditianilo, ditiolanilo, dihidropiranilo, dihidrotienilo, dihidrofuranilo, pirazolidinilo, imidazolinilo, imidazolidinilo, 3-azabiciclo[3.1.0]hexanilo, 3-azabiciclo[4.1.0]heptanilo, 3H-indolilo y quinolizinilo. Los ejemplos ilustrativos de grupos heterocicloalquilo, también conocidos como heterociclos no aromáticos, incluyen:



y

semejantes.

Los términos también incluyen todas las formas de anillo de los carbohidratos, incluyendo pero en un sentido no limitativo, los monosacáridos, los disacáridos y los oligosacáridos. En una forma de realización, el "heterociclilo no aromático" o "heteroaliciclilo" está sustituido. A menos que se indique de otra manera, el "heterociclilo no aromático" o "heteroaliciclilo" no está sustituido.

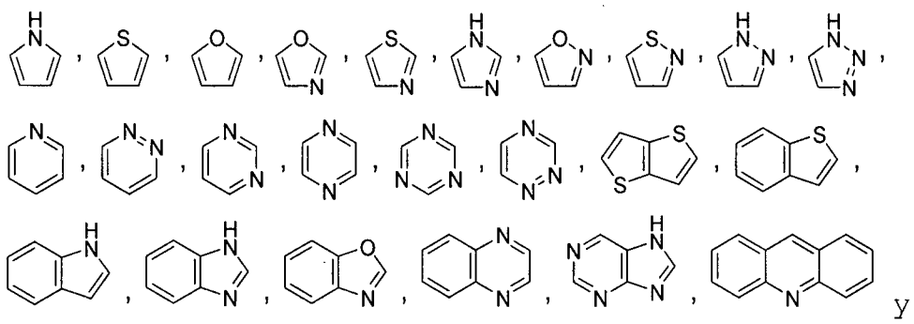
El término "arilo", según se usa en la presente, ya sea solo o en combinación, se refiere a un radical hidrocarbonado aromático de entre seis y veinte átomos del anillo de carbono aproximadamente, e incluye anillos de arilo fusionados y no fusionados. Un radical en anillo arilo fusionado contiene entre dos y cuatro anillos fusionados, donde el anillo de unión es un anillo arilo y los otros anillos individuales pueden ser alicíclicos, heterocíclicos, aromáticos, heteroaromáticos o cualquier combinación de los mismos. Además, el término arilo incluye anillos fusionados y no fusionados que contienen entre seis y doce átomos del anillo de carbono aproximadamente, así como los que contienen entre seis y diez átomos del anillo de carbono aproximadamente. Un ejemplo no limitativo de un grupo arilo de un solo anillo incluye fenilo; un grupo arilo de anillos fusionados incluye naftilo, fenantrenilo, antracenilo,

azulenilo; y un grupo bi-arilo no fusionado incluye bifenilo. En una forma de realización, el "arilo" está sustituido. A menos que se indique de otra manera, el "arilo" no está sustituido.

El término "heteroarilo", según se usa en la presente, ya sea solo o en combinación, se refiere a monoradicales aromáticos que contienen entre aproximadamente cinco y aproximadamente veinte átomos del esqueleto del anillo, donde uno o más de los átomos del anillo es un heteroátomo seleccionado de manera independiente entre oxígeno, nitrógeno, azufre, fósforo, silicona, selenio y estaño, pero sin limitaciones a estos átomos y con la condición que el anillo de dicho grupo no contenga dos átomos de adyacentes de O o S. En las realizaciones donde hay dos o más heteroátomos en el anillo, dichos dos o más heteroátomos pueden ser iguales entre sí o parte o todos dichos dos o más heteroátomos pueden ser diferentes entre sí. El término heteroarilo incluye radicales heteroarilo fusionados y no fusionados que contienen al menos un heteroátomo. El término heteroarilo también incluye heteroarilos fusionados y non-fusionados que tienen entre cinco y doce átomos del esqueleto del anillo aproximadamente, así como los que tienen entre cinco y diez átomos del esqueleto del anillo aproximadamente. La unión a un grupo heteroarilo puede ser a través de un átomo de carbono o de un heteroátomo. Por

consiguiente, a modo de ejemplo no limitante, un grupo imidazol se puede unir a una molécula parental a través de cualquiera de sus átomos de carbono (imidazol-2-ilo, imidazol-4-ilo o imidazol-5-ilo), o sus átomos de nitrógeno (imidazol-1-ilo o imidazol-3-ilo). Asimismo, un grupo heteroarilo puede estar sustituido en cualquiera o todos sus átomos de carbono y/o en cualquiera o todos sus heteroátomos. Un radical heteroarilo fusionado puede contener entre dos y cuatro anillos fusionados, donde el anillo de unión es un anillo heteroaromático y los otros anillos individuales pueden ser alicíclicos, heterocíclicos, aromáticos, heteroaromáticos o cualquier combinación de los mismos. Un ejemplo no limitativo de un grupo heteroarilo de un solo anillo incluye piridilo; los grupos heteroarilos de anillos fusionados incluyen benzimidazolilo, quinolinilo, acridinilo; y un grupo bi-heteroarilo no fusionado incluye bipiridinilo. Otros ejemplos de heteroarilos incluyen, sin limitaciones, furanilo, tienilo, oxazolilo, acridinilo, fenazinilo, benzimidazolilo, benzofuranilo, benzoxazolilo, benzotiazolilo, benzotiadiazolilo, benzotiofenilo, benzoxadiazolilo, benzotriazolilo, imidazolilo, indolilo, isoxazolilo, isoquinolinilo, indolizinilo, isotiazolilo, isoindoliloxadiazolilo, indazolilo, piridilo, piridazilo, pirimidilo, pirazinilo, pirrolilo, pirazinilo, pirazolilo, purinilo, ftalazinilo, pteridinilo, quinolinilo,

quinazolinilo, quinoxalinilo, triazolilo, tetrazolilo, tiazolilo, triazinilo, tiadiazolilo y semejantes, y sus óxidos, tal como por ejemplo piridil-N-óxido. Los ejemplos ilustrativos de grupos heteroarilo incluyen los siguientes grupos:



y semejantes.

En una forma de realización, el "heteroarilo" está sustituido. A menos que se indique de otra manera, el "heteroarilo" no está sustituido.

El término "heterociclilo", según se usa en la presente, ya sea solo o en combinación, se refiere en su conjunto a grupos heteroaliciclilo y heteroarilo. En la presente, cada vez que se indica la cantidad de átomos de carbono en un heterociclo (por ejemplo, $C_1$-$C_6$ heterociclo), debe estar presente al menos un átomo que no es carbono (el heteroátomo) en el anillo. Las denominaciones, tal como "$C_1$-$C_6$ heterociclo", solamente se refieren a la cantidad de átomos de carbono en el anillo y no se refieren a la cantidad total de átomos en el anillo. Las denominaciones tales como "heterociclo de 4-6 miembros" se refieren a la

cantidad total de átomos contenidos en el anillo (es decir, un anillo de cuatro, cinco o seis miembros, en donde al menos un átomo es un átomo de carbono, al menos un átomo es un heteroátomo y los restantes dos a cuatro átomos son ya sea átomos de carbono o heteroátomos). En los heterociclos que tienen dos o más heteroátomos, dichos dos o más heteroátomos pueden ser iguales o diferentes entre sí. Los grupos heterocíclicos no aromáticos incluyen grupos que contienen solamente tres átomos en el anillo, en tanto los grupos heterocíclicos aromáticos pueden contener al menos cinco átomos en el anillo. La unión (es decir, el enlace a una molécula parental u otra sustitución) a un heterociclo puede ser a través de un heteroátomo o de un átomo de carbono. En una forma de realización, el "heterociclilo" está sustituido. A menos que se indique de otra manera, el "heterociclilo" no está sustituido.

Los términos "halógeno", "halo" o "haluro", según se usa en la presente, ya sea solos o en combinación, se refieren a flúor, cloro, bromo y/o iodo.

El término "amino", según se usa en la presente, ya sea solo o en combinación, se refiere al monoradical $-NH_2$.

El término "alquilamino", según se usa en la presente, ya sea solo o en combinación, se refiere al monoradical -NH(alquilo), donde el alquilo es como se define en la presente.

El término "dialquilamino", según se usa en la presente, ya sea solo o en combinación, se refiere al monoradical -N(alquil)(alquilo), donde los alquilos pueden ser idénticos o no idénticos y son como se definen en la presente.

El término "diaminalquilo", según se usa en la presente, ya sea solo o en combinación, se refiere a un grupo alquilo que contiene dos grupos amina, en donde dichos grupos amina pueden ser sustituyentes sobre el grupo alquilo que pueden ser grupos amino, alquilamino o dialquilamino, o en donde uno o ambos grupos amina pueden formar parte de una cadena de alquilo para formar -alquilen-N(H o alquil)-alquilen-N(H o alquilo o alquilen-)(H o alquilo o alquilen-).

El término "hidroxi", según se usa en la presente, ya sea solo o en combinación, se refiere al monoradical -OH.

El término "ciano", según se usa en la presente, ya sea solo o en combinación, se refiere al monoradical -CN.

El término "cianometilo", según se usa en la presente, ya sea solo o en combinación, se refiere al monoradical -$CH_2CN$.

El término "nitro", según se usa en la presente, ya sea solo o en combinación, se refiere al monoradical -$NO_2$.

El término "oxi", según se usa en la presente, ya sea solo o en combinación, se refiere al diradical -O-.

El término "oxo", según se usa en la presente, ya sea solo o en combinación, se refiere al di-radical =O.

El término "carbonilo", según se usa en la presente, ya sea solo o en combinación, se refiere al di-radical -C(=O)-, que también se puede escribir como -C(O)-.

Los términos "carboxi" o "carboxilo", según se usa en la presente, ya sea solo o en combinación, se refiere a la porción -C(O)OH, que también se puede escribir como -COOH.

El término "alcoxi", según se usa en la presente, ya sea solo o en combinación, se refiere a un radical alquiléter, -O-alquilo, incluyendo los grupos -O-alifático y -O-carbociclilo, en donde los grupos alquilo, alifático y carbociclilo pueden estar sustituidos opcionalmente, y en donde los términos alquilo, alifático y carbociclilo son como se definen en la presente. Los ejemplos no limitativos de radicales alcoxi incluyen metoxi, etoxi, n-propoxi, isopropoxi, n-butoxi, iso-butoxi, sec-butoxi, tert-butoxi y semejantes.

El término "sulfinilo", según se usa en la presente, ya sea solo o en combinación, se refiere al diradical -S(=O)-.

El término "sulfonilo", según se usa en la presente, ya sea solo o en combinación, se refiere al diradical $-S(=O)_2-$.

Los términos "sulfonamida", "sulfonamido" y "sulfonamidilo", según se usan en la presente, ya sea solos o en combinación, se refieren a los grupos de diradicales -

$S(=O)_2$-NH- y -NH-$S(=O)_2$-.

Los términos "sulfamida", "sulfamido" y "sulfamidilo", según se usan en la presente, ya sea solos o en combinación, se refieren al grupo diradical -NH-$S(=O)_2$-NH-.

El término "reactivo", según se usa en la presente, se refiere a un nucleófilo o electrófilo usado para crear enlaces covalentes.

Se comprenderá que en aquellos casos donde se usan dos o más radicales, sucesivamente, para definir un sustituyente unido a una estructura, se considera que el radical nombrado en primer lugar es terminal y se considera que el radical nombrado en último lugar estará unido a la estructura en cuestión. Así, por ejemplo, el radical arilalquilo está unido a la estructura en cuestión por medio del grupo alquilo.

*Terminología farmacéutica*

El término "inhibidor de MEK", según se usa en la presente, se refiere a un compuesto que exhibe un valor de $IC_{50}$ con respecto a la actividad de MEK de no más de 100 μM aproximadamente o no más de 50 μM aproximadamente, medido en el ensayo de Mek1 quinasa que se describe en general en la presente. "$IC_{50}$" es aquella concentración de inhibidor que reduce la actividad de una enzima (por ejemplo, una Raf quinasa) al nivel de la mitad del máximo. Se descubrió que los compuestos que se describen en la presente presentan

inhibición de MEK. Los compuestos de la presente invención presentan preferentemente un valor de $IC_{50}$ con respecto a Raf de no más de 10 μM aproximadamente, más preferentemente de no más de 5 μM aproximadamente, aún más preferentemente de no más de 1 μM aproximadamente y con mayor preferencia de no más de 200 nM aproximadamente, medido en los ensayos de Raf quinasa que se describen en la presente.

El término "sujeto", "paciente" o "individuo", según se usa en la presente con referencia a individuos que sufren de un trastorno y semejantes, abarca mamíferos y no mamíferos. Los ejemplos de mamíferos incluyen, pero en un sentido no limitativo, cualquier miembro de la clase de los mamíferos: humanos, primates no humanos tales como chimpancés, y otras especies de simios y monos; animales de granja tales como ganado, caballos, ovejas, cabras, cerdos; animales domésticos tales como conejos, perros y gatos; animales de laboratorios incluyendo roedores, tales como ratas, ratones y cobayos, y semejantes. Los ejemplos de no mamíferos incluyen, pero en un sentido no limitativo, aves, peces y semejantes. En una forma de realización de los métodos y las composiciones provistas en la presente, el mamífero es un ser humano.

Los términos "tratar", "tratando" o "tratamiento", y otros equivalentes gramaticales usados en la presente, incluyen el alivio, la regresión o la mejora de los síntomas

de una enfermedad o condición, la prevención de síntomas adicionales, la mejora o prevención de las causas metabólicas de los síntomas, la inhibición de la enfermedad o condición, por ejemplo, el arresto del desarrollo de la enfermedad o condición, el alivio de la enfermedad o condición, causando la regresión de la enfermedad o condición, el alivio de una condición causada por la enfermedad o condición o la detención de los síntomas de la enfermedad o condición, y pretenden incluir la profilaxis. Los términos incluyen además lograr un beneficio terapéutico y/o un beneficio profiláctico. Un beneficio terapéutico se refiere a la erradicación o mejora del trastorno subyacente bajo tratamiento. Además, el beneficio terapéutico se logra con la erradicación o el alivio de uno o más de los síntomas fisiológicos asociados con el trastorno subyacente de manera tal que se observa una mejora en el paciente, no obstante lo cual el paciente aún puede padecer el trastorno subyacente. Para lograr un beneficio profiláctico, las composiciones se pueden administrar a un paciente con riesgo de desarrollar una enfermedad particular, o a un paciente que ha informado uno o más de los síntomas fisiológicos de una enfermedad, aún cuando no se haya realizado un diagnóstico de esta enfermedad.

Los términos "cantidad eficaz", "cantidad terapéuticamente eficaz" o "cantidad farmacéuticamente

eficaz", según se usan en la presente, se refieren a una cantidad de al menos un agente o compuesto que está siendo administrado que sea suficiente para tratar o prevenir la enfermedad o condición particular. El resultado puede ser una reducción y/o el alivio de los signos, síntomas o causas de una enfermedad, o cualquier otra alteración deseada de un sistema biológico. Por ejemplo, una "cantidad eficaz" para usos terapéuticos es la cantidad de la composición que comprende un compuesto divulgado en la presente necesario para proporcionar una disminución clínicamente significativa de una enfermedad. La cantidad "efectiva" apropiada en cualquier caso individual se puede determinar usando técnicas tales como un estudio de escalada de la dosis.

Los términos "sustancialmente libre de agua" y "sustancialmente libre de solvente", según se usan en la presente, se refieren a formas cristalinas polimorfas que comprenden menos que un 0,01, 0,1, 0,2, 0,3, 0,4, 0,5, 1 ó 2% en peso de agua o solvente, respectivamente.

El término "sustancialmente el mismo que", según se usa en la presente, se refiere a un patrón de difracción de rayos X de polvo o un patrón de calorimetría de barrido diferencial que puede no ser idéntico a los ilustrados en la presente, pero que se encuentra dentro de los límites del error experimental, cuando es considerado por un especialista en el arte.

Los términos "administrar", "administrando", "administración" y semejantes, según se usan en la presente, se refieren a los métodos que se pueden usar para suministrar los compuestos o las composiciones en el sitio deseado para la acción biológica. Estos métodos incluyen, pero en un sentido no limitativo, rutas orales, rutas intraduodenales, inyección parenteral (incluyendo intravenosa, subcutánea, intraperitoneal, intramuscular, intravascular o infusión), administración tópica y rectal. Los especialistas en el arte están familiarizados con las técnicas de administración que se pueden emplear con los compuestos y métodos que se describen en la presente, por ejemplo, como se describe en Goodman y Gilman, *The Pharmacological Basis of Therapeutics*, edición actual; Pergamon; y *Remington's, Pharmaceutical Sciences* (edición actual), Mack Publishing Co., Easton, Pa. En formas de realización preferidas, los compuestos y las composiciones que se describen en la presente se administran por vía oral.

El término "aceptable", según se usa en la presente, con respecto a una formulación, composición o ingrediente, significa que no tienen un efecto perjudicial persistente sobre el estado de salud general del sujeto bajo tratamiento.

El término "farmacéuticamente aceptable", según se usa en la presente, se refiere a un material, tal como un

vehículo o diluyente, que no afecta la actividad biológica o las propiedades de los compuestos que se describen en la presente, y que es relativamente no tóxico, es decir, que el material se pueda administrar a un individuo sin causar efectos biológicos indeseables o interactuar de una manera perjudicial con cualquiera de los componentes de la composición en la cual está contenido.

El término "composición farmacéutica", según se usa en la presente, se refiere a un compuesto biológicamente activo, opcionalmente mezclado con al menos un componente químico farmacéuticamente aceptable, tal como, aunque en un sentido no limitativo, vehículos, estabilizantes, diluyentes, agentes dispersantes, agentes de suspensión, agentes espesantes y/o excipientes.

El término "vehículo", según se usa en la presente, se refiere a compuestos o agentes químicos relativamente no tóxicos que facilitan la incorporación de un compuesto en células o tejidos.

El término "agonista", según se usa en la presente, se refiere a una molécula, tal como un compuesto, una droga, un activador de una enzima o un modulador de hormonas, que mejore la actividad de otra molécula o la actividad de un sitio receptor.

El término "antagonista", según se usa en la presente, se refiere a una molécula, tal como un compuesto, una droga,

un inhibidor de una enzima o un modulador de hormonas, que disminuye o impide la acción de otra molécula o la actividad de un sitio receptor.

El término "modular", según se usa en la presente, se refiere a la interacción con un blanco, ya sea de forma directa o indirecta, para alterar la actividad del blanco, incluyendo, a modo de ejemplo solamente, para mejorar la actividad del blanco, para inhibir la actividad del blanco, para limitar la actividad del blanco o para extender la actividad del blanco.

El término "modulador", según se usa en la presente, se refiere a una molécula que interactúa con un blanco, ya sea directa o indirectamente. Las interacciones incluyen, pero en un sentido no limitativo, las interacciones de un agonista y un antagonista.

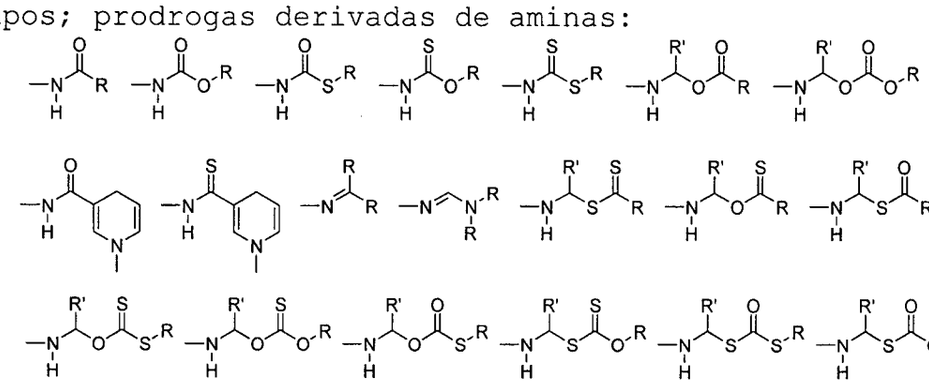
El término "derivado o prodroga farmacéuticamente aceptable", según se usa en la presente, se refiere a cualquier sal, éster, sal de un éster u otro derivado de un compuesto de la fórmula I se sea farmacéuticamente aceptable, que, luego de su administración a un receptor, pueda proporcionar, ya sea directa o indirectamente, un compuesto de esta invención o un metabolito o residuo farmacéuticamente activo del mismo. Los derivados o prodrogas particularmente favorecidos son aquellos que incrementan la biodisponibilidad de los compuestos de esta

invención cuando dichos compuestos son administrados a un paciente (por ejemplo, permitiendo que un compuesto administrado por vía oral sea absorbido más rápidamente en la sangre) o que mejora la administración del compuesto principal en un compartimiento biológico (por ejemplo, el cerebro o el sistema linfático).

Según se usa en la presente, una "prodroga" es un compuesto que se puede convertir en condiciones fisiológicas o por solvólisis en el compuesto específico o una sal de dicho compuesto farmacéuticamente aceptable. Las prodrogas incluyen compuestos en donde un residuo de aminoácido, o una cadena de polipéptidos de dos o más residuos de aminoácido, se une covalentemente a través de un enlace amida o éster a un grupo amino, hidroxi o ácido carboxílico libre de los compuestos de la fórmula I. Los residuos de aminoácidos contemplados incluyen, pero en un sentido no limitativo, los 20 aminoácidos naturales. Otros aminoácidos adecuados incluyen 4-hidroxiprolina, hidroxilisina, demosina, isodemosina, 3-metilhistidina, norvalina, β-alanina, ácido γ-aminobutírico, citrulina, homocisteína, homoserina, ornitina y metioninsulfona. Otros tipos de prodrogas son bien conocidos en el arte.

Las prodrogas farmacéuticamente aceptables de los compuestos que se describen en la presente incluyen, pero en un sentido no limitativo, ésteres, carbonatos,

tiocarbonatos, derivados N-acilo, derivados N-aciloxialquilo, derivados cuaternarios de aminas terciarias, bases de N-Mannich, bases de Schiff, conjugados de aminoácidos, ésteres de fosfato, sales de metales y ésteres de sulfonato. Existen diversas formas de prodrogas que son bien conocidas en el arte. Véase, por ejemplo *Design of Prodrugs*, Bundgaard, A. Ed., Elseview, 1985 y *Method in Enzymology*, Widder, K. *et al.*, Ed.; Academic, 1985, vol. 42, páginas 309-396; Bundgaard, H. "Design and Application of Prodrugs", en *A Textbook of Drug Design and Development*, Krosgaard-Larsen y H. Bundgaard, Ed., 1991, Capítulo 5, páginas 113-191; y Bundgaard, H., *Advanced Drug Delivery Review*, **1992**, *8*, 1-38, cada una de las cuales se incorpora en la presente a modo de referencia. Las prodrogas que se describen en la presente incluyen, pero en un sentido no limitativo, los siguientes grupos y combinaciones de estos grupos; prodrogas derivadas de aminas:



Las prodrogas de hidroxi incluyen, pero en un sentido no limitativo ésteres de aciloxialquilo, ésteres de

alcoxicarboniloxialquilo, ésteres de alquilo, ésteres de arilo y ésteres que contienen disulfuro.

El término "sal farmacéuticamente aceptable", según se usa en la presente, incluye sales que retienen la eficacia biológica de los ácidos y las bases libres del compuesto especificado y que no son biológicamente indeseables o inconvenientes de otra manera. Los compuestos descritos pueden contener grupos ácidos o básicos y por ello pueden reaccionar con cualquiera de numerosas bases inorgánicas u orgánicas y ácidos inorgánicos y orgánicos, para formar una sal farmacéuticamente aceptable. Los ejemplos de sales farmacéuticamente aceptables incluyen aquellas sales que se preparan por reacción de los compuestos descritos en la presente con un ácido mineral u orgánico o una base inorgánica, donde dichas sales incluyen, acetato, acrilato, adipato, alginato, aspartato, benzoato, bencensulfonato, bisulfato, bisulfito, bromuro, butirato, butin-1,4-dioato, alcanforato, alcanforsulfonato, caproato, caprilato, cloruros, clorobenzoato, cloruro, citrato, ciclopentanpropionato, decanoato, digluconato, fosfato diácido, dinitrobenzoato, dodecilsulfato, etansulfonato, formato, fumarato, glucoheptanoato, glicerofosfato, glicolato, hemisulfato, heptanoato, hexanoato, hexin-1,6-dioato, hidroxibenzoato, γ-hidroxibutirato, clorhidrato, bromhidrato, iodhidrato, 2-hidroxietansulfonato, ioduro,

isobutirato, lactato, maleato, malonato, metansulfonato, mandelato. metafosfato, metansulfonato, metoxibenzoato, metilbenzoato, fosfato monoácido, 1-naftalensulfonato, 2-naftalensulfonato, nicotinato, nitrato, oxalatos, palmoato, pectinato, persulfato, fenilacetatos, fenilpropionatos, 3-fenilpropionato, fosfato, picrato, pivalato, propionato, pirosulfato, pirofosfato, propiolato, propionatos, ftalato, fenilbutirato, propansulfonato, pirofosfatos, salicilato, succinato, sulfato, sulfito, succinato, suberato, sebacato, sulfonato, tartrato, tiocianato, tosilato, undeconato y xilensulfonato. Se pueden emplear otros ácidos, tal como oxálico, aunque no sean ellos mismos farmacéuticamente aceptables, en la preparación de sales de utilidad como intermediarios en la obtención de los compuestos de la invención y sus sales de adición ácida farmacéuticamente aceptables. (Véase, por ejemplo, Berge *et al.*, *J. Pharm. Sci.* **1977**, *66*, 1-19.) Además, aquellos compuestos que se describen en la presente que pueden comprender un grupo ácido libre, se pueden hacer reaccionar con una base adecuada, tal como el hidróxido, carbonato o bicarbonato de un catión de metal farmacéuticamente aceptable, con amoníaco, o con una amina orgánica primaria, secundaria o terciaria farmacéuticamente aceptable. Las sales de alcalinas o alcalino-térreas representativas incluyen sales de litio, sodio, potasio, calcio, magnesio y aluminio y

semejantes. Los ejemplos ilustrativos de bases incluyen hidróxido de sodio, hidróxido de potasio, hidróxido de colina, carbonato de sodio, $N^+(C_{1-4}$ alquilo$)_4$, y semejantes. Otras aminas orgánicas representativas de utilidad para la formación de sales de adición básica incluyen dietilamina, etilendiamina, etanolamina, dietanolamina, piperazina y semejantes. Se deberá comprender que los compuestos que se describen en la presente también incluyen la cuaternización de cualquier grupo que contiene nitrógeno básico que pudieran contener. Dicha cuaternización permite obtener productos solubles o dispersables en agua o aceite. Véase, por ejemplo, Berge *et al.*, *supra*. Estas sales se pueden preparar *in situ* durante el aislamiento y la purificación finales de los compuestos de la invención, o haciendo reaccionar por separado un compuesto purificado en su forma de base libre con un ácido orgánico o inorgánico adecuado, y aislando la sal así formada.

Los términos "mejorar" o "mejora", según se usa en la presente, significa incrementar o prolongar ya sea la potencia o duración de un efecto deseado. Por consiguiente, con respecto a la mejora del efecto de agentes terapéuticos, el término "mejora" se refiere a la capacidad para incrementar o prolongar, ya sea en cuanto a potencia o duración, el efecto de otros agentes terapéuticos sobre un sistema. Una "cantidad eficaz para lograr una mejora", según

se usa en la presente, se refiere a una cantidad adecuada para mejorar el efecto de otro agente terapéutico en un sistema deseado.

Los términos "combinación farmacéutica", "administrar una terapia adicional", "administrar un agente terapéutico adicional" y semejantes, según se usan en la presente, se refieren a una terapia farmacéutica que es el resultado del mezclado o la combinación de más de un ingrediente activo e incluye tanto combinaciones fijas como no fijas de los ingredientes activos. El término "combinación fija" significa que al menos uno de los compuestos descritos en la presente, y al menos un co-agente, se administran a un paciente simultáneamente en la forma de una sola entidad o dosificación. El término "combinación no fija" significa que al menos uno de los compuestos descritos en la presente, y al menos un co-agente, se administras a un paciente como entidades separadas ya sea de forma simultánea, concurrente o sucesiva, con límites de tiempo de intervención variables, en donde dicha administración provee niveles efectivos de dichos dos o más compuestos en el cuerpo del paciente. También se aplica a las terapias de cócteles como por ejemplo la administración de tres o más ingredientes activos.

Los términos "co-administración", "administrado en combinación con" y sus equivalentes gramaticales o

semejantes, según se usan en la presente, abarcan la administración de los agentes terapéuticos seleccionados a un solo paciente, y pretenden incluir regímenes de tratamiento en donde los agentes se administran por la misma ruta de administración o por una ruta diferente o al mismo tiempo o en tiempos diferentes. En algunas formas de realización los compuestos que se describen en la presente serán co-administrados con otros agentes. Estos términos abarcan la administración de dos o más agentes a un animal de modo que ambos agentes y/o sus metabolitos están presentes en el animal al mismo tiempo. Incluyen la administración simultánea en composiciones separadas, la administración en tiempos diferentes en composiciones separadas y/o la administración en una composición en la cual ambos agentes están presentes. Por consiguiente, en algunas formas de realización, los compuestos de la invención y el o los otros agentes se administran en una sola composición. En algunas formas de realización, los compuestos de la invención y el o los otros agentes se mezclan en la composición.

El término "metabolito", según se usa en la presente, se refiere a un derivado de un compuesto que se forma cuando el compuesto es metabolizado.

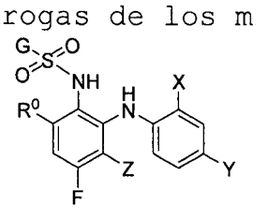
El término "metabolito activo", según se usa en la presente, se refiere a un derivado biológicamente activo de

un compuesto que se forma cuando el compuesto es metabolizado.

El término "metabolizado", según se usa en la presente, se refiere a la suma de los procesos (incluyendo, pero en un sentido no limitativo, reacciones de hidrólisis y reacciones catalizadas por enzimas) por los cuales una sustancia particular es cambiado por un organismo. Así, las enzimas pueden producir alteraciones estructurales específicas en un compuesto. Por ejemplo, el citocromo P450 cataliza una variedad de reacciones oxidantes y reductoras en tanto las uridina difosfato glucuroniltransferasas catalizan la transferencia de una molécula activada de ácido glucurónico en alcoholes aromáticos, alcoholes alifáticos, ácidos carboxílicos, aminas y grupos sulfhidrilo libres. Se puede consultar información adicional sobre metabolismo en *The Pharmacological Basis of Therapeutics*, 9a edición, McGraw-Hill (1996).

***Compuestos***

Se describen aquí compuestos de fórmula I, y sales aceptables farmacéuticamente, solvatos, polimorfos, ésteres, amidas, tautómeros o prodrogas de los mismos:




fórmula I

donde

Z es H o F;

X es F, Cl, $CH_3$, $CH_2OH$, $CH_2F$, $CHF_2$, o $CF_3$;

Y es I, Br, Cl, $CF_3$, $C_1$-$C_3$ alquilo, $C_2$-$C_3$ alquenilo, $C_2$-$C_3$ alquinilo, ciclopropilo, OMe, OEt, SMe, fenilo o Het, donde Het es un grupo heterocíclico mono o bicíclico de 5 a 10 miembros, el cual es saturado, olefínico o aromático, que contiene 1-5 heteroátomos en el anillo seleccionados en forma independiente entre N, O, y S; donde

todos dichos grupos fenilo o Het están opcionalmente sustituidos con F, Cl, Br, I, acetilo, metilo, CN, $NO_2$, $CO_2H$, $C_1$-$C_3$ alquilo, $C_1$-$C_3$ alcoxi, $C_1$-$C_3$ alquil-C(=O)-, $C_1$-$C_3$ alquil-C(=S)-, $C_1$-$C_3$ alcoxi-C(=S)-, $C_1$-$C_3$ alquil-C(=O)O-, $C_1$-$C_3$ alquil-O-(C=O)-, $C_1$-$C_3$ alquil-C(=O)NH-, $C_1$-$C_3$ alquil-C(=NH)NH-, $C_1$-$C_3$ alquil-NH-(C=O)-, di-$C_1$-$C_3$ alquil-N-(C=O)-, $C_1$-$C_3$ alquil-C(=O)N($C_1$-$C_3$ alquil)-, $C_1$-$C_3$ alquil-$S(=O)_2NH$- o trifluorometilo;

todos dichos grupos metilo, etilo, $C_1$-$C_3$ alquilo, y ciclopropilo están opcionalmente sustituidos con OH;

todos dichos grupos metilo están opcionalmente sustituidos con uno, dos o tres átomos de F;

$R^0$ es H, F, Cl, Br, I, $CH_3NH$-, $(CH_3)_2N$-, $C_1$-$C_6$ alquilo, $C_1$-$C_4$ alcoxi, $C_3$-$C_6$ cicloalquilo, $C_2$-$C_6$ alquenilo, $C_2$-$C_6$

alquinilo, fenilo, fenilo monosustituido, O($C_1$-$C_4$ alquilo),
O-C(=O)($C_1$-$C_4$ alquilo) o C(=O)O($C_1$-$C_4$ alquilo); donde

dichos grupos alquilo, alcoxi, cicloalquilo, alquenilo, alquinilo y fenilo están opcionalmente sustituidos con 1-3 sustituyentes seleccionados en forma independiente entre F, Cl, Br, I, OH, CN, cianometilo, nitro, fenilo y trifluorometilo;

dichos grupos $C_1$-$C_6$ alquilo y $C_1$-$C_4$ alcoxi también están opcionalmente sustituidos con $OCH_3$ o $OCH_2CH_3$;

G es $G_1$, $G_2$, $R_{1a}$, $R_{1b}$, $R_{1c}$, $R_{1d}$, $R_{1e}$, $Ar_1$, $Ar_2$ o $Ar_3$; donde

$G_1$ es $C_1$-$C_6$ alquilo opcionalmente sustituido con un grupo amino, $C_1$-$C_3$ alquilamino, o dialquilamino, dicho grupo dialquilamino comprende dos grupos $C_1$-$C_4$ alquilo los cuales pueden ser idénticos o no idénticos; o

$G_1$ es un grupo $C_3$-$C_8$ diaminoalquilo;

$G_2$ es un anillo de 5 o 6 miembros, el cual es saturado, no saturado o aromático, que contiene 1-3 heteroátomos en el anillo seleccionados en forma independiente entre N, O, y S, opcionalmente sustituidos con 1-3 sustituyentes seleccionados en forma independiente entre F, Cl, OH, O($C_1$-$C_3$ alquilo), $OCH_3$, $OCH_2CH_3$, $CH_3C(=O)NH$, $CH_3C(=O)O$, CN, $CF_3$, y un grupo heterocíclico aromático de 5 miembros que contiene 1-4 heteroátomos en el anillo seleccionados en forma

independiente entre N, O , y S;

$R_{1a}$ es metilo, opcionalmente sustituido con 1-3 átomos de flúor o 1-3 átomos de cloro, o con OH, ciclopropoxi, o $C_1$- $C_3$ alcoxi, donde dicho grupo ciclopropoxi o las unidades $C_1$-$C_3$ alquilo de dichos grupos $C_1$-$C_3$ alcoxi están opcionalmente sustituidos con un grupo hidroxi o metoxi, y donde todos los grupos $C_3$-alquilo dentro de dicho $C_1$- $C_4$ alcoxi están opcionalmente sustituidos adicionalmente con un segundo grupo OH;

$R_{1b}$ es $CH(CH_3)$-$C_{1-3}$ alquilo o $C_3$-$C_6$ cicloalquilo, dichos grupos alquilo y cicloalquilo opcionalmente sustituido con 1-3 sustituyentes seleccionados en forma independiente entre F, Cl, Br, I, OH, $OCH_3$, y CN;

$R_{1c}$ es $(CH_2)_nO_mR'$; donde

m es 0 o 1; y donde

cuando m es 0, n es 1 o 2;

cuando m es 1, n es 2 o 3;

R' es $C_1$-$C_6$ alquilo, opcionalmente sustituido con 1-3 sustituyentes seleccionados en forma independiente entre F, Cl, OH, $OCH_3$, $OCH_2CH_3$, y $C_3$-$C_6$ cicloalquilo;

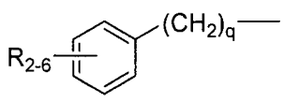
$R_{1d}$ es C(A)(A')(B)-; donde

B es H o $C_{1-4}$ alquilo, opcionalmente sustituido con uno o dos grupos OH;

A y A' son en forma independiente H o $C_{1-4}$ alquilo, opcionalmente sustituido con uno o dos grupos OH; o

A y A', junto con el átomo de carbono al cual se encuentran unidos, forman un anillo saturado de 3 a 6 miembros;

$R_{1e}$ es




**$R_{1e}$**

donde

q es 1 o 2;

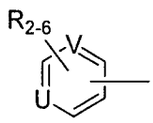
$R_2$ y $R_3$ son en forma independiente entre sí, H, F, Cl, Br, $CH_3$, $CH_2F$, $CHF_2$, $CF_3$ $OCH_3$, $OCH_2F$, $OCHF_2$, $OCF_3$, etilo, *n*-propilo, isopropilo, ciclopropilo, isobutilo, *sec*-butilo, *tert*-butilo o metilsulfonilo;

$R_4$ es H, F, Cl, Br, $CH_3$, $CH_2F$, $CHF_2$, $CF_3$ $OCH_3$, $OCH_2F$, $OCHF_2$, $OCF_3$, etilo, *n*-propilo, isopropilo, ciclopropilo, isobutilo, *sec*-butilo, *tert*-butilo, metilsulfonilo, nitro, acetamido, amidinilo, ciano, carbamoilo, metilcarbamoilo, dimetilcarbamoilo, 1,3,4-oxadiazol-2-ilo, 5-metil-1,3,4- oxadiazol, 1,3,4-tiadiazol, 5-metil-1,3,4-tiadiazol 1H-tetrazolilo, N-morfolilo carbonilo amino, N-morfolilsulfonilo y N-pirrolidinilcarbonilamino;

$R_5$ es H, F, Cl o metilo;

$R_6$ es H, F, Cl o metilo;

$Ar_1$ es




**$Ar_1$**

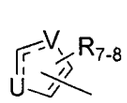
donde

U y V son, en forma independiente, N, $CR_2$ o $CR_3$;

$R_2$, $R_3$ y $R_4$ son, en forma independiente, H, F, Cl, Br, $CH_3$, $CH_2F$, $CHF_2$, $CF_3$ $OCH_3$, $OCH_2F$, $OCHF_2$, $OCF_3$, etilo, *n*-propilo, isopropilo, ciclopropilo, isobutilo, *sec*-butilo, *tert*-butilo, acetamido, amidinilo, ciano, carbamoilo, metilcarbamoilo, dimetilcarbamoilo, 1,3,4-oxadiazol-2-ilo, 5-metil-1,3,4-oxadiazolilo, 1,3,4-tiadiazolilo, 5-metil-1,3,4-tiadiazolilo, 1H-tetrazolilo, N-morfolilcarbonilamino, N-morfolilsulfonilo, N-pirrolidinilcarbonilamino, y metilsulfonilo;

$R_5$ y $R_6$ son, en forma independiente, H, F, Cl o metilo;

$Ar_2$ es




**$Ar_2$**

donde

la línea de guiones representa ubicaciones

formales alternativas para la unión doble del segundo anillo;

U es -S-, -O- o -N =, y donde

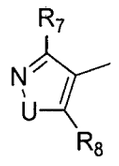
cuando U es -O- o -S-, V es -CH=, -CCl= o -N =;

cuando U es -N =, V es -CH=, -CCl=, o -N=;

$R_7$ es H o metilo;

$R_8$ es H, acetamido, metilo, F o Cl;

$Ar_3$ es




**$Ar_3$**

donde

U es -NH-, $-NCH_3-$ o -O-;

$R_7$ y $R_8$ son, en forma independiente, H, F, Cl, o metilo.

Además de las definiciones que se dan aquí para los grupos G, $R^0$, X, Y y Z, se incluyen sustituciones adicionales que pueden ser contempladas por aquellos versados en el arte químico y farmacéutico.

En algunas formas de realización, la invención provee un compuesto de fórmula I, donde G es $G_1$ o $G_2$. En otras realizaciones, G es $G_1$. En formas de realización adicionales, G es $G_2$.

En algunas formas de realización, la invención provee un compuesto de fórmula I, donde G es $R_{1a}$, $R_{1b}$, $R_{1c}$, $R_{1d}$, $R_{1e}$, $Ar_1$, $Ar_2$ o $Ar_3$. En formas de realización adicionales, G es $R_{1a}$, $R_{1b}$, $R_{1c}$, $R_{1d}$ o $R_{1e}$. En formas de realización adicionales, G es $R_{1a}$. En formas de realización adicionales, G es $R_{1b}$. En formas de realización adicionales, G es $R_{1c}$. En formas de realización adicionales, G es $R_{1d}$. En formas de realización adicionales, G es $R_{1e}$. En formas de realización adicionales, G es $Ar_1$, $Ar_2$ o $Ar_3$. En formas de realización adicionales, G es $Ar_1$. En formas de realización adicionales, G es $Ar_2$. En formas de realización adicionales, G es $Ar_3$

En algunas formas de realización se proveen compuestos de fórmula I, o sus sales aceptables farmacéuticamente. En formas de realización adicionales, se proveen aquí compuestos de fórmula I, o sus solvatos. En formas de realización adicionales, se proveen aquí compuestos de fórmula I o sus polimorfos. En formas de realización adicionales, se proveen aquí compuestos de fórmula I, o sus ésteres. En formas de realización adicionales, se proveen aquí compuestos de fórmula I, o sus amidas. En formas de realización adicionales, se proveen aquí compuestos de fórmula I o sus tautómeros. En formas de realización adicionales, se proveen aquí compuestos de fórmula I o sus prodrogas.

En algunas formas de realización, Z es H. En algunas

formas de realización, Z es F. En algunas formas de realización, X es F. En algunas formas de realización, X es Cl. En algunas formas de realización, X es $CH_3$. En algunas formas de realización, X es $CH_2OH$. En algunas formas de realización, X es $CH_2F$. En algunas formas de realización, X es $CHF_2$. En algunas formas de realización, X es $CF_3$. En algunas formas de realización, X es F, Cl, o $CH_3$.

En algunas formas de realización, G es $G_1$ o $G_2$, X es F, Cl, o $CH_3$; Y es I, Br, Cl, $CF_3$, $C_1$-$C_3$ alquilo, fenilo, piridilo, pirrolilo, pirazolilo, dichos grupos fenilo, piridilo, pirrolilo y pirazolilo están opcionalmente sustituidos con F, Cl, Br, I, acetilo, metilo, CN, $NO_2$, $CO_2H$, $C_1$-$C_3$ alquilo, $C_1$-$C_3$ alcoxi, $C_1$-$C_3$ alquil-C(=O)-, $C_1$-$C_3$ alquil-C(=S)-, $C_1$-$C_3$ alcoxi-C(=S)-, $C_1$-$C_3$ alquil-C(=O)O-, $C_1$-$C_3$ alquil-0-(C=O)-, $C_1$-$C_3$ alquil-C(=O)NH-, $C_1$-$C_3$ alquil-C(=NH)NH-, $C_1$-$C_3$ alquil-NH-(C=O)-, di-$C_1$-$C_3$ alquil-N-(C=O)-, $C_1$-$C_3$ alquil-C(=O)N($C_1$-$C_3$ alquil)-, $C_1$-$C_3$ alquil-$S(=O)_2NH$- o trifluorometilo; y Z es H o F. En formas de realización adicionales, G es $G_1$ o $G_2$, y $R^0$ es F, Cl, $C_1$-$C_4$ alquilo o $C_1$-$C_4$ alcoxi, dicho grupo $C_1$-$C_4$ alquilo y la porción $C_1$-$C_4$ alquilo de dicho grupo $C_1$-$C_4$ alcoxi están opcionalmente sustituidos con F, Cl, $OCH_3$, o $OCH_2CH_3$. En formas de realización adicionales, G es $G_1$ o $G_2$, y $R^0$ es H, F, Cl, $C_1$-$C_4$ alquilo, metoxi, etoxi, o 2-metoxi-etoxi.

En algunas formas de realización, $G_1$ es N-metil-2-

aminoetilo. En formas de realización adicionales, $G_1$ es $(CH_3)_2N-CH_2CH_2-NH-(CH_2)_n-$, donde n es 1, 2, o 3. En formas de realización adicionales, $G_1$is $(CH_3)_2N-CH_2CH_2-NH-(CH_2)_n-$, donde n es 1, 2, o 3, y X es F. En formas de realización adicionales, $G_1$is $(CH_3)_2N-CH_2CH_2-NH-(CH_2)_n-$, donde n es 1, 2, o 3, X es F y Z es F.

En algunas formas de realización, $G_2$ es 1-piperidilo, 2-piperidilo, 3-piperidilo, o 4-piperidilo. En formas de realización adicionales, $G_2$ es morfolilo, 1-piperazilo, o 2-piperazilo.

En algunas formas de realización, G es $R_{1a}$, $R_{1b}$, $R_{1c}$, $R_{1d}$, $R_{1e}$, $Ar_1$, $Ar_2$ o $Ar_3$ y X es F, Cl, o $CH_3$. En formas de realización adicionales, G es $R_{1a}$, $R_{1b}$, $R_{1c}$, $R_{1d}$, $R_{1e}$, $Ar_1$, $Ar_2$ o $Ar_3$, X es F, Cl, o $CH_3$ e Y es I, Br, Cl, $CF_3$, o $C_1$-$C_3$ alquilo En formas de realización adicionales, G es $R_{1a}$, $R_{1b}$, $R_{1c}$, $R_{1d}$, $R_{1e}$, $Ar_1$, $Ar_2$ o $Ar_3$, X es F, Cl, o $CH_3$, Y es I, Br, Cl, $CF_3$, o $C_1$-$C_3$ alquilo y Z es H o F

En formas de realización adicionales, G es $R_{1a}$, $R_{1b}$, $R_{1c}$, $R_{1d}$, $R_{1e}$, $Ar_1$, $Ar_2$ o $Ar_3$ y $R^0$ es F, Cl, $C_1$-$C_4$ alquilo o $C_1$-$C_4$ alcoxi, dicho grupo $C_1$-$C_4$ alquilo y la porción $C_1$-$C_4$ alquilo de dicho grupo $C_1$-$C_4$ alcoxi están opcionalmente sustituidos con F, Cl, $OCH_3$, o $OCH_2CH_3$. En formas de realización adicionales, G es $R_{1a}$, $R_{1b}$, $R_{1c}$, $R_{1d}$, $R_{1e}$, $Ar_1$, $Ar_2$ o $Ar_3$ y $R^0$ es H, F, Cl, $C_1$-$C_4$ alquilo, metoxi, etoxi, o 2- metoxi-etoxi.

En algunas formas de realización, G es $R_{1a}$; y Z es F. En formas de realización adicionales, G es $R_{1a}$ donde $R_{1a}$ es $CH_3$, $R^0$ es H; e Y es Br, I, $CF_3$, o $CH_3$.En algunas formas de realización, G es $R_{1b}$ y Z es F. En formas de realización adicionales, G es $R_{1b}$, Z es F, y $R^0$ es H, F, o $OCH_3$. En formas de realización adicionales, G es $R_{1b}$, Z es F, $R^0$ es H, F, o $OCH_3$, y X es F o $CH_3$. En formas de realización adicionales, G es $R_{1b}$, Z es F, $R^0$ es H, F, o $OCH_3$, X es F o $CH_3$ e Y es Br, I o $CH_3$. En formas de realización adicionales, G es $R_{1b}$ donde $R_{1b}$ es $C_3$-$C_6$ cicloalquilo. En formas de realización adicionales, G es $R_{1b}$ donde $R_{1b}$ es $C_3$-$C_6$ cicloalquilo sustituido. En formas de realización adicionales, G es $R_{1b}$ donde $R_{1b}$ es $C_3$-$C_6$ cicloalquilo no sustituido. En formas de realización adicionales, G es $R_{1b}$ donde $R_{1b}$ es $C_3$-$C_6$ cicloalquilo no sustituido y $R^0$ es H. En formas de realización adicionales, G es $R_{1b}$ donde $R_{1b}$ es isopropilo o ciclopropilo.

En algunas formas de realización, G es $R_{1c}$, e Y es I, Br, $CH_3$, o $CF_3$. En formas de realización adicionales, G es $R_{1c}$, Y es I, Br, $CH_3$, o $CF_3$, y Z es F. En formas de realización adicionales, G es $R_{1c}$, Y es I, Br, $CH_3$, o $CF_3$, Z es F y m es cero.

En algunas formas de realización, G es $R_{1d}$ y $R^0$ es fluoro, cloro, metilo, etilo, propilo, isopropilo, *sec*-butilo, *iso*-butilo, *tert*-butilo, ciclopropilo, ciclobutilo,

fluorometilo, metoxi, fluorometoxi, metilamino o dimetilamino. En formas de realización adicionales, G es $R_{1d}$, $R^0$ es fluoro, cloro, metilo, etilo, propilo, isopropilo, *sec*-butilo, *iso*-butilo, *tert*-butilo, ciclopropilo, ciclobutilo, fluorometilo, metoxi, fluorometoxi, metilamino o dimetilamino y X es F, Cl, $CH_3$, o mono-, di- o trifluorometilo. En formas de realización adicionales, G es $R_{1d}$, $R^0$ es fluoro, cloro, metilo, etilo, propilo, isopropilo, *sec*-butilo, *iso*-butilo, *tert*-butilo, ciclopropilo, ciclobutilo, fluorometilo, metoxi, fluorometoxi, metilamino o dimetilamino, X es F, Cl, $CH_3$, o mono-, di- o trifluorometilo e Y es I, Br, Cl, o mono-, di- o trifluorometilo. En formas de realización adicionales, G es $R_{1d}$, $R^0$ es fluoro, cloro, metilo, etilo, propilo, isopropilo, *sec*-butilo, *iso*-butilo, *tert*-butilo, ciclopropilo, ciclobutilo, fluorometilo, metoxi, fluorometoxi, metilamino o dimetilamino, X es F, Cl, $CH_3$, o mono-, di- o trifluorometilo, Y es I, Br, Cl, o mono-, di- o trifluorometilo y Z es H o F. En formas de realización adicionales, G es $R_{1d}$ y $R^0$ es F, Cl, metilo, etilo, metoxi, etoxi, o 2- metoxi-etoxi.

En formas de realización adicionales, G es $R_{1d}$, $R^0$ es F, Cl, metilo, etilo, metoxi, etoxi, o 2- metoxi-etoxi y X es F, Cl, o $CH_3$. En formas de realización adicionales, G es $R_{1d}$, $R^0$ es F, Cl, metilo, etilo, metoxi, etoxi, o 2- metoxi-

etoxi, X es F, Cl, o $CH_3$ e Y es I, Br, Cl, o mono-, di- o tri- fluorometilo. En formas de realización adicionales, G es $R_{1d}$, $R^0$ es F, Cl, metilo, etilo, metoxi, etoxi, o 2-metoxi-etoxi, X es F, Cl, o $CH_3$, Y es I, Br, Cl, o mono-, di- o tri- fluorometilo y Z es H o F. En formas de realización adicionales, G es $R_{1d}$ y $R^0$ es H; X es F, Cl, $CH_3$, o mono-, di- o tri- fluorometilo. En formas de realización adicionales, G es $R_{1d}$, $R^0$ es H; X es F, Cl, $CH_3$, o mono-, di- o tri- fluorometilo e Y es I, Br, Cl, o mono-, di- o tri-fluorometilo. En formas de realización adicionales, G es $R_{1d}$, $R^0$ es H; X es F, Cl, $CH_3$, o mono-, di- o tri-fluorometilo, Y es I, Br, Cl, o mono-, di- o tri-fluorometilo y Z es H o F.

En formas de realización adicionales, G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es $C_1$-$C_6$ cicloalquilo. En formas de realización adicionales, G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es $C_1$-$C_6$ cicloalquilo y B es H. En formas de realización adicionales, G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es $C_1$-$C_6$ cicloalquilo y B es metilo, etilo, 2-hidroxietilo, *n*-propilo, 3- hidroxipropilo, 2,3-dihidroxipropilo, 3,4-dihidroxibutilo, isopropilo, 1-metil-2-hidroxi etilo, n-butilo, sec-butilo, isobutilo, o 2-hidroximetil-3-hidroxi propilo.

En formas de realización adicionales, G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es $C_1$-$C_6$ cicloalquilo y B es 2,3-dihidroxipropilo o 3,4-dihidroxibutilo. En formas de

realización adicionales, G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es $C_1$-$C_6$ cicloalquilo y B es 2,3-dihidroxipropilo o 3,4-dihidroxibutilo, en el cual el carbono quiral en B es de configuración R. En formas de realización adicionales, G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es $C_1$-$C_6$ cicloalquilo y B es 2,3-dihidroxipropilo o 3,4-dihidroxibutilo, en el cual el carbono quiral en B es de configuración S. En formas de realización adicionales, G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es $C_1$-$C_6$ cicloalquilo y B es metilo, opcionalmente sustituido con un grupo OH, o $C_2$-$C_4$ alquilo, opcionalmente sustituido con uno o dos grupos OH. En formas de realización adicionales, G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es $C_1$-$C_6$ cicloalquilo y $R^0$ es fluoro, cloro, metilo, etilo, propilo, isopropilo, *sec*-butilo, *iso*-butilo, *tert*-butilo, ciclopropilo, ciclobutilo, fluorometilo, metoxi, fluorometoxi, metilamino o dimetilamino. En formas de realización adicionales, G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es $C_1$-$C_6$ cicloalquilo y $R^0$ es F, Cl, metilo, etilo, metoxi, etoxi, o 2- metoxi-etoxi. En formas de realización adicionales, G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es $C_1$-$C_6$ cicloalquilo y $R^0$ es H; X es F, Cl, $CH_3$, o mono-, di- o tri-fluorometilo.

En formas de realización adicionales, la invención provee una composición que comprende un compuesto de fórmula I, donde G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es $C_1$-$C_6$ cicloalquilo

y B es 2,3-dihidroxipropilo o 3,4-dihidroxibutilo, en el cual el carbono quiral en B es de configuración R, el cual se encuentra sustancialmente libre del isómero S. En formas de realización adicionales, la invención provee una composición que comprende un compuesto de fórmula I, donde G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es $C_1$-$C_6$ cicloalquilo y B es 2,3-dihidroxipropilo, en el cual el carbono quiral en B es de configuración R, el cual se encuentra sustancialmente libre del isómero S. En formas de realización adicionales, la invención provee una composición que comprende un compuesto de fórmula I, donde G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es $C_1$-$C_6$ cicloalquilo y B es 3,4-dihidroxibutilo, en el cual el carbono quiral en B es de configuración R, el cual se encuentra sustancialmente libre del isómero S. En formas de realización adicionales, la invención provee una composición que comprende un compuesto de fórmula I, donde G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es $C_1$-$C_6$ cicloalquilo y B es 2,3-dihidroxipropilo o 3,4-dihidroxibutilo, en el cual el carbono quiral en B es de configuración S, el cual se encuentra sustancialmente libre del isómero R. En formas de realización adicionales, la invención provee una composición que comprende un compuesto de fórmula I, donde G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es $C_1$-$C_6$ cicloalquilo y B es 2,3-dihidroxipropilo, en el cual el carbono quiral en B es de configuración S, el cual se encuentra sustancialmente libre

del isómero R. En formas de realización adicionales, la invención provee una composición que comprende un compuesto de fórmula I, donde G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es $C_1$-$C_6$ cicloalquilo y B es 3,4-dihidroxibutilo, en el cual el carbono quiral en B es de configuración S, el cual se encuentra sustancialmente libre del isómero R.

En formas de realización adicionales, G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es ciclopropilo. En formas de realización adicionales, G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es ciclopropilo y B es H. En formas de realización adicionales, G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es ciclopropilo y B es metilo, etilo, 2-hidroxietilo, *n*-propilo, 3- hidroxipropilo, 2,3-dihidroxipropilo, 3,4-dihidroxibutilo, isopropilo, 1-metil-2-hidroxi etilo, n-butilo, sec-butilo, isobutilo, o 2-hidroximetil-3-hidroxi propilo. En formas de realización adicionales, G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es ciclopropilo y B es 2,3-dihidroxipropilo o 3,4-dihidroxibutilo. En formas de realización adicionales, G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es ciclopropilo y B es 2,3-dihidroxipropilo o 3,4-dihidroxibutilo, en el cual el carbono quiral en B es de configuración R. En formas de realización adicionales, G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es ciclopropilo y B es 2,3-dihidroxipropilo o 3,4-dihidroxibutilo, en el cual el carbono quiral en B es de configuración S. En formas de realización adicionales, G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es

ciclopropilo y B es metilo, opcionalmente sustituido con un grupo OH, o $C_2$-$C_4$ alquilo, opcionalmente sustituido con uno o dos grupos OH. En formas de realización adicionales, G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es ciclopropilo y $R^0$ es fluoro, cloro, metilo, etilo, propilo, isopropilo, *sec*-butilo, *iso*-butilo, *tert*-butilo, ciclopropilo, ciclobutilo, fluorometilo, metoxi, fluorometoxi, metilamino o dimetilamino. En formas de realización adicionales, G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es ciclopropilo y $R^0$ es F, Cl, metilo, etilo, metoxi, etoxi, o 2- metoxi-etoxi. En formas de realización adicionales, G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es ciclopropilo y $R^0$ es H; X es F, Cl, $CH_3$, o mono-, di- o tri-fluorometilo.

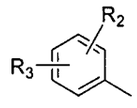
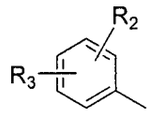
En formas de realización adicionales, la invención provee una composición que comprende un compuesto de fórmula I, donde G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es ciclopropilo y B es 2,3-dihidroxipropilo o 3,4-dihidroxibutilo, en el cual el carbono quiral en B es de configuración R, el cual se encuentra sustancialmente libre del isómero S. En formas de realización adicionales, la invención provee una composición que comprende un compuesto de fórmula I, donde G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es ciclopropilo y B es 2,3-dihidroxipropilo, en el cual el carbono quiral en B es de configuración R, el cual se encuentra sustancialmente libre del isómero S. En formas de realización adicionales, la

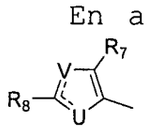
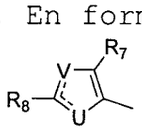
invención provee una composición que comprende un compuesto de fórmula I, donde G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es ciclopropilo y B es 3,4-dihidroxibutilo, en el cual el carbono quiral en B es de configuración R, el cual se encuentra sustancialmente libre del isómero S. En formas de realización adicionales, la invención provee una composición que comprende un compuesto de fórmula I, donde G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es ciclopropilo y B es 2,3-dihidroxipropilo o 3,4-dihidroxibutilo, en el cual el carbono quiral en B es de configuración S, el cual se encuentra sustancialmente libre del isómero R. En formas de realización adicionales, la invención provee una composición que comprende un compuesto de fórmula I, donde G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es ciclopropilo y B es 2,3-dihidroxipropilo, en el cual el carbono quiral en B es de configuración S, el cual se encuentra sustancialmente libre del isómero R. En formas de realización adicionales, la invención provee una composición que comprende un compuesto de fórmula I, donde G es $R_{1d}$ donde $R_{1d}$ es C(A)(A') es ciclopropilo y B es 3,4-dihidroxibutilo, en el cual el carbono quiral en B es de configuración S, el cual se encuentra sustancialmente libre del isómero R.

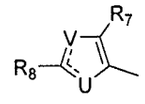
En algunas formas de realización, G es $R_{1e}$ y n es 1. En formas de realización adicionales, G es $R_{1e}$, $R^0$ es H, $R_{4-6}$ son H, $R_2$ y $R_3$ son, en forma independiente, H, F, Cl, Br, $CH_3$,

$CH_2F$, $CHF_2$, $CF_3$, O $CH_3$, $OCH_2F$, $OCHF_2$, $OCF_3$, etilo, *n*-propilo, isopropilo, ciclopropilo, isobutilo, *sec*-butilo, *tert*-butilo, y metilsulfonilo, X es F e Y es I.

En algunas formas de realización, G es $Ar_1$ donde $Ar_1$ es fenilo opcionalmente sustituido con un grupo seleccionado entre acetamido, amidinilo, ciano, carbamoilo, metilcarbamoilo, dimetilcarbamoilo, 1,3,4-oxadiazol-2-ilo, 5-metil-1,3,4-oxadiazolilo, 1,3,4-tiadiazolilo, 5 -metil-1,3,4- tiadiazolilo, 1H-tetrazolilo, N-morfolilcarbonilamino, N-morfolilsulfonilo, N-pirrolidinilcarbonilamino, y metilsulfonilo, opcionalmente sustituido con 1-3 sustituyentes seleccionados en forma independiente entre F, Cl, y $CH_3$. En formas de realización adicionales, G es $Ar_1$ donde $Ar_1$ es fenilo opcionalmente sustituido con un grupo seleccionado entre acetamido, amidinilo, ciano, carbamoilo, metilcarbamoilo, dimetilcarbamoilo, 1,3,4-oxadiazol-2-ilo, 5-metil-1,3,4-oxadiazolilo, 1,3,4-tiadiazolilo, 5 -metil- 1,3,4-tiadiazolilo, 1H-tetrazolilo, N-morfolilcarbonilamino, N-morfolilsulfonilo, N- pirrolidinilcarbonilamino, y metilsulfonilo, opcionalmente sustituido con 1-3 sustituyentes seleccionados en forma independiente entre F, Cl, y $CH_3$, $R^0$ es H, X es F, Cl, o metilo e Y es Br, I, $CF_3$, $C_1$-$C_3$ alquilo, $C_2$-$C_3$ alquenilo, $C_2$-$C_3$ alquinilo, ciclopropilo, O $CH_3$, $OCH_2CH_3$ o $SCH_3$. En algunas formas de realización, G es

$Ar_1$ donde $Ar_1$ es  y donde $R_2$ y $R_3$ son, en forma independiente, H, F, Cl, $CH_3$, $CF_3$, $OCH_3$. En formas de realización adicionales, G es $Ar_1$ donde $Ar_1$ es  y donde $R_2$ y $R_3$ son, en forma independiente, H, F, Cl, $CH_3$, $CF_3$, $OCH_3$, X es F o $CH_3$, Y es I, Br, o Cl; y Z es F. En formas de realización adicionales, G es $Ar_1$ donde $Ar_1$ es fenilo o fenilo monosustituido. En formas de realización adicionales, G es $Ar_1$ donde $Ar_1$ es fenilo o fenilo monosustituido, X es F o $CH_3$, Y es I, Br, o Cl, Z es F; y $R^0$ es F, metilo, etilo, metoxi, o 2-metoxi-etoxi. En formas de realización adicionales, G es $Ar_1$ donde U es N o $CR_2$ y V es N. En formas de realización adicionales, G es $Ar_1$ donde U es N o $CR_2$ y V es CR. En formas de realización adicionales, G es $Ar_1$ donde U es N o $CR_2$, V es CR, $R^0$ es H, X es F, Cl, o metilo e Y es Br, I, $CF_3$, $C_1$-$C_3$ alquilo, $C_2$-$C_3$ alquenilo, $C_2$-$C_3$ alquinilo, ciclopropilo, $OCH_3$, $OCH_2CH_3$ o $SCH_3$.

En algunas formas de realización, G es $Ar_2$ donde $Ar_2$ es  donde $R_7$ es H o metilo y $R_8$ es H, acetamido, metilo, F o Cl. En formas de realización adicionales, G es $Ar_2$ donde $Ar_2$ es  donde $R_7$ es H o metilo, $R_8$ es H, acetamido, metilo, F o Cl, $R^0$ es H, X es F, Cl, o metilo, Y es Br, I, $CF_3$, $C_1$-$C_3$ alquilo, $C_2$-$C_3$ alquenilo, $C_2$-$C_3$ alquinilo,

ciclopropilo, $OCH_3$, $OCH_2CH_3$ o $SCH_3$, y Z es F. En formas de realización adicionales, G es $Ar_2$ donde $Ar_2$ es  donde U es S o O, V es CH=, y $R_8$ es H o $CH_3$, $R_7$ es H o metilo, $R_8$ es H, acetamido, metilo, F o Cl, $R^0$ es H, X es F, Cl, o metilo, Y es Br, I, $CF_3$, $C_1$-$C_3$ alquilo, $C_2$-$C_3$ alquenilo, $C_2$-$C_3$ alquinilo, ciclopropilo, $OCH_3$, $OCH_2CH_3$ o $SCH_3$ y Z es F. En formas de realización adicionales, $R^0$ es H. En formas de realización adicionales, $R^0$ es H, X es F o Cl e Y es Br, I, $CH_2CH_3$ o $SCH_3$

En algunas formas de realización, G es $Ar_3$ donde U es -O-.

En formas de realización adicionales, G es $R_{1a}$, donde $R_{1a}$ es como se define precedentemente. En formas de realización adicionales, G es $R_{1a}$, y $R^0$ es H, donde $R_{1a}$ es como se define precedentemente. En formas de realización adicionales, G es $R_{1a}$ y $R^0$ es como se define precedentemente, diferente a H, y $R_{1a}$ es como se define precedentemente. En formas de realización adicionales, G es $R_{1a}$, donde $R_{1a}$ es metilo, monohalometilo, $C_1$-$C_3$ alcoximetilo, o ciclopropoximetilo. En formas de realización adicionales, G es $R_{1a}$, donde $R_{1a}$ es metilo, monohalometilo, $C_1$-$C_3$ alcoximetilo, o ciclopropoxi metilo y donde $R^0$ es F, Cl, $C_1$-$C_3$ alquilo, monocloro $C_1$-$C_3$ alquilo, $C_1$-$C_3$ alcoxi, trifluoro metoxi, o 2-metoxi-etoxi.

En formas de realización adicionales, G es $R_{1b}$, donde $R_{1b}$

es como se define precedentemente. En formas de realización adicionales, G es $R_{1b}$, y $R^0$ es H, donde $R_{1b}$ es como se define precedentemente. En formas de realización adicionales, G es $R_{1b}$, $R^0$ es H y Z es F, donde $R_{1b}$ es como se define precedentemente. En formas de realización adicionales, G es $R_{1b}$ y $R^0$ es como se define precedentemente, diferente a H, y $R_{1b}$ es como se define precedentemente. En formas de realización adicionales, G es $R_{1b}$, donde $R_{1b}$ es isopropilo, 2-butilo, 2-pentilo, ciclopropilo, ciclobutilo, ciclopentilo, o ciclohexilo, todo opcionalmente sustituido con 1 o 2 sustituyentes seleccionados en forma independiente entre F, Cl, OH, y $OCH_3$; Y es Br, I, metilo, o trifluorometilo. En formas de realización adicionales, G es $R_{1b}$, donde $R_{1b}$ es isopropilo, 2-butilo, 2-pentilo, ciclopropilo, ciclobutilo, ciclopentilo, o ciclohexilo, opcionalmente sustituido con 1 o 2 sustituyentes seleccionados en forma independiente entre F, Cl, OH, y $OCH_3$; Y es Br, I, metilo, o trifluorometilo; y $R^0$ es F, Cl, $C_1$-$C_3$ alquilo, monocloro $C_1$-$C_3$ alquilo, $C_1$-$C_3$ alcoxi, trifluorometoxi, o 2-metoxi- etoxi. En formas de realización adicionales, G es $R_{1b}$, donde $R_{1b}$ es isopropilo, 2-butilo, 2-pentilo, ciclopropilo, ciclobutilo, ciclopentilo, o ciclohexilo, todo opcionalmente sustituido con un Cl o con 1 o 2 grupos OH; e Y es Br, I, metilo, o trifluorometilo. En formas de realización adicionales, G es $R_{1b}$, donde $R_{1b}$ es

isopropilo, 2-butilo, 2-pentilo, ciclopropilo, ciclobutilo, ciclopentilo, o ciclohexilo, todo opcionalmente sustituido con un Cl o con 1 o 2 grupos OH; Y es Br, I, metilo, o trifluorometilo; y $R^0$ es F, Cl, $C_1$-$C_3$ alquilo, monocloro $C_1$-$C_3$ alquilo, $C_1$-$C_3$ alcoxi, trifluorometoxi, o 2-metoxi-etoxi.

En formas de realización adicionales, G es $R_{1c}$, donde $R_{1c}$ es como se define precedentemente. En formas de realización adicionales, G es $R_{1c}$, y $R^0$ es H, donde $R_{1c}$ es como se define precedentemente. En formas de realización adicionales, G es $R_{1c}$ y $R^0$ es como se define precedentemente, diferente a H, y $R_{1c}$ es como se define precedentemente. En formas de realización adicionales, G es $R_{1c}$, y $R^0$ es H, donde $R_{1c}$ es $(CH_2)_nO_mR'$, donde m es 0 o 1, n es 2 o 3 cuando m es 1, y n es 1 o 2 cuando m es 0, y R' es $C_1$-$C_6$ alquilo, opcionalmente sustituido con 1-3 sustituyentes seleccionados en forma independiente entre F, Cl, OH, $OCH_3$, $OCH_2CH_3$, y $C_3$-$C_6$ cicloalquilo. En otra forma de realización subgenérica más específica, m es cero, n es 1 o 2, y R' es $C_1$-$C_4$ alquilo, opcionalmente sustituido como se describe precedentemente. En otra forma de realización subgenérica más específica, m es 1, n es 2 o 3, y R' es $C_1$-$C_4$ alquilo, opcionalmente sustituido como se describe precedentemente. En una realización subgenérica aún más específica, m es cero, n es 1 o 2, y R' es $C_1$-$C_4$ alquilo, opcionalmente sustituido con 1 -3 grupos seleccionados entre OH, $OCH_3$, Cl, y ciclopropilo.

En formas de realización adicionales, G es $R_{1d}$, donde $R_{1d}$ es como se define precedentemente. En formas de realización adicionales, G es $R_{1d}$, y $R^0$ es H, donde $R_{1d}$ es como se define precedentemente. En formas de realización adicionales, G es $R_{1d}$ y $R^0$ es como se define precedentemente, diferente a H, y $R_{1d}$ es como se define precedentemente. En formas de realización adicionales, G es $R_{1d}$, y $R^0$ es H, donde $R_{1d}$ es C(A)(A')(B)- donde B, A, y A' son, en forma independiente, H o $C_{1-4}$ alquilo, opcionalmente sustituido con uno o dos grupos OH o átomos de halógeno, o A y $A^1$, junto con el átomo de carbono al cual se encuentran unidos, forman un anillo saturado de 3 a 6 miembros, dicho anillo contiene opcionalmente uno o dos heteroátomos seleccionados, en forma independiente, entre O, N, y S y opcionalmente sustituido con uno o dos grupos seleccionados en forma independiente entre metilo, etilo, fluoro, cloro, bromo y yodo.

En formas de realización adicionales, G es $R_{1e}$, donde $R_{1e}$ es como se define precedentemente. En formas de realización adicionales, G es $R_{1e}$, y $R^0$ es H, donde $R_{1e}$ es como se define precedentemente. En formas de realización adicionales, G es $R_{1e}$ y $R^0$ es como se define precedentemente, diferente a H, y $R_{1e}$ es como se define precedentemente.

En formas de realización adicionales, G es $Ar_1$, donde $Ar_1$ es como se define precedentemente. En formas de realización adicionales, G es $Ar_1$, y $R^0$ es H, donde $Ar_1$ es como se define

precedentemente. En formas de realización adicionales, G es $Ar_1$ y $R^0$ es como se define precedentemente, diferente a H, y $Ar_1$ es como se define precedentemente.

En formas de realización adicionales, G es $Ar_2$, donde $Ar_2$ es como se define precedentemente. En formas de realización adicionales, G es $Ar_2$, y $R^0$ es H, donde $Ar_2$ es como se define precedentemente. En formas de realización adicionales, G es $Ar_2$ y $R^0$ es como se define precedentemente, diferente a H, y $Ar_2$ es como se define precedentemente.

En formas de realización adicionales, X es F, Cl, o $CH_3$; Y es I, Br, Cl, $CF_3$ o $C_1$-$C_3$ alquilo, y Z es H o F. En formas de realización adicionales, X es F, Cl, o $CH_3$: Y es I, Br, Cl, $CF_3$, o $C_1$-$C_3$ alquilo, Z es H o F, y $R^0$ es halógeno, $C_1$-$C_6$ alquilo, monohalo $C_1$-$C_6$ alquilo, $C_3$-$C_6$ cicloalquilo, $C_2$-$C_6$ alquenilo, $C_2$-$C_6$ alquinilo, fenilo, fenilo monosustituido, $OR_3$, $O\text{-}C(=O)R_4$, o $C(=O)OR_5$. En formas de realización adicionales, X es F, Cl, o $CH_3$: Y es I, Br, Cl, $CF_3$, o $C_1$-$C_3$ alquilo, Z es H o F, y $R^0$ es furilo, tienilo, tiazolilo, isotiazolilo, oxazolilo, isoxazolilo, pirrolilo, o pirazolilo. En formas de realización adicionales, X es F, Cl, o $CH_3$: Y es I, Br, Cl, $CF_3$, o $C_1$-$C_3$ alquilo, Z es H o F, y $R^0$ es F, Cl, $C_1$-$C_4$ alquilo, $C_1$-$C_3$ alcoxi, trifluorometoxi, o 2- metoxi-etoxi.

En otra forma de realización subgenérica más específica, $R_{1\,d}$ es cicloalquilo o 1-alquil-cicloalquilo, en el cual el

grupo 1-alquilo se sustituye opcionalmente con uno o dos grupos OH o con uno o dos átomos de halógeno.

En otra forma de realización subgenérica más específica, $R^0$ es halógeno, $C_1$-$C_6$ alquilo, monohalo $C_1$-$C_6$ alquilo, $C_3$-$C_6$ cicloalquilo, $C_2$-$C_6$ alquenilo, $C_2$-$C_6$ alquinilo, fenilo, fenilo monosustituido, $OR_3$, $O$-$C(=O)R_4$, o $C(=O)OR_5$; y $R_{1d}$ es cicloalquilo o 1-alquil-cicloalquilo, en el cual el grupo 1-alquilo se sustituye opcionalmente con uno o dos grupos OH o con uno o dos átomos de halógeno.

En otra forma de realización subgenérica más específica, $R^0$ es furilo, tienilo, tiazolilo, isotiazolilo, oxazolilo, isoxazolilo, pirrolilo, o pirazolilo; y $R_{1d}$ es cicloalquilo o 1-alquil-cicloalquilo, en el cual el grupo 1-alquilo se sustituye opcionalmente con uno o dos grupos OH o uno o dos átomos de halógeno.

En otra forma de realización subgenérica más específica, $R_{1d}$ es cicloalquilo o 1-alquil-cicloalquilo, en el cual el grupo 1-alquilo se sustituye opcionalmente con uno o dos grupos OH, y donde Y es Br, I, metilo, o trifluorometilo. En otra forma de realización subgenérica más específica, $R_{1d}$ es cicloalquilo o 1-alquil-cicloalquilo, en el cual el grupo 1-alquilo se sustituye opcionalmente con uno o dos átomos de flúor o de cloro, y donde Y es Br, I, metilo, o trifluorometilo. En otra forma de realización subgenérica más específica, $R_{1d}$ es cicloalquilo o (1-alquil)-

cicloalquilo, en el cual el grupo 1-alquilo se sustituye opcionalmente con uno o dos grupos OH, y donde $R^{0'}$ es F, Cl, $C_1$-$C_3$ alquilo, monocloro $C_1$-$C_3$ alquilo, $C_1$-$C_3$ alcoxi, trifluorometoxi, o 2-metoxi-etoxi. En otra forma de realización subgenérica más específica, $R_{1d}$ es tetrahidrofurilo, tetrahidrotienilo, pirrolidilo, piperidilo, piperazinilo, o morfolilo, cada uno opcionalmente sustituido como se describe precedentemente, y donde Y es Br, I, metilo, o trifluorometilo. En otra forma de realización subgenérica más específica, $R_{1d}$ es oxazolidinilo, tiazolidinilo, isoxazolidinilo, isotiazolidinilo, tetrahidrofurilo, tetrahidrotienilo, pirrolidilo, piperidilo, piperazinilo, o morfolilo, cada uno opcionalmente sustituido como se describe precedentemente, y donde Y es Br, I, metilo, o trifluorometilo. En otra forma de realización subgenérica más específica, $R_{1d}$ es ciclopropilo o 1-alquil-ciclopropilo, en el cual el grupo 1-alquilo se sustituye opcionalmente con uno o dos grupos OH, y donde $R^{0'}$ es F, Cl, metilo, etilo, clorometilo, $C_1$-$C_2$ alcoxi, trifluorometoxi, o 2-metoxi-etoxi. En una realización aún más específica, $R_{1d}$ es 1-(monohidroxialquilo) cicloalquilo. En otra forma de realización más específica, $R_{1d}$ es 1-(monohidroxialquilo) cicloalquilo, donde $R^{0'}$ es F, Cl, metilo, etilo, clorometilo, $C_1$-$C_2$ alcoxi, trifluorometoxi, o 2-metoxi-

etoxi. En una realización aún más específica, $R_{1d}$ es 1-(dihidroxialquilo) cicloalquilo. En otra forma de realización más específica, $R_{1d}$ es 1-(dihidroxialquilo) cicloalquilo, donde $R^{0'}$ es F, Cl, metilo, etilo, clorometilo, $C_1$-$C_2$ alcoxi, trifluorometoxi, o 2-metoxi-etoxi.

En una realización subgenérica más específica U es $CR_2$ y V es N. En otra forma de realización subgenérica más específica, U y V son ambos N. En una realización subgenérica más específica, U es $CR_2$ y V es $CR_3$.

En una realización subgenérica aún más específica, esta invención provee un compuesto de fórmula I, donde G es $Ar_1$ y $Ar_1$ es fenilo o fenilo monosustituido, $R^0$ es F, metilo, etilo, $C_1$-$C_3$ alcoxi, trifluorometoxi, o 2-metoxi-etoxi; X es F, Cl, o $CH_3$; Y es I; y Z es F. En otra forma de realización subgenérica, esta invención provee un compuesto de fórmula I, donde G es $Ar_1$, donde $Ar_1$ es fenilo o fenilo monosustituido, $R^0$ es halógeno, $C_1$-$C_6$ alquilo, $C_3$-$C_6$ cicloalquilo, $C_2$-$C_6$ alquenilo, $C_2$-$C_6$ alquinilo, todos dichos grupos alquilo, cicloalquilo, alquenilo, y alquinilo están opcionalmente sustituidos con 1-3 sustituyentes seleccionados en forma independiente entre halógeno, OH, CN, cianometilo, nitro, fenilo, y trifluorometilo; o $R^0$ es fenilo, $OR_3$, furilo, tienilo, tiazolilo, isotiazolilo, oxazolilo, isoxazolilo, pirrolilo, o pirazolilo. En una

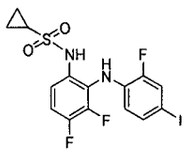
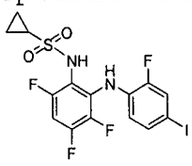
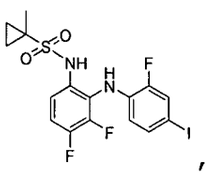
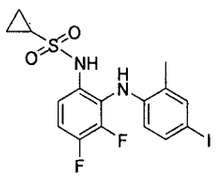
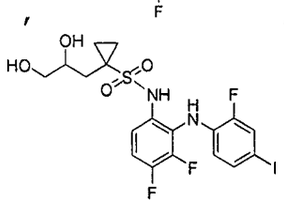
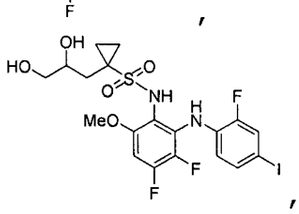
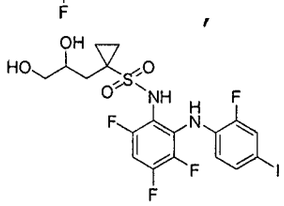
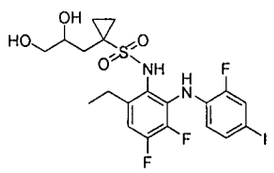
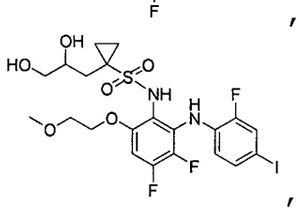
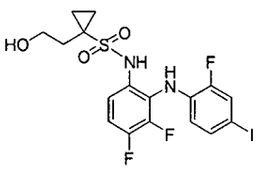
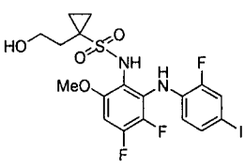
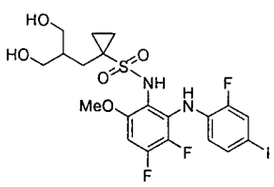
realización subgenérica más específica, esta invención provee un compuesto de fórmula I, donde A es $Ar_1$, donde $Ar_1$ es fenilo o fenilo monosustituido, $R^0$ es F, Cl, $C_1$-$C_3$ alquilo, $C_1$-$C_3$ alcoxi, 2-metoxietoxi, $C_2$-$C_3$ alquenilo, $C_2$-$C_3$ alquinilo, trifluorometilo, fenilo, furilo, o tienilo, tiazolilo, isotiazolilo, oxazolilo, isoxazolilo, pirrolilo, o pirazolilo; X es F, Cl, o metilo; Y es I, Br, Cl, $CF_3$, o $C_1$-$C_3$ alquilo; y Z es F.

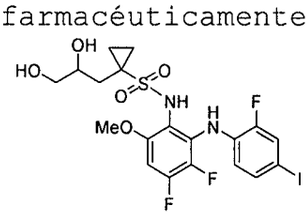
En otra forma de realización subgenérica aún más específica, esta invención provee un compuesto de fórmula I, donde G es $Ar_1$, donde $Ar_1$ es fenilo o fenilo monosustituido, $R^0$ es H; X es F, Cl, o $CH_3$; Y es Br o I; y Z es F.

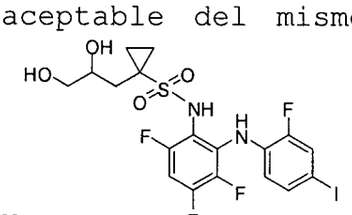
En otra forma de realización subgenérica esta invención provee un compuesto de fórmula I, donde G es $Ar_2$, donde $Ar_2$ es 2-tienilo, 2-furilo, 3 -tienilo, 3 -furilo, 2-pirrolilo, o 3 -pirrolilo, todo opcionalmente sustituido con metoxicarbonilo, metilcarbamoilo, acetamido, acetilo, metilo, etilo, trifluorometilo, o halógeno. En una realización subgenérica más específica esta invención provee un compuesto de fórmula I, donde G es $Ar_2$, donde $Ar_2$ es 2-tienilo, 2-furilo, 3-tienilo, 3-furilo, 2-pirrolilo, o 3-pirrolilo, todo opcionalmente sustituido con metoxicarbonilo, metilcarbamoilo, acetamido, acetilo, metilo, etilo, trifluorometilo, o halógeno; $R^0$ no es H; X es F, Cl, o $CH_3$: Y es I, Br, Cl, $CF_3$, o $C_1$-$C_3$ alquilo, y Z es H

o F. En otra forma de realización subgenérica esta invención provee un compuesto de fórmula I, donde G es $Ar_2$, donde $Ar_2$ es 2-tienilo, 2-furilo, 3-tienilo, 3-furilo, 2-pirrolilo, o 3-pirrolilo, todo opcionalmente sustituido con metoxicarbonilo, metilcarbamoilo, acetamido, acetilo, metilo, etilo, trifluorometilo, o halógeno; $R^0$ es F, Cl, $C_1$-$C_3$ alquilo, monocloro $C_1$-$C_3$ alquilo, $C_1$-$C_3$ alcoxi, trifluorometoxi, metiloxi-metoxi, o 2-metoxi-etoxi; X es F, Cl, o $CH_3$: Y es I, Br, Cl, $CF_3$, o $C_1$-$C_3$ alquilo, y Z es H o F. En otra forma de realización subgenérica esta invención provee un compuesto de fórmula I, donde G es $Ar_2$, donde $Ar_2$ es 2-tienilo, 2-furilo, 3-tienilo, 3-furilo, 2-pirrolilo, o 3-pirrolilo, todo opcionalmente sustituido con metoxicarbonilo, metilcarbamoilo, acetamido, acetilo, metilo, etilo, trifluorometilo, o halógeno; $R^0$ es H; X es F, Cl, o $CH_3$: Y es I, Br, Cl, $CF_3$, o $C_1$-$C_3$ alquilo, y Z es H o F. En otra forma de realización subgenérica esta invención provee un compuesto de fórmula I, donde G es $Ar_2$, donde $Ar_2$ es tiazolilo, isotiazolilo, oxazolilo, isoxazolilo, pirrolilo, o pirazolilo, todo opcionalmente sustituido con metoxicarbonilo, metilcarbamoilo, acetamido, acetilo, metilo, etilo, trifluorometilo, o halógeno; $R^0$ es H o metoxi; X es F, Cl, o $CH_3$: Y es I, Br, Cl, $CF_3$, o $C_1$-$C_3$ alquilo, y Z es H o F.

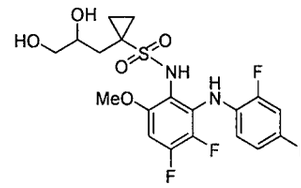
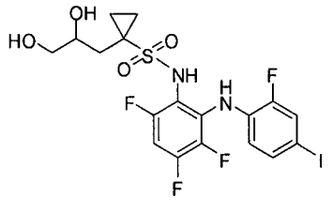
En algunas formas de realización, el compuesto de

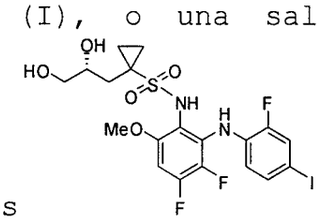
fórmula (I), o una sal farmacéuticamente aceptable del mismo, se selecciona entre  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , y  .

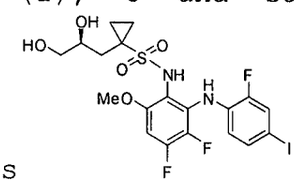
En algunas formas de realización, la invención provee un compuesto de fórmula I, o una sal farmacéuticamente aceptable del mismo, seleccionado entre: 

y  , donde el carbono 2-OH es de configuración R.

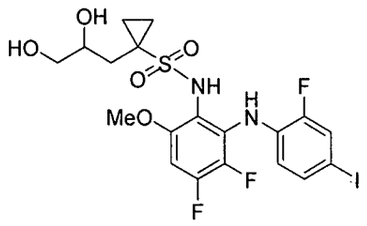
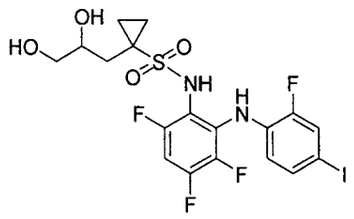
En algunas formas de realización, la invención provee un

compuesto de fórmula I, o una sal farmacéuticamente aceptable del mismo, seleccionado entre:  y  , donde el carbono 2-OH es de configuración S.

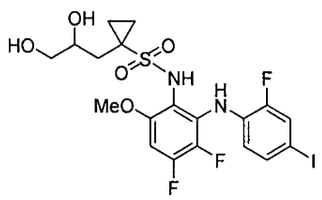
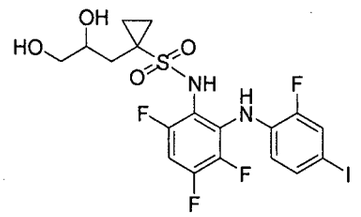
En formas de realización adicionales, el compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, es  .

En formas de realización adicionales, el compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, es  .

En algunas formas de realización, la invención provee una composición que comprende un compuesto de fórmula I, seleccionado entre aquellos que se muestran a continuación, donde el carbono 2-OH es de configuración R, sustancialmente libre del isómero S.

En algunas formas de realización, la invención provee una composición que comprende un compuesto de fórmula I, seleccionado entre aquellos que se muestran a continuación, donde el carbono 2-OH es de configuración S, sustancialmente libre del isómero R.

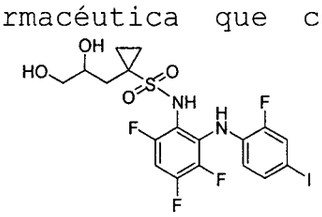
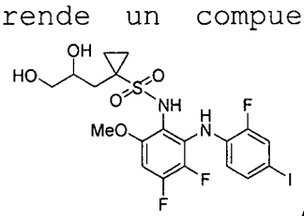



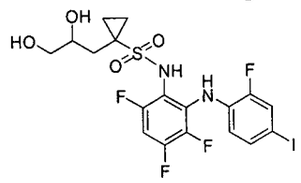
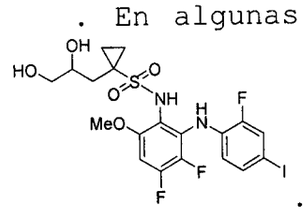
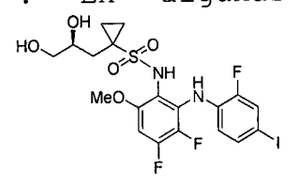
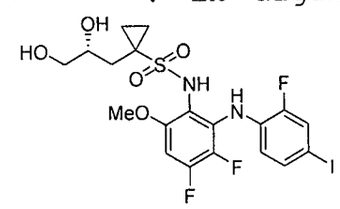
En algunas formas de realización, esta invención provee un compuesto de fórmula I, donde Y es fenilo, piridilo, o pirazolilo. En otra forma de realización subgenérica, esta invención provee un compuesto de fórmula I, donde Y es fenilo, piridilo, o pirazolilo sustituido. En aún otra forma de realización subgenérica, esta invención provee un compuesto de fórmula I, donde Y es Br o I. En una realización subgenérica, esta invención provee un compuesto de fórmula I, donde G es 1-piperidilo, 2-piperidilo, 3-piperidilo, o 4-piperidilo. En otra forma de realización subgenérica, esta invención provee un compuesto de fórmula I, donde G es 1-piperazilo o 2-piperazilo. En otra forma de realización subgenérica, esta invención provee un compuesto

de fórmula I, donde G es morfolilo. En otra forma de realización subgenérica, esta invención provee un compuesto de fórmula I, donde G es N-metil-2-aminoetilo. En una realización subgenérica, esta invención provee un compuesto de fórmula I, donde G es N-metil-3-amino-n-propilo. En otra forma de realización subgenérica, esta invención provee un compuesto de fórmula I, donde G es $(CH_3)_2N-CH_2CH_2-NH-(CH_2)_n-$, donde n es 1, 2, o 3. En otra forma de realización subgenérica, esta invención provee un compuesto de fórmula I, donde G es $(CH_3CH_2)_2N-CH_2CH_2-NH-(CH_2)_n-$, donde n es 1 o 2. En una realización subgenérica más específica, esta invención provee un compuesto de fórmula I, donde G es 1-piperidilo, 2-piperidilo, 3-piperidilo, o 4-piperidilo; $R^o$ es H, halo, o metoxi; X es F; e Y es I. En otra forma de realización subgenérica más específica, esta invención provee un compuesto de fórmula I, donde G es 1-piperazilo o 2-piperazilo; $R^o$ es H, halo, o metoxi; X es F; e Y es I. En otra forma de realización subgenérica más específica, esta invención provee un compuesto de fórmula I, donde G es morfolilo; $R^o$ es H, halo, o metoxi; X es F; e Y es I. En otra forma de realización subgenérica más específica, esta invención provee un compuesto de fórmula I, donde G es N-metil-2-aminoetilo; $R^o$ es H, halo, o metoxi; X es F; e Y es I En otra forma de realización subgenérica más específica, esta invención provee un compuesto de fórmula I, donde G es

N-metil-3-amino-n-propilo; $R^o$ es H, halo, o metoxi; X es F; e Y es I. En otra forma de realización subgenérica más específica, esta invención provee un compuesto de fórmula I, donde G es $(CH_3)_2N-CH_2CH_2-NH-(CH_2)_n-$, donde n es 1, 2, o 3; $R^o$ es H, halo, o metoxi; X es F; e Y es I. En otra forma de realización subgenérica más específica, esta invención provee un compuesto de fórmula I, donde G es $(CH_3CH_2)_2N-CH_2CH_2-NH-(CH_2)_n-$, donde n es 1 o 2; $R^o$ es H, halo, o metoxi; X es F; e Y es I.

En algunas formas de realización, la invención provee una composición farmacéutica que comprende un compuesto de fórmula I o una sal farmacéuticamente aceptable, solvato, polimorfo, éster, amida, tautómero o prodroga del mismo. En algunas formas de realización la composición farmacéutica comprende además al menos un vehículo farmacéuticamente aceptable.

En algunas formas de realización, la invención provee una composición farmacéutica que comprende un compuesto seleccionado entre:  y  , o una sal farmacéuticamente aceptable, solvato, polimorfo, éster, amida, tautómero o prodroga del mismo. En algunas formas de realización, la composición farmacéutica comprende además al menos un vehículo farmacéuticamente aceptable. En

algunas formas de realización, el compuesto es de configuración R. En algunas formas de realización, el compuesto es de configuración R, sustancialmente libre del isómero S. En algunas formas de realización, el compuesto es de configuración S. En algunas formas de realización, el compuesto es de configuración S, sustancialmente libre del isómero R. En algunas formas de realización, el compuesto es:  . En algunas formas de realización, el compuesto es:  . En algunas formas de realización, el compuesto es:  . En algunas formas de realización, el compuesto es:  .

**Tablas con ejemplos no limitantes de Compuestos de fórmula I**

Las tablas a continuación muestran ejemplos de compuestos individuales que se proveen o se contemplan en esta invención. Estos ejemplos de ninguna manera deben considerarse limitantes.

La Tabla 1 muestra formas de realización de esta invención que son compuestos de fórmula I, donde $R^0$ es como se define aquí, G es $R_{1a}$ donde $R_{1a}$ es como se define en la tabla y X, Y y Z se definen en la tabla.

**Tabla 1**

| $R_{1a}$ | X | Y |
|---|---|---|
| | | |
| $CH_3$ | F | I |
| $CH_3$ | Cl | I |
| $CH_3$ | F | Br |
| $CH_3$ | Cl | Br |
| $CH_3$ | F | $CH_3$ |
| $CH_3$ | Cl | $CH_3$ |
| $CH_3$ | F | $CF_3$ |
| $CH_3$ | Cl | $CF_3$ |
| $CH_3$ | F | C≡CH |
| $CH_3$ | Cl | C≡CH |
| $CH_3$ | F | $SCH_3$ |
| $CH_3$ | Cl | $SCH_3$ |
| $CH_3$ | F | $(CH_2)_2CH_3$ |
| $CH_3$ | Cl | $(CH_2)_2CH_3$ |
| $CH_3$ | F | $CH_2CH_3$ |
| $CH_3$ | Cl | $CH_2CH_3$ |

| $R_{1a}$ | X | Y |
|---|---|---|
| $CH_3$ | F | $CH_2OH$ |
| $CH_3$ | Cl | $CH_2OH$ |
| $CH_3$ | F | ▷ |
| $CH_3$ | Cl | ▷ |
| $CH_3$ | $CH_3$ | $CH=CH_2$ |
| $CH_3$ | $CH_3$ | C≡CH |
| $CH_3$ | $CH_3$ | $SCH_3$ |
| $CH_2F$ | F | I |
| $CH_2F$ | Cl | I |
| $CH_2F$ | F | Br |
| $CH_2F$ | Cl | Br |
| $CH_2F$ | F | $CH_3$ |
| $CH_2F$ | Cl | $CH_3$ |
| $CH_2F$ | F | $CF_3$ |
| $CH_2F$ | Cl | $CF_3$ |
| $CF_3$ | F | I |
| $CF_3$ | Cl | I |

4961

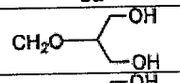
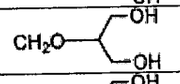
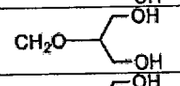
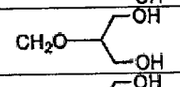
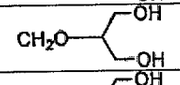
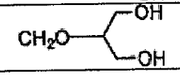
| $R_{1a}$ | X | Y |
|---|---|---|
| $CF_3$ | F | Br |
| $CF_3$ | Cl | Br |
| $CF_3$ | F | $CH_3$ |
| $CF_3$ | Cl | $CH_3$ |
| $CF_3$ | F | $CF_3$ |
| $CF_3$ | Cl | $CF_3$ |
| $CH_2Cl$ | F | I |
| $CH_2Cl$ | Cl | I |
| $CH_2Cl$ | F | Br |
| $CH_2Cl$ | Cl | Br |
| $CH_2Cl$ | F | $CH_3$ |
| $CH_2Cl$ | Cl | $CH_3$ |
| $CH_2Cl$ | F | $CF_3$ |
| $CH_2Cl$ | Cl | $CF_3$ |
| $CHCl_2$ | F | I |
| $CHCl_2$ | Cl | I |
| $CHCl_2$ | F | Br |
| $CHCl_2$ | Cl | Br |
| $CHCl_2$ | F | $CH_3$ |
| $CHCl_2$ | Cl | $CH_3$ |
| $CHCl_2$ | F | $CF_3$ |
| $CHCl_2$ | Cl | $CF_3$ |
| $CCl_3$ | F | I |

| $R_{1a}$ | X | Y |
|---|---|---|
| $CCl_3$ | Cl | I |
| $CCl_3$ | F | Br |
| $CCl_3$ | Cl | Br |
| $CCl_3$ | F | $CH_3$ |
| $CCl_3$ | Cl | $CH_3$ |
| $CCl_3$ | F | $CF_3$ |
| $CCl_3$ | Cl | $CF_3$ |
| $CH_2OH$ | F | I |
| $CH_2OH$ | Cl | I |
| $CH_2OH$ | F | Br |
| $CH_2OH$ | Cl | Br |
| $CH_2OH$ | F | $CH_3$ |
| $CH_2OH$ | Cl | $CH_3$ |
| $CH_2OH$ | F | $CF_3$ |
| $CH_2OH$ | Cl | $CF_3$ |
| $CH_2OMe$ | F | I |
| $CH_2OMe$ | Cl | I |
| $CH_2OMe$ | F | Br |
| $CH_2OMe$ | Cl | Br |
| $CH_2OMe$ | F | $CH_3$ |
| $CH_2OMe$ | Cl | $CH_3$ |
| $CH_2OMe$ | F | $CF_3$ |
| $CH_2OMe$ | Cl | $CF_3$ |

4462

| $R_{1a}$ | X | Y |
|---|---|---|
| $CH_2OMe$ | F | C≡CH |
| $CH_2OMe$ | Cl | $SCH_3$ |
| $CH_2OMe$ | $CH_3$ | $CF_3$ |
| $CH_2OMe$ | $CH_3$ | C≡CH |
| $CH_2OEt$ | F | I |
| $CH_2OEt$ | Cl | I |
| $CH_2OEt$ | F | Br |
| $CH_2OEt$ | Cl | Br |
| $CH_2OEt$ | F | $CH_3$ |
| $CH_2OEt$ | Cl | $CH_3$ |
| $CH_2OEt$ | F | $CF_3$ |
| $CH_2OEt$ | Cl | $CF_3$ |
| $CH_2O$-◁ | F | I |
| $CH_2O$-◁ | Cl | I |
| $CH_2O$-◁ | F | Br |
| $CH_2O$-◁ | Cl | Br |
| $CH_2O$-◁ | F | $CH_3$ |
| $CH_2O$-◁ | Cl | $CH_3$ |
| $CH_2O$-◁ | F | $CF_3$ |
| $CH_2O$-◁ | Cl | $CF_3$ |
| $CH_2O$-  | F | I |
| $CH_2O$-  | Cl | I |
| $CH_2O$-  | F | Br |

| $R_{1a}$ | X | Y |
|---|---|---|
| $CH_2O$-  | Cl | Br |
| $CH_2O$-  | F | $CH_3$ |
| $CH_2O$-  | Cl | $CH_3$ |
| $CH_2O$-  | F | $CF_3$ |
| $CH_2O$-  | Cl | $CF_3$ |
| $CH_2O$-  | F | I |
| $CH_2O$-  | Cl | I |
| $CH_2O$-  | F | Br |
| $CH_2O$-  | Cl | Br |
| $CH_2O$-  | F | $CH_3$ |
| $CH_2O$-  | Cl | $CH_3$ |
| $CH_2O$-  | F | $CF_3$ |
| $CH_2O$-  | Cl | $CF_3$ |
| $CH_2O$-  | F | I |
| $CH_2O$-  | Cl | I |
| $CH_2O$-  | F | Br |
| $CH_2O$-  | Cl | Br |
| $CH_2O$-  | F | $CH_3$ |
| $CH_2O$-  | Cl | $CH_3$ |
| $CH_2O$-  | F | $CF_3$ |
| $CH_2O$-  | Cl | $CF_3$ |
| $CH_2O$-  | F | I |
| $CH_2O$-  | Cl | I |

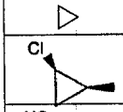
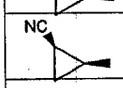
| $R_{1a}$ | X | Y |
|---|---|---|
|  | F | Br |
|  | Cl | Br |
|  | F | $CH_3$ |
|  | Cl | $CH_3$ |
|  | F | $CF_3$ |
|  | Cl | $CF_3$ |
| $CH_3$ | F | fenilo |
| $CH_3$ | Cl | fenilo |
| $CH_3$ | $CH_3$ | fenilo |
| $CH_3$ | F | 3-piridilo |
| $CH_3$ | Cl | 3-piridilo |
| $CH_3$ | $CH_3$ | 4-piridilo |
| $CH_3$ | F | pirazolilo |
| $CH_3$ | Cl | pirazolilo |
| $CH_3$ | F | 4-piridilo |
| $CH_3$ | Cl | 4-piridilo |
| $CH_3$ | $CH_3$ | 2-($CH_3$-$SO_2$-NH)-fenilo |
| $CH_3$ | $CH_3$ | 3-($CH_3$-$SO_2$-NH)-fenilo |

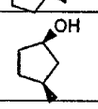
| $R_{1a}$ | X | Y |
|---|---|---|
| $CH_3$ | Cl | 3-($CH_3$-$SO_2$-NH)-fenilo |
| $CH_3$ | F | 3-($CH_3$-$SO_2$-NH)-fenilo |

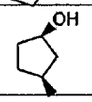
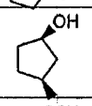
La Tabla 2 muestra formas de realización de esta invención que son compuestos de fórmula I, donde $R^0$ es como se define aquí, G es $R_{1b}$ donde $R_{1b}$ es como se define en la tabla y X, Y y Z se definen en la tabla.

**Tabla 2**

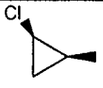
| $R_{1b}$ | X | Y | Z |
|---|---|---|---|
| ▷ | F | I | F |
| ▷ | Cl | I | F |
| ▷ | F | Br | F |
| ▷ | Cl | Br | F |
| ▷ | F | $CH_3$ | F |
| ▷ | Cl | $CH_3$ | F |
| ▷ | F | $CF_3$ | F |
| ▷ | Cl | $CF_3$ | F |
| ▷ | F | C≡CH | F |
| ▷ | Cl | C≡CH | F |
| ▷ | F | $SCH_3$ | F |
| ▷ | Cl | $SCH_3$ | F |
| ▷ | F | $CH_2OH$ | F |
| ▷ | Cl | $CH_2OH$ | F |
| ▷ | F | $(CH_2)_3OH$ | F |
| ▷ | Cl | $(CH_2)_3OH$ | F |
| ▷ | F | $(CH_2)_2CH_3$ | F |
| ▷ | Cl | $(CH_2)_2CH_3$ | F |

| $R_{1b}$ | X | Y | Z |
|---|---|---|---|
| ▷ | F | $CH_2CH_3$ | F |
| ▷ | Cl | $CH_2CH_3$ | F |
| ▷ | F | $(CH_2)_2CH_3$ | F |
| ▷ | Cl | $(CH_2)_2CH_3$ | F |
| ▷ | $CH_3$ | I | F |
| ▷ | $CH_3$ | Br | F |
| ▷ | $CH_3$ | $CH_3$ | F |
| ▷ | $CH_3$ | $CF_3$ | F |
| ▷ | $CH_3$ | $CH_2CH_3$ | F |
| ▷ | $CH_3$ | $(CH_2)_2CH_3$ | F |
| ▷ | $CH_3$ | C≡CH | F |
| ▷ | $CH_3$ | $SCH_3$ | F |
|  | $CH_3$ | $(CH_2)_2CH_3$ | F |
|  | $CH_3$ | I | F |
| ▷ | F | $CH=CH_2$ | F |
| ▷ | Cl | $CH=CH_2$ | F |
| ▷ | $CH_3$ | $CH=CH_2$ | F |
| ▷ | F | ▷ | F |

| $R_{1b}$ | X | Y | Z |
|---|---|---|---|
| ▷ | F | $OCH_3$ | F |
| ▷ | Cl | $(CH_2)_2CH_2OH$ | F |
| ◇ | F | I | F |
| | | | F |
| ◇ | Cl | I | F |
| ◇ | F | Br | F |
| ◇ | Cl | Br | F |
| ◇ | F | $CH_3$ | F |
| ◇ | Cl | $CH_3$ | F |
| ◇ | F | $CF_3$ | F |
| ◇ | Cl | $CF_3$ | F |
| ⬠ | F | I | F |
| ⬠ | Cl | I | F |
| ⬠ | F | Br | F |
| ⬠ | Cl | Br | F |
| ⬠ | F | $CH_3$ | F |
| ⬠ | Cl | $CH_3$ | F |
| ⬠ | F | $CF_3$ | F |
| ⬠ | Cl | $CF_3$ | F |
| ⬠ | Cl | ▷ | F |
|  | F | $(CH_2)_2CH_3$ | F |
|  | Cl | C≡CH | F |
|  | $CH_3$ | $SCH_3$ | F |

| $R_{1b}$ | X | Y | Z |
|---|---|---|---|
|  | Cl | $CF_3$ | F |
|  | $CH_3$ | $CH_3$ | F |
|  | F | $CH_2OH$ | F |
|  | Cl | $(CH_2)_3OH$ | F |
|  | F | $OCH_2CH_3$ | F |
| ⬡ | F | I | F |
| ⬡ | Cl | I | F |
| ⬡ | F | Br | F |
| ⬡ | Cl | Br | F |
| ⬡ | F | $CH_3$ | F |
| ⬡ | Cl | $CH_3$ | F |
| ⬡ | F | $CF_3$ | F |
| ⬡ | Cl | $CF_3$ | F |
| | | | |
| ▷ | F | fenilo | F |
| ▷ | Cl | fenilo | F |
| ▷ | F | 3-piridilo | F |
| ▷ | Cl | 3-piridilo | F |
| ▷ | F | pirazol-4-ilo | F |
| ▷ | Cl | pirazol-4-ilo | F |
| ▷ | F | 4-piridilo | F |

| $R_{1b}$ | X | Y | Z |
|---|---|---|---|
| ▷ | Cl | 4-piridilo | F |
| ▷ | F | 1-metil-pirazol-4-ilo | F |
| ▷ | Cl | 1-metil-pirazol-4-ilo | F |
| ▷ | F | pirazol-3-ilo | F |
| ▷ | Cl | pirazol-3-ilo | F |
| ▷ | F | 2-($CH_3$-$SO_2$-NH)-fenilo | F |
| ▷ | Cl | 2-($CH_3$-$SO_2$-NH)-fenilo | F |
| ▷ | F | 3-($CH_3$-$SO_2$-NH)-fenilo | F |
| ▷ | Cl | 3-($CH_3$-$SO_2$-NH)-fenilo | F |

| $R_{1b}$ | X | Y | Z |
|---|---|---|---|
| ▷ | $CH_3$ | 2-($CH_3$-$SO_2$-NH)-fenilo | F |
| ▷ | $CH_3$ | 3-($CH_3$-$SO_2$-NH)-fenilo | F |
| ▷ | F | 4-$CF_3O$-fenilo | F |
| ▷ | Cl | 4-$CF_3O$-fenilo | F |
| ▷ | $CH_3$ | 4-$CF_3O$-fenilo | F |
|  | Cl | 2-($CH_3$-$SO_2$-NH)-fenilo | F |
| ◇ | F | fenilo | F |
| ◇ | | fenilo | |
| ◇ | Cl | 3-piridilo | F |
| ◇ | F | 3-piridilo | F |
| ◇ | Cl | pirazol-4-ilo | F |
| ◇ | F | pirazol-4-ilo | F |

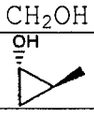
| $R_{1b}$ | X | Y | Z |
|---|---|---|---|
|  | Cl | 4-piridilo | F |
|  | F | 4-piridilo | F |
|  | Cl | 1-metil-pirazol-4-ilo | F |
|  | $CH_3$ | 1-metil-pirazol-4-ilo | F |
|  | F | pirazol-3-ilo | F |
|  | Cl | pirazol-3-ilo | F |
|  | F | 2-($CH_3$-$SO_2$-NH)-fenilo | F |
|  | Cl | 2-($CH_3$-$SO_2$-NH)-fenilo | F |
|  | F | fenilo | F |
|  | Cl | fenilo | F |
|  | F | 3-piridilo | F |
|  | Cl | 3-piridilo | F |

| $R_{1b}$ | X | Y | Z |
|---|---|---|---|
|  | Cl | pirazol-3-ilo | F |

Tabla 3 muestra formas de realización de esta invención que son compuestos de fórmula I, donde $R^0$ es como se define aquí, G es $R_{1c}$ donde $R_{1c}$ es como se define en la tabla y X, Y y Z se definen en la tabla.

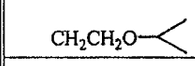
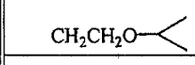
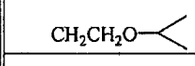
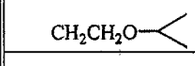
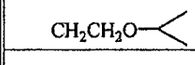
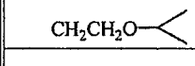
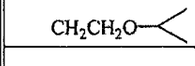
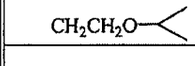
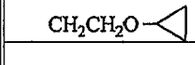
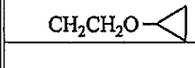
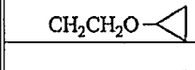
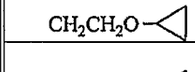
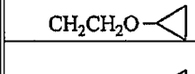
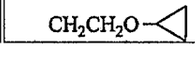
**Tabla 3**

| $R_{1c}$ | X | Y | Z | $R_{1c}$ | X | Y | Z |
|---|---|---|---|---|---|---|---|
| $CH_2CH_3$ | F | I | F | $CH(CH_3)_2$ | F | $OCH_3$ | F |
| $CH_2CH_3$ | Cl | I | F | $CH(CH_3)_2$ | Cl | $OCH_3$ | F |
| $CH_2CH_3$ | F | Br | F | $CH(CH_3)_2$ | F | I | F |
| $CH_2CH_3$ | Cl | Br | F | $CH(CH_3)_2$ | Cl | I | F |
| $CH_2CH_3$ | F | $CH_3$ | F | $CH(CH_3)_2$ | F | Br | F |
| $CH_2CH_3$ | Cl | $CH_3$ | F | $CH(CH_3)_2$ | Cl | Br | F |
| $CH_2CH_3$ | F | $CF_3$ | F | $CH(CH_3)_2$ | F | $CH_3$ | F |
| $CH_2CH_3$ | Cl | $CF_3$ | F | $CH(CH_3)_2$ | Cl | $CH_3$ | F |
| $CH_2CH_3$ | $CH_3$ | $CH_3$ | F | $CH(CH_3)_2$ | F | $CH_2CH_3$ | F |
| $CH_2CH_3$ | $CH_3$ | $CH_3$ | F | $CH(CH_3)_2$ | Cl | $CH_2CH_3$ | F |
| $CH_2CH_3$ | $CH_3$ | C≡CH | F | $CH(CH_3)_2$ | $CH_3$ | $CH_2CH_3$ | F |
| $CH_2CH_3$ | $CH_3$ | $SCH_3$ | F | $CH(CH_3)_2$ | Cl | $CH_2CH_3$ | F |
| $CH_2CH_3$ | F | C≡CH | F | $CH(CH_3)_2$ | Fl | $CH(CH_3)_2$ | F |
| $CH_2CH_3$ | Cl | $SCH_3$ | F | $CH(CH_3)_2$ | Cl | $CH(CH_3)_2$ | F |
| $CH_2CH_3$ | F | ▷ | F | $CH(CH_3)_2$ | F | $CF_3$ | F |
| $CH_2CH_3$ | Cl | ▷ | F | $CH(CH_3)_2$ | Cl | $CH_3$ | F |
| $CH_2CH_3$ | $CH_3$ | ▷ | F | $CH(CH_3)_2$ | $CH_3$ | Br | F |

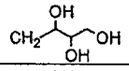
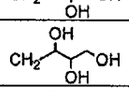
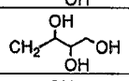
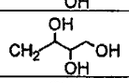
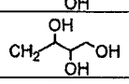
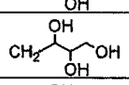
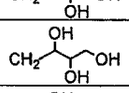
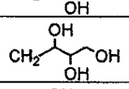
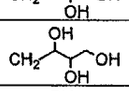
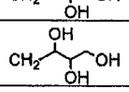
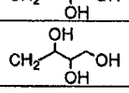
| $R_{1c}$ | X | Y | Z |
|---|---|---|---|
| $CH(CH_3)_2$ | $CH_3$ | C≡CH | F |
| $CH(CH_3)_2$ | $CH_3$ | $SCH_3$ | F |
| $CH(CH_3)_2$ | $CH_3$ | ▷ | F |
| $CH(CH_3)_2$ | F | $CH_2OH$ | F |
| $CH(CH_3)_2$ | Cl |  | F |
| *n*-butilo | F | I | F |
| *n*-butilo | Cl | I | F |
| *n*-butilo | F | Br | F |
| *n*-butilo | Cl | Br | F |
| *n*-butilo | F | $CH_3$ | F |
| *n*-butilo | Cl | $CH_3$ | F |
| *n*-butilo | F | $OCH_3$ | F |
| *n*-butilo | Cl | $OCH_3$ | F |
| *n*-butilo | $CH_3$ | $OCH_3$ | F |
| *n*-butilo | Cl | $OCH_2CH_3$ | F |
| *n*-butilo | F | $OCH_2CH_3$ | F |
| *n*-butilo | $CH_3$ | $OCH_2CH_3$ | F |
| *n*-butilo | F | $OCH_2CH_2OH$ | F |
| *n*-butilo | F | $CF_3$ | F |
| *n*-butilo | Cl | $CF_3$ | F |
| *sec*-butilo | F | I | F |
| *sec*-butilo | Cl | I | F |
| *sec*-butilo | F | Br | F |

| $R_{1c}$ | X | Y | Z |
|---|---|---|---|
| *sec*-butilo | Cl | Br | F |
| *sec*-butilo | F | $CH_3$ | F |
| *sec*-butilo | Cl | $CH_3$ | F |
| *sec*-butilo | F | $CF_3$ | F |
| *sec*-butilo | Cl | $CF_3$ | F |
| $CH_2CF_3$ | F | I | F |
| $CH_2CF_3$ | Cl | I | F |
| $CH_2CF_3$ | F | Br | F |
| $CH_2CF_3$ | Cl | Br | F |
| $CH_2CF_3$ | F | $CH_3$ | F |
| $CH_2CF_3$ | Cl | $CH_3$ | F |
| $CH_2CF_3$ | F | $CF_3$ | F |
| $CH_2CF_3$ | Cl | $CF_3$ | F |
| $CH_2CCl_3$ | F | I | F |
| $CH_2CCl_3$ | Cl | I | F |
| $CH_2CCl_3$ | F | Br | F |
| $CH_2CCl_3$ | Cl | Br | F |
| $CH_2CCl_3$ | F | $CH_3$ | F |
| $CH_2CCl_3$ | Cl | $CH_3$ | F |
| $CH_2CCl_3$ | F | $CF_3$ | F |
| $CH_2CCl_3$ | Cl | $CF_3$ | F |
| $CH_2$-◁ | F | I | F |
| $CH_2$-◁ | Cl | I | F |

| $R_{1c}$ | X | Y | Z | $R_{1c}$ | X | Y | Z |
|---|---|---|---|---|---|---|---|
| $CH_2$-◁ | F | Br | F | $CH_2CH_2CH_2Cl$ | Cl | I | F |
| $CH_2$-◁ | Cl | Br | F | $CH_2CH_2CH_2Cl$ | F | Br | F |
| $CH_2$-◁ | F | $CH_3$ | F | $CH_2CH_2CH_2Cl$ | Cl | Br | F |
| $CH_2$-◁ | Cl | $CH_3$ | F | $CH_2CH_2CH_2Cl$ | F | $CH_3$ | F |
| $CH_2$-◁ | F | $CF_3$ | F | $CH_2CH_2CH_2Cl$ | Cl | $CH_3$ | F |
| $CH_2$-◁ | Cl | $CF_3$ | F | $CH_2CH_2CH_2Cl$ | F | $CF_3$ | F |
| $CH_2CH_2F$ | F | I | F | $CH_2CH_2CH_2Cl$ | Cl | $CF_3$ | F |
| $CH_2CH_2F$ | Cl | I | F | $CH_2CH_2OH$ | F | I | F |
| $CH_2CH_2F$ | F | Br | F | $CH_2CH_2OH$ | Cl | I | F |
| $CH_2CH_2F$ | Cl | Br | F | $CH_2CH_2OH$ | F | Br | F |
| $CH_2CH_2F$ | F | $CH_3$ | F | $CH_2CH_2OH$ | Cl | Br | F |
| $CH_2CH_2F$ | Cl | $CH_3$ | F | $CH_2CH_2OH$ | F | $CH_3$ | F |
| $CH_2CH_2F$ | F | $CF_3$ | F | $CH_2CH_2OH$ | Cl | $CH_3$ | F |
| $CH_2CH_2F$ | Cl | $CF_3$ | F | $CH_2CH_2OH$ | F | $CF_3$ | F |
| $CH_2CH_2Cl$ | F | I | F | $CH_2CH_2OH$ | Cl | $CF_3$ | F |
| $CH_2CH_2Cl$ | Cl | I | F | $CH_2CH_2CH_2OH$ | F | I | F |
| $CH_2CH_2Cl$ | F | Br | F | $CH_2CH_2CH_2OH$ | Cl | I | F |
| $CH_2CH_2Cl$ | Cl | Br | F | $CH_2CH_2CH_2OH$ | F | Br | F |
| $CH_2CH_2Cl$ | F | $CH_3$ | F | $CH_2CH_2CH_2OH$ | Cl | Br | F |
| $CH_2CH_2Cl$ | Cl | $CH_3$ | F | $CH_2CH_2CH_2OH$ | F | $CH_3$ | F |
| $CH_2CH_2Cl$ | F | $CF_3$ | F | $CH_2CH_2CH_2OH$ | Cl | $CH_3$ | F |
| $CH_2CH_2Cl$ | Cl | $CF_3$ | F | $CH_2CH_2CH_2OH$ | F | $CF_3$ | F |
| $CH_2CH_2CH_2Cl$ | F | I | F | $CH_2CH_2CH_2OH$ | Cl | $CF_3$ | F |

| $R_{1c}$ | X | Y | Z | $R_{1c}$ | X | Y | Z |
|---|---|---|---|---|---|---|---|
| $(CH_2)_4OH$ | F | I | F | $(CH_2)_3OCH_3$ | Cl | $CF_3$ | F |
| $(CH_2)_4OH$ | Cl | I | F | $CH_2CH_2OEt$ | F | I | F |
| $(CH_2)_4OH$ | F | Br | F | $CH_2CH_2OEt$ | Cl | I | F |
| $(CH_2)_4OH$ | Cl | Br | F | $CH_2CH_2OEt$ | F | Br | F |
| $(CH_2)_4OH$ | F | $CH_3$ | F | $CH_2CH_2OEt$ | Cl | Br | F |
| $(CH_2)_4OH$ | Cl | $CH_3$ | F | $CH_2CH_2OEt$ | F | $CH_3$ | F |
| $(CH_2)_4OH$ | F | $CF_3$ | F | $CH_2CH_2OEt$ | Cl | $CH_3$ | F |
| $(CH_2)_4OH$ | Cl | $CF_3$ | F | $CH_2CH_2OEt$ | F | $CF_3$ | F |
| $CH_2CH_2OCH_3$ | F | I | F | $CH_2CH_2OEt$ | Cl | $CF_3$ | F |
| $CH_2CH_2OCH_3$ | Cl | I | F |  | F | I | F |
| $CH_2CH_2OCH_3$ | F | Br | F |  | Cl | I | F |
| $CH_2CH_2OCH_3$ | Cl | Br | F |  | F | Br | F |
| $CH_2CH_2OCH_3$ | F | $CH_3$ | F |  | Cl | Br | F |
| $CH_2CH_2OCH_3$ | Cl | $CH_3$ | F |  | F | $CH_3$ | F |
| $CH_2CH_2OCH_3$ | F | $CF_3$ | F |  | Cl | $CH_3$ | F |
| $CH_2CH_2OCH_3$ | Cl | $CF_3$ | F |  | F | $CF_3$ | F |
| $(CH_2)_3OCH_3$ | F | I | F |  | Cl | $CF_3$ | F |
| $(CH_2)_3OCH_3$ | Cl | I | F |  | F | I | F |
| $(CH_2)_3OCH_3$ | F | Br | F |  | Cl | I | F |
| $(CH_2)_3OCH_3$ | Cl | Br | F |  | F | Br | F |
| $(CH_2)_3OCH_3$ | F | $CH_3$ | F |  | Cl | Br | F |
| $(CH_2)_3OCH_3$ | Cl | $CH_3$ | F |  | F | $CH_3$ | F |
| $(CH_2)_3OCH_3$ | F | $CF_3$ | F |  | Cl | $CH_3$ | F |

| $R_{1c}$ | X | Y | Z | $R_{1c}$ | X | Y | Z |
|---|---|---|---|---|---|---|---|
| $CH_2CH_2O$-cyclopropyl | F | $CF_3$ | F | $CH_2CH_2CH_2O$-cyclopropyl | Cl | $CH_3$ | F |
| $CH_2CH_2O$-cyclopropyl | Cl | $CF_3$ | F | $CH_2CH_2CH_2O$-cyclopropyl | F | $CF_3$ | F |
| $CH_2CH_2CH_2OEt$ | F | I | F | $CH_2CH_2CH_2O$-cyclopropyl | Cl | $CF_3$ | F |
| $CH_2CH_2CH_2OEt$ | Cl | I | F | $CH_2CH_2O$-glycerol | F | I | F |
| $CH_2CH_2CH_2OEt$ | F | Br | F | $CH_2CH_2O$-glycerol | Cl | I | F |
| $CH_2CH_2CH_2OEt$ | Cl | Br | F | $CH_2CH_2O$-glycerol | F | Br | F |
| $CH_2CH_2CH_2OEt$ | F | $CH_3$ | F | $CH_2CH_2O$-glycerol | Cl | Br | F |
| $CH_2CH_2CH_2OEt$ | Cl | $CH_3$ | F | $CH_2CH_2O$-glycerol | F | $CH_3$ | F |
| $CH_2CH_2CH_2OEt$ | F | $CF_3$ | F | $CH_2CH_2O$-glycerol | Cl | $CH_3$ | F |
| $CH_2CH_2CH_2OEt$ | Cl | $CF_3$ | F | $CH_2CH_2O$-glycerol | F | $CF_3$ | F |
| $CH_2CH_2CH_2O$-isopropyl | F | I | F | $CH_2CH_2O$-glycerol | Cl | $CF_3$ | F |
| $CH_2CH_2CH_2O$-isopropyl | Cl | I | F | 1,3-propanediol | F | I | F |
| $CH_2CH_2CH_2O$-isopropyl | F | Br | F | 1,3-propanediol | Cl | I | F |
| $CH_2CH_2CH_2O$-isopropyl | Cl | Br | F | 1,3-propanediol | F | Br | F |
| $CH_2CH_2CH_2O$-isopropyl | F | $CH_3$ | F | 1,3-propanediol | Cl | Br | F |
| $CH_2CH_2CH_2O$-isopropyl | Cl | $CH_3$ | F | 1,3-propanediol | F | $CH_3$ | F |
| $CH_2CH_2CH_2O$-isopropyl | F | $CF_3$ | F | 1,3-propanediol | Cl | $CH_3$ | F |
| $CH_2CH_2CH_2O$-isopropyl | Cl | $CF_3$ | F | 1,3-propanediol | F | $CF_3$ | F |
| $CH_2CH_2CH_2O$-cyclopropyl | F | I | F | 1,3-propanediol | Cl | $CF_3$ | F |
| $CH_2CH_2CH_2O$-cyclopropyl | Cl | I | F | 1,2,3-propanetriol | F | I | F |
| $CH_2CH_2CH_2O$-cyclopropyl | F | Br | F | 1,2,3-propanetriol | Cl | I | F |
| $CH_2CH_2CH_2O$-cyclopropyl | Cl | Br | F | 1,2,3-propanetriol | $CH_3$ | I | F |
| $CH_2CH_2CH_2O$-cyclopropyl | F | $CH_3$ | F | 1,2,3-propanetriol | F | Br | F |

| $R_{1c}$ | X | Y | Z |
|---|---|---|---|
|  | Cl | Br | F |
|  | $CH_3$ | Br | F |
|  | F | $CH_3$ | F |
|  | Cl | $CH_3$ | F |
|  | $CH_3$ | $CH_3$ | F |
|  | F | C≡CH | F |
|  | F | $SCH_3$ | F |
|  | F | $CH_2CH_2CH_3$ | F |
|  | Cl | $CH_2CH(OH)CH_3$ | F |
|  | F | $CH(CH_3)_2$ | F |
|  | Cl | $CF_3$ | F |
| $CH_2CH_3$ | F | fenilo | F |
| $CH_2CH_3$ | Cl | fenilo | F |
| $CH_2CH_3$ | F | fenilo | F |
| $CH_2CH_3$ | Cl | 3-piridilo | F |
| $CH_2CH_3$ | F | 3-piridilo | F |
| $CH_2CH_3$ | Cl | 4-piridilo | F |
| $CH_2CH_3$ | F | pirazolilo | F |
| $CH_2CH_3$ | Cl | pirazolilo | F |
| $CH_2CH_3$ | $CH_3$ | 4-piridilo | F |
| $CH_2CH_3$ | $CH_3$ | 4-piridilo | F |
| $CH_2CH_3$ | $CH_3$ | 2-($CH_3$-$SO_2$-NH)-fenilo | F |

| $R_{1c}$ | X | Y | Z |
|---|---|---|---|
| $CH_2CH_3$ | $CH_3$ | 3-($CH_3$-$SO_2$-NH)-fenilo | F |
| $CH_2CH_3$ | F | 3-($CH_3$-$SO_2$-NH)-fenilo | F |
| $CH_2CH_3$ | Cl | 3-($CH_3$-$SO_2$-NH)-fenilo | F |
| $CH_2CH_3$ | F | fenilo | F |
| $CH_2CH_3$ | Cl | fenilo | F |
| $CH_2CH_3$ | $CH_3$ | fenilo | F |
| | | 3-piridilo | |
| $CH(CH_3)_2$ | F | 3-piridilo | F |
| $CH(CH_3)_2$ | Cl | 4-piridilo | F |
| $CH(CH_3)_2$ | F | pirazolilo | F |
| $CH(CH_3)_2$ | Cl | pirazolilo | F |
| $CH(CH_3)_2$ | F | 4-piridilo | F |
| $CH(CH_3)_2$ | Cl | 4-piridilo | F |
| $CH(CH_3)_2$ | F | 2-($CH_3$-$SO_2$-NH)-fenilo | F |
| $CH(CH_3)_2$ | Cl | 3-($CH_3$-$SO_2$-NH)-fenilo | F |
| $CH(CH_3)_2$ | F | 3-($CH_3$-$SO_2$-NH)-fenilo | F |

| $R_{1c}$ | X | Y | Z |
|---|---|---|---|
| $CH(CH_3)_2$ | Cl | 3-($CH_3$-$SO_2$-NH)-fenilo | F |
| $CH(CH_3)_2$ | $CH_3$ | fenilo | F |
| $CH(CH_3)_2$ | Cl | fenilo | F |
| $CH(CH_3)_2$ | Fl | fenilo | F |
| $CH(CH_3)_2$ | Cl | 3-piridilo | F |
| | | 3-piridilo | |
| $CH(CH_3)_2$ | F | 4-piridilo | F |
| $CH(CH_3)_2$ | Cl | pirazolilo | F |
| $CH(CH_3)_2$ | $CH_3$ | pirazolilo | F |
| $CH(CH_3)_2$ | $CH_3$ | 4-piridilo | F |
| $CH(CH_3)_2$ | $CH_3$ | 4-piridilo | F |
| $CH(CH_3)_2$ | $CH_3$ | 2-($CH_3$-$SO_2$-NH)-fenilo | F |
| $CH(CH_3)_2$ | F | 3-($CH_3$-$SO_2$-NH)-fenilo | F |
| $CH(CH_3)_2$ | Cl | 3-($CH_3$-$SO_2$-NH)-fenilo | F |
| | | 3-($CH_3$-$SO_2$-NH)-fenilo | |
| *n*-butilo | F | fenilo | F |
| *n*-butilo | Cl | fenilo | F |
| *n*-butilo | F | fenilo | F |

| $R_{1c}$ | X | Y | Z |
|---|---|---|---|
| *n*-butilo | Cl | 3-piridilo | F |
| *n*-butilo | F | 3-piridilo | F |
| *n*-butilo | Cl | 4-piridilo | F |
| *n*-butilo | F | pirazolilo | F |
| *n*-butilo | Cl | pirazolilo | F |
| *n*-butilo | $CH_3$ | 4-piridilo | F |
| *n*-butilo | Cl | 4-piridilo | F |
| *n*-butilo | F | 2-($CH_3$-$SO_2$-NH)-fenilo | F |
| *n*-butilo | $CH_3$ | 3-($CH_3$-$SO_2$-NH)-fenilo | F |
| *n*-butilo | F | 3-($CH_3$-$SO_2$-NH)-fenilo | F |
| | | 3-($CH_3$-$SO_2$-NH)-fenilo | |
| *n*-butilo | F | fenilo | F |
| *n*-butilo | Cl | fenilo | F |
| | | fenilo | |
| *sec*-butilo | F | 3-piridilo | F |
| *sec*-butilo | Cl | 3-piridilo | F |
| *sec*-butilo | F | 4-piridilo | F |
| *sec*-butilo | Cl | pirazolilo | F |
| *sec*-butilo | F | pirazolilo | F |

| $R_{1c}$ | X | Y | Z | $R_{1c}$ | X | Y | Z |
|---|---|---|---|---|---|---|---|
| *sec*-butilo | Cl | 4-piridilo | F | $CH_2CCl_3$ | Cl | fenilo | F |
| *sec*-butilo | F | 4-piridilo | F | | | 3-piridilo | |
| sec-butilo | Cl | $CF_3$ | F | $CH_2$-◁ | F | 3-piridilo | F |
| $CH_2CF_3$ | F | fenilo | F | $CH_2$-◁ | Cl | 4-piridilo | F |
| $CH_2CF_3$ | Cl | fenilo | F | $CH_2$-◁ | F | pirazolilo | F |
| $CH_2CF_3$ | F | fenilo | F | $CH_2$-◁ | Cl | pirazolilo | F |
| $CH_2CF_3$ | Cl | 3-piridilo | F | $CH_2$-◁ | F | 4-piridilo | F |
| $CH_2CF_3$ | F | 3-piridilo | F | $CH_2$-◁ | Cl | 4-piridilo | F |
| $CH_2CF_3$ | Cl | 4-piridilo | F | $CH_2$-◁ | F | 2-($CH_3$-$SO_2$-NH)-fenilo | F |
| $CH_2CF_3$ | F | pirazolilo | F | | | | |
| $CH_2CF_3$ | Cl | pirazolilo | F | $CH_2$-◁ | Cl | 3-($CH_3$-$SO_2$-NH)-fenilo | F |
| | | 4-piridilo | | | | | |
| $CH_2CCl_3$ | F | 4-piridilo | F | | | 3-($CH_3$-$SO_2$-NH)-fenilo | |
| $CH_2CCl_3$ | Cl | 2-($CH_3$-$SO_2$-NH)-fenilo | F | $CH_2CH_2F$ | F | 3-($CH_3$-$SO_2$-NH)-fenilo | F |
| $CH_2CCl_3$ | F | 3-($CH_3$-$SO_2$-NH)-fenilo | F | $CH_2CH_2F$ | Cl | fenilo | F |
| $CH_2CCl_3$ | Cl | 3-($CH_3$-$SO_2$-NH)-fenilo | F | $CH_2CH_2F$ | F | fenilo | F |
| | | | | $CH_2CH_2F$ | Cl | fenilo | F |
| $CH_2CCl_3$ | F | 3-($CH_3$-$SO_2$-NH)-fenilo | F | $CH_2CH_2F$ | F | 3-piridilo | F |
| | | | | $CH_2CH_2F$ | Cl | 3-piridilo | F |
| $CH_2CCl_3$ | Cl | fenilo | F | $CH_2CH_2F$ | F | 4-piridilo | F |
| $CH_2CCl_3$ | F | fenilo | F | $CH_2CH_2F$ | Cl | pirazolilo | F |

| $R_{1c}$ | X | Y | Z |
|---|---|---|---|
| | | pirazolilo | |
| $CH_2CH_2Cl$ | F | 4-piridilo | F |
| $CH_2CH_2Cl$ | Cl | 4-piridilo | F |
| $CH_2CH_2Cl$ | F | 2-($CH_3$-$SO_2$-NH)-fenilo | F |
| $CH_2CH_2Cl$ | Cl | 3-($CH_3$-$SO_2$-NH)-fenilo | F |
| $CH_2CH_2Cl$ | F | 3-($CH_3$-$SO_2$-NH)-fenilo | F |
| $CH_2CH_2Cl$ | Cl | 3-($CH_3$-$SO_2$-NH)-fenilo | F |
| $CH_2CH_2Cl$ | F | fenilo | F |
| $CH_2CH_2Cl$ | Cl | fenilo | F |
| | | fenilo | |
| $CH_2CH_2CH_2Cl$ | F | 3-piridilo | F |
| $CH_2CH_2CH_2Cl$ | Cl | 3-piridilo | F |
| $CH_2CH_2CH_2Cl$ | F | 4-piridilo | F |
| $CH_2CH_2CH_2Cl$ | Cl | pirazolilo | F |
| $CH_2CH_2CH_2Cl$ | F | pirazolilo | F |
| $CH_2CH_2CH_2Cl$ | Cl | 4-piridilo | F |
| $CH_2CH_2CH_2Cl$ | F | 4-piridilo | F |
| $CH_2CH_2CH_2Cl$ | Cl | 2-($CH_3$-$SO_2$-NH)-fenilo | F |

| $R_{1c}$ | X | Y | Z |
|---|---|---|---|
| | | 3-($CH_3$-$SO_2$-NH)-fenilo | |
| $CH_2CH_2OH$ | F | 3-($CH_3$-$SO_2$-NH)-fenilo | F |
| $CH_2CH_2OH$ | Cl | 3-($CH_3$-$SO_2$-NH)-fenilo | F |
| $CH_2CH_2OH$ | F | fenilo | F |
| $CH_2CH_2OH$ | Cl | fenilo | F |
| $CH_2CH_2OH$ | F | fenilo | F |
| $CH_2CH_2OH$ | Cl | 3-piridilo | F |
| $CH_2CH_2OH$ | F | 3-piridilo | F |
| $CH_2CH_2OH$ | Cl | 4-piridilo | F |
| | | pirazolilo | |
| $CH_2CH_2CH_2OH$ | F | pirazolilo | F |
| $CH_2CH_2CH_2OH$ | Cl | 4-piridilo | F |
| $CH_2CH_2CH_2OH$ | F | 4-piridilo | F |
| $CH_2CH_2CH_2OH$ | Cl | 2-($CH_3$-$SO_2$-NH)-fenilo | F |
| $CH_2CH_2CH_2OH$ | F | 3-($CH_3$-$SO_2$-NH)-fenilo | F |
| $CH_2CH_2CH_2OH$ | Cl | 3-($CH_3$-$SO_2$-NH)-fenilo | F |

| $R_{1c}$ | X | Y | Z |
|---|---|---|---|
| $CH_2CH_2CH_2OH$ | F | 3-($CH_3$-$SO_2$-NH)-fenilo | F |
| $CH_2CH_2CH_2OH$ | Cl | fenilo | F |
| | | fenilo | |
| $(CH_2)_4OH$ | F | fenilo | F |
| $(CH_2)_4OH$ | Cl | 3-piridilo | F |
| $(CH_2)_4OH$ | F | 3-piridilo | F |
| $(CH_2)_4OH$ | Cl | 4-piridilo | F |
| $(CH_2)_4OH$ | F | pirazolilo | F |
| $(CH_2)_4OH$ | Cl | pirazolilo | F |
| $(CH_2)_4OH$ | F | 4-piridilo | F |
| $(CH_2)_4OH$ | Cl | 4-piridilo | F |
| | | 2-($CH_3$-$SO_2$-NH)-fenilo | |
| $CH_2CH_2OCH_3$ | F | 3-($CH_3$-$SO_2$-NH)-fenilo | F |
| $CH_2CH_2OCH_3$ | Cl | 3-($CH_3$-$SO_2$-NH)-fenilo | F |
| $CH_2CH_2OCH_3$ | F | 3-($CH_3$-$SO_2$-NH)-fenilo | F |
| $CH_2CH_2OCH_3$ | Cl | fenilo | F |
| $CH_2CH_2OCH_3$ | F | fenilo | F |
| $CH_2CH_2OCH_3$ | Cl | fenilo | F |

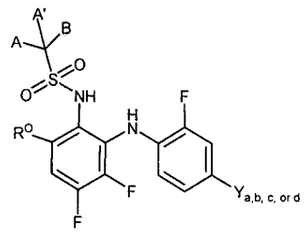
| $R_{1c}$ | X | Y | Z |
|---|---|---|---|
| $CH_2CH_2OCH_3$ | F | 3-piridilo | F |
| $CH_2CH_2OCH_3$ | Cl | 3-piridilo | F |
| | | 4-piridilo | |
| $(CH_2)_3OCH_3$ | F | pirazolilo | F |
| $(CH_2)_3OCH_3$ | Cl | pirazolilo | F |
| $(CH_2)_3OCH_3$ | F | 4-piridilo | F |
| $(CH_2)_3OCH_3$ | Cl | 4-piridilo | F |
| $(CH_2)_3OCH_3$ | F | 2-($CH_3$-$SO_2$-NH)-fenilo | F |
| $(CH_2)_3OCH_3$ | Cl | 3-($CH_3$-$SO_2$-NH)-fenilo | F |
| $(CH_2)_3OCH_3$ | F | 3-($CH_3$-$SO_2$-NH)-fenilo | F |
| $(CH_2)_3OCH_3$ | Cl | 3-($CH_3$-$SO_2$-NH)-fenilo | F |
| | | fenilo | |
| $CH_2CH_2OEt$ | F | fenilo | F |
| $CH_2CH_2OEt$ | Cl | fenilo | F |
| $CH_2CH_2OEt$ | F | 3-piridilo | F |
| $CH_2CH_2OEt$ | Cl | 3-piridilo | F |
| $CH_2CH_2OEt$ | F | 4-piridilo | F |
| $CH_2CH_2OEt$ | Cl | pirazolilo | F |
| $CH_2CH_2OEt$ | F | pirazolilo | F |

| $R_{1c}$ | X | Y | Z |
|---|---|---|---|
| $CH_2CH_2OEt$ | Cl | 4-piridilo | F |

479

Las Tablas 4a y 4b muestran formas de realización de esta invención que son compuestos de fórmula I, donde G = $R_{1d}$, Z es F, X es F y $R_{1d}$ y $R^0$ se definen en la tabla. Cada línea en la tabla corresponde a cinco especies que difieren sólo en la posición Y.

**Tabla 4a**




$Y_a$ = $CH_3$; $Y_b$ = Br; $Y_c$ = I; $Y_d$ = Cl;

| COMPUESTO NÚMERO | A, A' | B | $R^0$ |
|---|---|---|---|
| 1(a-d) | H, H | H | $OCH_3$ |
| 2(a-d) | H, H | H | $NHCH_3$ |
| 3(a-d) | H, H | H | $CH_2CH_3$ |
| 4(a-d) | H, H | H | $CH_2CH=CH_2$ |
| 5(a-d) | H, H | H | CN |
| 6(a-d) | H, H | H | $CF_3$ |
| 7(a-d) | H, H | H | F |
| 8(a-d) | H, H | H | $C_6H_6$ |
| 9(a-d) | H, H | $-CH_2CH(OH)CH_2OH$ | $OCH_3$ |
| 10(a-d) | H, H | $-CH_2CH(OH)CH_2OH$ | $NHCH_3$ |
| 11(a-d) | H, H | $-CH_2CH(OH)CH_2OH$ | $CH_2CH_3$ |
| 12(a-d) | $-(CH_2)_2-$ | $-CH_2(C_3H_5)$ | $OCH_3$ |

| COMPUESTO NÚMERO | A, A' | B | $R^0$ |
|---|---|---|---|
| 13(a-d) | $-(CH_2)_2-$ | $-CH_2(C_3H_5)$ | $NHCH_3$ |
| 14(a-d) | $-(CH_2)_2-$ | $-CH_2(C_3H_5)$ | $CH_2CH_3$ |
| 15(a-d) | $-(CH_2)_2-$ | $CH_3$ | F |
| 16(a-d) | $-(CH_2)_2-$ | $-CH_2CH_2OH$ | F |
| 17(a-d) | $-(CH_2)_2-$ | $-(CH_2)_2CH(OH)CH_2OH$ | F |
| 18(a-d) | $CH_3$, H | $-(CH_2)_2CH(OH)CH_2OH$ | F |
| 19(a-d) | $-(CH_2)_2-$ | $CH_3$ | $OCH_3$ |
| 20(a-d) | $-(CH_2)_2-$ | $-CH_2CH_2OH$ | $OCH_3$ |
| 21(a-d) | $-(CH_2)_2-$ | $-(CH_2)_2CH(OH)CH_2OH$ | $OCH_3$ |
| 22(a-d) | $CH_3$, H | $-(CH_2)_2CH(OH)CH_2OH$ | $OCH_3$ |
| 23(a-d) | $-(CH_2)_2-$ | $CH_3$ | H |
| 24(a-d) | $-(CH_2)_2-$ | $-CH_2CH_2OH$ | H |
| 25(a-d) | $-(CH_2)_2-$ | $-(CH_2)_2CH(OH)CH_2OH$ | H |
| 26(a-d) | $CH_3$, H | $-(CH_2)_2CH(OH)CH_2OH$ | H |
| 27(a-d) | H, H | H | $OCH_3$ |
| 28(a-d) | H, H | H | $NHCH_3$ |
| 29(a-d) | H, H | H | $CH_2CH_3$ |
| 30(a-d) | H, H | H | $CH_2CH=CH_2$ |
| 31(a-d) | H, H | H | CN |
| 32(a-d) | H, H | H | $CF_3$ |
| 33(a-d) | H, H | H | F |
| 34(a-d) | H, H | H | $C_6H_6$ |

| COMPUESTO NÚMERO | A, A' | B | $R^0$ |
|---|---|---|---|
| 35 (a-d) | H, H | $-CH_2CH(OH)CH_2OH$ | $OCH_3$ |
| 36 (a-d) | H, H | $-CH_2CH(OH)CH_2OH$ | $NHCH_3$ |
| 37 (a-d) | H, H | $-CH_2CH(OH)CH_2OH$ | $CH_2CH_3$ |
| 38 (a-d) | $-(CH_2)_2-$ | $-CH_2(C_3H_5)$ | $OCH_3$ |
| 39 (a-d) | $-(CH_2)_2-$ | $-CH_2(C_3H_5)$ | $NHCH_3$ |
| 40 (a-d) | $-(CH_2)_2-$ | $-CH_2(C_3H_5)$ | $CH_2CH_3$ |
| 41 (a-d) | $-(CH_2)_2-$ | $CH_3$ | F |
| 42 (a-d) | $-(CH_2)_2-$ | $-CH_2CH_2OH$ | F |
| 43 (a-d) | $-(CH_2)_2-$ | $-(CH_2)_2CH(OH)CH_2OH$ | F |
| 44 (a-d) | $CH_3$, H | $-(CH_2)_2CH(OH)CH_2OH$ | F |
| 45 (a-d) | $-(CH_2)_2-$ | $CH_3$ | $OCH_3$ |
| 46 (a-d) | $-(CH_2)_2-$ | $-CH_2CH_2OH$ | $OCH_3$ |
| 47 (a-d) | $-(CH_2)_2-$ | $-(CH_2)_2CH(OH)CH_2OH$ | $OCH_3$ |
| 48 (a-d) | $CH_3$, H | $-(CH_2)_2CH(OH)CH_2OH$ | $OCH_3$ |
| 49 (a-d) | $-(CH_2)_2-$ | $CH_3$ | H |
| 50 (a-d) | $-(CH_2)_2-$ | $-CH_2CH_2OH$ | H |
| 51 (a-d) | $-(CH_2)_2-$ | $-(CH_2)_2CH(OH)CH_2OH$ | H |
| 52 (a-d) | $CH_3$, H | $-(CH_2)_2CH(OH)CH_2OH$ | H |

**Tabla 4b**

| COMPUESTO NÚMERO | A, A' | B | $R^0$ |
|---|---|---|---|
| 1 (a-d) | H, H | H | 2-furanilo |

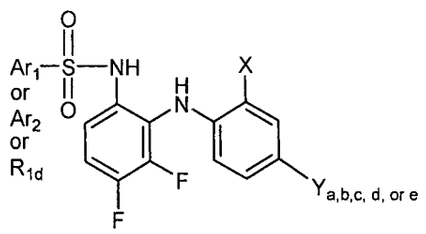
| COMPUESTO NÚMERO | A, A' | B | $R^0$ |
|---|---|---|---|
| 2(a-d) | H, H | H | 1,2,3 triazolil-4-ilo |
| 3(a-d) | H, H | H | 4-imidazolilo |
| 4(a-d) | H, H | H | 2-furanilo |
| 5(a-d) | H, H | H | 1,2,3 triazolil-4-ilo |
| 6(a-d) | H, H | H | 4-imidazolilo |
| 7(a-d) | H, H | $-(CH_2)_2CH(OH)CH_2OH$ | 2-furanilo |
| 8(a-d) | H, H | $-(CH_2)_2CH(OH)CH_2OH$ | 1,2,3 triazolil-4-ilo |
| 9(a-d) | H, H | $-(CH_2)_2CH(OH)CH_2OH$ | 4-imidazolilo |
| 10(a-d) | $-(CH_2)_2-$ | $-CH_2(C_3H_5)$ | 2-furanilo |
| 11(a-d) | $-(CH_2)_2-$ | $-CH_2(C_3H_5)$ | 1,2,3 triazolil-4-ilo |
| 12(a-d) | $-(CH_2)_2-$ | $-CH_2(C_3H_5)$ | 4-imidazolilo |
| 13(a-d) | $-(CH_2)_2-$ | $CH_3$ | 4-tiazolilo |
| 14(a-d) | $-(CH_2)_2-$ | $-CH_2CH_2OH$ | 4-tiazolilo |
| 15(a-d) | $-(CH_2)_2-$ | $-(CH_2)_2CH(OH)CH_2OH$ | 4-tiazolilo |
| 16(a-d) | $CH_3$, H | $-(CH_2)_2CH(OH)CH_2OH$ | 4-tiazolilo |
| 17(a-d) | $-(CH_2)_2-$ | $CH_3$ | 2-oxazolilo |
| 18(a-d) | $-(CH_2)_2-$ | $-CH_2CH_2OH$ | 2-oxazolilo |
| 19(a-d) | $-(CH_2)_2-$ | $-(CH_2)_2CH(OH)CH_2OH$ | 2-oxazolilo |

| COMPUESTO NÚMERO | A, A' | B | $R^0$ |
|---|---|---|---|
| 20(a-d) | $CH_3$, H | $-(CH_2)_2CH(OH)CH_2OH$ | 2-oxazolilo |
| 21(a-d) | H, H | H | 2-furanilo |
| 22(a-d) | H, H | H | 1,2,3 triazolil-4-ilo |
| 23(a-d) | H, H | H | 4-imidazolilo |
| 24(a-d) | H, H | H | 2-furanilo |
| 25(a-d) | H, H | H | 1,2,3 triazolil-4-ilo |
| 26(a-d) | H, H | H | 4-imidazolilo |
| 27(a-d) | H, H | $-CH_2CH(OH)CH_2OH$ | 2-furanilo |
| 28(a-d) | H, H | $-CH_2CH(OH)CH_2OH$ | 1,2,3 triazolil-4-ilo |
| 29(a-d) | H, H | $-CH_2CH(OH)CH_2OH$ | 4-imidazolilo |
| 30(a-d) | $-(CH_2)_2-$ | $-CH_2(C_3H_5)$ | 2-furanilo |
| 31(a-d) | $-(CH_2)_2-$ | $-CH_2(C_3H_5)$ | 1,2,3 triazolil-4-ilo |
| 32(a-d) | $-(CH_2)_2-$ | $-CH_2(C_3H_5)$ | 4-imidazolilo |
| 33(a-d) | $-(CH_2)_2-$ | $CH_3$ | 4-tiazolilo |
| 34(a-d) | $-(CH_2)_2-$ | $-CH_2CH_2OH$ | 4-tiazolilo |
| 35(a-d) | $-(CH_2)_2-$ | $-(CH_2)_2CH(OH)CH_2OH$ | 4-tiazolilo |
| 36(a-d) | $CH_3$, H | $-(CH_2)_2CH(OH)CH_2OH$ | 4-tiazolilo |
| 37(a-d) | $-(CH_2)_2-$ | $CH_3$ | 2-oxazolilo |

| COMPUESTO NÚMERO | A, A' | B | $R^0$ |
|---|---|---|---|
| **38(a-d)** | $-(CH_2)_2-$ | $-CH_2CH_2OH$ | 2-oxazolilo |
| **39(a-d)** | $-(CH_2)_2-$ | $-(CH_2)_2CH(OH)CH_2OH$ | 2-oxazolilo |
| **40(a-d)** | $CH_3$, H | $-(CH_2)_2CH(OH)CH_2OH$ | 2-oxazolilo |

La Tabla 5a muestra formas de realización de esta invención que son compuestos de fórmula I, donde G es $Ar_1$, $Ar_2$ o $R_{1d}$, y donde $R^0$ es H, Z es F y G y X se definen en la tabla. Cada línea en la tabla corresponde a cinco especies ($Y_a$, $Y_b$, $Y_c$, $Y_d$ e $Y_e$) que difieren sólo en la posición Y, donde $Y_a$ = $SCH_3$; $Y_b$ = Br; $Y_c$ = I; $Y_d$ = Cl; $Y_e$ = $CH_3$.

**Tabla 5a**




$Y_a$ = $SCH_3$; $Y_b$ = Br; $Y_c$ = I; $Y_d$ = Cl; $Y_e$ = $CH_3$

| Compuesto Nro. | G = $R_{1d}$, $Ar_1$, o $Ar_2$ | X |
|---|---|---|
| 1 (a-e) | fenilo | Cl |
| 2 (a-e) | fenilo | F |
| 3 (a-e) | 2-F-fenilo | Cl |
| 4 (a-e) | 2-F-fenilo | F |
| 5 (a-e) | 3-F-fenilo | Cl |
| 6 (a-e) | 3-F-fenilo | F |

485

| Compuesto Nro. | G = $R_{1d}$, $Ar_1$, o $Ar_2$ | X |
|---|---|---|
| 7 (a-e) | 4-F-fenilo | Cl |
| 8 (a-e) | 4-F-fenilo | F |
| 9 (a-e) | 2,4-di-F-fenilo | Cl |
| 10 (a-e) | 2,4-di-F-fenilo | F |
| 11 (a-e) | 2,5-di-F-fenilo | Cl |
| 12 (a-e) | 2,5-di-F-fenilo | F |
| 13 (a-e) | 2,6-di-F-fenilo | Cl |
| 14 (a-e) | 2,6-di-F-fenilo | F |
| 15 (a-e) | 3,4-di-F-fenilo | Cl |
| 16 (a-e) | 3,4-di-F-fenilo | F |
| 17 (a-e) | 3,5-di-F-fenilo | Cl |
| 18 (a-e) | 3,5-di-F-fenilo | F |
| 19 (a-e) | 2,6-di-F-fenilo | Cl |
| 20 (a-e) | 2,6-di-F-fenilo | F |
| 21 (a-e) | 2,3,4-tri-F-fenilo | Cl |
| 22 (a-e) | 2,3,4-tri-F-fenilo | F |
| 23 (a-e) | 3,4,5-tri-F-fenilo | Cl |
| 24 (a-e) | 3,4,5-tri-F-fenilo | F |
| 25 (a-e) | penta-F-fenilo | Cl |
| 26 (a-e) | penta-F-fenilo | F |
| 27 (a-e) | 3-Cl-4-F-fenilo | Cl |
| 28 (a-e) | 3-Cl-4-F-fenilo | F |

486

| Compuesto Nro. | G = $R_{1d}$, $Ar_1$, o $Ar_2$ | X |
|---|---|---|
| 29 (a-e) | 2-Cl-4-F-fenilo | Cl |
| 30 (a-e) | 2-Cl-4-F-fenilo | F |
| 31 (a-e) | 2-F-3-Cl-fenilo | Cl |
| 32 (a-e) | 2-F-3-Cl-fenilo | F |
| 33 (a-e) | 2-F-4-Cl-fenilo | Cl |
| 34 (a-e) | 2-F-4-Cl-fenilo | F |
| 35 (a-e) | 2-F-5-Cl-fenilo | Cl |
| 36 (a-e) | 2-F-5-Cl-fenilo | F |
| 37 (a-e) | 3-ciano-4-F-fenilo | Cl |
| 38 (a-e) | 3-ciano-4-F-fenilo | F |
| 39 (a-e) | 2-Cl-fenilo | Cl |
| 40 (a-e) | 2-Cl-fenilo | F |
| 41 (a-e) | 3-Cl-fenilo | Cl |
| 42 (a-e) | 3-Cl-fenilo | F |
| 43 (a-e) | 4-Cl-fenilo | Cl |
| 44 (a-e) | 4-Cl-fenilo | F |
| 45 (a-e) | 2,3-di-Cl-fenilo | Cl |
| 46 (a-e) | 2,3-di-Cl-fenilo | F |
| 47 (a-e) | 2,5-di-Cl-fenilo | Cl |
| 48 (a-e) | 2,5-di-Cl-fenilo | F |
| 49 (a-e) | 2,6-di-Cl-fenilo | Cl |
| 50 (a-e) | 2,6-di-Cl-fenilo | F |

487

| Compuesto Nro. | G = $R_{1d}$, $Ar_1$, o $Ar_2$ | X |
|---|---|---|
| 51 (a-e) | 3,5-di-Cl-fenilo | Cl |
| 52 (a-e) | 3,5-di-Cl-fenilo | F |
| 53 (a-e) | 2,4-di-Cl-fenilo | Cl |
| 54 (a-e) | 2,4-di-Cl-fenilo | F |
| 55 (a-e) | 3,4-di-Cl-fenilo | Cl |
| 56 (a-e) | 3,4-di-Cl-fenilo | F |
| 57 (a-e) | 2,4,6-tri-Cl-fenilo | Cl |
| 58 (a-e) | 2,4,6-tri-Cl-fenilo | F |
| 59 (a-e) | 2-Cl-4-$CF_3$-fenilo | Cl |
| 60 (a-e) | 2-Cl-4-$CF_3$-fenilo | F |
| 61 (a-e) | 2-$CF_3$-fenilo | Cl |
| 62 (a-e) | 2-$CF_3$-fenilo | F |
| 63 (a-e) | 3-$CF_3$-fenilo | Cl |
| 64 (a-e) | 3-$CF_3$-fenilo | F |
| 65 (a-e) | 4-$CF_3$-fenilo | Cl |
| 66 (a-e) | 4-$CF_3$-fenilo | F |
| 67 (a-e) | 2-$CF_3O$ fenilo | Cl |
| 68 (a-e) | 2-$CF_3O$ fenilo | F |
| 69 (a-e) | 3-$CF_3O$ fenilo | Cl |
| 70 (a-e) | 3-$CF_3O$ fenilo | F |
| 71 (a-e) | 4-$CF_3O$ fenilo | Cl |
| 72 (a-e) | 4-$CF_3O$ fenilo | F |

| Compuesto Nro. | G = $R_{1d}$, $Ar_1$, o $Ar_2$ | X |
|---|---|---|
| 73 (a-e) | 2-$CHF_2O$ fenilo | Cl |
| 74 (a-e) | 2-$CHF_2O$ fenilo | F |
| 75 (a-e) | 2-metil-5-nitro-fenilo | Cl |
| 76 (a-e) | 2-metil-5-nitro-fenilo | F |
| 77 (a-e) | 2-ciano-fenilo | Cl |
| 78 (a-e) | 2-ciano-fenilo | F |
| 79 (a-e) | 3-ciano-fenilo | Cl |
| 80 (a-e) | 3-ciano-fenilo | F |
| 81 (a-e) | 4-ciano-fenilo | Cl |
| 82 (a-e) | 4-ciano-fenilo | F |
| 83 (a-e) | 4-metoxi-fenilo | Cl |
| 84 (a-e) | 4-metoxi-fenilo | F |
| 85 (a-e) | 3,4-dimetoxi-fenilo | Cl |
| 86 (a-e) | 3,4-dimetoxi-fenilo | F |
| 87 (a-e) | 3-carbamil-fenilo | Cl |
| 88 (a-e) | 3-carbamil-fenilo | F |
| 89 (a-e) | 3-carboxil-fenilo | Cl |
| 90 (a-e) | 3-carboxil-fenilo | F |
| 91 (a-e) | 3-(N,N-dimetilcarbamoil)fenilo | Cl |
| 92 (a-e) | 3-(N,N-dimetilcarbamoil)fenilo | F |
| 93 (a-e) | 4-metilsulfonil-fenilo | Cl |
| 94 (a-e) | 4-metilsulfonil-fenilo | F |

2189

| Compuesto Nro. | G = $R_{1d}$, $Ar_1$, o $Ar_2$ | X |
|---|---|---|
| 95 (a-e) | 3-(1,3,4 oxadiazol-2-il)fenilo | Cl |
| 96 (a-e) | 3-(1,3,4 oxadiazol-2-il)fenilo | F |
| 97 (a-e) | 3-(1,3,4 tiadiazol-2-il)fenilo | Cl |
| 98 (a-e) | 3-(1,3,4 tiadiazol-2-il)fenilo | F |
| 99 (a-e) | 3-(5-metil-1-1,3,4-oxadiazol)fenilo | Cl |
| 100 (a-e) | 3-(5-metil-1-1,3,4-oxadiazol)fenilo | F |
| 101 (a-e) | 3-(5-metil-1-1,3,4-tiadiazol)fenilo | Cl |
| 102 (a-e) | 3-(5-metil-1-1,3,4-tiadiazol)fenilo | F |
| 103 (a-e) | 3-amidinil-fenilo | Cl |
| 104 (a-e) | 3-amidinil-fenilo | F |
| 105 (a-e) | 3-(1H-tetrazolil)fenilo | Cl |
| 106 (a-e) | 3-(1H-tetrazolil)fenilo | F |
| 107 (a-e) | 4-acetamido-fenilo | Cl |
| 108 (a-e) | 4-acetamido-fenilo | F |
| 109 (a-e) | 3-Cl-4-[(N-morfolinilcarbonil)amino]fenilo | Cl |
| 110 (a-e) | 3-Cl-4-[(N-morfolinilcarbonil)amino]fenilo | F |
| 111 (a-e) | 3-Cl-4-[(N-pirrolidinilcarbonil)amino]fenilo | Cl |
| 112 (a-e) | 3-Cl-4-[(N-pirrolidinilcarbonil)amino]fenilo | F |

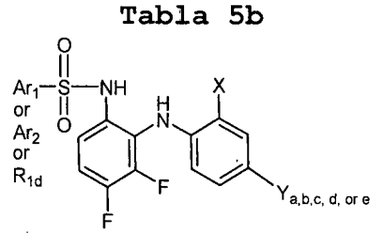
| Compuesto Nro. | G = $R_{1d}$, $Ar_1$, o $Ar_2$ | X |
|---|---|---|
| 113 (a-e) | 3,5-dimetilisoxazolilo | Cl |
| 114 (a-e) | 3,5-dimetilisoxazolilo | F |
| 115 (a-e) | 4-(N-morfolinilsulfonil)fenilo | Cl |
| 116 (a-e) | 4-(N-morfolinilsulfonil)fenilo | F |
| 117 (a-e) | 3-F-bencilo | Cl |
| 118 (a-e) | 3-F-bencilo | F |
| 119 (a-e) | 4-F-bencilo | Cl |
| 120 (a-e) | 4-F-bencilo | F |
| 121 (a-e) | 3-F-fenil-etilo | Cl |
| 122 (a-e) | 3-F-fenil-etilo | F |
| 123 (a-e) | 4-F-fenil-etilo | Cl |
| 124 (a-e) | 4-F-fenil-etilo | F |
| 125 (a-e) | 8-quinolinilo | Cl |
| 126 (a-e) | 8-quinolinilo | F |
| 127 (a-e) | 2-tienilo | Cl |
| 128 (a-e) | 2-tienilo | F |
| 129 (a-e) | 2,3-di-Cl-tien-5-ilo | Cl |
| 130 (a-e) | 2,3-di-Cl-tien-5-ilo | F |
| 131 (a-e) | 1,3,5 trimetil-1H-pirazolilo | Cl |
| 132 (a-e) | 1,3,5 trimetil-1H-pirazolilo | F |
| 133 (a-e) | 1,3-dimetil-5-Cl-1H-pirazolilo | Cl |
| 134 (a-e) | 1,3-dimetil-5-Cl-1H-pirazolilo | F |

491

| Compuesto Nro. | G = $R_{1d}$, $Ar_1$, o $Ar_2$ | X |
|---|---|---|
| 135 (a-e) | 1-metil-3$CF_3$-1H-pirazol-4-ilo | Cl |
| 136 (a-e) | 1-metil-3$CF_3$-1H-pirazol-4-ilo | F |
| 137 (a-e) | 2-acetamido-4-metil-tiazol-5-ilo | Cl |
| 138 (a-e) | 2-acetamido-4-metil-tiazol-5-ilo | F |
| 139 (a-e) | 2,4-dimetil-tiazol-5-ilo | Cl |
| 140 (a-e) | 2,4-dimetil-tiazol-5-ilo | F |
| 141 (a-e) | 1,2-dimetil-1H-imidazol-4-ilo | Cl |
| 142 (a-e) | 1,2-dimetil-1H-imidazol-4-ilo | F |

La Tabla 5b muestra formas de realización de esta invención que son compuestos de fórmula I, donde G es $Ar_1$, $Ar_2$ o $R_{1d}$, y donde $R^0$ es H, Z es F y G y X se definen en la tabla. Cada línea en la tabla corresponde a cinco especies ($Y_a$, $Y_b$, $Y_c$, $Y_d$ e $Y_e$) que difieren sólo en la posición Y, donde $Y_a$ = fenilo; $Y_b$ = fenilo 3-sustituido; $Y_c$ = 3-piridilo; $Y_d$ = 4-piridilo; $Y_e$ = 3-pirazolilo.

**Tabla 5b**




$Y_a$ = fenilo; $Y_b$ = fenilo 3-sustituido; $Y_c$ = 3-piridilo; $Y_d$ = 4-piridilo; $Y_e$ = 3-pirazolilo

| Compuesto Nro | G = $R_{1d}$, $Ar_1$, o $Ar_2$ | X |
|---|---|---|

492

| Compuesto Nro | G = $R_{1d}$, $Ar_1$, o $Ar_2$ | X |
|---|---|---|
| 1 (a-e) | fenilo | Cl |
| 2 (a-e) | fenilo | F |
| 3 (a-e) | 2-F-fenilo | Cl |
| 4 (a-e) | 2-F-fenilo | F |
| 5 (a-e) | 3-F-fenilo | Cl |
| 6 (a-e) | 3-F-fenilo | F |
| 7 (a-e) | 4-F-fenilo | Cl |
| 8 (a-e) | 4-F-fenilo | F |
| 9 (a-e) | 2,4-di-F-fenilo | Cl |
| 10 (a-e) | 2,4-di-F-fenilo | F |
| 11 (a-e) | 2,5-di-F-fenilo | Cl |
| 12 (a-e) | 2,5-di-F-fenilo | F |
| 13 (a-e) | 2,6-di-F-fenilo | Cl |
| 14 (a-e) | 2,6-di-F-fenilo | F |
| 15 (a-e) | 3,4-di-F-fenilo | Cl |
| 16 (a-e) | 3,4-di-F-fenilo | F |
| 17 (a-e) | 3,5-di-F-fenilo | Cl |
| 18 (a-e) | 3,5-di-F-fenilo | F |
| 19 (a-e) | 2,6-di-F-fenilo | Cl |
| 20 (a-e) | 2,6-di-F-fenilo | F |
| 21 (a-e) | 2,3,4-tri-F-fenilo | Cl |
| 22 (a-e) | 2,3,4-tri-F-fenilo | F |
| 23 (a-e) | 3,4,5-tri-F-fenilo | Cl |

| Compuesto Nro | G = $R_{1d}$, $Ar_1$, o $Ar_2$ | X |
|---|---|---|
| 24 (a-e) | 3,4,5-tri-F-fenilo | F |
| 25 (a-e) | penta-F-fenilo | Cl |
| 26 (a-e) | penta-F-fenilo | F |
| 27 (a-e) | 3-Cl-4-F-fenilo | Cl |
| 28 (a-e) | 3-Cl-4-F-fenilo | F |
| 29 (a-e) | 2-Cl-4-F-fenilo | Cl |
| 30 (a-e) | 2-Cl-4-F-fenilo | F |
| 31 (a-e) | 2-F-3-Cl-fenilo | Cl |
| 32 (a-e) | 2-F-3-Cl-fenilo | F |
| 33 (a-e) | 2-F-4-Cl-fenilo | Cl |
| 34 (a-e) | 2-F-4-Cl-fenilo | F |
| 35 (a-e) | 2-F-5-Cl-fenilo | Cl |
| 36 (a-e) | 2-F-5-Cl-fenilo | F |
| 37 (a-e) | 3-ciano-4-F-fenilo | Cl |
| 38 (a-e) | 3-ciano- 4-F-fenilo | F |
| 39 (a-e) | 2-Cl-fenilo | Cl |
| 40 (a-e) | 2-Cl-fenilo | F |
| 41 (a-e) | 3-Cl-fenilo | Cl |
| 42 (a-e) | 3-Cl-fenilo | F |
| 43 (a-e) | 4-Cl-fenilo | Cl |
| 44 (a-e) | 4-Cl-fenilo | F |
| 45 (a-e) | 2,3-di-Cl-fenilo | Cl |
| 46 (a-e) | 2,3-di-Cl-fenilo | F |

494

| Compuesto Nro | G = $R_{1d}$, $Ar_1$, o $Ar_2$ | X |
|---|---|---|
| 47 (a-e) | 2,5-di-Cl-fenilo | Cl |
| 48 (a-e) | 2,5-di-Cl-fenilo | F |
| 49 (a-e) | 2,6-di-Cl-fenilo | Cl |
| 50 (a-e) | 2,6-di-Cl-fenilo | F |
| 51 (a-e) | 3,5-di-Cl-fenilo | Cl |
| 52 (a-e) | 3,5-di-Cl-fenilo | F |
| 53 (a-e) | 2,4-di-Cl-fenilo | Cl |
| 54 (a-e) | 2,4-di-Cl-fenilo | F |
| 55 (a-e) | 3,4-di-Cl-fenilo | Cl |
| 56 (a-e) | 3,4-di-Cl-fenilo | F |
| 57 (a-e) | 2,4,6-tri-Cl-fenilo | Cl |
| 58 (a-e) | 2,4,6-tri-Cl-fenilo | F |
| 59 (a-e) | 2-Cl-4-$CF_3$-fenilo | Cl |
| 60 (a-e) | 2-Cl-4-$CF_3$-fenilo | F |
| 61 (a-e) | 2-$CF_3$-fenilo | Cl |
| 62 (a-e) | 2-$CF_3$-fenilo | F |
| 63 (a-e) | 3-$CF_3$-fenilo | Cl |
| 64 (a-e) | 3-$CF_3$-fenilo | F |
| 65 (a-e) | 4-$CF_3$-fenilo | Cl |
| 66 (a-e) | 4-$CF_3$-fenilo | F |
| 67 (a-e) | 2-$CF_3O$ fenilo | Cl |
| 68 (a-e) | 2-$CF_3O$ fenilo | F |
| 69 (a-e) | 3-$CF_3O$ fenilo | Cl |

2495

| Compuesto Nro | G = $R_{1d}$, $Ar_1$, o $Ar_2$ | X |
|---|---|---|
| 70 (a-e) | 3-$CF_3O$ fenilo | F |
| 71 (a-e) | 4-$CF_3O$ fenilo | Cl |
| 72 (a-e) | 4-$CF_3O$ fenilo | F |
| 73 (a-e) | 4-$CHF_2O$-fenilo | Cl |
| 74 (a-e) | 4-$CHF_2O$-fenilo | F |
| 75 (a-e) | 2-metil-5-nitro-fenilo | Cl |
| 76 (a-e) | 2-metil-5-nitro-fenilo | F |
| 77 (a-e) | 2-ciano-fenilo | Cl |
| 78 (a-e) | 2-ciano-fenilo | F |
| 79 (a-e) | 3-ciano-fenilo | Cl |
| 80 (a-e) | 3-ciano-fenilo | F |
| 81 (a-e) | 4-ciano-fenilo | Cl |
| 82 (a-e) | 4-ciano-fenilo | F |
| 83 (a-e) | 4-metoxi-fenilo | Cl |
| 84 (a-e) | 4-metoxi-fenilo | F |
| 85 (a-e) | 3,4-dimetoxi-fenilo | Cl |
| 86 (a-e) | 3,4-dimetoxi-fenilo | F |
| 87 (a-e) | 3-carbamil-fenilo | Cl |
| 88 (a-e) | 3-carbamil-fenilo | F |
| 89 (a-e) | 3-carboxil-fenilo | Cl |
| 90 (a-e) | 3-carboxil- fenilo | F |
| 91 (a-e) | 3-(N,N-dimetilcarbamoil)fenilo | Cl |

| Compuesto Nro | G = $R_{1d}$, $Ar_1$, o $Ar_2$ | X |
|---|---|---|
| 92 (a-e) | 3-(N,N-dimetilcarbamoil)fenilo | F |
| 93 (a-e) | 4-metilsulfonil-fenilo | Cl |
| 94 (a-e) | 4-metilsulfonil-fenilo | F |
| 95 (a-e) | 3-(1,3,4 oxadiazol-2-il)fenilo | Cl |
| 96 (a-e) | 3-(1,3,4 oxadiazol-2-il)fenilo | F |
| 97 (a-e) | 3-(1,3,4 tiadiazol-2-il)fenilo | Cl |
| 98 (a-e) | 3-(1,3,4 tiadiazol-2-il)fenilo | F |
| 99 (a-e) | 3-(5-metil-1,3,4-oxadiazol)fenilo | Cl |
| 100 (a-e) | 3-(5-metil-1,3,4-oxadiazol)fenilo | F |
| 101 (a-e) | 3-(5-metil-1,3,4-tiadiazol)fenilo | Cl |
| 102 (a-e) | 3-(5-metil-1,3,4-tiadiazol)fenilo | F |
| 103 (a-e) | 3-amidinil-fenilo | Cl |
| 104 (a-e) | 3-amidinil-fenilo | F |
| 105 (a-e) | 3-(1H-tetrazolil)fenilo | Cl |

497

| Compuesto Nro | G = $R_{1d}$, $Ar_1$, o $Ar_2$ | X |
|---|---|---|
| 106 (a-e) | 3-(1H-tetrazolil)fenilo | F |
| 107 (a-e) | 4-acetamido-fenilo | Cl |
| 108 (a-e) | 4-acetamido-fenilo | F |
| 109 (a-e) | 3-Cl-4-[(N-morfolinilcarbonilo) amino]fenilo | Cl |
| 110 (a-e) | 3-Cl-4-[(N-morfolinilcarbonilo) amino]fenilo | F |
| 111 (a-e) | 3-Cl-4-[(N-pirrolidinilcarbonilo) amino]fenilo | Cl |
| 112 (a-e) | 3-Cl-4-[(N-pirrolidinilcarbonilo) amino]fenilo | F |
| 113 (a-e) | 3,5-dimetilisoxazolilo | Cl |
| 114 (a-e) | 3,5-dimetilisoxazolilo | F |
| 115 (a-e) | 4-(N-morfolinilsulfonil)fenilo | Cl |
| 116 (a-e) | 4-(N-morfolinilsulfonil)fenilo | F |
| 117 (a-e) | 3-F-bencilo | Cl |
| 118 (a-e) | 3-F-bencilo | F |

498

| Compuesto Nro | G = $R_{1d}$, $Ar_1$, o $Ar_2$ | X |
|---|---|---|
| 119 (a-e) | 4-F-bencilo | Cl |
| 120 (a-e) | 4-F-bencilo | F |
| 121 (a-e) | 3-F-fenil-etilo | Cl |
| 122 (a-e) | 3-F-fenil-etilo | F |
| 123 (a-e) | 4-F-fenil-etilo | Cl |
| 124 (a-e) | 4-F-fenil-etilo | F |
| 125 (a-e) | 8-quinolinilo | Cl |
| 126 (a-e) | 8-quinolinilo | F |
| 127 (a-e) | 2-tienilo | Cl |
| 128 (a-e) | 2-tienilo | F |
| 129 (a-e) | 2,3-di-Cl-tien-5-ilo | Cl |
| 130 (a-e) | 2,3-di-Cl-tien-5-ilo | F |
| 131 (a-e) | 1,3,5 trimetil-1H-pirazolilo | Cl |
| 132 (a-e) | 1,3,5 trimetil-1H-pirazolilo | F |
| 133 (a-e) | 1,3-dimetil-5-Cl-1H-pirazolilo | Cl |
| 134 (a-e) | 1,3-dimetil-5-Cl-1H-pirazolilo | F |
| 135 (a-e) | 1-metil-3-$CF_3$-1H-pirazol-4-ilo | Cl |
| 136 (a-e) | 1-metil-3-$CF_3$-1H-pirazol-4-ilo | F |
| 137 (a-e) | 2-acetamido-4-metil-tiazol- | Cl |

| Compuesto Nro | G = $R_{1d}$, $Ar_1$, o $Ar_2$ | X |
|---|---|---|
| | 5-ilo | |
| 138 (a-e) | 2-acetamido-4-metil-tiazol-5-ilo | F |
| 139 (a-e) | 2,4-dimetil-tiazol-5-ilo | Cl |
| 140 (a-e) | 2,4-dimetil-tiazol-5-ilo | F |
| 141 (a-e) | 1,2-dimetil-1H-imidazol-4-ilo | Cl |
| 142 (a-e) | 1,2-dimetil-1H-imidazol-4-ilo | F |
| 143 (a-e) | 1-(2-hidroxietilo) ciclopropilo | F |
| 144 (a-e) | 1-(3-hidroxipropil)ciclopropilo | F |
| 145 (a-e) | 1-(2,3-dihidroxipropil)ciclopropilo | F |
| 146 (a-e) | 1-(3,4-dihidroxibutilo) ciclopropilo | F |
| 147 (a-e) | 1-(2,3-dihidroxipropil)ciclobutilo | F |

***Procedimientos de síntesis***

En otro aspecto, se proveen métodos para sintetizar los compuestos descritos aquí. En algunas formas de realización, los compuestos descritos aquí se pueden obtener según los métodos que se describen a continuación. La intención de los

procedimientos y ejemplos siguientes es ilustrar dichos métodos. Ni los procedimientos ni los ejemplos deben considerarse como limitantes de la invención en sentido alguno. Los compuestos descritos aquí también se pueden sintetizar usando técnicas sintéticas estándar conocidas por aquellos versados en el arte o usando métodos conocidos en el arte en combinación con métodos descritos aquí. Además, los solventes, temperaturas y otras condiciones de reacción que se presentan aquí pueden variar de acuerdo a la práctica y el conocimiento de aquellos versados en el arte.

Los materiales de partida para la síntesis de los compuestos como se describe en la presente se pueden obtener de fuentes comerciales, tales como Aldrich Chemical Co. (Milwaukee, Wis.), Sigma Chemical Co. (St. Louis, Mo.), o los materiales de partida se pueden sintetizar. Los compuestos descritos aquí, y otros compuestos con diferentes sustituyentes se pueden sintetizar usando técnicas y materiales conocidos por aquellos versados en el arte, tal como se describe, por ejemplo, en March, ADVANCED ORGANIC CHEMISTRY 4th Ed., (Wiley 1992); Carey y Sundberg, ADVANCED ORGANIC CHEMISTRY 4th Ed., Vols. A y B (Plenum 2000, 2001), y Green y Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS 3rd Ed., (Wiley 1999) (todos lo cuales se incorporan como referencia en su totalidad). Los métodos generales para la preparación de compuestos como se revela aquí pueden derivarse de

501

reacciones conocidas en el campo, y las reacciones se pueden modificar mediante el uso de reactivos y condiciones apropiadas, según será reconocible por la persona versada en el arte, para la introducción de varias porciones encontradas en las fórmulas según se provee aquí. A modo de guía se pueden utilizar los siguientes métodos sintéticos.

Formación de uniones covalentes mediante la reacción de un electrófilo con un nucleófilo

Los compuestos descritos aquí se pueden modificar usando diversos electrófilos o nucleófilos para formar nuevos grupos funcionales o sustituyentes. La tabla siguiente titulada "Ejemplos de uniones covalentes y sus precursores" enumera ejemplos seleccionados de uniones covalentes y grupos funcionales precursores los cuales proveen y pueden usarse como guía para la variedad de combinaciones de electrófilos y nucleófilos disponibles. Los grupos funcionales precursores se muestran como grupos electrofílicos y grupos nucleofílicos.

| producto de la unión covalente | Electrófilo | Nucleófilo |
|---|---|---|
| Carboxamidas | ésteres activados | Aminas/anilinas |
| Carboxamidas | azidas de acilo | Aminas/anilinas |
| Carboxamidas | Halogenuros de | Aminas/anilinas |

502

| | | |
|---|---|---|
| | acilo | |
| Ésteres | Halogenuros de acilo | Alcoholes/fenoles |
| Ésteres | Nitrilos de acilo | Alcoholes/fenoles |
| Carboxamidas | Nitrilos de acilo | Aminas/anilinas |
| Iminas | Aldehidos | Aminas/anilinas |
| Hidrazones | Aldehidos o cetonas | Hidrazines |
| Oximes | Aldehidos o cetonas | Hidroxilaminas |
| Alquilo aminas | Halogenuros de alquilo | Aminas/anilinas |
| Ésteres | Halogenuros de alquilo | Ácidos carboxílicos |
| Tioéteres | Halogenuros de alquilo | Tioles |
| Éteres | Halogenuros de alquilo | Alcoholes/fenoles |
| Tioéteres | Sulfonatos de alquilo | Tioles |
| Ésteres | Sulfonatos de alquilo | Ácidos carboxílicos |

503

| | | |
|---|---|---|
| Éteres | Sulfonatos de alquilo | Alcoholes/fenoles |
| Ésteres | Anhídridos | Alcoholes/fenoles |
| Carboxamidas | Anhídridos | Aminas/anilinas |
| Tiofenoles | Halogenuros de arilo | Tioles |
| Arilo aminas | Halogenuros de arilo | Aminas |
| Tioéteres | Aziridinas | Tioles |
| ésteres de boronato | Boronatos | Glicoles |
| Carboxamidas | Ácidos carboxílicos | Aminas/anilinas |
| Ésteres | Ácidos carboxílicos | Alcoholes |
| Hidrazinas | Hidrazidas | Ácidos carboxílicos |
| *N*-acilureas o Anhídridos | Carbodiimidas | Ácidos carboxílicos |
| Ésteres | Diazoalcanos | Ácidos carboxílicos |
| Tioéteres | Epóxidos | Tioles |
| Tioéteres | Haloacetamidas | Tioles |
| Ammotriazinas | Halotriazinas | Aminas/anilinas |

504

| | | |
|---|---|---|
| éteres de triazinilo | Halotriazinas | Alcoholes/fenoles |
| Amidinas | Imido ésteres | Aminas/anilinas |
| Ureas | Isocianatos | Aminas/anilinas |
| Uretanos | Isocianatos | Alcoholes/fenoles |
| Tioureas | Isotiocianatos | Aminas/anilinas |
| Tioéteres | Maleimidas | Tioles |
| ésteres de fosfito | Fosforamiditas | Alcoholes |
| éteres de sililo | Haluro de sililo | Alcoholes |
| Alquil aminas | Ésteres de sulfonato | Aminas/anilinas |
| Tioéteres | Ésteres de sulfonato | Tioles |
| Ésteres | Ésteres de sulfonato | Ácidos carboxílicos |
| Éteres | Ésteres de sulfonato | Alcoholes |
| Sulfonamidas | Halogenuros de sulfonilo | Aminas/anilinas |
| Ésteres de sulfonato | Halogenuros de sulfonilo | Fenoles/alcoholes |

*Ejemplos de uniones covalentes y sus precursores*

Uso de grupos protectores

En las reacciones descritas, puede ser necesario proteger grupos funcionales reactivos, por ejemplo grupos hidroxi, amino, imino, tio o carboxi, cuando se desea que éstos se encuentren en el producto final, para evitar su participación indeseada en las reacciones. Los grupos protectores se usan para bloquear algunos o todos los grupos reactivos y para impedir que dichos grupos participen en reacciones químicas hasta que se remueva el grupo protector. En algunas formas de realización, cada grupo protector puede removerse por un medio diferente. Los grupos protectores que son clivados bajo condiciones de reacción totalmente dispares cumplen con el requerimiento de remoción diferencial. Los grupos protectores se pueden remover mediante ácidos, bases e hidrogenólisis. Los grupos tales como tritilo, dimetoxitritilo, acetal y t-butildimetilsililo son lábiles a ácidos y se pueden usar para proteger grupos carboxi e hidroxi reactivos en la presencia de grupos amino protegidos con grupos Cbz, que son removibles mediante hidrogenólisis, y grupos Fmoc, que son lábiles a bases. Los grupos de ácido carboxílico e hidroxi reactivos se pueden bloquear con grupos lábiles a bases tales como, pero en un sentido no limitativo, metilo, etilo y acetilo en la presencia de aminas bloqueadas con grupos lábiles a ácidos tal como carbamato de t-butilo o con carbamatos que son

566

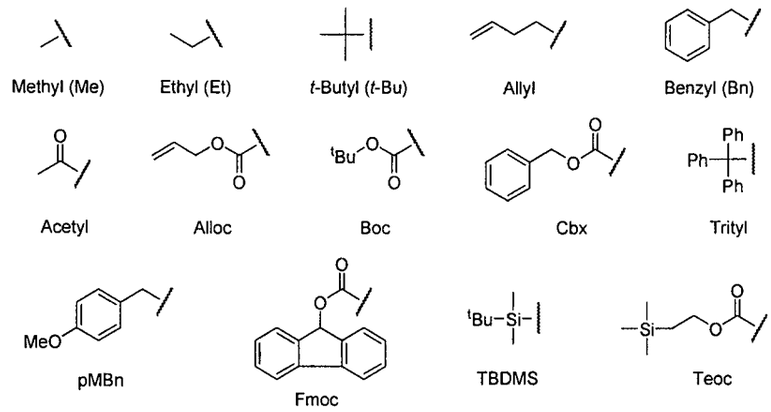
estables a ácidos y bases pero que se pueden remover hidrolíticamente.

Los grupos de ácido carboxílico e hidroxi reactivos también se pueden bloquear con grupos protectores removibles hidrolíticamente tal como el grupo bencilo, en tanto los grupos amina capaces de formar puente de hidrógeno con ácidos se pueden bloquear con grupos lábiles a bases, tal como Fmoc. Los grupos de acido carboxílico reactivo se pueden proteger por conversión en simples compuestos éster según se ejemplifica en la presente, o se pueden bloquear con grupos protectores removibles oxidativamente, tal como 2,4-dimetoxibencilo, en tanto los grupos amino co-existentes se pueden bloquear con carbamatos de sililo lábiles a fluoruros.

Los grupos bloqueantes de alilo son de utilidad en la presencia de grupos protectores de ácidos y bases dado que los primeros son estables y se pueden remover subsiguientemente mediante catalizadores de metales o de ácido pi. Por ejemplo, un ácido carboxílico bloqueado con alilo se puede desproteger con una reacción catalizada por Pd en la presencia de grupos protectores de carbamato de t-butilo lábil a ácidos o de acetato de amina lábil a bases. Aún otra forma de grupo protector es una resina a la cual se puede unir un compuesto o intermediario. En tanto el residuo permanezca unido a la resina, dicho grupo funcional está

bloqueado y no puede reaccionar. Una vez liberada de la resina, el grupo funcional está disponible para reaccionar.

Los grupos protectores o bloqueantes se pueden seleccionar entre:




Otros grupos protectores, además de una descripción detallada de las técnicas que se pueden aplicar en la creación de grupos protectores y su eliminación, se describen en Greene y Wuts, *Protective Groups in Organic Synthesis*, 3ª Ed., John Wiley & Sons, Nueva York, NY, 1999, y Kocienski, *Protective Groups*, Thieme Verlag, Nueva York, NY, 1994, que se incorporan por completo en la presente a modo de referencia.

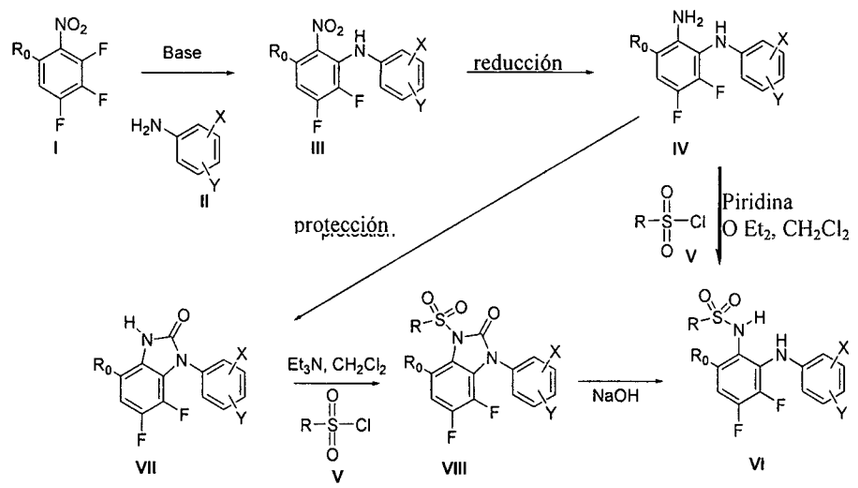
Elaboración de los compuestos de la fórmula I

Los compuestos de esta invención se pueden elaborar utilizando diversos métodos. Los siguientes procedimientos pretenden ilustrar tales métodos, y los ejemplos indicados pretenden ilustrar el alcance de esta invención. Ninguno de los métodos ni los ejemplos deberían considerarse como

568

limitativos de la invención en modo alguno.

**I.** La preparación de un compuesto de la fórmula VI se indica a continuación

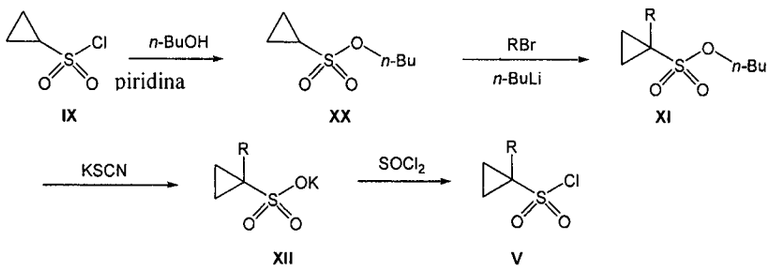



El esquema I anterior ilustra un método para elaborar los derivados sulfonamida de la fórmula VI. 1.2. El derivado diamina (fórmula IV) se puede preparar fácilmente en dos pasos a partir de los derivados nitro deseados (fórmula I). Los compuestos de la fórmula IV se pueden hacer reaccionar con los derivados de cloruro de sulfonilo (fórmula V, véase el esquema siguiente) para formar la sulfonamida deseada. Como alternativa, los derivados 1,2-diamina IV se pueden proteger como una imidazolidona (fórmula VII), antes de hacerlos reaccionar con el correspondiente cloruro de sulfonilo. La desprotección de la 1,2-diamina VIII bajo condiciones básicas proporcionó el material VI deseado.

**II.** La ruta general para sintetizar un compuesto de la

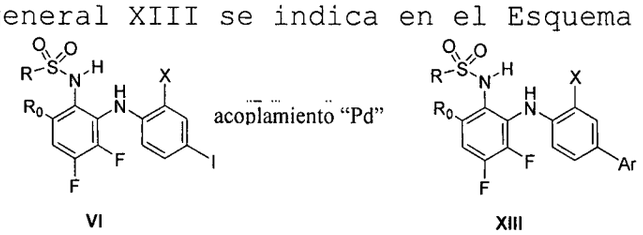
509

fórmula general V se indica a continuación




El esquema II anterior muestra un ejemplo de la preparación del cloruro de sulfonilo complejo. El compuesto XX se puede sintetizar a partir de IX, alquilar y convertir en la sal de potasio XII. El tratamiento de la sal con $SOCl_2$ o $POCl_3$ permite obtener los compuestos deseados. En la sección experimental la se describen otros procedimientos más específicos para preparar derivados únicos de cloruro de sulfonilo.

**III**. La ruta general para sintetizar un compuesto de la fórmula general XIII se indica en el Esquema 3.

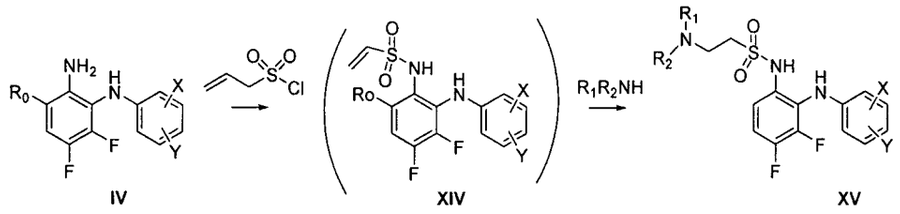



El esquema III anterior ilustra la preparación de derivados sulfonamida de la fórmula general XIII. Por ejemplo, estos compuestos se pueden obtener fácilmente por reacción del compuesto VI con un ácido borónico usando un catalizador de paladio bajo condiciones de Suzuki.

**IV**. La ruta general para sintetizar un compuesto de la

510

fórmula general XIII se indica en el Esquema 4.




IV XIV XV

El esquema IV anterior ilustra la preparación de derivados sulfonamida de la fórmula general XV. La vinilsulfonamida (XIV) se hace reaccionar con aminas para formar derivados de la fórmula general XV.

*Otras formas de los compuestos de la fórmula I*

Isómeros de los compuestos de la fórmula I

Los compuestos que se describen en la presente pueden existir como isómeros geométricos. Los compuestos descritos en la presente pueden contener uno o más enlaces dobles. Los compuestos presentados aquí incluyen todos los isómeros cis, trans, syn, anti, *entgegen* (E) y *zusammen* (Z), así como las correspondientes mezclas de los mismos. En algunas situaciones, los compuestos pueden existir como tautómeros. Los compuestos que se describen en la presente incluyen todos los posibles tautómeros dentro de las fórmulas descritas en la presente. Los compuestos que se describen en la presente pueden tener uno o más centros quirales y cada centro puede existir en la configuración R o S. Los compuestos que se describen en la presente incluyen todas las formas diastereoméricas, enantioméricas y epiméricas,

S11

así como las correspondientes mezclas de los mismos. En formas de realización adicionales de los compuestos y métodos provistos en la presente, las mezclas de enantiómeros y/o diastereoisómeros, que resultan de un solo paso preparativo, la combinación o la interconversión también pueden ser de utilidad en las aplicaciones descritas en la presente. Los compuestos que se describen en la presente se pueden preparar como sus estereoisómeros individuales por reacción de una mezcla racémica del compuesto con un agente de resolución ópticamente activo para formar un par de compuestos diastereoisoméricos, separación de los diastereómeros y recuperación de los enantiómeros ópticamente puros. La resolución de los enantiómeros se puede realizar usando derivados diastereoméricos covalentes de los compuestos que se describen en la presente o se pueden usar complejos disociables (por ejemplo, sales diastereoisoméricas cristalinas). Los diastereómeros tienen propiedades físicas diferentes (por ejemplo, puntos de fusión, puntos de ebullición, solubilidades, reactividades, etcétera), y se pueden separar fácilmente aprovechando estas diferencias. Los diastereómeros se pueden separar por cromatografía quiral o mediante técnicas de separación/resolución basadas en las diferencias de solubilidad. Después se recuperan los enantiómeros ópticamente puros, junto con el agente de

SR

resolución, empleando cualquier medio apropiado que no produzca racemización. Por una descripción más detallada de los procedimientos que se pueden usar para resolver estereoisómeros de compuestos a partir de su mezcla racémica véase Jean Jacques Andre Collet, Samuel H. Wilen, *Enantiomers, Racemates and Resolutions*, John Wiley & Sons, Inc., 1981, incorporada por completo en la presente a modo de referencia.

Compuestos marcados de la fórmula I

En la presente también se describen compuestos de la fórmula I marcados con isótopos y métodos de tratamiento de trastornos. Por ejemplo, la invención provee métodos de tratamiento de enfermedades que comprenden administrar los compuestos de la fórmula I marcados con isótopos. Los compuestos de la fórmula I marcados con isótopos se pueden administrar como composiciones farmacéuticas. Por consiguiente, los compuestos de la fórmula I también incluyen los compuestos marcados con isótopos, que son estructuralmente idénticos a aquellos que se revelaron en la presente, excepto por el hecho de que se han reemplazado uno o más átomos por un átomo que tiene una masa atómica o número másico diferente de la masa atómica o el número másico que habitualmente se encuentra en la naturaleza. Los ejemplos de isótopos que se pueden incorporar en los compuestos de la invención incluyen isótopos de hidrógeno,

513

carbono, nitrógeno, oxígeno, fósforo, azufre, flúor y cloro, como por ejemplo $^{2}H$, $^{3}H$, $^{13}C$, $^{14}C$, $^{15}N$, $^{18}O$, $^{17}O$, $^{31}P$, $^{32}P$, $^{35}S$, $^{18}F$ y $^{36}Cl$, respectivamente. Los compuestos que se describen en la presente, las sales farmacéuticamente aceptables de los mismos que contienen a los isótopos mencionados precedentemente y/u otros isótopos de otros átomos se encuentran dentro del alcance de esta invención. Determinados compuestos de la fórmula I marcados con isótopos, por ejemplo aquellos en los cuales se incorporan isótopos radioactivos tales como $^{3}H$ y $^{14}C$, son útiles para ensayos de distribución de la droga y/o en tejidos sustrato. Los isótopos tritio, es decir, $^{3}H$, y carbono-14, es decir, $^{14}C$, a menudo se preparan y detectan con facilidad. Además, la sustitución por isótopos más pesados tales como deuterio, es decir, $^{2}H$, puede proporcionar ciertas ventajas terapéuticas producto de una mayor estabilidad metabólica, por ejemplo una mayor vida media *in vivo* o menores requerimientos de dosificación y, por lo tanto, en algunas circunstancias pueden ser deseables. Los compuestos marcados con isótopos y las sales farmacéuticamente aceptables de los mismos en general se pueden preparar mediante los procedimientos que se describen en la presente, por sustitución de un reactivo no marcado con isótopos fácilmente disponible por un reactivo marcado con isótopos.

Los compuestos que se describen en la presente se

514

pueden marcar de otra manera, incluyendo, pero en un sentido no limitativo, el uso de cromóforos o grupos fluorescentes, marcas bioluminescentes o marcas quimioluminiscentes.

Sales farmacéuticamente aceptables de los compuestos de la fórmula I

En la presente también se describen sales farmacéuticamente aceptables de los compuestos de la fórmula I y métodos de tratamiento de trastornos. Por ejemplo, la invención provee métodos de tratamiento de enfermedades, que comprenden administrar sales farmacéuticamente aceptables de los compuestos de la fórmula I. Las sales farmacéuticamente aceptables de los compuestos de la fórmula I se pueden administrar como composiciones farmacéuticas.

Así, los compuestos que se describen en la presente se pueden preparar como sales farmacéuticamente aceptables formadas cuando se reemplaza un protón ácido presente en el compuesto parental por un ion de metal, por ejemplo un ion de un metal alcalino, un ion alcalino térreo o un ion de aluminio; o cuando se coordina con una base orgánica. Las sales de adición básica también se pueden preparar haciendo reaccionar la forma de ácido libre de los compuestos que se describen en la presente con una base inorgánica u orgánica farmacéuticamente aceptable, incluyendo, pero en un sentido no limitativo, bases orgánicas tales como etanolamina, dietanolamina, trietanolamina, trometamina, N-metilglucamina

S17

y semejantes y bases inorgánicas tales como hidróxido de aluminio, hidróxido de calcio, hidróxido de potasio, carbonato de sodio, hidróxido de sodio y semejantes. Además, las formas de sales de los compuestos se pueden preparar usando sales de los materiales de partida o de los intermediarios.

Además, los compuestos que se describen en la presente se pueden preparar como sales farmacéuticamente aceptables formadas por reacción de la forma de la base libre del compuesto con un ácido inorgánico u orgánico farmacéuticamente aceptable, incluyendo, pero en un sentido no limitativo, ácidos inorgánicos tales como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido nítrico, ácido fosfórico, ácido metafosfórico y semejantes; y ácidos orgánicos tales como ácido acético, ácido propiónico, ácido hexanoico, ácido ciclopentanpropiónico, ácido glicólico, ácido pirúvico, ácido láctico, ácido malónico, ácido succínico, ácido málico, ácido maleico, ácido fumárico, ácido p-toluensulfónico, ácido tartárico, ácido trifluoroacético, ácido cítrico, ácido benzoico, ácido 3-(4-hidroxibenzoil)benzoico, ácido cinámico, ácido mandélico, ácido arilsulfónico, ácido metansulfónico, ácido etansulfónico, ácido 1,2-etandisulfónico, ácido 2-hidroxietansulfónico, ácido bencensulfónico, ácido 2-naftalensulfónico, ácido 4-metilbiciclo-[2,2,2]oct-2-en-1-

316

carboxílico, ácido glucoheptónico, ácido 4,4'-metilenbis-(3-hidroxi-2-en-1-carboxílico), ácido 3-fenilpropiónico, ácido trimetilacético, ácido butilacético terciario, ácido laurilsulfúrico, ácido glucónico, ácido glutámico, ácido hidroxinaftoico, ácido salicílico, ácido esteárico y ácido mucónico.

Solvatos de los compuestos de la fórmula I

En la presente también se describen solvatos de los compuestos de la fórmula I y métodos de tratamiento de trastornos. Por ejemplo, la invención provee métodos de tratamiento de enfermedades, que comprenden administrar solvatos de los compuestos de la fórmula I. Los solvatos de los compuestos de la fórmula I se pueden administrar como composiciones farmacéuticas.

Los solvatos contienen cantidades estequiométricas o no estequiométricas de un solvente, y se pueden formar durante el proceso de cristalización con solventes farmacéuticamente aceptables, tales como agua, etanol y semejantes. Los hidratos se forman cuando el solvente es agua o se forman alcoholatos cuando el solvente es alcohol. Los solvatos de los compuestos que se describen en la presente se pueden preparar o formar convenientemente durante los procesos que se describen en la presente. A modo de ejemplo solamente, los hidratos de los compuestos que se describen en la presente se pueden preparar convenientemente por

SA

recristalización a partir de una mezcla de solventes acuosos/orgánicos, usando solventes orgánicos incluyendo, pero en un sentido no limitativo, dioxano, tetrahidrofurano o metanol. Además, los compuestos provistos en la presente pueden existir en formas no solvatadas así como solvatadas. En general, las formas solvatadas se consideran equivalentes a las formas no solvatadas a los efectos de los compuestos y métodos provistos en la presente.

Polimorfos de los compuestos de la fórmula I

En la presente también se describen polimorfos de los compuestos de la fórmula I y métodos de tratamiento de trastornos. Por ejemplo, la invención provee métodos de tratamiento de enfermedades, que comprenden administrar polimorfos de los compuestos de la fórmula I. Los polimorfos de los compuestos de la fórmula I se pueden administrar como composiciones farmacéuticas.

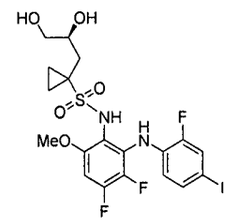
Por consiguiente, los compuestos que se describen en la presente incluyen todas sus formas cristalinas, conocidas como polimorfos. Los polimorfos incluyen los diferentes ordenamientos de empaquetamiento de cristales de la misma composición elemental de un compuesto. Los polimorfos pueden tener diferentes patrones de difracción de rayos X, espectros infrarrojos, puntos de fusión, densidad, dureza, forma cristalina, propiedades ópticas y eléctricas, estabilidad y solubilidad. Hay diversos factores, tales como

58

el solvente de recristalización, velocidad de cristalización y temperatura de almacenamiento, que pueden causar que predomine una sola forma cristalina.

**Polimorfo cristalino de forma de N-(S)-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida**

La invención también se relaciona con un polimorfo cristalino de forma A de N-(S)-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida:




que exhibe un patrón de difracción de los rayos X en polvo específico. En algunas formas de realización, el patrón de difracción de rayos X en polvo contiene al menos aproximadamente 50% de los picos que se muestran en **FIG. 5**. En algunas formas de realización, el patrón de difracción de rayos X en polvo contiene al menos aproximadamente 70% de los picos que se muestran en **FIG. 5**. En algunas formas de realización, el patrón de difracción de rayos X en polvo contiene al menos aproximadamente 90% de los picos que se muestran en **FIG. 5**. En algunas formas de realización, el patrón de difracción de rayos X en polvo es sustancialmente igual el patrón de difracción de rayos X en polvo que se

S 19

muestra en **FIG. 5.**

La invención también se relaciona con un polimorfo cristalino de forma A de N-(S)-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida que exhibe un patrón de calorimetría diferencial de barrido específico. En algunas formas de realización, el patrón de calorimetría diferencial de barrido específico es sustancialmente el mismo que el patrón de calorimetría diferencial de barrido que se muestra en **FIG. 6.** En algunas formas de realización el polimorfo cristalino de forma A tiene una temperatura del comienzo de la fusión según se determinó mediante calorimetría diferencial de barrido en aproximadamente 143°C.

La invención también se relaciona con una forma polimórfica de N-(S)-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida realizada mediante un método que comprende el paso de cristalizar N-(S)-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida amorfa a partir de un solvente. La invención también se relaciona con una forma polimórfica de N-(S)-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida realizada mediante

520

un método que comprende el paso de cristalizar N-(S)-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida amorfa a partir de una mezcla de hexano y acetato de etilo.

La invención también se relaciona con composiciones farmacéuticas que comprenden una cantidad efectiva de polimorfo cristalino de forma A de N-(S)-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida y un vehículo farmacéuticamente aceptable. Otros aspectos de la invención se relacionan con una composición farmacéutica que comprende el polimorfo cristalino de forma A y al menos un excipiente o vehículo.

El polimorfo cristalino de forma A de N-(S)-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida es útil para el tratamiento o prevención de cáncer o una enfermedad inflamatoria. La invención además se relaciona con métodos para el tratamiento o la prevención de cáncer o una enfermedad inflamatoria, que comprende administrar una cantidad efectiva de un polimorfo cristalino de forma A de N-(S)-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida a un sujeto en necesidad del mismo. Aún otros aspectos de la invención se relacionan con métodos para el

521

tratamiento o profilaxis de una enfermedad inflamatoria que comprende administrar a un sujeto en necesidad del mismo una cantidad efectiva del polimorfo cristalino- Aspectos adicionales de la invención se relacionan con métodos para el tratamiento o profilaxis de una enfermedad proliferativa que comprende administrar a un sujeto en necesidad del mismo una cantidad efectiva del polimorfo cristalino.

Prodrogas de los compuestos de la fórmula I

En la presente también se describen prodrogas de los compuestos de la fórmula I y métodos de tratamiento de trastornos. Por ejemplo, la invención provee métodos de tratamiento de enfermedades, que comprenden administrar prodrogas de los compuestos de la fórmula I. Las prodrogas de los compuestos de la fórmula I se pueden administrar como composiciones farmacéuticas.

Las prodrogas son generalmente precursores de drogas que, luego de su administración a un sujeto y la subsiguiente absorción, son convertidas en una especie activa, o una especie más activa, por medio de algún proceso, tal como conversión por una vía metabólica. Algunas prodrogas contienen un grupo químico en la prodroga que las vuelve menos activas y/o que confiere solubilidad o alguna otra propiedad a la droga. Una vez que se ha clivado y/o modificado el grupo químico de la prodroga se genera la droga activa. Las prodrogas son a menudo de gran utilidad

522

porque, en algunas situaciones, pueden ser más fáciles de administrar que la droga parental. Por ejemplo, las mismas pueden estar biodisponibles para una administración por vía oral, en tanto la parental no lo está. La prodroga también puede presentar una solubilidad mejorada en las composiciones farmacéuticas ante la droga principal. Un ejemplo, en un sentido no limitativo, de una prodroga sería un compuesto descrito en la presente que es administrado como un éster (la "prodroga") para facilitar el paso a través de una membrana celular donde la solubilidad es perjudicial para la movilidad pero que luego es hidrolizado metabólicamente en el ácido carboxílico, la entidad activa, una vez que está adentro de la célula donde la solubilidad en resulta beneficiosa. Un ejemplo adicional de una prodroga podría ser un péptido corto (poliaminoácido) unido a un grupo ácido, donde dicho péptido es metabolizado para revelar el grupo activo.

Las prodrogas se pueden diseñar como derivados reversibles de la droga, para su uso como modificadores para mejorar el transporte de la droga a los tejidos específicos. El diseño de prodrogas ha buscado hasta la fecha incrementar la solubilidad efectiva en agua del compuesto terapéutico para dirigirlas a las regiones donde el agua es el solvente principal. Véase, por ejemplo, Fedorak et al., *Am. J. Physiol.*, 269:G210-218 (1995); McLoed et al., *Gastroenterol*,

573

106:405-413 (1994); Hochhaus et al., *Biomed. Chrom.*, 6:283-286 (1992); J. Larsen y H. Bundgaard, *Int. J. Pharmaceutics*, 37, 87 (1987); J. Larsen et al., *Int. J. Pharmaceutics*, 47, 103 (1988); Sinkula et al., *J. Pharm. Sci.*, 64:181-210 (1975); T. Higuchi y V. Stella, *Pro-drugs as Novel Delivery Systems*, Vol. 14 de la serie de A.C.S. Symposium; y Edward B. Roche, *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association y Pergamon Press, 1987, todas incorporadas por completo en la presente.

Además, se pueden preparar derivados de prodrogas de los compuestos que se describen aquí empleando métodos conocidos por los especialistas en el arte (por ejemplo, por detalles adicionales, véase Saulnier *et al.* (1994), *Bioorganic and Medicinal Chemistry Letters*, Vol. 4, página 1985). A modo de ejemplo solamente, las prodrogas apropiadas se pueden preparar por reacción de un compuesto no derivatizado de la fórmula I con un agente carbamilante adecuado, tal como, pero en un sentido no limitativo, 1,1-aciloxialquilcarbanocloridato, carbonato de para-nitrofenilo o semejantes. Las formas de prodrogas de los compuestos descritos en la presente, en donde la prodroga es metabolizada *in vivo* para producir un derivado indicado en la presente están incluidas dentro del alcance de las reivindicaciones. Aún más, algunos de los compuestos que se describen en la presente pueden ser una prodroga para otro

524

derivado o compuesto activo.

En algunas formas de realización, las prodrogas incluyen compuestos en donde un residuo de aminoácido, o una cadena polipeptídica de dos o más (por ejemplo, dos, tres o cuatro) residuos de aminoácido se une covalentemente, a través de un enlace amida o éster, a un grupo hidroxilo o ácido carboxílico libre de los compuestos de la presente invención. Los residuos de aminoácido incluyen, pero en un sentido no limitativo, los 20 aminoácidos naturales que se designan comúnmente mediante símbolos de tres letras y también incluyen 4-hidroxiprolina, hidroxilisina, demosina, isodemosina, 3-metilhistidina, norvalina, beta-alanina, ácido gama-aminobutírico, citrulina, homocisteína, homoserina, ornitina y sulfona de metionina. También están abarcados otros tipos de prodrogas.

Los compuestos de la fórmula I que contienen grupos amino, amido, hidroxi o carboxílico libres se pueden convertir en prodrogas. Por ejemplo, los grupos carboxilo libres se pueden derivatizar como amidas o ésteres de alquilo. Los grupos hidroxilo libres se pueden derivatizar usando grupos que incluyen, pero en un sentido no limitativo, hemisuccinatos, ésteres de fosfato, dimetilaminoacetatos, y fosforiloximetiloxicarbonilos, como se expone en *Advanced Drug Delivery Reviews* (Resúmenes de administración de drogas avanzado), **1996**, *19*, 115 15. Las

525

prodrogas de carbamato de grupos hidroxilo y amino también están incluidas, como así también las prodrogas de carbonato, ésteres de sulfonato y ésteres de sulfato de grupos hidroxilo.

También está incluida la derivatización de los grupos hidroxilo como éteres de (aciloxi)metilo y (aciloxi)etilo, en donde el grupo acilo puede ser un éster de alquilo sustituido opcionalmente con grupos que incluyen, pero en un sentido no limitativo, funciones éter, amino, ácido carboxílico, o en donde el grupo acilo es un éster de aminoácido como se describió más arriba. Las prodrogas de este tipo se describen en *J. Med. Chem., 1996, 39,* 10. Las aminas libres también se pueden derivatizar como amidas, sulfonamidas o fosfonamidas. Todos estos grupos de prodrogas pueden incorporar grupos que incluyen, pero en un sentido no limitativo, funciones éter, amina y ácido carboxílico.

Hay sitios sobre porciones del anillo aromático de los compuestos de la fórmula I que pueden ser susceptibles a diversas reacciones metabólicas, por lo cual la incorporación de los sustituyentes apropiados sobre estructuras del anillo aromático, puede reducir, minimizar o eliminar esta vía metabólica.

*Composiciones farmacéuticas*

En la presente se describen composiciones farmacéuticas. En algunas formas de realización, las

526

composiciones farmacéuticas comprenden una cantidad eficaz de un compuesto de la fórmula I, o una sal farmacéuticàmente aceptable del mismo. En algunas formas de realización, las composiciones farmacéuticas comprenden una cantidad eficaz de un compuesto fórmula I, o una sal, solvato, polimorfo, éster, amida, tautómero, prodroga, hidrato o derivado farmacéuticamente aceptable del mismo y al menos un vehículo farmacéuticamente aceptable. En algunas formas de realización, las composiciones farmacéuticas son para el tratamiento de trastornos. En algunas formas de realización, las composiciones farmacéuticas son para el tratamiento de trastornos en un mamífero. En algunas formas de realización, las composiciones farmacéuticas son para el tratamiento de trastornos en un ser humano.

En aspectos adicionales, la presente invención está dirigida a una composición farmacéutica que comprende un compuesto de la fórmula I o una sal, solvato, polimorfo, éster, amida, tautómero o prodroga farmacéuticamente aceptable del mismo. En algunas formas de realización, las composiciones farmacéuticas comprenden además un vehículo farmacéuticamente aceptable. Dichas composiciones pueden contener adyuvantes, excipientes y conservantes, agentes para demorar la absorción, rellenos, aglutinantes, adsorbentes, soluciones amortiguadoras, agentes desintegrantes, agentes solubilizantes, otros vehículos y

527

otros ingredientes inertes. Los métodos de formulación de dichas composiciones son bien conocidos en el arte.

En algunas formas de realización, la composición farmacéutica se encuentra en una forma adecuada para una administración oral. En otras formas de realización o adicionales, la composición farmacéutica se encuentra en la forma de una tableta, cápsula, píldora, polvo, formulación de liberación sostenida, solución, suspensión, como una solución, suspensión o emulsión estéril para una inyección parenteral, como un ungüento o crema para una administración tópica o como un supositorio para una administración rectal.

En otras formas de realización o adicionales, la composición farmacéutica se encuentra en formas de dosificación unitarias adecuadas para la administración individual de dosificaciones precisas. En otras formas de realización o adicionales, la cantidad del compuesto de la fórmula I se encuentra en el rango de entre aproximadamente 0,001 y aproximadamente 1000 mg/kg de peso corporal/día. En otras formas de realización o adicionales, la cantidad del compuesto de la fórmula I se encuentra en el rango de entre aproximadamente 0,5 y aproximadamente 50 mg/kg/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,001 y aproximadamente 7 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de

528

entre aproximadamente 0,002 y aproximadamente 6 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,005 y aproximadamente 5 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,01 y aproximadamente 5 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,02 y aproximadamente 5 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,05 y aproximadamente 2,5 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,1 y aproximadamente 1 g/día. En otras formas de realización o adicionales, serán más que adecuados los niveles de dosificación inferiores al límite inferior del rango mencionado previamente. En otras formas de realización o adicionales, pueden ser necesarios niveles de dosificación superiores al límite superior del rango mencionado previamente.

En otras formas de realización o adicionales, el compuesto de la fórmula I se administra en una sola dosis, una vez por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra en múltiples dosis, más de una vez por día. En otras formas de

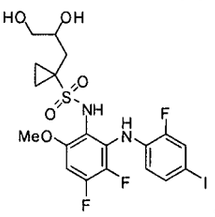
529

realización o adicionales, el compuesto de la fórmula I se administra dos veces por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra tres veces por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra cuatro veces por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra más de cuatro veces por día. En algunas formas de realización, la composición farmacéutica es para la administración a un mamífero. En otras formas de realización o adicionales, el mamífero es un ser humano.

En otras formas de realización o adicionales, la composición farmacéutica comprende además un vehículo, excipiente y/o adyuvante farmacéutico. En otras formas de realización o adicionales, la composición farmacéutica comprende además al menos un agente terapéutico. En otras formas de realización o adicionales, el agente terapéutico se selecciona del grupo de agentes citotóxicos, agentes anti-angiogénesis y agentes anti-neoplásicos. En otras formas de realización o adicionales, el agente anti-neoplásico se selecciona del grupo que consiste de agentes alquilantes, anti-metabolitos, epidofilotoxinas; enzimas antineoplásicas, inhibidores de topoisomerasa, procarbazinas, mitoxantronas, complejos de coordinación de platino, modificadores de la respuesta biológica e

536

inhibidores del crecimiento, agentes terapéuticos hormonales/anti-hormonales y factores de crecimiento hematopoyéticos. En otras formas de realización o adicionales, el agente terapéutico es taxol, bortezomib o ambos. En otras formas de realización o adicionales, la composición farmacéutica se administra en combinación con una terapia adicional. En otras formas de realización o adicionales, la terapia adicional es una terapia por radiación, quimioterapia, cirugía o cualquier combinación de las mismas. En otras formas de realización o adicionales, la composición farmacéutica comprende una sal farmacéuticamente aceptable de un compuesto de la fórmula I.

La invención también se relaciona con una composición que comprende  . En algunas formas de realización, el carbono 2-OH del compuesto se encuentra en la configuración R. En algunas formas de realización, la composición está sustancialmente libre del isómero S del compuesto. En algunas formas de realización, el compuesto contiene menos que un 10% del isómero S del compuesto. En algunas formas de realización, el compuesto contiene menos que un 5% del isómero S del compuesto. En algunas formas de realización, el compuesto contiene menos que un 1% del

531

isómero S del compuesto. En algunas formas de realización, el compuesto se encuentra en la configuración R.

En algunas formas de realización, el carbono 2-OH del compuesto se encuentra en la configuración S. En algunas formas de realización, la composición está sustancialmente libre del isómero R del compuesto. En algunas formas de realización, el compuesto contiene menos que un 10% del isómero R del compuesto. En algunas formas de realización, el compuesto contiene menos que un 5% del isómero R del compuesto. En algunas formas de realización, el compuesto contiene menos que un 1% del isómero R del compuesto. En algunas formas de realización, el compuesto se encuentra en la configuración S.

En algunas formas de realización, la composición contiene al menos aproximadamente 50% de un compuesto que exhibe un patrón de difracción de rayos X de polvo que comprende al menos un 50% de los picos identificados en el patrón de difracción de rayos X de polvo que se muestra en la FIG. **5**. En algunas formas de realización, el patrón de difracción de rayos X de polvo comprende al menos un 70% de los picos identificados en el patrón de difracción de rayos X de polvo que se muestra en la FIG. **5**. En algunas formas de realización, el patrón de difracción de rayos X de polvo comprende al menos un 90% de los picos identificados en la FIG **5**. En algunas formas de realización, el patrón de

532

difracción de rayos X de polvo es sustancialmente el mismo que el patrón de difracción de rayos X de polvo que se muestra en la FIG. **5**.

En algunas formas de realización, la composición contiene al menos aproximadamente 75% de un compuesto que exhibe un patrón de difracción de rayos X de polvo que comprende al menos un 50% de los picos identificados en el patrón de difracción de rayos X de polvo que se muestra en la FIG. **5**. En algunas formas de realización, el patrón de difracción de rayos X de polvo comprende al menos un 70% de los picos identificados en el patrón de difracción de rayos X de polvo que se muestra en la FIG. **5**. En algunas formas de realización, el patrón de difracción de rayos X de polvo comprende al menos un 90% de los picos identificados en la FIG **5**. En algunas formas de realización, el patrón de difracción de rayos X de polvo es sustancialmente el mismo que el patrón de difracción de rayos X de polvo que se muestra en la FIG. **5**.

En algunas formas de realización, la composición contiene al menos aproximadamente 90% de un compuesto que exhibe un patrón de difracción de rayos X de polvo que comprende al menos un 50% de los picos identificados en el patrón de difracción de rayos X de polvo que se muestra en la FIG. **5**. En algunas formas de realización, el patrón de difracción de rayos X de polvo comprende al menos un 70% de

533

los picos identificados en el patrón de difracción de rayos X de polvo que se muestra en la FIG. **5**. En algunas formas de realización, el patrón de difracción de rayos X de polvo comprende al menos un 90% de los picos identificados en la FIG **5**. En algunas formas de realización, el patrón de difracción de rayos X de polvo es sustancialmente el mismo que el patrón de difracción de rayos X de polvo que se muestra en la FIG. **5**.

En algunas formas de realización, sustancialmente todo el compuesto en la composición exhibe un patrón de difracción de rayos X de polvo que comprende al menos un 50% de los picos identificados en el patrón de difracción de rayos X de polvo que se muestra en la FIG. **5**. En algunas formas de realización, el patrón de difracción de rayos X de polvo comprende al menos un 70% de los picos identificados en el patrón de difracción de rayos X de polvo que se muestra en la FIG. **5**. En algunas formas de realización, el patrón de difracción de rayos X de polvo comprende al menos un 90% de los picos identificados en la FIG. **5**. En algunas formas de realización, el patrón de difracción de rayos X de polvo es sustancialmente el mismo que el patrón de difracción de rayos X de polvo que se muestra en la FIG. **5**.

En algunas formas de realización, el polimorfo cristalino presente en la composición tiene un punto de fusión que comienza, determinado por calorimetría de barrido

534

diferencial, en 143°C aproximadamente. En algunas formas de realización, el polimorfo cristalino está sustancialmente libre de agua. En algunas formas de realización, el polimorfo cristalino está sustancialmente libre de solvente.

En algunas formas de realización, la composición contiene al menos un 50% aproximadamente de un compuesto que exhibe un patrón de calorimetría de barrido diferencial sustancialmente igual el patrón de calorimetría de barrido diferencial que se muestra en la FIG. 6. En algunas formas de realización, el polimorfo cristalino tiene un punto de fusión que comienza, determinado por calorimetría de barrido diferencial, en 143°C aproximadamente. En algunas formas de realización, el polimorfo cristalino está sustancialmente libre de agua. En algunas formas de realización, el polimorfo cristalino está sustancialmente libre de solvente.

En algunas formas de realización, la composición contiene al menos un 75% aproximadamente de un compuesto que exhibe un patrón de calorimetría de barrido diferencial sustancialmente igual el patrón de calorimetría de barrido diferencial que se muestra en la FIG. 6. En algunas formas de realización, el polimorfo cristalino tiene un punto de fusión que comienza, determinado por calorimetría de barrido diferencial, en 143°C aproximadamente. En algunas formas de realización, el polimorfo cristalino está sustancialmente libre de agua. En algunas formas de realización, el

535

polimorfo cristalino está sustancialmente libre de solvente.

En algunas formas de realización, la composición contiene al menos un 90% aproximadamente de un compuesto que exhibe un patrón de calorimetría de barrido diferencial sustancialmente igual el patrón de calorimetría de barrido diferencial que se muestra en la FIG. 6. En algunas formas de realización, el polimorfo cristalino tiene un punto de fusión que comienza, determinado por calorimetría de barrido diferencial, en 143°C aproximadamente. En algunas formas de realización, el polimorfo cristalino está sustancialmente libre de agua. En algunas formas de realización, el polimorfo cristalino está sustancialmente libre de solvente.

En algunas formas de realización, sustancialmente todo el compuesto en la composición exhibe un patrón de calorimetría de barrido diferencial sustancialmente igual al patrón de calorimetría de barrido diferencial que se muestra en la FIG. **6**. En algunas formas de realización, el polimorfo cristalino tiene un punto de fusión que comienza, determinado por calorimetría de barrido diferencial, en 143°C aproximadamente. En algunas formas de realización, el polimorfo cristalino está sustancialmente libre de agua. En algunas formas de realización, el polimorfo cristalino está sustancialmente libre de solvente.

En algunas formas de realización, la forma polimórfica de N-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-

536

metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida se elabora mediante un método que comprende el paso de cristalizar la forma amorfa de N-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida. En algunas formas de realización, el paso de cristalización comprende una cristalización a partir de una mezcla de acetato de etilo y heptano, por ejemplo, una mezcla de acetato de etilo y heptano en una relación de entre 1-4 partes de acetato de etilo aproximadamente y 2-10 partes de heptano aproximadamente o más específicamente, una relación de entre 2 partes de acetato de etilo aproximadamente y 5 partes de heptano aproximadamente.

En algunas formas de realización, el compuesto se formula para una liberación inmediata del compuesto. En algunas formas de realización, el compuesto se formula para una liberación sostenida del compuesto. En otras formas de realización, el compuesto se formula para una liberación extendida del compuesto.

En algunas formas de realización, la composición se encuentra en una forma de dosificación como una tableta. En otras formas de realización, la composición se encuentra en una forma de dosificación como una cápsula. La composición se puede conformar en una forma de dosificación como una cápsula o tableta y se puede emplear un amplio rango de

537

composiciones y enfoques de elaboración alternativos. Referencias: (1) *Remington, The Science and Practice of Pharmacy*, 20ª edición, 2000, (2) *Pharmaceutical Dosage Forms: Tablets*. Volúmenes 1-3, 1989, y (3) *Modern Pharmaceuticals*, 4ª edición, 2002. Se puede emplear un rango de enfoques de elaboración incluyendo procesos de mezclado en seco, granulación en húmedo, compactación con rodillos, extrusión, esferonización, recubrimiento y secado por aspersión. También es posible emplear formulación y enfoques de elaboración de geles blandos.

En algunas formas de realización, la composición incluye un relleno o diluyente. En diversas formas de realización, el relleno o diluyente se selecciona entre celulosa microcristalina, celulosa microcristalina silicificada, lactosa, manitol, azúcar compresible, fosfato de calcio, sulfato de calcio, carbonato de calcio, silicato de calcio y almidón. En otras formas de realización, el relleno o diluyente es celulosa microcristalina.

En algunas formas de realización, la composición incluye un desintegrante. En diversas formas de realización, el desintegrante se selecciona entre croscarmellosa sódica, glicolato de almidón sódico, crospovidona, metilcelulosa, ácido algínico, alginato de sodio, derivados de almidón, bentonita y goma Vee [*veegum*]. En algunas formas de realización, el desintegrante es

538

croscarmellosa sódica.

En algunas formas de realización, la composición incluye un lubricante. En diversas formas de realización, el lubricante se selecciona entre estearato de magnesio, estearatos de metales, talco, estearilfumarato de sodio y ácido esteárico. En algunas formas de realización, el lubricante es estearato de magnesio.

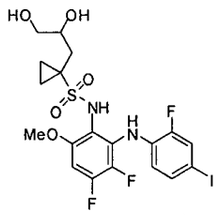
En algunas formas de realización, la composición incluye un agente humectante o un agente tensioactivo. En diversas formas de realización, el agente humectante o el agente tensioactivo se selecciona entre laurilsulfato de sodio, glicerol, oleatos de sorbitán, estearatos de sorbitán, laurato, palmitato, estearato, oleato o hexaloato de sorbitán polioxietilenado, alcohol polioxietilenestearílico y monolaurato de sorbitán. En algunas formas de realización, el agente humectante o el agente tensioactivo es laurilsulfato de sodio.

También se pueden agregar excipientes adicionales tales como deslizantes, saborizantes y colorantes. Se pueden consultar excipientes alternativos adicionales en *The Handbook of Pharmaceutical Excipients*, 5ª edición, 2005 y la base de datos de ingredientes inactivos de la FDA.

La invención también se relaciona con una composición que comprende:

aproximadamente 1 mg de un compuesto de la siguiente

539

estructura:  (definida en cualquiera de las formas de realización precedentes);

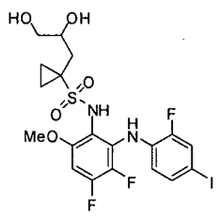
aproximadamente 222,2 mg de celulosa microcristalina;

aproximadamente 12,0 mg de croscarmellosa sódica;

aproximadamente 2,4 mg de laurilsulfato de sodio; y

aproximadamente 2,4 mg de estearato de magnesio.

La invención también se relaciona con una composición que comprende:

aproximadamente 10 mg de un compuesto de la siguiente estructura:  (definida en cualquiera de las formas de realización precedentes);

aproximadamente 213,2 mg de celulosa microcristalina;

aproximadamente 12,0 mg de croscarmellosa sódica;

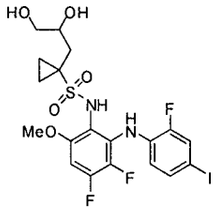
aproximadamente 2,4 mg de laurilsulfato de sodio; y

aproximadamente 2,4 mg de estearato de magnesio.

La invención también se relaciona con una composición que comprende:

aproximadamente 20 mg de un compuesto de la siguiente

5110

estructura:  (definida en cualquiera de las formas de realización precedentes);

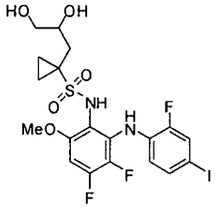
aproximadamente 203,2 mg de celulosa microcristalina;

aproximadamente 12,0 mg de croscarmellosa sódica;

aproximadamente 2,4 mg de laurilsulfato de sodio; y

aproximadamente 2,4 mg de estearato de magnesio.

La invención también se relaciona con una composición que comprende:

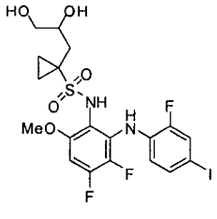
aproximadamente 40 mg de un compuesto de la siguiente estructura:  (definida en cualquiera de las formas de realización precedentes);

aproximadamente 183,2 mg de celulosa microcristalina;

aproximadamente 12,0 mg de croscarmellosa sódica;

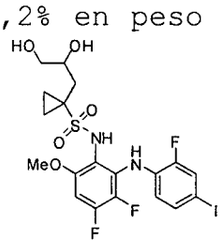
aproximadamente 2,4 mg de laurilsulfato de sodio; y

aproximadamente 2,4 mg de estearato de magnesio.

La invención también se relaciona con una composición que comprende: aproximadamente 0,4% en peso de un compuesto de la siguiente estructura:  (definida en

541

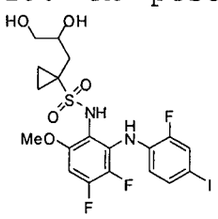
cualquiera de las formas de realización precedentes), y aproximadamente 99,6% en peso de un transportador o vehículo farmacéuticamente aceptable. En algunas formas de realización, el transportador o vehículo farmacéuticamente aceptable comprende celulosa microcristalina. En otras formas de realización o adicionales, la celulosa microcristalina comprende aproximadamente 92,6% en peso de la composición. En otras formas de realización o adicionales, la composición comprende además: aproximadamente un 5% en peso de croscarmellosa sódica; aproximadamente un 1% en peso de laurilsulfato de sodio; y aproximadamente un 1% en peso de estearato de magnesio.

La invención también se relaciona con una composición que comprende: aproximadamente 4,2% en peso de un compuesto de la siguiente estructura:  (definida en cualquiera de las formas de realización precedentes); y aproximadamente 95,8% en peso de un transportador o vehículo farmacéuticamente aceptable. En algunas formas de realización, el transportador o vehículo farmacéuticamente aceptable comprende celulosa microcristalina. En otras formas de realización o adicionales, la celulosa microcristalina comprende aproximadamente 88,8% en peso de

542

la composición. En otras formas de realización o adicionales, la composición comprende además: aproximadamente un 5% en peso de croscarmellosa sódica; aproximadamente un 1% en peso de laurilsulfato de sodio; y aproximadamente un 1% en peso de estearato de magnesio.

La invención también se relaciona con una composición que comprende: entre aproximadamente 2% y aproximadamente 10% en peso de un compuesto de la siguiente estructura:

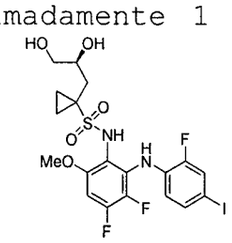



(definida en cualquiera de las formas de realización precedentes); y entre aproximadamente 98% y aproximadamente 90% en peso de un transportador o vehículo farmacéuticamente aceptable. En algunas formas de realización, el transportador o vehículo farmacéuticamente aceptable comprende celulosa microcristalina. En otras formas de realización o adicionales, la celulosa microcristalina comprende entre aproximadamente 85% y aproximadamente 95% en peso de la composición. En otras formas de realización o adicionales, la composición comprende además: entre aproximadamente 1% y aproximadamente 6% en peso de croscarmellosa sódica; entre aproximadamente 0,1% y aproximadamente 2% en peso de laurilsulfato de sodio; y entre aproximadamente 0,25% y aproximadamente 1,5% en peso

513

de estearato de magnesio. En algunas formas de realización, el transportador o vehículo farmacéuticamente aceptable comprende celulosa microcristalina. En otras formas de realización o adicionales, la celulosa microcristalina comprende entre aproximadamente 85% y aproximadamente 95% en peso de la composición. En otras formas de realización o adicionales, la composición comprende además: entre aproximadamente 1% y aproximadamente 6% en peso de croscarmellosa sódica; y entre aproximadamente 0,25% y aproximadamente 1,5% en peso de estearato de magnesio.

La invención también se relaciona con una composición que comprende:

aproximadamente 1 mg de un compuesto de la siguiente estructura: 

;

aproximadamente 222,2 mg de celulosa microcristalina;

aproximadamente 12,0 mg de croscarmellosa sódica;

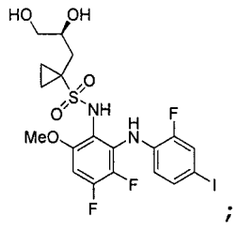
aproximadamente 2,4 mg de laurilsulfato de sodio; y

aproximadamente 2,4 mg de estearato de magnesio.

La invención también se relaciona con una composición que comprende:

aproximadamente 10 mg de un compuesto de la siguiente

544

estructura:  ;

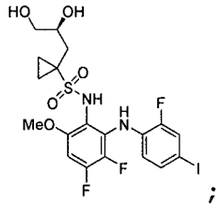
aproximadamente 213,2 mg de celulosa microcristalina;

aproximadamente 12,0 mg de croscarmellosa sódica;

aproximadamente 2,4 mg de laurilsulfato de sodio; y

aproximadamente 2,4 mg de estearato de magnesio.

La invención también se relaciona con una composición que comprende:

aproximadamente 20 mg de un compuesto de la siguiente estructura:  ;

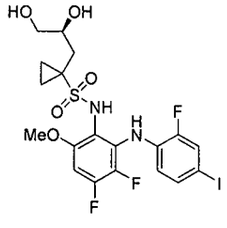
aproximadamente 203,2 mg de celulosa microcristalina;

aproximadamente 12,0 mg de croscarmellosa sódica;

aproximadamente 2,4 mg de laurilsulfato de sodio; y

aproximadamente 2,4 mg de estearato de magnesio.

La invención también se relaciona con una composición que comprende:

aproximadamente 40 mg de un compuesto de la siguiente estructura:  ;

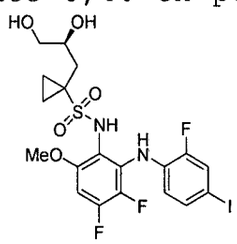
aproximadamente 183,2 mg de celulosa microcristalina;

545

aproximadamente 12,0 mg de croscarmellosa sódica;

aproximadamente 2,4 mg de laurilsulfato de sodio; y

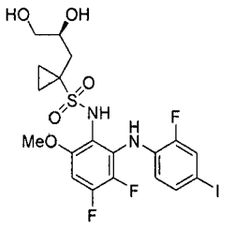
aproximadamente 2,4 mg de estearato de magnesio.

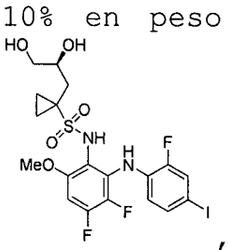
La invención también se relaciona con una composición que comprende: aproximadamente 0,4% en peso de un compuesto de la siguiente estructura: 

, y aproximadamente 99,6% en peso de un transportador o vehículo farmacéuticamente aceptable. En algunas formas de realización, el transportador o vehículo farmacéuticamente aceptable comprende celulosa microcristalina. En otras formas de realización o adicionales, la celulosa microcristalina comprende aproximadamente 92,6% en peso de la composición. En otras formas de realización o adicionales, la composición comprende además: aproximadamente un 5% en peso de croscarmellosa sódica; aproximadamente un 1% en peso de laurilsulfato de sodio; y aproximadamente un 1% en peso de estearato de magnesio.

La invención también se relaciona con una composición que comprende: aproximadamente 4,2% en peso de un compuesto

546

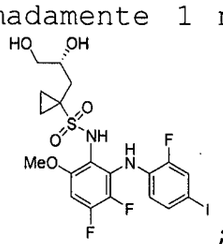
de la siguiente estructura:  , y aproximadamente 95,8 % en peso de un transportador o vehículo farmacéuticamente aceptable. En algunas formas de realización, el transportador o vehículo farmacéuticamente aceptable comprende celulosa microcristalina. En otras formas de realización o adicionales, la celulosa microcristalina comprende aproximadamente 88,8% en peso de la composición. En otras formas de realización o adicionales, la composición comprende además: aproximadamente un 5% en peso de croscarmellosa sódica; aproximadamente un 1% en peso de laurilsulfato de sodio; y aproximadamente un 1% en peso de estearato de magnesio.

La invención también se relaciona con una composición que comprende: entre aproximadamente 2% y aproximadamente 10% en peso de un compuesto de la siguiente estructura:  , y entre aproximadamente 98% y aproximadamente 90% en peso de un transportador o vehículo farmacéuticamente aceptable. En algunas formas de realización, el transportador o vehículo farmacéuticamente aceptable comprende celulosa microcristalina. En otras formas de

347

realización o adicionales, la celulosa microcristalina comprende entre aproximadamente 85% y aproximadamente 95% en peso de la composición. En otras formas de realización o adicionales, la composición comprende además: entre aproximadamente 1% y aproximadamente 6% en peso de croscarmellosa sódica; entre aproximadamente 0,1% y aproximadamente 2% en peso de laurilsulfato de sodio; y entre aproximadamente 0,25% y aproximadamente 1,5% en peso de estearato de magnesio. En algunas formas de realización, el transportador o vehículo farmacéuticamente aceptable comprende celulosa microcristalina. En otras formas de realización o adicionales, la celulosa microcristalina comprende entre aproximadamente 85% y aproximadamente 95% en peso de la composición. En otras formas de realización o adicionales, la composición comprende además: entre aproximadamente 1% y aproximadamente 6% en peso de croscarmellosa sódica; y entre aproximadamente 0,25% y aproximadamente 1,5% en peso de estearato de magnesio.

La invención también se relaciona con una composición que comprende:

aproximadamente 1 mg de un compuesto de la siguiente estructura: 

;

548

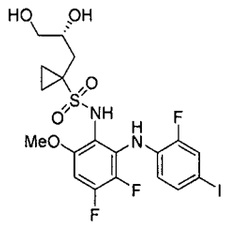
aproximadamente 222,2 mg de celulosa microcristalina;

aproximadamente 12,0 mg de croscarmellosa sódica;

aproximadamente 2,4 mg de laurilsulfato de sodio; y

aproximadamente 2,4 mg de estearato de magnesio.

La invención también se relaciona con una composición que comprende:

aproximadamente 10 mg de un compuesto de la siguiente estructura:  ;

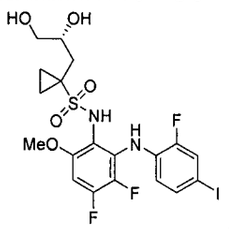
aproximadamente 213,2 mg de celulosa microcristalina;

aproximadamente 12,0 mg de croscarmellosa sódica;

aproximadamente 2,4 mg de laurilsulfato de sodio; y

aproximadamente 2,4 mg de estearato de magnesio.

La invención también se relaciona con una composición que comprende:

aproximadamente 20 mg de un compuesto de la siguiente estructura:  ;

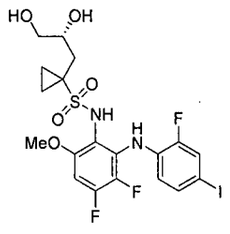
aproximadamente 203,2 mg de celulosa microcristalina;

aproximadamente 12,0 mg de croscarmellosa sódica;

aproximadamente 2,4 mg de laurilsulfato de sodio; y

aproximadamente 2,4 mg de estearato de magnesio.

La invención también se relaciona con una composición que comprende:

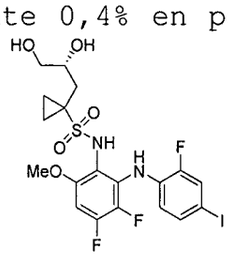
aproximadamente 40mg de un compuesto de la siguiente estructura:  ;

aproximadamente 183,2 mg de celulosa microcristalina;

aproximadamente 12,0 mg de croscarmellosa sódica;

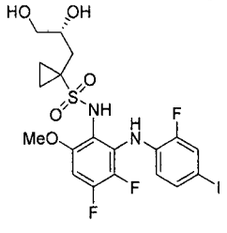
aproximadamente 2,4 mg de laurilsulfato de sodio; y

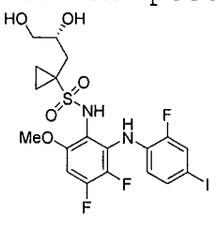
aproximadamente 2,4 mg de estearato de magnesio.

La invención también se relaciona con una composición que comprende: aproximadamente 0,4% en peso de un compuesto de la siguiente estructura:  , y aproximadamente 99,6% en peso de un transportador o vehículo farmacéuticamente aceptable. En algunas formas de realización, el transportador o vehículo farmacéuticamente aceptable comprende celulosa microcristalina. En otras formas de realización o adicionales, la celulosa microcristalina comprende aproximadamente 92,6% en peso de la composición. En otras formas de realización o adicionales, la composición comprende además: aproximadamente un 5% en peso de croscarmellosa sódica;

550

aproximadamente un 1% en peso de laurilsulfato de sodio; y aproximadamente un 1% en peso de estearato de magnesio.

La invención también se relaciona con una composición que comprende: aproximadamente 4,2% en peso de un compuesto de la siguiente estructura:  , y aproximadamente 95,8 % en peso de un transportador o vehículo farmacéuticamente aceptable. En algunas formas de realización, el transportador o vehículo farmacéuticamente aceptable comprende celulosa microcristalina. En otras formas de realización o adicionales, la celulosa microcristalina comprende aproximadamente 88,8% en peso de la composición. En otras formas de realización o adicionales, la composición comprende además: aproximadamente un 5% en peso de croscarmellosa sódica; aproximadamente un 1% en peso de laurilsulfato de sodio; y aproximadamente un 1% en peso de estearato de magnesio.

La invención también se relaciona con una composición que comprende: entre aproximadamente 2% y aproximadamente 10% en peso de un compuesto de la siguiente estructura:  , y entre aproximadamente 98% y aproximadamente

551

90% en peso de un transportador o vehículo farmacéuticamente aceptable. En algunas formas de realización, el transportador o vehículo farmacéuticamente aceptable comprende celulosa microcristalina. En otras formas de realización o adicionales, la celulosa microcristalina comprende entre aproximadamente 85% y aproximadamente 95% en peso de la composición. En otras formas de realización o adicionales, la composición comprende además: entre aproximadamente 1% y aproximadamente 6% en peso de croscarmellosa sódica; entre aproximadamente 0,1% y aproximadamente 2% en peso de laurilsulfato de sodio; y entre aproximadamente 0,25% y aproximadamente 1,5% en peso de estearato de magnesio. En algunas formas de realización, el transportador o vehículo farmacéuticamente aceptable comprende celulosa microcristalina. En otras formas de realización o adicionales, la celulosa microcristalina comprende entre aproximadamente 85% y aproximadamente 95% en peso de la composición. En otras formas de realización o adicionales, la composición comprende además: entre aproximadamente 1% y aproximadamente 6% en peso de croscarmellosa sódica; y entre aproximadamente 0,25% y aproximadamente 1,5% en peso de estearato de magnesio.

En la presente también se describen composiciones farmacéuticas que comprenden una cantidad eficaz de un polimorfo cristalino, la forma A, de N-(S)-(3,4-difluoro-2-

(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida. En algunas formas de realización, las composiciones farmacéuticas comprenden una cantidad eficaz de un polimorfo cristalino, la forma A, de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida, y al menos un vehículo farmacéuticamente aceptable. En algunas formas de realización, las composiciones farmacéuticas son para el tratamiento de trastornos. En algunas formas de realización, las composiciones farmacéuticas son para el tratamiento de trastornos en un mamífero. En algunas formas de realización, las composiciones farmacéuticas son para el tratamiento de trastornos en un ser humano. En algunas formas de realización las composiciones farmacéuticas son para el tratamiento o la profilaxis de enfermedades inflamatorias. En algunas formas de realización, las composiciones farmacéuticas son para el tratamiento o la profilaxis de enfermedades proliferativas.

*Métodos de uso de los compuestos, incluyendo formas polimórficas, y de las composiciones*

En otros aspectos, la presente invención está dirigida a un método para lograr un efecto en un paciente, que comprende la administración de una cantidad eficaz de un compuesto de la fórmula I o una sal, solvato, polimorfo,

553

éster, amida, tautómero o prodroga farmacéuticamente aceptable del mismo, a un paciente, en donde el efecto se selecciona del grupo que consiste de inhibición de distintos tipos de cáncer, enfermedades inmunológicas y enfermedades inflamatorias. En algunas formas de realización, el compuesto o una sal, solvato, polimorfo, éster, amida, tautómero o prodroga farmacéuticamente aceptable del mismo, se administra como un componente de una composición que comprende además un transportador o vehículo farmacéuticamente aceptable. En algunas formas de realización, el efecto es la inhibición de distintos tipos de cáncer. En otras formas de realización o adicionales, el efecto es la inhibición de enfermedades inmunológicas. En otras formas de realización o adicionales, el efecto es la inhibición enfermedades inflamatorias.

Se puede usar cualquiera de las composiciones que se describen y reivindican en la presente en los métodos provistos en esta sección.

En algunas formas de realización, la composición que comprende un compuesto de la fórmula I se administra en combinación con una terapia adicional. En otras formas de realización o adicionales, la terapia adicional es una terapia por radiación, quimioterapia o cirugía o cualquier combinación de las mismas. En otras formas de realización o adicionales, la composición que comprende un compuesto de la

554

fórmula I se administra en combinación con al menos un agente terapéutico.

En algunas formas de realización, la composición se administra por vía oral, intraduodenal, parenteral (incluyendo intravenosa, subcutánea, intramuscular, intravascular o por infusión), tópica o rectal. En otras formas de realización o adicionales, la cantidad del compuesto de la fórmula I se encuentra en el rango de entre aproximadamente 0,001 y aproximadamente 1000 mg/kg de peso corporal/día. En otras formas de realización o adicionales, la cantidad del compuesto de la fórmula I se encuentra en el rango de entre aproximadamente 0,5 y aproximadamente 50 mg/kg/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,001 y aproximadamente 7 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,01 y aproximadamente 7 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,02 y aproximadamente 5 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,05 y aproximadamente 2,5 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,1 y aproximadamente 1 g/día. En

555

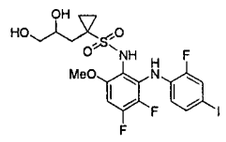
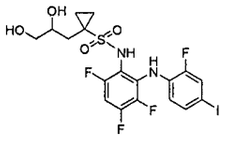
otras formas de realización o adicionales, serán más que adecuados los niveles de dosificación inferiores al límite inferior del rango mencionado previamente. En otras formas de realización o adicionales, pueden ser necesarios niveles de dosificación superiores al límite superior del rango mencionado previamente.

En algunas formas de realización de las composiciones y los métodos provistos en la presente, se proporcionan inhibidores de MEK proteína quinasa que además comprende un compuesto de la fórmula I, en donde el compuesto de la fórmula I está presente en una cantidad de entre aproximadamente 0,1 mg y aproximadamente 200 mg. En otras formas de realización, el inhibidor de MEK proteína quinasa comprende un compuesto de la fórmula I y está presente en una cantidad de entre aproximadamente 0,2 mg y aproximadamente 100 mg. En otras formas de realización, el inhibidor de MEK proteína quinasa comprende un compuesto de la fórmula I y está presente en una cantidad de entre aproximadamente 0,3 mg y aproximadamente 90 mg. En otras formas de realización, el inhibidor de MEK proteína quinasa comprende un compuesto de la fórmula I y está presente en una cantidad de entre aproximadamente 0,4 mg y aproximadamente 80 mg. En otras formas de realización, el inhibidor de MEK proteína quinasa comprende un compuesto de la fórmula I y está presente en una cantidad de entre

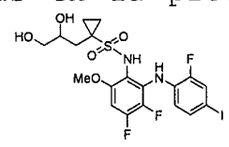
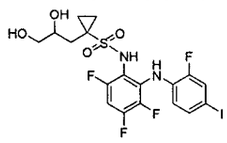
556

aproximadamente 0,5 mg y aproximadamente 70 mg. En otras formas de realización, el inhibidor de MEK proteína quinasa comprende un compuesto de la fórmula I y está presente en una cantidad de entre aproximadamente 0,4 mg y aproximadamente 80 mg. En otras formas de realización, el inhibidor de MEK proteína quinasa comprende un compuesto de la fórmula I y está presente en una cantidad de entre aproximadamente 0,5 mg y aproximadamente 70 mg. En otras formas de realización, el inhibidor de MEK proteína quinasa comprende un compuesto de la fórmula I y está presente en una cantidad de entre aproximadamente 1 mg y aproximadamente 60 mg. En otras formas de realización, el inhibidor de MEK proteína quinasa comprende un compuesto de la fórmula I y está presente en una cantidad de entre aproximadamente 1,5 mg y aproximadamente 50 mg. En otras formas de realización, el inhibidor de MEK proteína quinasa comprende un compuesto de la fórmula I y está presente en una cantidad de entre aproximadamente 2 mg y aproximadamente 45 mg. En otras formas de realización, el inhibidor de MEK proteína quinasa comprende un compuesto de la fórmula I y está presente en una cantidad de entre aproximadamente 2,5 mg y aproximadamente 40 mg. En otras formas de realización, el inhibidor de MEK proteína quinasa además comprende el compuesto de la fórmula I presente en las cantidades de dosificación provistas en la presente se selecciona del

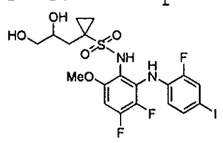
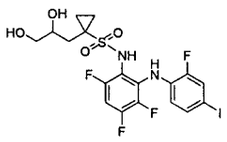
557

grupo que consiste de:  , y  .

En algunas formas de realización de las composiciones y los métodos provistos en la presente, se proporcionan inhibidores de MEK proteína quinasa que además comprenden un compuesto de la fórmula I, en donde el compuesto de la fórmula I está presente en una cantidad de aproximadamente 0,1 mg, aproximadamente 0,2 mg, aproximadamente 0,25 mg, aproximadamente 0,3 mg, aproximadamente 0,4 mg, aproximadamente 0,5 mg, aproximadamente 0,6 mg, aproximadamente 0,7 mg, aproximadamente 0,8 mg, aproximadamente 0,9 mg, aproximadamente 1 mg, aproximadamente 1,5 mg, aproximadamente 2 mg, aproximadamente 2,5 mg, aproximadamente 3 mg, aproximadamente 3,5 mg, aproximadamente 4,0 mg, aproximadamente 4,5 mg, aproximadamente 5 mg, aproximadamente 5,5 mg, aproximadamente 6 mg, aproximadamente 6,5 mg, aproximadamente 7 mg, aproximadamente 7,5 mg, aproximadamente 8 mg, aproximadamente 8,5 mg, aproximadamente 9 mg, aproximadamente 9,5 mg, aproximadamente 10 mg, aproximadamente 10,5 mg, aproximadamente 11 mg, aproximadamente 11,5 mg, aproximadamente 12 mg, aproximadamente 12,5 mg y/o aproximadamente 13 mg, aproximadamente 14 mg o aproximadamente 15 mg. En otras

formas de realización, el compuesto de la fórmula I presente en las cantidades de dosificación provistas en la presente se selecciona del grupo que consiste de:  , y  .

En algunas formas de realización de las composiciones y los métodos provistos en la presente, se proporcionan inhibidores de MEK proteína quinasa que además comprenden un compuesto de la fórmula I, en donde el compuesto de la fórmula I está presente en una cantidad de aproximadamente 15 mg, aproximadamente 20 mg, aproximadamente 25 mg, aproximadamente 30 mg, aproximadamente 35 mg, aproximadamente 40 mg, aproximadamente 45 mg, aproximadamente 50 mg, aproximadamente 55 mg, aproximadamente 60 mg, aproximadamente 65 mg, aproximadamente 75 mg, aproximadamente 80 mg, aproximadamente 85 mg, aproximadamente 90 mg, aproximadamente 95 mg, aproximadamente 100 mg, aproximadamente 110 mg, aproximadamente 120 mg, aproximadamente 125 mg, aproximadamente 130 mg, aproximadamente 140 mg, aproximadamente 150 mg, aproximadamente 160 mg, aproximadamente 170 mg, aproximadamente 175 mg, aproximadamente 180 mg,

aproximadamente 190 mg o aproximadamente 200 mg. En otras formas de realización, el compuesto de la fórmula I presente en las cantidades de dosificación provistas en la presente se selecciona del grupo que consiste de:  , y  .

En otras formas de realización o adicionales, el compuesto de la fórmula I se administra en una sola dosis, una vez por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra en múltiples dosis, más de una vez por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra dos veces por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra tres veces por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra cuatro veces por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra más de cuatro veces por día. En algunas formas de realización, el individuo que sufre de cáncer es un mamífero. En otras formas de realización o adicionales, el individuo es un ser humano. En otras formas de realización o adicionales, se administra una cantidad eficaz de una composición que

560

comprende una sal farmacéuticamente aceptable de un compuesto de la fórmula I.

En algunos aspectos, la presente invención está dirigida a un método de tratamiento de una enfermedad en un individuo que sufre de dicha enfermedad que comprende administrarle a dicho individuo una cantidad eficaz de una composición que comprende un compuesto de la fórmula I o una sal, solvato, polimorfo, éster, tautómero o prodroga farmacéuticamente aceptable del mismo.

En otros aspectos, la presente invención está dirigida a un método de tratamiento de un trastorno en un mamífero, que comprende administrarle a dicho mamífero una cantidad terapéuticamente eficaz del compuesto de la fórmula I o una sal, solvato, polimorfo, éster, tautómero o prodroga farmacéuticamente aceptable del mismo

En otros aspectos, la presente invención está dirigida a un método de tratamiento de un trastorno en un se humano, que comprende administrarle a dicho mamífero una cantidad terapéuticamente eficaz del compuesto de la fórmula I o una sal, solvato, polimorfo, éster, tautómero o prodroga farmacéuticamente aceptable del mismo

Enfermedades y trastornos modulados por MEK

En la presente también se describen métodos para modular la actividad MEK que comprende poner MEK en contacto con una cantidad de un compuesto de la fórmula I que sea

561

suficiente para modular la actividad de MEK. La modulación puede comprender inhibir o activar la actividad MEK. En algunas formas de realización, la invención provee métodos para inhibir la actividad MEK por contacto de MEK con una cantidad de un compuesto de la fórmula I que sea suficiente para inhibir la actividad de MEK. En algunas formas de realización, la invención provee métodos para inhibir la actividad MEK en una solución por contacto de dicha solución con una cantidad de un compuesto de la fórmula I que sea suficiente para inhibir la actividad de MEK en dicha solución. En algunas formas de realización, la invención provee métodos para inhibir la actividad MEK en una célula por contacto de dicha célula con una cantidad de un compuesto descrito en la presente que sea suficiente para inhibir la actividad de MEK en dicha célula. En algunas formas de realización, la invención provee métodos para inhibir la actividad MEK en un tejido por contacto de dicho tejido con una cantidad de un compuesto descrito en la presente que sea suficiente para inhibir la actividad de MEK en dicho tejido. En algunas formas de realización, la invención provee métodos para inhibir la actividad MEK en un organismo por contacto de dicho organismo con una cantidad de un compuesto descrito en la presente que sea suficiente para inhibir la actividad de MEK en dicho organismo. En algunas formas de realización, la invención provee métodos

562

para inhibir la actividad MEK en un animal por contacto de dicho animal con una cantidad de un compuesto descrito en la presente que sea suficiente para inhibir la actividad de MEK en dicho animal. En algunas formas de realización, la invención provee métodos para inhibir la actividad MEK en un mamífero por contacto de dicho mamífero con una cantidad de un compuesto descrito en la presente que sea suficiente para inhibir la actividad de MEK en dicho mamífero. En algunas formas de realización, la invención provee métodos para inhibir la actividad MEK en un ser humano por contacto de dicho humano con una cantidad de un compuesto descrito en la presente que sea suficiente para inhibir la actividad de MEK en dicho ser humano.

Los compuestos de la fórmula I, y las composiciones que contienen un compuesto de la fórmula I, y sales, solvatos, polimorfos, ésteres, amidas, tautómeros o prodrogas farmacéuticamente aceptables del mismo, pueden modular la actividad de las enzimas MEK; y, como tales, son de utilidad para el tratamiento de enfermedades o condiciones en las cuales la actividad aberrante de la enzima MEK contribuya en la patología y/o los síntomas de una enfermedad o condición.

En algunos aspectos, la presente invención está dirigida a un método de tratamiento de un trastorno o condición que es modulada por la cascada MEK en un mamífero, incluyendo un ser humano, que comprende administrarle a

563

dicho mamífero una cantidad del compuesto de la fórmula I, o una sal, éster, prodroga, solvato, hidrato o derivado farmacéuticamente aceptable del mismo, eficaz para modular dicha cascada. La dosificación apropiada para un paciente particular puede ser determinada, de acuerdo con métodos conocidos, por los especialistas en el arte.

En otros aspectos, la presente invención está dirigida a un método para inhibir una enzima MEK. En algunas formas de realización, el método comprende poner dicha enzima MEK en contacto con una cantidad de una composición que comprende un compuesto de la fórmula I o una sal, solvato, polimorfo, éster, amida, tautómero o prodroga farmacéuticamente aceptable del mismo, suficiente para inhibir dicha enzima, en donde dicha enzima es inhibida. En otras formas de realización o adicionales, la enzima se inhibe en al menos un 1% aproximadamente. En otras formas de realización o adicionales, la enzima se inhibe en al menos un 2% aproximadamente. En otras formas de realización o adicionales, la enzima se inhibe en al menos un 3% aproximadamente. En otras formas de realización o adicionales, la enzima se inhibe en al menos un 4% aproximadamente. En otras formas de realización o adicionales, la enzima se inhibe en al menos un 5% aproximadamente. En otras formas de realización o adicionales, la enzima se inhibe en al menos un 10%

564

aproximadamente. En otras formas de realización o adicionales, la enzima se inhibe en al menos un 20% aproximadamente. En otras formas de realización o adicionales, la enzima se inhibe en al menos un 25% aproximadamente. En otras formas de realización o adicionales, la enzima se inhibe en al menos un 30% aproximadamente. En otras formas de realización o adicionales, la enzima se inhibe en al menos un 40% aproximadamente. En otras formas de realización o adicionales, la enzima se inhibe en al menos un 50% aproximadamente. En otras formas de realización o adicionales, la enzima se inhibe en al menos un 60% aproximadamente. En otras formas de realización o adicionales, la enzima se inhibe en al menos un 70% aproximadamente. En otras formas de realización o adicionales, la enzima se inhibe en al menos un 75% aproximadamente. En otras formas de realización o adicionales, la enzima se inhibe en al menos un 80% aproximadamente. En otras formas de realización o adicionales, la enzima se inhibe en al menos un 90% aproximadamente. En otras formas de realización o adicionales, la enzima es inhibida esencialmente por completo. En otras formas de realización o adicionales, la enzima MEK es la MEK quinasa. En otras formas de realización o adicionales, la enzima MEK es MEK1. En otras formas de

563

realización o adicionales, la enzima MEK es MEK2. En otras formas de realización o adicionales, el contacto tiene lugar dentro de una célula. En otras formas de realización o adicionales, la célula es una célula de mamífero. En otras formas de realización o adicionales, la célula de mamífero es una célula humana. En otras formas de realización o adicionales, la enzima MEK es inhibida con una composición que comprende una sal farmacéuticamente aceptable de un compuesto de la fórmula I.

En otros aspectos o adicionales, la presente invención está dirigida a un método de tratamiento de un trastorno mediado por MEK en un individuo que sufre de dicho trastorno que comprende administrarle a dicho individuo una cantidad eficaz de una composición que comprende un compuesto de la fórmula I o una sal, solvato, polimorfo, éster, amida, tautómero o prodroga farmacéuticamente aceptable del mismo. En algunas formas de realización, la composición que comprende un compuesto de la fórmula I se administra por vía oral, intraduodenal, parenteral (incluyendo intravenosa, subcutánea, intramuscular, intravascular o por infusión), tópica o rectal. En algunas formas de realización, la composición farmacéutica se encuentra en una forma adecuada para una administración oral. En otras formas de realización o adicionales, la composición farmacéutica se encuentra en la forma de una tableta, cápsula, píldora, polvo,

566

formulaciones de liberación sostenida, solución, suspensión, como una solución, suspensión o emulsión estéril para una inyección parenteral, como un ungüento o crema para una administración tópica o como un supositorio para una administración rectal. En otras formas de realización o adicionales, la composición farmacéutica se encuentra en formas de dosificación unitarias adecuadas para la administración individual de dosificaciones precisas. En otras formas de realización o adicionales, la composición farmacéutica comprende además un vehículo, excipiente y/o adyuvante farmacéutico.

En otras formas de realización o adicionales, la cantidad del compuesto de la fórmula I se encuentra en el rango de entre aproximadamente 0,001 y aproximadamente 1000 mg/kg de peso corporal/día. En otras formas de realización o adicionales, la cantidad del compuesto de la fórmula I se encuentra en el rango de entre aproximadamente 0,5 y aproximadamente 50 mg/kg/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,001 y aproximadamente 7 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,01 y aproximadamente 7 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,02 y aproximadamente 5 g/día. En

567

otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,05 y aproximadamente 2,5 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,1 y aproximadamente 1 g/día. En otras formas de realización o adicionales, serán más que adecuados los niveles de dosificación inferiores al límite inferior del rango mencionado previamente. En otras formas de realización o adicionales, pueden ser necesarios niveles de dosificación superiores al límite superior del rango mencionado previamente.

En otras formas de realización o adicionales, el compuesto de la fórmula I se administra en una sola dosis, una vez por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra en múltiples dosis, más de una vez por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra dos veces por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra tres veces por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra cuatro veces por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra más de cuatro veces por día. En algunas formas de realización, el individuo que sufre del trastorno mediado por MEK es un

368

mamífero. En otras formas de realización o adicionales, el individuo es un ser humano.

En algunas formas de realización, la composición que comprende un compuesto de la fórmula I se administra en combinación con una terapia adicional. En otras formas de realización o adicionales, la terapia adicional es una terapia por radiación, quimioterapia, cirugía o cualquier combinación de las mismas. En otras formas de realización o adicionales, la composición que comprende un compuesto de la fórmula I se administra en combinación con al menos un agente terapéutico. En otras formas de realización o adicionales, el agente terapéutico se selecciona del grupo de agentes citotóxicos, agentes anti-angiogénesis y agentes anti-neoplásicos. En otras formas de realización o adicionales, el agente anti-neoplásico se selecciona del grupo que consiste de agentes alquilantes, anti-metabolitos, epidofilotoxinas; enzimas antineoplásicas, inhibidores de topoisomerasa, procarbazinas, mitoxantronas, complejos de coordinación de platino, modificadores de la respuesta biológica e inhibidores del crecimiento, agentes terapéuticos hormonales/anti-hormonales y factores de crecimiento hematopoyéticos. En otras formas de realización o adicionales, el agente terapéutico se selecciona entre taxol, bortezomib o ambos.

En algunas formas de realización, el trastorno mediado

569

por MEK se selecciona del grupo que consiste de enfermedades inflamatorias, infecciones, trastornos autoinmunes, accidente cerebrovascular, isquemia, trastornos cardíacos, trastornos neurológicos, trastornos fibrogenéticos, trastornos proliferativos, trastornos hiperproliferativos, trastornos hiperproliferativos no cancerosos, tumores, leucemias, neoplasmas, distintos tipos de cáncer, carcinomas, enfermedades metabólicas, enfermedad maligna, restenosis vascular, psoriasis, aterosclerosis, artritis reumatoide, osteoartritis, insuficiencia cardíaca, dolor crónico, dolor neuropático, síndrome de ojo seco, glaucoma de ángulo cerrado y glaucoma de ángulo amplio. En otras formas de realización o adicionales, el trastorno mediado por MEK es una enfermedad inflamatoria. En otras formas de realización o adicionales, el trastorno mediado por MEK es una enfermedad hiperproliferativa. En otras formas de realización o adicionales, el trastorno mediado por MEK se selecciona del grupo que consiste de tumores, leucemias, neoplasmas, distintos tipos de cáncer, carcinomas y enfermedad maligna. En otras formas de realización o adicionales, comprende cáncer de estómago, cáncer de cerebro, cáncer de mama, cáncer de pulmón, cáncer de ovario, cáncer pancreático, cáncer de próstata, cáncer renal, cáncer colorrectal o leucemia. En otras formas de realización o adicionales, el trastorno fibrogenético es escleroderma,

570

polimiositis, lupus sistémica, artritis reumatoide, cirrosis hepática, formación de queloides, nefritis intersticial o fibrosis pulmonar. En otras formas de realización o adicionales, se administra una cantidad eficaz de una composición que comprende una sal farmacéuticamente aceptable de un compuesto de la fórmula I.

La invención también se relaciona con métodos para modular la actividad MEK que comprende el contacto de MEK con una cantidad de un polimorfo cristalino, forma A, de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida que sea suficiente para modular la actividad de MEK. La modulación puede comprender inhibir o activar la actividad MEK. En algunas formas de realización, la invención provee métodos para inhibir la actividad MEK por contacto de MEK con una cantidad de un polimorfo cristalino, forma A, de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida que sea suficiente para inhibir la actividad de MEK. En algunas formas de realización, la invención provee métodos para inhibir la actividad de MEK en una solución por contacto de dicha solución con una cantidad de un polimorfo cristalino, forma A, de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-

571

sulfonamida que sea suficiente para inhibir la actividad de MEK en dicha solución. En algunas formas de realización, la invención provee métodos para inhibir la actividad de MEK en una célula por contacto de dicha célula con una cantidad de un polimorfo cristalino, forma A, de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida que sea suficiente para inhibir la actividad de MEK en dicha célula. En algunas formas de realización, la invención provee métodos para inhibir la actividad de MEK en un tejido por contacto de dicho tejido con una cantidad de un polimorfo cristalino, forma A, de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida que sea suficiente para inhibir la actividad de MEK en dicho tejido. En algunas formas de realización, la invención provee métodos para inhibir la actividad de MEK en un organismo por contacto de dicho organismo con una cantidad de un polimorfo cristalino, forma A, de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida que sea suficiente para inhibir la actividad de MEK en dicho organismo. En algunas formas de realización, la invención provee métodos para inhibir la actividad de MEK en un animal por contacto de dicho animal con una cantidad de un polimorfo cristalino,

S-72

forma A, de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida que sea suficiente para inhibir la actividad de MEK en dicho animal. En algunas formas de realización, la invención provee métodos para inhibir la actividad de MEK en un mamífero por contacto de dicho mamífero con una cantidad de un polimorfo cristalino, forma A, de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida que sea suficiente para inhibir la actividad de MEK en dicho mamífero. En algunas formas de realización, la invención provee métodos para inhibir la actividad de MEK en un ser humano por contacto de dicho humano con una cantidad de un polimorfo cristalino, forma A, de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida que sea suficiente para inhibir la actividad de MEK en dicho ser humano.

Cáncer

En otros aspectos, la presente invención está dirigida a un método para el tratamiento, la prevención o la profilaxis de cáncer en un individuo que comprende administrarle a dicho individuo una cantidad eficaz de un compuesto de la fórmula I o una sal, solvato, polimorfo, éster, amida, tautómero o prodroga farmacéuticamente

573

aceptable del mismo. En algunas formas de realización, el compuesto o una sal, solvato, polimorfo, éster, amida, tautómero o prodroga farmacéuticamente aceptable del mismo, se administra como un componente de una composición que comprende además un transportador o vehículo farmacéuticamente aceptable. En otras formas de realización o adicionales, el cáncer es cáncer de cerebro, cáncer de mama, cáncer de pulmón, cáncer de ovario, cáncer pancreático, cáncer de próstata, cáncer renal, cáncer de estómago, cáncer colorrectal o leucemia. En otras formas de realización o adicionales, el trastorno fibrogenético es escleroderma, polimiositis, lupus sistémica, artritis reumatoide, cirrosis hepática, formación de queloides, nefritis intersticial o fibrosis pulmonar. En otras formas de realización o adicionales, el cáncer es cáncer de cerebro, cáncer de mama, cáncer de pulmón, cáncer de ovario, cáncer pancreático, cáncer de próstata, cáncer renal, cáncer colorrectal, leucemia, melanoma, cáncer de tiroides o carcinoma de células basales. En otras formas de realización o adicionales, el cáncer es cáncer de cerebro o carcinoma adrenocortical. En otras formas de realización o adicionales, el cáncer es cáncer de mama. En otras formas de realización o adicionales, el cáncer es cáncer de ovario. En otras formas de realización o adicionales, el cáncer es cáncer pancreático. En otras formas de realización o

574

adicionales, el cáncer es cáncer de próstata. En otras formas de realización o adicionales, el cáncer es cáncer renal. En otras formas de realización o adicionales, el cáncer es cáncer colorrectal. En otras formas de realización o adicionales, el cáncer es leucemia mieloide. En otras formas de realización o adicionales, el cáncer es glioblastoma. En otras formas de realización o adicionales, el cáncer es linfoma folicular. En otras formas de realización o adicionales, el cáncer es leucemia aguda pre-B. En otras formas de realización o adicionales, el cáncer es leucemia linfocítica B crónica. En otras formas de realización o adicionales, el cáncer es mesotelioma. En otras formas de realización o adicionales, el cáncer es cáncer de pulmón de células pequeñas. En algunas formas de realización, el cáncer es cáncer de estómago.

En algunas formas de realización, la composición que comprende un compuesto de la fórmula I se administra en combinación con una terapia adicional. En otras formas de realización o adicionales, la terapia adicional es una terapia por radiación, quimioterapia, cirugía o cualquier combinación de las mismas. En otras formas de realización o adicionales, la composición que comprende un compuesto de la fórmula I se administra en combinación con al menos un agente terapéutico. En otras formas de realización o adicionales, el agente terapéutico se selecciona del grupo

de agentes citotóxicos, agentes anti-angiogénesis y agentes anti-neoplásicos. En otras formas de realización o adicionales, el agente anti-neoplásico se selecciona del grupo que consiste de agentes alquilantes, anti-metabolitos, epidofilotoxinas; enzimas antineoplásicas, inhibidores de topoisomerasa, procarbazinas, mitoxantronas, complejos de coordinación de platino, modificadores de la respuesta biológica e inhibidores del crecimiento, agentes terapéuticos hormonales/anti-hormonales y factores de crecimiento hematopoyéticos. En otras formas de realización o adicionales, el agente terapéutico se selecciona entre taxol, bortezomib o ambos.

En otras formas de realización o adicionales, la cantidad del compuesto de la fórmula I se encuentra en el rango de entre aproximadamente 0,001 y aproximadamente 1000 mg/kg de peso corporal/día. En otras formas de realización o adicionales, la cantidad del compuesto de la fórmula I se encuentra en el rango de entre aproximadamente 0,5 y aproximadamente 50 mg/kg/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,001 y aproximadamente 7 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,01 y aproximadamente 7 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de

576

entre aproximadamente 0,02 y aproximadamente 5 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,05 y aproximadamente 2,5 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,1 y aproximadamente 1 g/día. En otras formas de realización o adicionales, serán más que adecuados los niveles de dosificación inferiores al límite inferior del rango mencionado previamente. En otras formas de realización o adicionales, pueden ser necesarios niveles de dosificación superiores al límite superior del rango mencionado previamente.

En algunas formas de realización, la composición se administra por vía oral, intraduodenal, parenteral (incluyendo intravenosa, subcutánea, intramuscular, intravascular o por infusión), tópica o rectal. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra en una sola dosis, una vez por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra en múltiples dosis, más de una vez por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra dos veces por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra tres veces por día. En otras formas de realización o adicionales, el compuesto

de la fórmula I se administra cuatro veces por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra más de cuatro veces por día. En algunas formas de realización, el individuo que sufre de cáncer es un mamífero. En otras formas de realización o adicionales, el individuo es un ser humano. En otras formas de realización o adicionales, se administra una cantidad eficaz de una composición que comprende una sal farmacéuticamente aceptable de un compuesto de la fórmula I.

Crecimiento celular anormal

En la presente también se describen compuestos, composiciones farmacéuticas y métodos para inhibir un crecimiento celular anormal. En algunas formas de realización, el crecimiento celular anormal es en un mamífero. Los métodos para inhibir un crecimiento celular anormal comprenden administrar una cantidad eficaz de un compuesto de la fórmula I, o una sal, solvato, polimorfo, éster, amida, tautómero, prodroga, hidrato o derivado farmacéuticamente aceptable del mismo, en donde se inhibe el crecimiento celular anormal. Los métodos para inhibir el crecimiento celular anormal en un mamífero comprenden administrarle al mamífero una cantidad de un compuesto de la fórmula I, o una sal, solvato, polimorfo, éster, amida, tautómero, prodroga, hidrato o derivado farmacéuticamente aceptable del mismo, en donde las cantidades del compuesto,

o la sal, son eficaces para inhibir el crecimiento celular anormal en el mamífero.

En algunas formas de realización, los métodos comprenden administrar una cantidad eficaz de un compuesto de la fórmula I, o una sal, solvato, polimorfo, éster, amida, tautómero, prodroga, hidrato o derivado farmacéuticamente aceptable del mismo, en combinación con una cantidad de un quimioterapéutico, en donde las cantidades del compuesto, o su sal, solvato, polimorfo, éster, amida, tautómero, prodroga, hidrato o derivado del mismo y el quimioterapéutico son eficaces juntos para inhibir el crecimiento celular anormal. Actualmente se conocen muchos quimioterapéuticos en el arte y se pueden usar en combinación con los compuestos de la invención. En algunas formas de realización, el quimioterapéutico se selecciona del grupo que consiste de inhibidores mitóticos, agentes alquilantes, anti-metabolitos, antibióticos intercalantes, inhibidores de factores de crecimiento, inhibidores del ciclo celular, enzimas, inhibidores de topoisomerasa, modificadores de la respuesta biológica, anti-hormonas, inhibidores de la angiogénesis y anti-andrógenos.

También se describen métodos para inhibir un crecimiento celular anormal en un mamífero que comprenden administrarle al mamífero una cantidad de un compuesto de la

S79

fórmula I, o una sal, solvato, polimorfo, éster, amida, tautómero, prodroga, hidrato o derivado farmacéuticamente aceptable del mismo, en combinación con una terapia por radiación, en donde las cantidades del compuesto, o su sal, solvato, polimorfo, éster, amida, tautómero, prodroga, hidrato o un derivado del mismo se combinan con la terapia por radiación eficaz para inhibir el crecimiento celular anormal o tratar el trastorno hiperproliferativo en el mamífero. Las técnicas de administración de una terapia por radiación son conocidas en el arte, y estas técnicas se pueden usar en la terapia combinada que se describe en la presente. La administración del compuesto de la fórmula I en esta terapia combinada se puede determinar como se describe en la presente.

La invención también se relaciona con un método y una composición farmacéutica para inhibir el crecimiento celular anormal en un mamífero que comprende una cantidad de un compuesto de la fórmula I, o una sal, solvato, polimorfo, éster, amida, tautómero, prodroga, hidrato o derivado farmacéuticamente aceptable del mismo, o un derivado marcado con isótopos del mismo, y una cantidad de una o más sustancias seleccionadas entre agentes anti-angiogénesis, inhibidores de la transducción de señales y agentes antiproliferativos.

Los agentes anti-angiogénesis, tales como inhibidores

S80

de MMP-2 (metaloproteinasa de la matriz 2), inhibidores de MMP-9 (metaloproteinasa de la matriz 9) e inhibidores de COX-11 (ciclooxigenasa 11), se pueden usar junto con un compuesto de la presente invención y las composiciones farmacéuticas que se describen en la presente. Los ejemplos de inhibidores de COX-II que son de utilidad incluyen CELEBREX™ (alecoxib), valdecoxib y rofecoxib. Los ejemplos de inhibidores de metaloproteinasa de la matriz que son de utilidad se describen en WO 96/33172 (publicada el 24 de octubre,1996), WO 96/27583 (publicada el 7 de marzo, 1996), Solicitud de Patente de Europa N°: 97304971.1 (presentada el 8 de julio, 1997), Solicitud de Patente de Europa N°: 99308617.2 (presentada el 29 de octubre, 1999), WO 98/07697 (publicada el 26 de febrero, 1998), WO 98/03516 (publicada el 29 de enero, 1998), WO 98/34918 (publicada el 13 de agosto, 1998), WO 98/34915 (publicada el 13 de agosto,1998), WO 98/33768 (publicada el 6 de agosto, 1998), WO 98/30566 (publicada el 16 de julio, 1998), publicación de Patente de Europa 606.046 (publicada el 13 de julio,1994), publicación de Patente de Europa 931.788 (publicada el 28 de julio, 1999), WO 90/05719 (publicada el 31 de mayo, 1990), WO 99/52910 (publicada el 21 de octubre,1999), WO 99/52889 (publicada el 21 de octubre, 1999), WO 99/29667 (publicada el 17 de junio, 1999), Solicitud Internacional PCT N°: PCT/IB98/01113 (presentada el 21 de julio, 1998), Solicitud

381

de Patente de Europa N°: 99302232.1 (presentada el 25 de marzo, 1999), Solicitud de Patente de Gran Bretaña N°: 9912961,1 (presentada el 3 de junio, 1999), Solicitud Provisional de Patente de los EE.UU. N°: 60/148.464 (presentada el 12 de agosto, 1999), Patente de los EE.UU. N°: 5.863.949 (presentada el 26 de enero, 1999), Patente de los EE.UU. N°: 5.861.510 (presentada el 19 de enero, 1999) y publicación de Patente de Europa 780.386 (publicada el 25 de junio, 1997), todas las cuales se incorporan por completo en la presente a modo de referencia. Algunos inhibidores de MMP-2 y MMP-9 tienen poca o ninguna actividad inhibidora de MMP-1, en tanto algunos inhiben selectivamente a MMP-2 y/o AMP-9 con relación a las otras metaloproteinasas de la matriz (es decir, MAP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP- 7, MMP-8, MMP-10, MMP-11, MMP-12 y MMP-13). Algunos ejemplos específicos de inhibidores de MMP que son de utilidad en la presente invención son AG-3340, RO 32-3555 y RS 13-0830.

En otros aspectos, la presente invención está dirigida a un método para degradar, inhibir el crecimiento o matar una célula cancerosa que comprende poner dicha célula en contacto con una cantidad de una composición que sea eficaz para degradar, inhibir el crecimiento o matar dicha célula, donde la composición comprende un compuesto de la fórmula I o una sal, solvato, polimorfo, éster, amida, tautómero o prodroga farmacéuticamente aceptable del mismo. En algunas

582

formas de realización, las células cancerosas comprenden células de cáncer de cerebro, de mama, de pulmón, de ovario, pancreático, de próstata, renal o colorrectal.

En otras formas de realización o adicionales, la composición se administra junto con al menos un agente terapéutico. En otras formas de realización o adicionales, el agente terapéutico es taxol, bortezomib o ambos. En otras formas de realización o adicionales, el agente terapéutico se selecciona del grupo que consiste de agentes citotóxicos, agentes anti-angiogénesis y agentes anti-neoplásicos. En otras formas de realización o adicionales, los agentes anti-neoplásicos se seleccionan del grupo que consiste de agentes alquilantes, anti-metabolitos, epidofilotoxinas; enzimas antineoplásicas, inhibidores de topoisomerasa, procarbazinas, mitoxantronas, complejos de coordinación de platino, modificadores de la respuesta biológica e inhibidores del crecimiento, agentes terapéuticos hormonales/anti-hormonales y factores de crecimiento hematopoyéticos.

En algunas formas de realización, las células cancerosas se degradan. En otras formas de realización o adicionales, se degrada el 1% de las células cancerosas. En otras formas de realización o adicionales, se degrada el 2% de las células cancerosas. En otras formas de realización o adicionales, se degrada el 3% de las células cancerosas. En

S83

otras formas de realización o adicionales, se degrada el 4% de las células cancerosas. En otras formas de realización o adicionales, se degrada el 5% de las células cancerosas. En otras formas de realización o adicionales, se degrada el 10% de las células cancerosas. En otras formas de realización o adicionales, se degrada el 20% de las células cancerosas. En otras formas de realización o adicionales, se degrada el 25% de las células cancerosas. En otras formas de realización o adicionales, se degrada el 30% de las células cancerosas. En otras formas de realización o adicionales, se degrada el 40% de las células cancerosas. En otras formas de realización o adicionales, se degrada el 50% de las células cancerosas. En otras formas de realización o adicionales, se degrada el 60% de las células cancerosas. En otras formas de realización o adicionales, se degrada el 70% de las células cancerosas. En otras formas de realización o adicionales, se degrada el 75% de las células cancerosas. En otras formas de realización o adicionales, se degrada el 80% de las células cancerosas. En otras formas de realización o adicionales, se degrada el 90% de las células cancerosas. En otras formas de realización o adicionales, se degrada el 100% de las células cancerosas. En otras formas de realización o adicionales, se degradan esencialmente todas las células cancerosas.

En algunas formas de realización, se matan las células cancerosas. En otras formas de realización o adicionales, se

584

mata el 1% de las células cancerosas. En otras formas de realización o adicionales, se mata el 2% de las células cancerosas. En otras formas de realización o adicionales, se mata el 3% de las células cancerosas. En otras formas de realización o adicionales, se mata el 4% de las células cancerosas. En otras formas de realización o adicionales, se mata el 5% de las células cancerosas. En otras formas de realización o adicionales, se mata el 10% de las células cancerosas. En otras formas de realización o adicionales, se mata el 20% de las células cancerosas. En otras formas de realización o adicionales, se mata el 25% de las células cancerosas. En otras formas de realización o adicionales, se mata el 30% de las células cancerosas. En otras formas de realización o adicionales, se mata el 40% de las células cancerosas. En otras formas de realización o adicionales, se mata el 50% de las células cancerosas. En otras formas de realización o adicionales, se mata el 60% de las células cancerosas. En otras formas de realización o adicionales, se mata el 70% de las células cancerosas. En otras formas de realización o adicionales, se mata el 75% de las células cancerosas. En otras formas de realización o adicionales, se mata el 80% de las células cancerosas. En otras formas de realización o adicionales, se mata el 90% de las células cancerosas. En otras formas de realización o adicionales, se mata el 100% de las células cancerosas. En otras formas de

585

realización o adicionales, se matan esencialmente todas las células cancerosas.

En otras formas de realización o adicionales, se inhibe el crecimiento de las células cancerosas. En otras formas de realización o adicionales, se inhibe el crecimiento de las células cancerosas en un 1% aproximadamente. En otras formas de realización o adicionales, se inhibe el crecimiento de las células cancerosas en un 2% aproximadamente. En otras formas de realización o adicionales, se inhibe el crecimiento de las células cancerosas en un 3% aproximadamente. En otras formas de realización o adicionales, se inhibe el crecimiento de las células cancerosas en un 4% aproximadamente. En otras formas de realización o adicionales, se inhibe el crecimiento de las células cancerosas en un 5% aproximadamente. En otras formas de realización o adicionales, se inhibe el crecimiento de las células cancerosas en un 10% aproximadamente. En otras formas de realización o adicionales, se inhibe el crecimiento de las células cancerosas en un 20% aproximadamente. En otras formas de realización o adicionales, se inhibe el crecimiento de las células cancerosas en un 25% aproximadamente. En otras formas de realización o adicionales, se inhibe el crecimiento de las células cancerosas en un 30% aproximadamente. En otras formas de realización o adicionales, se inhibe el

crecimiento de las células cancerosas en un 40% aproximadamente. En otras formas de realización o adicionales, se inhibe el crecimiento de las células cancerosas en un 50% aproximadamente. En otras formas de realización o adicionales, se inhibe el crecimiento de las células cancerosas en un 60% aproximadamente. En otras formas de realización o adicionales, se inhibe el crecimiento de las células cancerosas en un 70% aproximadamente. En otras formas de realización o adicionales, se inhibe el crecimiento de las células cancerosas en un 75% aproximadamente. En otras formas de realización o adicionales, se inhibe el crecimiento de las células cancerosas en un 80% aproximadamente. En otras formas de realización o adicionales, se inhibe el crecimiento de las células cancerosas en un 90% aproximadamente. En otras formas de realización o adicionales, se inhibe el crecimiento de las células cancerosas en un 100% aproximadamente. En otras formas de realización o adicionales, se utiliza una composición que comprende una sal farmacéuticamente aceptable de un compuesto de la fórmula I.

En la presente también se describen métodos para inhibir un crecimiento celular anormal. En algunas formas de realización, el crecimiento celular anormal es en un mamífero. Los métodos para inhibir el crecimiento celular

anormal comprenden administrar una cantidad eficaz de un polimorfo cristalino, forma A, de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida, en donde se inhibe el crecimiento celular anormal. Los métodos para inhibir un crecimiento celular anormal en un mamífero comprenden administrarle al mamífero una cantidad de un polimorfo cristalino, forma A, de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida, en donde la cantidad de dicho polimorfo cristalino, forma A, de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida es eficaz para inhibir el crecimiento celular anormal en el mamífero.

En algunas formas de realización, los métodos comprenden administrar una cantidad eficaz de un polimorfo cristalino, forma A, de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida en combinación con una cantidad de un quimioterapéutico, en donde las cantidades del polimorfo cristalino, forma A, de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida y del quimioterapéutico son eficaces juntos para inhibir el crecimiento celular anormal.

Actualmente se conocen muchos quimioterapéuticos en el arte y se pueden usar en combinación con los compuestos y las composiciones de la invención. En algunas formas de realización, el quimioterapéutico se selecciona del grupo que consiste de inhibidores mitóticos, agentes alquilantes, anti-metabolitos, antibióticos intercalantes, inhibidores de factores de crecimiento, inhibidores del ciclo celular, enzimas, inhibidores de topoisomerasa, modificadores de la respuesta biológica, anti-hormonas, inhibidores de la angiogénesis y anti-andrógenos.

En algunas formas de realización, los métodos para inhibir un crecimiento celular anormal en un mamífero comprenden administrarle al mamífero una cantidad de un polimorfo cristalino, forma A, de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida en combinación con una terapia por radiación, en donde la cantidad de polimorfo cristalino, forma A, de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida en combinación con la terapia por radiación es eficaz para inhibir el crecimiento celular anormal. Las técnicas de administración de una terapia por radiación son conocidas en el arte, y estas técnicas se pueden usar en la terapia combinada que se describe en la presente.

589

Tratamiento de un trastorno hiperproliferativo

En otros aspectos, la presente invención está dirigida a un método de tratamiento de un trastorno hiperproliferativo en un mamífero, incluyendo un ser humano, que comprende administrarle a dicho mamífero una cantidad terapéuticamente eficaz del compuesto de la fórmula I o una sal, solvato, polimorfo, éster, tautómero o prodroga farmacéuticamente aceptable del mismo.

En otros aspectos, la presente invención está dirigida a un método para el tratamiento, la prevención o la profilaxis de una enfermedad proliferativa en un individuo que comprende administrarle a dicho individuo una cantidad eficaz de un compuesto de la fórmula I o una sal, solvato, polimorfo, éster, amida, tautómero o prodroga farmacéuticamente aceptable del mismo. En algunas formas de realización, el compuesto o una sal, solvato, polimorfo, éster, amida, tautómero o prodroga farmacéuticamente aceptable del mismo, se administra como un componente de una composición que comprende además un transportador o vehículo farmacéuticamente aceptable. En algunas formas de realización, la enfermedad proliferativa es cáncer, psoriasis, restenosis, una enfermedad autoinmune o aterosclerosis. En otras formas de realización o adicionales, la enfermedad proliferativa es una enfermedad hiperproliferativa. En otras formas de realización o

590

adicionales, la enfermedad proliferativa se selecciona del grupo que consiste de tumores, leucemias, neoplasmas, distintos tipos de cáncer, carcinomas y una enfermedad maligna. En otras formas de realización o adicionales, el cáncer es cáncer de cerebro, cáncer de mama, cáncer de pulmón, cáncer de ovario, cáncer pancreático, cáncer de próstata, cáncer renal, cáncer de estómago, cáncer colorrectal o leucemia. En otras formas de realización o adicionales, el trastorno fibrogenético es escleroderma, polimiositis, lupus sistémica, artritis reumatoide, cirrosis hepática, formación de queloides, nefritis intersticial o fibrosis pulmonar. En otras formas de realización o adicionales, el cáncer es cáncer de cerebro, cáncer de mama, cáncer de pulmón, cáncer de ovario, cáncer de estómago, cáncer pancreático, cáncer de próstata, cáncer renal, cáncer colorrectal o leucemia. En otras formas de realización o adicionales, el cáncer es cáncer de cerebro o carcinoma adrenocortical. En otras formas de realización o adicionales, el cáncer es cáncer de mama. En otras formas de realización o adicionales, el cáncer es cáncer de ovario. En otras formas de realización o adicionales, el cáncer es cáncer pancreático. En otras formas de realización o adicionales, el cáncer es cáncer de próstata. En otras formas de realización o adicionales, el cáncer es cáncer renal. En otras formas de realización o adicionales, el

591

cáncer es cáncer colorrectal. En otras formas de realización o adicionales, el cáncer es leucemia mieloide. En otras formas de realización o adicionales, el cáncer es glioblastoma. En otras formas de realización o adicionales, el cáncer es linfoma folicular. En otras formas de realización o adicionales, el cáncer es leucemia aguda pre-B. En otras formas de realización o adicionales, el cáncer es leucemia linfocítica B crónica. En otras formas de realización o adicionales, el cáncer es mesotelioma. En otras formas de realización o adicionales, el cáncer es cáncer de pulmón de células pequeñas. En algunas formas de realización, el cáncer es cáncer de estómago.

En algunas formas de realización, la composición que comprende un compuesto de la fórmula I se administra en combinación con una terapia adicional. En otras formas de realización o adicionales, la terapia adicional es una terapia por radiación, quimioterapia, cirugía o una combinación de las mismas. En otras formas de realización o adicionales, la composición que comprende un compuesto de la fórmula I se administra en combinación con al menos un agente terapéutico. En otras formas de realización o adicionales, el agente terapéutico se selecciona del grupo de agentes citotóxicos, agentes anti-angiogénesis y agentes anti-neoplásicos. En otras formas de realización o adicionales, el agente anti-neoplásico se selecciona del

592

grupo que consiste de agentes alquilantes, anti-metabolitos, epidofilotoxinas; enzimas antineoplásicas, inhibidores de topoisomerasa, procarbazinas, mitoxantronas, complejos de coordinación de platino, modificadores de la respuesta biológica e inhibidores del crecimiento, agentes terapéuticos hormonales/anti-hormonales y factores de crecimiento hematopoyéticos. En otras formas de realización o adicionales, el agente terapéutico se selecciona entre taxol, bortezomib o ambos.

En algunas formas de realización, la composición se administra por vía oral, intraduodenal, parenteral (incluyendo intravenosa, subcutánea, intramuscular, intravascular o por infusión), tópica o rectal. En otras formas de realización o adicionales, la cantidad del compuesto de la fórmula I se encuentra en el rango de entre aproximadamente 0,001 y aproximadamente 1000 mg/kg de peso corporal/día. En otras formas de realización o adicionales, la cantidad del compuesto de la fórmula I se encuentra en el rango de entre aproximadamente 0,5 y aproximadamente 50 mg/kg/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,001 y aproximadamente 7 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,01 y aproximadamente 7 g/día. En otras formas de realización o

593

adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,02 y aproximadamente 5 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,05 y aproximadamente 2,5 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,1 y aproximadamente 1 g/día. En otras formas de realización o adicionales, serán más que adecuados los niveles de dosificación inferiores al límite inferior del rango mencionado previamente. En otras formas de realización o adicionales, pueden ser necesarios niveles de dosificación superiores al límite superior del rango mencionado previamente.

En otras formas de realización o adicionales, el compuesto de la fórmula I se administra en una sola dosis, una vez por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra en múltiples dosis, más de una vez por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra dos veces por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra tres veces por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra cuatro veces por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra más

594

de cuatro veces por día. En algunas formas de realización, el individuo que sufre de la enfermedad proliferativa es un mamífero. En otras formas de realización o adicionales, el individuo es un ser humano. En otras formas de realización o adicionales, se administra una cantidad eficaz de una composición que comprende una sal farmacéuticamente aceptable de un compuesto de la fórmula I.

Tamaño tumoral

En otros aspectos, la presente invención está dirigida a un método para reducir el tamaño de un tumor, inhibir el incremento del tamaño tumoral, reducir la proliferación del tumor o prevenir la proliferación del tumor en un individuo, que comprende administrarle a dicho individuo una cantidad eficaz de un compuesto de la fórmula I o una sal, solvato, polimorfo, éster, amida, tautómero o prodroga farmacéuticamente aceptable del mismo. En algunas formas de realización, el compuesto o una sal, solvato, polimorfo, éster, amida, tautómero o prodroga farmacéuticamente aceptable del mismo, se administra como un componente de una composición que comprende además un transportador o vehículo farmacéuticamente aceptable. En algunas formas de realización, se reduce el tamaño de un tumor. En otras formas de realización o adicionales, el tamaño de un tumor se reduce en al menos un 1%. En otras formas de realización o adicionales, el tamaño de un tumor se reduce en al menos

395

un 2%. En otras formas de realización o adicionales, el tamaño de un tumor se reduce en al menos un 3%. En otras formas de realización o adicionales, el tamaño de un tumor se reduce en al menos un 4%. En otras formas de realización o adicionales, el tamaño de un tumor se reduce en al menos un 5%. En otras formas de realización o adicionales, el tamaño de un tumor se reduce en al menos un 10%. En otras formas de realización o adicionales, el tamaño de un tumor se reduce en al menos un 20%. En otras formas de realización o adicionales, el tamaño de un tumor se reduce en al menos un 25%. En otras formas de realización o adicionales, el tamaño de un tumor se reduce en al menos un 30%. En otras formas de realización o adicionales, el tamaño de un tumor se reduce en al menos un 40%. En otras formas de realización o adicionales, el tamaño de un tumor se reduce en al menos un 50%. En otras formas de realización o adicionales, el tamaño de un tumor se reduce en al menos un 60%. En otras formas de realización o adicionales, el tamaño de un tumor se reduce en al menos un 70%. En otras formas de realización o adicionales, el tamaño de un tumor se reduce en al menos un 75%. En otras formas de realización o adicionales, el tamaño de un tumor se reduce en al menos un 80%. En otras formas de realización o adicionales, el tamaño de un tumor se reduce en al menos un 85%. En otras formas de realización o adicionales, el tamaño de un tumor se reduce en al menos

596

un 90%. En otras formas de realización o adicionales, el tamaño de un tumor se reduce en al menos un 95%. En otras formas de realización o adicionales, el tumor es erradicado. En algunas formas de realización, no aumenta el tamaño de un tumor.

En algunas formas de realización, se reduce la proliferación del tumor. En algunas formas de realización, la proliferación del tumor se reduce en al menos un 1%. En algunas formas de realización, la proliferación del tumor se reduce en al menos un 2 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos un 3 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos un 4 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos un 5 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos un 10 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos un 20 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos un 25 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos un 30 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos un 40 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos un 50 %. En algunas formas de realización, la proliferación del tumor se

597

reduce en al menos un 60 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos un 70 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos un 75 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos un 75 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos un 80 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos un 90 %. En algunas formas de realización, la proliferación del tumor se reduce en al menos un 95 %. En algunas formas de realización, se previene la proliferación del tumor.

En algunas formas de realización, la composición que comprende un compuesto de la fórmula I se administra en combinación con una terapia adicional. En otras formas de realización o adicionales, la terapia adicional es una terapia por radiación, quimioterapia, cirugía o cualquier combinación de las mismas. En otras formas de realización o adicionales, la composición que comprende un compuesto de la fórmula I se administra en combinación con al menos un agente terapéutico. En otras formas de realización o adicionales, el agente terapéutico se selecciona del grupo de agentes citotóxicos, agentes anti-angiogénesis y agentes anti-neoplásicos. En otras formas de realización o adicionales, el agente anti-neoplásico se selecciona del

grupo que consiste de agentes alquilantes, anti-metabolitos, epidofilotoxinas; enzimas antineoplásicas, inhibidores de topoisomerasa, procarbazinas, mitoxantronas, complejos de coordinación de platino, modificadores de la respuesta biológica e inhibidores del crecimiento, agentes terapéuticos hormonales/anti-hormonales y factores de crecimiento hematopoyéticos. En otras formas de realización o adicionales, el agente terapéutico se selecciona entre taxol, bortezomib o ambos.

En algunas formas de realización, la composición se administra por vía oral, intraduodenal, parenteral (incluyendo intravenosa, subcutánea, intramuscular, intravascular o por infusión), tópica o rectal. En otras formas de realización o adicionales, la cantidad del compuesto de la fórmula I se encuentra en el rango de entre aproximadamente 0,001 y aproximadamente 1000 mg/kg de peso corporal/día. En otras formas de realización o adicionales, la cantidad del compuesto de la fórmula I se encuentra en el rango de entre aproximadamente 0,5 y aproximadamente 50 mg/kg/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,001 y aproximadamente 7 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,01 y aproximadamente 7 g/día. En otras formas de realización o

599

adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,02 y aproximadamente 5 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,05 y aproximadamente 2,5 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,1 y aproximadamente 1 g/día. En otras formas de realización o adicionales, serán más que adecuados los niveles de dosificación inferiores al límite inferior del rango mencionado previamente. En otras formas de realización o adicionales, pueden ser necesarios niveles de dosificación superiores al límite superior del rango mencionado previamente.

En otras formas de realización o adicionales, el compuesto de la fórmula I se administra en una sola dosis, una vez por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra en múltiples dosis, más de una vez por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra dos veces por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra tres veces por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra cuatro veces por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra más

660

de cuatro veces por día. En algunas formas de realización, el individuo que sufre de cáncer es un mamífero. En otras formas de realización o adicionales, el individuo es un ser humano. En otras formas de realización o adicionales, se administra una cantidad eficaz de una composición que comprende una sal farmacéuticamente aceptable de un compuesto de la fórmula I.

Enfermedad inflamatoria

En otros aspectos, la presente invención está dirigida a un método para el tratamiento, la prevención o la profilaxis de una enfermedad inflamatoria en un individuo que comprende administrarle a dicho individuo una cantidad eficaz de un compuesto de la fórmula I o una sal, solvato, polimorfo, éster, amida, tautómero o prodroga farmacéuticamente aceptable del mismo. En algunas formas de realización, el compuesto o una sal, solvato, polimorfo, éster, amida, tautómero o prodroga farmacéuticamente aceptable del mismo, se administra como un componente de una composición que comprende además un transportador o vehículo farmacéuticamente aceptable. En otras formas de realización o adicionales, la enfermedad inflamatoria se selecciona entre enfermedades inflamatorias crónicas, artritis reumatoide, artritis reumatoide, espondiloartropatías, espondilitis anquilosante, gota, tendonitis, bursitis, ciática, artritis gotosa, osteoartritis, artritis juvenil,

artritis reumática aguda, artritis enteropática, artritis neuropática, artritis psoriática, artritis piogénica, aterosclerosis, lupus sistémica eritematosa, enfermedad de intestino inflamatorio, síndrome de intestino irritable, colitis ulcerosa, esofagitis por reflujo, enfermedad de Crohn, gastritis, asma, alergias, síndrome de dificultad respiratoria, pancreatitis, enfermedad pulmonar obstructiva crónica, fibrosis pulmonar, psoriasis, eczema o escleroderma.

En algunas formas de realización, la composición que comprende un compuesto de la fórmula I se administra en combinación con una terapia adicional. En otras formas de realización o adicionales, la composición que comprende un compuesto de la fórmula I se administra en combinación con al menos un agente terapéutico. En algunas formas de realización, la composición se administra por vía oral, intraduodenal, parenteral (incluyendo intravenosa, subcutánea, intramuscular, intravascular o por infusión), tópica o rectal. En otras formas de realización o adicionales, la cantidad del compuesto de la fórmula I se encuentra en el rango de entre aproximadamente 0,001 y aproximadamente 1000 mg/kg de peso corporal/día. En otras formas de realización o adicionales, la cantidad del compuesto de la fórmula I se encuentra en el rango de entre aproximadamente 0,5 y aproximadamente 50 mg/kg/día. En otras

602

formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,001 y aproximadamente 7 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,01 y aproximadamente 7 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,02 y aproximadamente 5 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,05 y aproximadamente 2,5 g/día. En otras formas de realización o adicionales la cantidad de compuesto de la fórmula I es de entre aproximadamente 0,1 y aproximadamente 1 g/día. En otras formas de realización o adicionales, serán más que adecuados los niveles de dosificación inferiores al límite inferior del rango mencionado previamente. En otras formas de realización o adicionales, pueden ser necesarios niveles de dosificación superiores al límite superior del rango mencionado previamente.

En otras formas de realización o adicionales, el compuesto de la fórmula I se administra en una sola dosis, una vez por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra en múltiples dosis, más de una vez por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se

603

administra dos veces por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra tres veces por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra cuatro veces por día. En otras formas de realización o adicionales, el compuesto de la fórmula I se administra más de cuatro veces por día. En algunas formas de realización, el individuo que sufre de la enfermedad inflamatoria es un mamífero. En otras formas de realización o adicionales, el individuo es un ser humano. En otras formas de realización o adicionales, se administra una cantidad eficaz de una composición que comprende una sal farmacéuticamente aceptable de un compuesto de la fórmula I.

*Modos de administración*

En la presente se describen compuestos de la fórmula I o una sal, solvato, polimorfo, éster, amida, tautómero, prodroga, hidrato o derivado farmacéuticamente aceptable del mismo. También se describen composiciones farmacéuticas que comprenden un compuesto de la fórmula I o una sal, solvato, polimorfo, éster, amida, tautómero, prodroga, hidrato o derivado farmacéuticamente aceptable del mismo. Los compuestos y las composiciones que se describen en la presente se pueden administrar ya sea solos o en combinación con vehículos, excipientes o diluyentes farmacéuticamente aceptables, en una composición farmacéutica, de acuerdo con

604

la práctica farmacéutica estándar.

En la presente también se describen composiciones farmacéuticas que comprenden al polimorfo cristalino N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida (Forma A). Los compuestos y las composiciones que se describen en la presente se pueden administrar ya sea solos o en combinación con vehículos, excipientes o diluyentes farmacéuticamente aceptables, en una composición farmacéutica, de acuerdo con la práctica farmacéutica estándar. La administración se puede efectuar mediante cualquier método que permita suministrar los compuestos en el sitio de acción. Estos métodos incluyen, aunque en un sentido no limitativo, el suministro mediante administración por las rutas enterales (incluyendo oral, gástrica o tubo de alimentación duodenal, supositorio rectal y enema rectal), las rutas parenterales (inyección o infusión, incluyendo intraarterial, intracardíaca, intradérmica, intraduodenal, intramedular, intramuscular, intraósea, intraperitoneal, intratecal, intravascular, intravenosa, intravítrea, epidural y subcutánea), por inhalación, transdérmica, transmucosa, sublingual, bucal y tópica (incluyendo epicutánea, dérmica, enema, gotas oftálmicas, gotas óticas, intranasal, vaginal), aunque la ruta más adecuada puede depender, por ejemplo, la condición y el trastorno del receptor. Los especialistas en

665

el arte estarán familiarizados con las técnicas de administración que se pueden emplear con los compuestos y los métodos de la invención. A modo de ejemplo solamente, los compuestos que se describen en la presente se pueden administrar localmente en el área que necesita del tratamiento, por ejemplo, mediante infusión local durante una cirugía, aplicación tópica tal como cremas o ungüentos, inyección, catéter o implante, donde dicho implante es, por ejemplo, de un material poroso, no poroso o gelatinoso, incluyendo membranas, tal como membranas sialásticas, o fibras. La administración también puede ser por inyección directa en el sitio de un tejido u órgano enfermo.

La administración de los compuestos y las composiciones que se describen en la presente se puede efectuar mediante cualquier método que permita suministrar los compuestos en el sitio de acción. Estos métodos incluyen rutas orales, rutas intraduodenales, inyección parenteral (incluyendo intravenosa, subcutánea, intraperitoneal, intramuscular, intravascular o infusión), administración tópica y rectal. Por ejemplo, los compuestos que se describen en la presente se pueden administrar localmente en el área que necesita del tratamiento. Esto se puede lograr, por ejemplo, pero en un sentido no limitativo, mediante infusión local durante una cirugía, aplicación tópica, por ejemplo, con una crema, ungüento, inyección, catéter o implante, donde dicho

606

implante es, por ejemplo, de un material poroso, no poroso o gelatinoso, incluyendo membranas, tal como membranas sialásticas, o fibras. La administración también puede ser mediante inyección directa en el sitio (o sitio anterior) de un tumor o tejido neoplásico o pre-neoplásico. Los especialistas en el arte están familiarizados con las técnicas de formulación y administración que se pueden emplear con los compuestos y métodos de la invención, por ejemplo, como se describe en Goodman y Gilman, *The Pharmacological Basis of Therapeutics*, edición actual; Pergamon; y *Remington's, Pharmaceutical Sciences* (edición actual), Mack Publishing Co., Easton, Pa.

Las formulaciones incluyen aquellas que son adecuadas para una administración oral, parenteral (incluyendo subcutánea, intradérmica, intramuscular, intravenosa, intraarticular e intramedular), intraperitoneal, transmucosa, transdérmica, rectal y tópica (incluyendo dérmica, bucal, sublingual e intraocular), aunque la ruta más adecuada puede depender, por ejemplo, de la condición y el trastorno del receptor. Las formulaciones se pueden presentar convenientemente en formas de dosificación unitarias y se pueden preparar mediante cualquiera de los métodos bien conocidos en el arte de la farmacia. Todos los métodos incluyen el paso de asociar un compuesto de la presente invención, o una sal, solvato, polimorfo, éster,

667

amida, tautómero, prodroga, hidrato o derivado farmacéuticamente aceptable del mismo ("ingrediente activo"), con el vehículo que constituye uno o más ingredientes accesorios. En general, las formulaciones se preparan asociando uniforme e íntimamente el ingrediente activo con vehículos líquidos, vehículos sólidos finamente divididos o ambos, y luego dando forma al producto en la formulación deseada, de ser necesario.

Las formulaciones apropiadas para la administración oral se pueden presentar como unidades discretas tales como cápsulas, obleas o tabletas, cada una de las cuales contiene una cantidad predeterminada de ingrediente activo; como un polvo o como gránulos; como una solución o una suspensión en un líquido acuoso o no acuoso; o como una emulsión líquida de aceite en agua o una emulsión líquida de agua en aceite. El ingrediente activo también se puede presentar como un bolo, electuario o pasta.

Las preparaciones farmacéuticas que son útiles para una administración oral incluyen tabletas, cápsulas a presión de gelatina dura, así como cápsulas blandas, selladas hechas de gelatina y un plastificante, como por ejemplo glicerol o sorbitol. Las tabletas se pueden preparar por compresión o moldeado, opcionalmente con uno o más ingredientes accesorios. Las tabletas comprimidas se pueden preparar efectuando una compresión del agente activo, en una forma de

flujo libre, tal como polvo o gránulos, en una máquina apropiada, mezclado opcionalmente con aglutinantes, diluyentes inertes o agentes lubricantes, tensioactivos o dispersantes. Se pueden preparar tabletas moldeadas efectuando un moldeo de una mezcla del compuesto en polvo, humedecido con un diluyente líquido inerte, en una máquina apropiada. Opcionalmente, las tabletas se pueden recubrir o marcar y se pueden formular para proporcionar una liberación lenta o controlada del ingrediente activo en la misma. Todas las formulaciones para la administración oral deberían presentarse en dosificaciones apropiadas para dicha administración. Las tabletas o cápsulas a presión pueden contener al ingrediente activo; mezclado con un relleno tal como celulosa microcristalina, celulosa microcristalina silicificada, almidón pregelatinizado, lactosa, fosfato dicálcico o azúcar compresible; un aglutinante tal como hipromelosa, povidona o pasta de almidón; un desintegrante tal como croscarmellosa sódica, crospovidona o glicolato de almidón sódico; un agente tensioactivo tal como laurilsulfato de sodio y/o lubricantes y auxiliares de procesamiento tal como talco, estearato de magnesio, ácido esteárico o dióxido de silicona coloidal y, opcionalmente, estabilizantes. En las cápsulas blandas, los compuestos activos pueden estar disueltos o suspendidos en líquidos apropiados, como por ejemplo aceites grasos, parafina

609

líquida o polietilenglicoles líquidos. Además, se pueden agregar estabilizantes. Los núcleos de grageas se suministran con recubrimientos apropiados. Para tal fin, son de utilidad las soluciones concentradas de azúcares, que opcionalmente pueden contener goma arábiga, talco, polivinilpirrolidona, gel carbopol, polietilenglicol y/o dióxido titanio, soluciones de laca y solventes orgánicos adecuados o mezclas de solventes. A los recubrimientos de tabletas o grageas se les pueden agregar tinturas o pigmentos para su identificación o para caracterizar diferentes combinaciones de dosis de compuesto activo.

Las preparaciones farmacéuticas se pueden formular para una administración parenteral por inyección, por ejemplo, por inyección de bolo o infusión continua. Las formulaciones para inyección se pueden presentar en una forma de dosificación unitaria (por ejemplo, en ampollas o recipientes con dosificaciones múltiples) con adición de un conservante. Las composiciones pueden tomar formas tales como suspensiones, soluciones o emulsiones en vehículos al aceite o acuosos, y pueden contener agentes de la formulación tales como agentes de suspensión, estabilizantes y/o dispersantes. Las formulaciones se pueden presentar en recipientes de dosis unitarias o de múltiples dosis, por ejemplo ampollas y viales sellados, y se pueden almacenar en la forma de un polvo o en un estado liofilizado que

610

solamente requiere de la adición del vehículo líquido estéril, por ejemplo, salina o agua estéril libre de pirógenos, inmediatamente antes del uso. Las soluciones y suspensiones inyectables extemporáneas se pueden preparar a partir de polvos, gránulos y tabletas estériles, del tipo que se describió previamente.

Las formulaciones para una administración parenteral incluyen soluciones para inyecciones acuosas y no acuosas (oleosas) estériles que pueden contener antioxidantes, soluciones amortiguadoras del pH, bacteriostáticos y solutos que vuelven a la formulación isotónica con respecto a la sangre del recipiente al que se aplicará; y suspensiones estériles acuosas y no acuosas que pueden incluir agentes de suspensión y agentes espesantes. Los solventes o vehículos lipofílicos apropiados incluyen aceites grasos tales como aceite de sésamo, o ésteres sintéticos de ácidos grasos, como por ejemplo oleato de etilo o triglicéridos, o liposomas. Las suspensiones acuosas inyectables pueden contener sustancias que incrementan la viscosidad de la suspensión, tal como carboximetilcelulosa sódica, sorbitol o dextrano. Opcionalmente, la suspensión también puede contener estabilizantes apropiados o agentes que aumenten la solubilidad de los compuestos para permitir la preparación de soluciones altamente concentradas.

Las preparaciones farmacéuticas también se pueden

611

formular como una preparación depot. Dichas formulaciones de acción prolongada pueden ser administradas mediante implantes (por ejemplo, subcutáneos o intramusculares) o por inyección intramuscular. Así, por ejemplo, los compuestos se pueden formular con materiales poliméricos o hidrofóbicos adecuados (por ejemplo, como una emulsión en un aceite aceptable) o con resinas de intercambio iónico o como derivados escasamente solubles, por ejemplo, como una forma salina escasamente soluble.

Para una administración por vía bucal o sublingual, las composiciones pueden tomar la forma de tabletas, grageas, pastillas o geles formulados de manera convencional. Dichas composiciones pueden comprender al ingrediente activo en una base saborizada, tal como sacarosa y acacia o tragacanto.

Las preparaciones farmacéuticas también se pueden formular en composiciones para la vía rectal, tales como supositorios o enemas de retención, por ejemplo, que contienen bases para supositorios convencionales tales como manteca de cacao, polietilenglicol u otros glicéridos.

Las preparaciones farmacéuticas se pueden administrar por vía tópica, es decir, mediante una administración no sistémica. Esto incluye la aplicación de un compuesto de la presente invención externamente, a la epidermis o en la cavidad bucal y la instilación de dicho un compuesto en el oído, el ojo y la nariz, de modo tal que el compuesto no

612

ingrese significativamente en el torrente sanguíneo. Por el contrario, la administración sistémica se refiere a una administración oral, intravenosa, intraperitoneal e intramuscular.

Las preparaciones farmacéuticas adecuadas para una administración tópica incluyen preparaciones líquidas o semilíquidas adecuada para la penetración a través de la piel en el sitio de la inflamación tales como geles, linimentos, lociones, cremas, ungüentos o pastas, y gotas adecuadas para una administración en el ojo, el oído o la nariz. El ingrediente activo puede comprender, para una administración tópica, entre 0,001% y 10% p/p, por ejemplo entre 1% y 2% en peso de la formulación. Sin embargo puede comprender tanto como un 10% p/p o puede comprender menos que un 5% p/p o entre 0,1% y 1% p/p de la formulación.

Las preparaciones farmacéuticas para una administración por inhalación se administran convenientemente mediante un insuflador, envase nebulizador presurizado u otro medio conveniente para suministrar un rocío en aerosol. Los envases presurizados pueden comprender un propelente adecuado, tal como diclorodifluorometano, triclorofluorometano, diclorotetrafluoroetano, dióxido de carbono u otro gas adecuado. En el caso de un aerosol presurizado, la unidad de dosificación puede ser determinada con una válvula para administrar una cantidad medida. Como

613

alternativa, para una administración por inhalación o insuflación, las preparaciones farmacéuticas pueden tomar la forma de una composición de un polvo seco, por ejemplo una mezcla en polvo del compuesto y una base de polvo adecuada tal como lactosa o almidón. La composición en polvo se puede presentar en formas de dosificación unitarias, por ejemplo, en cápsulas, cartuchos, gelatina o envases de blísters, con los cuales se puede administrar el polvo con la ayuda de un inhalador o insuflador.

Se deberá comprender que además de los ingredientes ya mencionados particularmente, los compuestos y las composiciones que se describen en la presente pueden incluir otros agentes convencionales en el arte referidos al tipo de formulación en cuestión, por ejemplo los que son adecuados para una administración oral pueden incluir agentes saborizantes.

*Formulaciones*

Se debe tener en cuenta que se puede utilizar cualquiera de las composiciones y los compuestos que se describen en la presente en cualquiera de las formulaciones que se describen en esta sección, que no pretende ser limitativo y no debería considerarse en tal sentido.

Los compuestos o las composiciones que se describen en la presente se pueden suministrar en una vesícula, por ejemplo, un liposoma (véase, por ejemplo, Langer, *Science*

614

**1990**, *249*,1527-1533; Treat et al., *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Bernstein y Fidler, Ed., Liss, N.Y., páginas 353-365, 1989). Los compuestos y las composiciones farmacéuticas que se describen en la presente también se pueden suministrar en un sistema de liberación controlada. En una forma de realización, se puede usar una bomba (véase, Sefton, 1987, *CRC Crit. Ref. Biomed. Eng.* 14:201; Buchwald et al. *Surgery*, **1980** *88*, 507; Saudek et al. *N. Engl. J. Med.* **1989**, *321*, (574). Además, se puede ubicar un sistema de liberación controlada próximo al blanco terapéutico. (Véase, Goodson, *Medical Applications of Controlled Release*, 1984, Vol. 2, páginas 115-138). Las composiciones farmacéuticas descritas en la presente también pueden contener al ingrediente activo en una forma adecuada para uso oral, por ejemplo, como tabletas, comprimidos, pastillas, suspensiones acuosas u oleosas, polvos o gránulos dispersables, emulsiones, cápsulas duras o blandas, o jarabes o elixires. Los composiciones pretendidas para el uso oral se pueden preparar de acuerdo con cualquier método conocido en la técnica para la elaboración de composiciones farmacéuticas, y dichas composiciones pueden contener uno o más agentes seleccionados del grupo formado por agentes edulcorantes, agentes saborizantes, agentes colorantes y agentes conservantes con el fin de proveer preparaciones farmacéuticamente elegantes y de buen sabor. Las tabletas

6N

contienen al ingrediente activo mezclado con excipientes no tóxicos farmacéuticamente aceptables que son adecuados para la elaboración de tabletas. Estos excipientes pueden ser, por ejemplo, diluyentes inertes, tal como carbonato de calcio, carbonato de sodio, lactosa, fosfato de calcio o fosfato de sodio; agentes de granulación y de desintegración; rellenos tales como celulosa microcristalina, celulosa microcristalina silicificada, almidón pregelatinizado, lactosa, fosfato dicálcico o azúcar compresible; aglutinantes tales como hipromelosa, povidona o pasta de almidón; desintegrantes tales como croscarmellosa sódica, crospovidona o glicolato de almidón sódico; un agente tensioactivo tal como laurilsulfato de sodio y/o lubricantes y auxiliares de procesamiento tales como talco, croscarmellosa sódica, almidón de maíz, o ácido algínico; agentes de unión, por ejemplo almidón, gelatina, polivinilpirrolidona o acacia, y agentes lubricantes, por ejemplo estearato de magnesio, ácido esteárico o dióxido de silicona coloidal y, opcionalmente, talco. Las tabletas se pueden recubrir, o no, mediante técnicas conocidas para enmascarar el sabor de la droga o demorar la desintegración y absorción en el tracto gastrointestinal y así proporcionar una acción sostenida sobre un período más prolongado. Por ejemplo, sería apropiado el uso de un material enmascarador del sabor soluble en agua, tal como

616

hidroxipropilmetilcelulosa o hidroxipropilcelulosa, o un material retardante en el tiempo tal como etilcelulosa o acetato butirato de celulosa. Las formulaciones de uso oral también se pueden presentar en la forma de cápsulas de gelatina dura, donde el ingrediente activo está mezclado en un diluyente sólido inerte, por ejemplo, carbonato de calcio, fosfato de calcio o caolín, o como cápsulas de gelatina blanda, donde el ingrediente activo está mezclado con un vehículo soluble en agua, tal como polietilenglicol, o con un medio oleoso, por ejemplo, aceite de maní, parafina líquida o aceite de oliva. Las formas de dosificación en cápsulas y tabletas se pueden preparar mediante diversas técnicas de procesamiento incluyendo técnicas de mezclado en seco y de granulación en húmedo. En el método de elaboración de de mezclado en seco, la droga se puede incorporar en la forma de dosificación mediante mezclado en seco con los excipientes seguido por encapsulamiento en un recubrimiento para cápsulas o por compresión en una forma de tableta. La operación de mezclado en seco puede efectuarse por pasos e incluye pasos de tamizado entre los pasos de mezclado para facilitar la formación de una mezcla uniforme. En el método de elaboración de granulación en húmedo, la droga se puede agregar a los excipientes secos y mezclar antes de agregar la solución aglutinante o la droga se puede disolver y agregar como una solución formando parte de la

6A

granulación. En la técnica de granulación en húmedo, el agente tensioactivo, si se usa, se puede agregar a los excipientes secos o se puede agregar a la solución aglutinante e incorporar en la forma de una solución. Las formas de dosificación como cápsulas también se pueden elaborar disolviendo la droga en un material que se pueda rellenar y que sea compatible con los recubrimientos de las cápsulas de gelatina dura que luego se pueden marcar con bandas y sellar. Las formas de dosificación en cápsulas y tabletas también se pueden producir disolviendo la droga en un material tal como la forma fundida de un polietilenglicol de alto peso molecular y enfriándola en una forma sólida, para luego moler e incorporar este material en los procesos de elaboración de cápsulas y tabletas convencionales.

Las suspensiones acuosas contienen al material activo mezclado con excipientes adecuados para la elaboración de suspensiones acuosas. Dichos excipientes son agentes de suspensión, por ejemplo carboximetilcelulosa de sodio, metilcelulosa, hidroxipropilmetilcelulosa, alginato de sodio, polivinilpirrolidona, goma tragacanto y goma acacia; los agentes dispersantes o humectantes pueden ser fosfátidos naturales, por ejemplo, lecitina, o productos de condensación de un óxido de alquileno con ácidos grasos, por ejemplo, estearato de polioxietileno, o productos de condensación de óxido de etileno con alcoholes alifáticos de

618

cadena larga, por ejemplo, heptadecaetilenoxicetanol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y un hexitol, tal como monooleato de polioxietilensorbitol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo, monooleato de polietilensorbitano. Las suspensiones acuosas pueden contener uno o más conservantes, por ejemplo, p-hidroxibenzoato de etilo o *n*-propilo; uno o más agentes colorantes; uno o más agentes saborizantes; y uno o más agentes saborizantes, tales como sacarosa, sacarina o aspartame.

Las suspensiones oleosas se pueden formular suspendiendo el ingrediente activo en un aceite vegetal, por ejemplo, aceite de maní, aceite de oliva, aceite de sésamo o aceite de coco, en un aceite mineral, como por ejemplo parafina líquida. Las suspensiones oleosas pueden contener un agente espesante, por ejemplo, cera de abeja, parafina dura o alcohol cetílico. Se pueden agregar agentes edulcorantes como por ejemplo aquellos que se mencionaron antes, y agentes saborizantes para proveer un preparado oral de sabor aceptable. Estas composiciones se pueden conservar por adición de un antioxidante, tal como hidroxianisol butilado o alfa-tocoferol.

Los polvos y los gránulos dispersables apropiados para

619

la preparación de una suspensión acuosa mediante la adición de agua proporcionan el ingrediente activo en combinación con un agente dispersante o humectante, un agente de suspensión y uno o más conservantes. Los ejemplos de agentes dispersantes o humectantes y de suspensión apropiados son aquellos que se mencionaron con anterioridad. También pueden haber presentes otros excipientes adicionales como por ejemplo agentes edulcorantes, saborizantes y colorantes. Dichas composiciones se pueden conservar agregando un antioxidante como por ejemplo ácido ascórbico.

Las composiciones farmacéuticas también se pueden encontrar en la forma de emulsiones de aceite en agua. La fase acuosa puede ser un aceite vegetal, por ejemplo, aceite de oliva o aceite de maní, o un aceite mineral, por ejemplo, parafina líquida o mezclas de los mismos. Los agentes emulsionantes apropiados pueden ser fosfátidos naturales, por ejemplo, lecitina de soja, y ésteres o ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo, monooleato de sorbitán, y productos de condensación de dichos ésteres parciales con óxido de etileno, por ejemplo, monooleato de polioxietilen sorbitán. Las emulsiones también pueden contener agentes edulcorantes, agentes saborizantes, conservantes y antioxidantes.

Los jarabes y elixires se pueden formular con agentes edulcorantes, por ejemplo glicerol, propilenglicol, sorbitol

676

o sacarosa. Dichas formulaciones también pueden contener un emoliente, un conservante y agentes saborizantes y antioxidantes.

Las composiciones farmacéuticas se pueden encontrar en la forma de una solución acuosa inyectable estéril. Los vehículos y solventes aceptables que se pueden emplear comprenden agua, solución de Ringer y solución de cloruro de sodio isotónica. La preparación inyectable estéril también puede ser una microemulsión de aceite-en-agua inyectable estéril, donde el ingrediente activo está disuelto en la fase oleosa. Por ejemplo, el ingrediente activo se puede disolver primero en una mezcla de aceite de soja y lecitina. La solución de aceite se introduce luego en una mezcla de agua y glicerol y se procesa para formar una microemulsión. Las soluciones o microemulsiones inyectables se pueden introducir en el torrente sanguíneo de un paciente mediante inyección local de un bolo. Como alternativa, puede resultar ventajoso administrar la solución o microemulsión de una manera tal que se mantenga una concentración constante en la circulación del compuesto de la invención. Con el fin de mantener dicha concentración constante, se puede utilizar un dispositivo de administración intravenosa continua. Un ejemplo de un dispositivo tal es la bomba intravenosa Deltec CADD-PLUS™ modelo 5400. Las composiciones farmacéuticas se pueden encontrar en la forma de una suspensión inyectable

621

acuosa u oleaginosa estéril para una administración intramuscular y subcutánea. Esta suspensión se puede formular de acuerdo con la técnica conocida usando los agentes dispersantes o humectantes y los agentes de suspensión adecuados que se mencionaron con anterioridad. El preparado inyectable estéril también puede ser una solución o suspensión inyectable estéril en un diluyente o solvente no tóxico aceptable para el uso por vía parenteral, por ejemplo como una solución en 1,3-butandiol. Además, convencionalmente se emplean aceites fijos estériles como solventes o medios de suspensión. Para tal fin, se puede emplear cualquier aceite blando fijo, incluyendo mono o diglicéridos sintéticos. Además, en la preparación de inyectables se pueden usar ácidos grasos, tales como ácido oleico.

Las composiciones farmacéuticas también se pueden administrar bajo la forma de supositorios, para efectuar la administración de la droga por vía rectal. Estas composiciones se pueden preparar mezclando los inhibidores con un excipiente adecuado no irritante que sea sólido a temperaturas comunes pero líquido a la temperatura rectal y por ello se fundirá en el recto liberando la droga. Tales materiales incluyen manteca de cacao, gelatina glicerinada, aceites vegetales hidrogenados, mezclas de polietilenglicoles de diversos pesos moleculares y ésteres

622

de ácidos grasos de polietilenglicol.

Para uso tópico, son de utilidad las cremas, los ungüentos, las gelatinas, soluciones o suspensiones, *etc.*, que contienen un compuesto o composición de la invención para dicha administración tópica. Según se usa en la presente, la aplicación tópica puede incluir enjuagues bucales.

Las composiciones farmacéuticas se pueden administrar en una forma intranasal mediante el uso tópico de vehículos y dispositivos de administración intranasales adecuados, o por medio de rutas transdérmicas, usando las formas de parches transdérmicos bien conocidas por los especialistas en el arte.

Las formulaciones se pueden presentar convenientemente en formas de dosificación unitarias y se pueden preparar mediante cualquiera de los métodos bien conocidos en el arte de la farmacia. Todos los métodos incluyen el paso de asociar un compuesto de la presente invención, o una sal, éster, prodroga o solvato farmacéuticamente aceptable del mismo ("ingrediente activo"), con el vehículo que comprende uno o más ingredientes accesorios. En general, las formulaciones se preparan asociando de manera uniforme e íntima el ingrediente activo con vehículos líquidos, vehículos sólidos finamente divididos o ambos, y luego dando forma al producto en la formulación deseada, de ser

623

necesario. Los métodos para preparar diversas composiciones farmacéuticas con una cantidad específica de compuesto activo son conocidos, o resultarán evidentes para los especialistas en este arte. Para una forma de administración transdérmica, la forma de dosificación será, por supuesto, continua en lugar de intermitente para todo el régimen de dosificación.

*Dosis*

La cantidad de las composiciones farmacéuticas administrada dependerá en primer lugar del mamífero bajo tratamiento. En los casos donde las composiciones farmacéuticas son administradas a un sujeto humano, la dosificación diaria será determinada normalmente por el médico a cargo, donde la dosificación en general varía de acuerdo con la edad, el sexo, la dieta, el peso, el estado de salud general y la respuesta de cada paciente individual, la severidad de los síntomas del paciente, la indicación o condición precisa bajo tratamiento, la severidad de la indicación o condición bajo tratamiento, el momento de la administración, la ruta de administración, la disposición de la composición, la velocidad de excreción, la combinación de drogas y a discreción del médico a cargo que la prescribe. Además, la ruta de administración puede variar dependiendo de la condición y su severidad. La composición farmacéutica se puede encontrar como una forma de dosificación unitaria.

624

En dicha forma, la preparación se subdivide en dosis unitarias que contienen cantidades apropiadas del componente activo, por ejemplo, una cantidad eficaz para el propósito deseado. La determinación de la dosificación apropiada para una situación particular se encuentra dentro del conocimiento del arte. En general, el tratamiento se inicia con dosificaciones menores que comprenden menos que la dosis óptima del compuesto. Posteriormente, se aumenta la dosis en pequeñas cantidades hasta alcanzar el efecto óptimo teniendo en cuenta las circunstancias. Para mayor conveniencia, la dosificación diaria total se puede dividir y administrar en porciones a lo largo del día si así se desea. La cantidad y frecuencia de administración de los compuestos que se describen en la presente, y si corresponde otros agentes y/o terapias terapéuticas, serán reguladas de acuerdo con el buen juicio del clínico (médico) teniendo en cuenta factores como los que se describieron previamente. Por lo tanto, la cantidad de composición farmacéutica que será administrada puede variar ampliamente. La administración puede comprender una cantidad de entre aproximadamente 0,001 mg/kg de peso corporal y aproximadamente 100 mg/kg de peso corporal por día (administrados en una sola dosis o en dosis divididas) o al menos aproximadamente 0,1 mg/kg de peso corporal por día. Una dosificación terapéutica particular puede incluir, por ejemplo, entre aproximadamente 0,01 mg y aproximadamente

675

7000 mg de compuesto o, por ejemplo, entre aproximadamente 0,05 mg y aproximadamente 2500 mg. La cantidad de compuesto activo en una dosis unitaria de preparación se puede variar o ajustar entre aproximadamente 0,1 mg y 1000 mg, entre aproximadamente 1 mg y 300 mg o entre 10 mg y 200 mg, de acuerdo con la aplicación particular. En algunos casos, será más adecuado emplear niveles de dosificación por debajo del límite inferior del rango mencionado previamente, en tanto en otros casos se pueden utilizar dosis aún más grandes sin causar ningún efecto secundario perjudicial, por ejemplo dividiendo tales dosis mayores en varias dosis menores para su administración a lo largo del día. La cantidad administrada varía dependiendo del valor de $IC_{50}$ particular del compuesto usado. En las aplicaciones combinadas, en las cuales el compuesto no es la única terapia, sería posible administrar cantidades menores del compuesto y aún ofrecer un efecto terapéutico o profiláctico.

Se proveen dosificaciones adicionales en toda la memoria descriptiva y las reivindicaciones.

*Formas de dosificación*

La composición farmacéutica se puede encontrar, por ejemplo, en una forma adecuada para una administración oral como una tableta, una cápsula, una píldora, un polvo, formulaciones de liberación sostenida, una solución, una suspensión, para inyecciones parenterales como una solución,

626

suspensión o emulsión estéril, para una administración tópica como un ungüento o crema; o para una administración rectal como un supositorio. La composición farmacéutica se puede encontrar en formas de dosificación unitarias adecuadas para la administración individual de dosificaciones precisas. La composición farmacéutica incluirá un vehículo o excipiente farmacéutico convencional y un compuesto de acuerdo con la invención como ingrediente activo. Además, puede incluir otros agentes medicinales o farmacéuticos, vehículos, adyuvantes, etc.

Los ejemplos de formas de administración parenteral incluyen soluciones o suspensiones de compuestos activos en soluciones acuosas estériles, por ejemplo, soluciones acuosas de propilenglicol o dextrosa. Si se desea, se puede regular convenientemente el pH de las formas de dosificación.

Los vehículos farmacéuticos adecuados incluyen diluyentes inertes o rellenos, agua y diversos solventes orgánicos. Si se desea, las composiciones farmacéuticas pueden contener ingredientes adicionales tales como saborizantes, aglutinantes, excipientes y semejantes. Así, para una administración oral, se pueden emplear tabletas que contienen diversos excipientes, tal como ácido cítrico, junto con distintos desintegrantes tales como almidón, ácido algínico y determinados silicatos complejos y con agentes de

67

unión tales como sacarosa, gelatina y acacia. Además, a menudo puede ser de utilidad emplear agentes lubricantes, tales como estearato de magnesio, laurilsulfato de sodio y talco, para la formación de tabletas. También se pueden emplear composiciones sólidas de un tipo similar en cápsulas de gelatina rellenas duras y blandas, que incluyen lactosa o azúcar lácteo y también polietilenglicoles de alto peso molecular. Cuando se desean suspensiones acuosas o elixires para una administración oral, el compuesto activo contenido se puede combinar con diversos agentes edulcorantes o saborizantes, materiales colorantes o tinturas y, si se desea, agentes emulsionantes o agentes de suspensión, junto con diluyentes tales como agua, etanol, propilenglicol, glicerina o combinaciones de los mismos.

Los métodos para preparar distintas composiciones farmacéuticas con una cantidad específica del compuesto activo son conocidos o resultarán evidentes para los especialistas en este arte. Por ejemplos de ellos, véase *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Ester, Pa., 18ª edición (1990).

*Terapias combinadas*

Los compuestos que se describen en la presente, o una sal, solvato, polimorfo, éster, amida, tautómero, prodroga, hidrato o derivado farmacéuticamente aceptable del mismo, se pueden administrar como una terapia única. Los compuestos

678

que se describen en la presente, o una sal, solvato, polimorfo, éster, amida, tautómero, prodroga, hidrato o derivado farmacéuticamente aceptable del mismo, también se pueden administrar en combinación con una o más terapias adicionales.

En la presente también se describe la N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida (Forma A) que se puede administrar como una terapia única. El polimorfo cristalino, forma A, de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida también se puede administrar en combinación con uno o más terapias adicionales.

A modo de ejemplo solamente, si uno de los efectos secundarios experimentados por un paciente luego de recibir la administración de los compuestos que se describen en la presente es hipertensión, entonces sería apropiado administrar una agente anti-hipertensivo en combinación con el compuesto. O bien, a modo de ejemplo solamente, se puede mejorar la eficacia terapéutica de uno de los compuestos que se describen en la presente mediante la administración de un adyuvante (es decir, por sí mismo el adyuvante solamente tendrá un beneficio terapéutico mínimo, pero en combinación con otro agente terapéutico, mejora el beneficio terapéutico

629

global para el paciente). O bien, a modo de ejemplo solamente, es posible incrementar el beneficio experimentado por un paciente con la administración de uno de los compuestos que se describen en la presente con otro agente terapéutico (con su régimen terapéutico) que también tiene un beneficio terapéutico. A modo de ejemplo solamente, en un tratamiento de diabetes que comprende la administración de uno de los compuestos que se describen en la presente, se podría lograr un mayor beneficio terapéutico si también se le suministra al paciente otro agente terapéutico para la diabetes. En cualquier caso, en forma independiente de la enfermedad, el trastorno o la condición bajo tratamiento, el beneficio global experimentado por el paciente simplemente puede ser la suma de los dos agentes terapéuticos o el paciente puede experimentar un beneficio sinérgico.

Otras terapias incluyen, pero en un sentido no limitativo, la administración de otros agentes terapéuticos, terapia por radiación o ambos. En los casos donde los compuestos que se describen en la presente se administran con otros agentes terapéuticos, no es necesario administrar los compuestos que se describen en la presente en la misma composición farmacéutica que los otros agentes terapéuticos y pueden administrarse, debido a características físicas y químicas diferentes, por una ruta diferente. Por ejemplo, los compuestos/composiciones pueden administrarse por vía

oral para generar y mantener niveles sanguíneos buenos de los mismos, en tanto el otro agente terapéutico puede administrarse por vía intravenosa. La determinación del modo de administración y la conveniencia de la administración, cuando fuera posible, en la misma composición farmacéutica, es propia del conocimiento del clínico especialista en el tema. La administración inicial puede efectuarse según los protocolos establecidos conocidos en el arte y luego, en base a los efectos observados, la dosificación, los modos de administración y los tiempos de administración, puede ser modificada por el clínico. La elección particular del compuesto (y cuando fuera apropiado, otro agente terapéutico y/o radiación) dependerá del diagnóstico de los médicos a cargo y su buen juicio de la condición del paciente y el protocolo de tratamiento apropiado. Otros agentes terapéuticos pueden incluir agentes quimioterapéuticos, tales como sustancias anti-tumorales, por ejemplo las que se seleccionan entre inhibidores mitóticos, por ejemplo vinblastina; agentes alquilantes, por ejemplo cis-platino, carboplatino y ciclofosfamida; anti-metabolitos, por ejemplo 5-fluorouracilo, citosina arabinósido e hidroxiurea o, por ejemplo, un anti-metabolito divulgado en la Solicitud de Patente de Europa N°: 239362 tal como ácido N-(5-[N-(3,4-dihidro-2-metil-4-oxoquinazolin-6-ilmetil)-N-metilamino]-2-tenoil)-L-glutámico; inhibidores de factores de crecimiento;

631

inhibidores del ciclo celular; antibióticos intercalantes, por ejemplo adriamicina y bleomicina; enzimas, por ejemplo, interferón; y anti-hormonas, por ejemplo anti-estrógenos tal como Nolvadex™ (tamoxifeno) o, por ejemplo, anti-andrógenos tal como Casodex™ (4'-ciano-3-(4-fluorofenilsulfonil)-2-hidroxi-2-metil-3'-(trifluorometil) propionanilida). Dicho tratamiento conjunto se puede lograr administrando una dosificación simultánea, consecutiva o separada de los componentes individuales del tratamiento.

Los compuestos y las composiciones que se describen en la presente (y cuando fuera apropiado un agente quimioterapéutico y/o radiación) se pueden administrar de manera concurrente (por ejemplo, simultánea, esencialmente simultánea o dentro del mismo protocolo de tratamiento) o sucesiva, dependiendo de la naturaleza de la enfermedad, la condición del paciente y la elección del agente quimioterapéutico y/o radiación que será administrado junto (es decir, dentro de un único protocolo de tratamiento) con el compuesto/composición.

En las aplicaciones y los usos combinados, no es necesario administrar el compuesto/composición y el agente quimioterapéutico y/o radiación de forma simultánea o esencialmente simultánea, y el orden inicial de administración del compuesto/composición y del agente quimioterapéutico y/o radiación posiblemente no sea

632

importante. Por consiguiente, los compuestos/composiciones de la invención se pueden administrar primero seguido por la administración del agente quimioterapéutico y/o la radiación; o el agente quimioterapéutico y/o radiación se pueden administrar primero seguido por la administración de los compuestos/composiciones de la invención. Esta administración alternada puede repetirse para un único protocolo de tratamiento. La determinación del orden de administración, y la cantidad de repeticiones de administración de cada agente terapéutico durante un protocolo de tratamiento es propia del conocimiento del médico experimentado después de evaluar la enfermedad bajo tratamiento y la condición del paciente. Por ejemplo, el agente quimioterapéutico y/o la radiación se pueden administrar primero, en especial si es un agente citotóxico, y luego se puede continuar el tratamiento con la administración de los compuestos/composiciones de la invención seguido por, cuando se considerara ventajoso, la administración del agente quimioterapéutico y/o la radiación, y así sucesivamente hasta completar el protocolo de tratamiento. Por consiguiente, de acuerdo con la experiencia y el conocimiento, el médico a cargo puede modificar cada protocolo para la administración de un compuesto/composición en el tratamiento de acuerdo con las necesidades individuales del paciente, a medida que avanza

633

el tratamiento. El clínico a cargo, en el momento de juzgar si un tratamiento es eficaz a la dosificación administrada, tendrá en cuenta el bienestar general del paciente así como signos más definidos tales como el alivio de los síntomas relacionados con la, la inhibición del crecimiento tumoral, la disminución real del tumor o la inhibición de metástasis. El tamaño del tumor se puede medir usando métodos estándar, tales como estudios radiológicos, por ejemplo, escaneado MRI o CAT, y las mediciones sucesivas se pueden usar para juzgar si el crecimiento del tumor ha sido retardado o aún revertido, o no. El alivio de los síntomas relacionados tal como dolor, y la mejora en la condición global también se pueden emplear al juzgar la eficacia del tratamiento.

Los ejemplos específicos, no limitativos, de posibles terapias combinadas incluyen el uso de los compuestos de la invención con los agentes agrupados en las siguientes clasificaciones farmacoterapéuticas que se indican más adelante. Estos listados no deben considerarse cerradas, sino que deberían servir como ejemplos ilustrativos comunes al área terapéutico relevante actualmente. Más aún, los regímenes combinados pueden incluir una variedad de rutas de administración y deberían incluir las vías oral, intravenosa, intraocular, subcutánea, dérmica y tópica inhalada.

Para el tratamiento de enfermedades oncológicas,

634

trastornos proliferativos y distintos tipos de cáncer, los compuestos de acuerdo con la presente invención se pueden administrar con un agente seleccionado del grupo que comprende: inhibidores de aromatasa, antiestrógenos, anti-andrógenos, corticosteroides, agonistas de gonadorelina, inhibidores de topoisomerasa 1 y 2, agentes activos contra microtúbulos, agentes alquilantes, nitrosoureas, antimetabolitos antineoplásicos, compuestos que contienen platino, agentes dirigidos contra lípidos o proteína quinasas, IMiD, agentes dirigidos contra proteína o lípido fosfatasa, agentes anti-angiogénicos, inhibidores de Akt, inhibidores de IGF-I, moduladores de FGF3, inhibidores de mTOR, Smac miméticos, inhibidores de HDAC, agentes que inducen diferenciación celular, antagonistas del receptor de bradiquinina 1, antagonistas de angiotensina II, inhibidores de ciclooxigenasa, inhibidores de heparanasa, inhibidores de linfoquina, inhibidores de citoquinas, inhibidores de IKK, inhibidores de P38MAPK, ARRY-797, inhibidores de HSP90, inhibidores de multiquinasa, bisfosfanatos, derivados de rapamicina, inhibidores de la vía anti-apoptótica, agonistas de la vía apoptótica, agonistas de PPAR, agonistas de RAR, inhibidores de isoformas Ras, inhibidores de telomerasa, inhibidores de proteasa, inhibidores de metaloproteinasas, inhibidores de aminopeptidasas, activadores de SHIP - AQX-MN100, Humax-CD20 (ofatumumab), antagonistas de CD20,

~~B35~~
635

fusiones de la toxina de la difteria-IL2.

Para el tratamiento de enfermedades oncológicas, trastornos proliferativos y distintos tipos de cáncer, los compuestos de acuerdo con la presente invención se pueden administrar con un agente seleccionado del grupo que comprende: dacarbazina (DTIC), actinomicinas $C_2$, $C_3$, D y $F_1$, ciclofosfamida, melfalán, estramustina, maitansinol, rifamicina, estreptovaricina, doxorubicina, daunorubicina, epirubicina, idarubicina, detorubicina, carminomicina, idarubicina, epirubicina, esorubicina, mitoxantrona, bleomicinas A, $A_2$ y B, camptotecina, Irinotecan$^{MR}$, Topotecan$^{MR}$, 9-aminocamptotecina, 10,11-metilendioxicamptotecina, 9-nitrocamptotecina, bortezomib, temozolomida, TAS103, NPI0052, combretastatina, combretastatina A-2, combretastatina A-4, calicheamicinas, neocarcinostatinas, epotilonas A B, C, y variantes semisintéticas, Herceptin$^{MR}$, Rituxan$^{MR}$, anticuerpos CD40, asparaginasa, interleuquinas, interferones, leuprolida y pegaspargasa, 5-fluorouracilo, fluorodeoxiuridina, ptorafur, 5'-deoxifluorouridina, UFT, MITC, S-1 capecitabina, dietilestilbestrol, tamoxifeno, toremefine, tolmudex, timitaq, flutamida, fluoximesterona, bicalutamida, finasteride, estradiol, trioxifeno, dexametasona, acetato de leuprorelina, estramustina, droloxifeno, medroxiprogesterona, acetato de megesterol,

636

aminoglutetimida, testolactona, testosterona, dietilestilbestrol, hidroxiprogesterona, mitomicinas A, B y C, porfiromicina, cisplatino, carboplatino, oxaliplatino, tetraplatino, platino-DACH, ormaplatino, talidomida, lenalidomida, CI-973, telomestatina, CHIR258, Rad 001, SAHA, Tubacina, 17-AAG, sorafenib, JM-216, podofilotoxina, epipodofilotoxina, etopósido, tenipósido, Tarceva$^{MR}$, Iressa$^{MR}$, Imatinib$^{MR}$, Miltefosina$^{MR}$, Perifosina$^{MR}$, aminopterina, metotrexato, metopterina, dicloro-metotrexato, 6-mercaptopurina, tioguanina, azatuoprina, alopurinol, cladribina, fludarabina, pentostatina, 2-cloroadenosina, deoxicitidina, citosina arabinósido, citarabina, azacitidina, 5-azacitosina, gencitabina, 5-azacitosina-arabinósido, vincristina, vinblastina, vinorelbina, leurosina, leurosidina y vindesina, paclitaxel, taxotere y docetaxel.

Para el tratamiento de enfermedades inflamatorias o dolor, los compuestos y sales farmacéuticamente aceptables de los compuestos de acuerdo con la presente invención se pueden administrar con un agente seleccionado del grupo que comprende: corticosteroides, anti-inflamatorios no esteroides, relajantes musculares y combinaciones de los mismos con otros agentes, anestésicos y combinaciones de los mismos con otros agentes, expectorantes y combinaciones de los mismos con otros agentes, antidepresivos,

637

anticonvulsivantes y combinaciones de los mismos; antihipertensivos, opioides, canabinoides tópicos, capsaicina, dipropionato de betametasona (aumentado y no aumentado), valerato de betametasona, propionato de clobetasol, prednisona, metilprednisolona, diacetato de diflorasona, propionato de halobetasol, amcinonida, dexametasona, dexosimetasona, fluocinolona acetononida, fluocinonida, halocinonida, pivalato de clocortalona, dexosimetasona, flurandrenalida, salicilatos, ibuprofeno, ketoprofeno, etodolac, diclofenac, meclofenamato sódico, naproxeno, piroxicam, celecoxib, ciclobenzaprina, baclofeno, ciclobenzaprina/lidocaína, baclofeno/ciclobenzaprina, ciclobenzaprina/lidocaína/ketoprofeno, lidocaína, lidocaína/deoxi-D-glucosa, prilocaína, crema EMLA (mezcla eutéctica de anestésicos locales (lidocaína 2,5% y prilocaína 2,5%), guaifenesina, guaifenesina/ketoprofeno/ciclobenzaprina, amitriptilina, doxepina, desipramina, imipramina, amoxapina, clomipramina, nortriptilina, protriptilina, duloxetina, mirtazepina, nisoxetina, maprotilina, reboxetina, fluoxetina, fluvoxamina, carbamazepina, felbamato, lamotrigina, topiramato, tiagabina, oxcarbazepina, carbamezipina, zonisamida, mexiletina, gabapentina/clonidina, gabapentina/carbamazepina, carbamazepina/ciclobenzaprina, antihipertensivos incluyendo clonidina, codeína, loperamida,

638

tramadol, morfoína, fentanilo, oxicodona, hidrocodona, levorfanol, butorfanol, mentol, aceite de gaulteria, alcanfor, aceite de eucalipto, aceite de terpentina; ligandos de CB1/CB2, acetaminofeno, infliximab, inhibidores de óxido nítrico sintasa, en particular inhibidores de la óxido nítrico sintasa inducible, inhibidores de PDE4 - mecanismo similar a Ibudilast (AV-411), CDC-801, inhibidores de JNK - CC-401, inhibidores de la combinación TNF/PDE4 - CDC-998, antagonistas de IL1 por ejemplo Anakinra - Kineret, AMG 108, (mAb) contra IL-1, activadores de SHIP - AQX-MN100, antagonistas de C5, inhibidores de C5a, Pexelizumab, inhibidores de la síntesis de pirimidina, inhibidores de linfoquina, inhibidores de citoquina, inhibidores de IKK, inhibidores de P38MAPK, ARRY-797, inhibidores de HSP90, inhibidores de multiquinasa, bisfosfanatos, agonistas de PPAR, inhibidores de Cox1 y Cox2, terapia anti-CD4, inhibidores de células B, inhibidores dobles de COX/LOX, agentes inmunosupresores, inhibidores de iNOS, NSAID, inhibidores de sPLA2, colchicina, alopurinol, oxipurinol, oro, Ridaura - Auranofin, febuxostat, Puricasa, formulaciones de PEG-uricasa, Benzbromarona, agonistas de beta-2 de acción prolongada (LABA), salmeterol (Serevent Diskus) y formoterol (Foradil), modificadores de leucotrieno incluyendo montelukast (Singulair) y zafirlukast (Accolate). Cromolina inhalada (Intal) o nedocromilo (Tilade),

639

Teofilina. Agonistas de beta-2 de corta acción, Ipratropio (Atrovent), Inmunoterapia-(aplicaciones de desensibilización-alergia), anticuerpos monoclonales anti-IgE - Xolair, DMARDs comunes que incluyen hidroxicloroquina (Plaquenil), el compuesto de oro auranofina (Ridaura), sulfasalazina (Azulfidine), minociclina (Dynacin, Minocin) y metotrexato (Rheumatrex), leflunomida (Arava), azatioprina (Imuran), ciclosporina (Neoral, Sandimmune) y ciclofosfamida (Cytoxan), antibióticos, antagonistas de CD80, antagonistas de factores co-estimulantes, Humax-CD20 (ofatumumab); antagonistas de CD20, inhibidores de MEK, inhibidores de NF kappa B, anticuerpos anti-células B, denosumab, mAb dirigido específicamente contra el activador del receptor del ligando del factor nuclear kappa B (RANKL). anticuerpos inactivantes de IL17, antagonistas/inhibidores del receptor de IL-17, inhibidores de CTLA, inhibidores de CD20, receptores de VEGFR-1 soluble, anticuerpos anti-receptor de VEGFR-1, anticuerpos anti-VEGF, antagonista del receptor de integrina, inhibidores de selectina, inhibidores de P-selectina y E-selectina, inhibidores de fosfolipasa A2, inhibidores de lipoxigenasa, antagonistas/anticuerpos de RANKL y RANK, antagonistas de osteoprotegerina, inhibidores de linfotoxina, estimulador de linfocitos-B, inhibidores de MCP-1, inhibidores de MIF, inhibidores de: CD2, CD3, CD4, CD25, CD40 y CD40 ligando CD152 (CTLA4), inmunosupresores de

640

macrólidos, inhibidores selectivos del metabolismo de nucleótidos, inhibidores de la quimiotaxis, inhibidores del receptor de CXC y del ligando de CXC, antagonistas de quimioquinas, inhibidores de la quimiotaxis de leucocitos, bloqueantes de moléculas de adhesión, selectinas, antagonistas del antígeno-1 de la función de linfocitos, antagonistas del antígeno-4 muy tardío (VLA-4), inhibidores de metaloproteasas de la matriz, inhibidores de elastasa, inhibidores de catepsina.

Para el tratamiento de trastornos oftalmológicos y enfermedades oculares, los compuestos y sales farmacéuticamente aceptables de los compuestos de acuerdo con la presente invención se pueden administrar con un agente seleccionado del grupo que comprende: beta-bloqueantes, inhibidores de anhidrasa carbónica, antagonistas alfa y beta-adrenérgicos incluyendo antagonistas alfa1-adrenérgicos, agonistas alfa2, mitóticos, análogos de prostaglandina, corticosteroides y agentes inmunosupresores.

Para el tratamiento de trastornos oftalmológicos y enfermedades oculares, los compuestos y sales farmacéuticamente aceptables de los compuestos de acuerdo con la presente invención se pueden administrar con un agente seleccionado del grupo que comprende: timolol, betaxolol, levobetaxolol, carteolol, levobunolol,

641

propranolol, brinzolamida, dorzolamida, nipradilol, iopidina, brimonidina, pilocarpina, epinefrina, latanoprost, travoprost, bimatoprost, unoprostona, dexametasona, prednisona, metilprednisolona, azatioprina, ciclosporina e inmunoglobulinas.

Para el tratamiento de trastornos autoinmunes, los compuestos y sales farmacéuticamente aceptables de los compuestos de acuerdo con la presente invención se pueden administrar con un agente seleccionado del grupo que comprende: corticosteroides, inmunosupresores, análogos de prostaglandina y antimetabolitos.

Para el tratamiento de trastornos autoinmunes, los compuestos de acuerdo con la presente invención se pueden administrar con un agente seleccionado del grupo que comprende: dexametasona, prednisona, metilprednisolona, azatioprina, ciclosporina, inmunoglobulinas, latanoprost, travoprost, bimatoprost, unoprostona, infliximab, rutuximab, metotrexato, anti-inflamatorios no esteroides, relajantes musculares y combinaciones de los mismos con otros agentes, anestésicos y combinaciones de los mismos con otros agentes, expectorantes y combinaciones de los mismos con otros agentes, antidepresivos, anticonvulsivantes y combinaciones de los mismos; antihipertensivos, opioides, canabinoides tópicos, capsaicina, dipropionato de betametasona (aumentado y no aumentado), valerato de betametasona, propionato de

AR

clobetasol, prednisona, metilprednisolona, diacetato de diflorasona, propionato de halobetasol, amcinonida, dexametasona, dexosimetasona, fluocinolona acetononida, fluocinonida, halocinonida, pivalato de clocortalona, dexosimetasona, flurandrenalida, salicilatos, ibuprofeno, ketoprofeno, etodolac, diclofenac, meclofenamato sódico, naproxeno, piroxicam, celecoxib, ciclobenzaprina, baclofen, ciclobenzaprina/lidocaína, baclofen/ciclobenzaprina, ciclobenzaprina/lidocaína/ketoprofeno, lidocaína, lidocaína/deoxi-D-glucosa, prilocaína, crema EMLA (mezcla eutéctica de anestésicos locales (lidocaína 2,5% y prilocaína 2,5%), guaifenesina, guaifenesina/ketoprofeno/ciclobenzaprina, amitriptilina, doxepina, desipramina, imipramina, amoxapina, clomipramina, nortriptilina, protriptilina, duloxetina, mirtazepina, nisoxetina, maprotilina, reboxetina, fluoxetina, fluvoxamina, carbamazepina, felbamato, lamotrigina, topiramato, tiagabina, oxcarbazepina, carbamezipina, zonisamida, mexiletina, gabapentina/clonidina, gabapentina/carbamazepina, carbamazepina/ciclobenzaprina, antihipertensivos incluyendo clonidina, codeína, loperamida, tramadol, morfoína, fentanilo, oxicodona, hidrocodona, levorfanol, butorfanol, mentol, aceite de gaulteria, alcanfor, aceite de eucalipto, aceite de terpentina; ligandos de CB1/CB2, acetaminofeno, infliximab, inhibidores

643

de óxido nítrico sintasa, en particular inhibidores de la óxido nítrico sintasa inducible,; y otros agentes, tal como capsaicina, inhibidores de PDE4 - mecanismo similar a Ibudilast (AV-411), CDC-801, inhibidores de JNK - CC-401, inhibidores de la combinación TNF/PDE4 - CDC-998, antagonistas de IL1 por ejemplo Anakinra - Kineret, AMG 108, (mAb) contra IL-1, activadores de SHIP - AQX-MN100, antagonistas de C5, inhibidores de C5a, Pexelizumab, inhibidores de la síntesis de pirimidina, inhibidores de linfoquina, inhibidores de citoquina, inhibidores de IKK, inhibidores de P38MAPK, ARRY-797, inhibidores de HSP90, inhibidores de multiquinasa, bisfosfanatos, agonistas de PPAR, inhibidores de Cox1 y Cox2, terapia anti-CD4, inhibidores de células B, inhibidores dobles de COX/LOX, agentes inmunosupresores, inhibidores de iNOS, NSAID, inhibidores de sPLA2, colchicina, alopurinol, oxipurinol, oro, Ridaura - Auranofin, febuxostat, Puricasa, formulaciones de PEG-uricasa, Benzbromarona, agonistas de beta-2 de acción prolongada (LABA), salmeterol (Serevent Diskus) y formoterol (Foradil), modificadores de leucotrieno incluyendo montelukast (Singulair) y zafirlukast (Accolate). Cromolina inhalada (Intal) o nedocromilo (Tilade), Teofilina. agonistas de beta-2 de corta acción, Ipratropio (Atrovent), Inmunoterapia-(aplicaciones de desensibilización-alergia), anticuerpos monoclonales anti-

644

IgE - Xolair, DMARDs comunes que incluyen hidroxicloroquina (Plaquenil), el compuesto de oro auranofina (Ridaura), sulfasalazina (Azulfidine), minociclina (Dynacin, Minocin) y metotrexato (Rheumatrex), leflunomida (Arava), azatioprine (Imuran), ciclosporina (Neoral, Sandimmune) y ciclofosfamida (Cytoxan), antibióticos, antagonistas de CD80, antagonistas de factores co-estimulantes, Humax-CD20 (ofatumumab); antagonistas de CD20, inhibidores de MEK, inhibidores de NF kappa B, anticuerpos anti-células B, denosumab, mAb dirigido específicamente contra el activador del receptor del ligando del factor nuclear kappa B (RANKL). anticuerpos inactivantes de IL17, antagonistas/inhibidores del receptor de IL-17, inhibidores de CTLA, inhibidores de CD20, receptores de VEGFR-1 soluble, anticuerpos anti-receptor de VEGFR-1, anticuerpos anti-VEGF, antagonista del receptor de integrina, inhibidores de selectina, inhibidores de P-selectina y E-selectina, inhibidores de fosfolipasa A2, inhibidores de lipoxigenasa, antagonistas/anticuerpos de RANKL y RANK, antagonistas de osteoprotegerina, inhibidores de linfotoxina, estimulador de linfocitos-B, inhibidores de MCP-1, inhibidores de MIF, inhibidores de: CD2, CD3, CD4, CD25, CD40 y CD40 ligando CD152 (CTLA4), inmunosupresores de macrólidos, inhibidores selectivos del metabolismo de nucleótidos, inhibidores de la quimiotaxis, inhibidores del receptor de CXC y del ligando de CXC, antagonistas de

645

quimioquinas, inhibidores de la quimiotaxis de leucocitos, bloqueantes de moléculas de adhesión, selectinas, antagonistas del antígeno-1 de la función de linfocitos, antagonistas del antígeno-4 muy tardío (VLA-4), inhibidores de metaloproteasas de la matriz, inhibidores de elastasa, inhibidores de catepsina.

Para el tratamiento de trastornos metabólicos, los compuestos y sales farmacéuticamente aceptables de los compuestos de acuerdo con la presente invención se pueden administrar con un agente seleccionado del grupo que comprende: insulina, derivados y miméticos de insulina, secretagogos de insulina, sensibilizadores de insulina, agentes de biguanida, inhibidores de alfa-glucosidasa, ligandos del receptor de sulfonilurea insulinotrópico, inhibidores de la proteína tirosina fosfatasa-1B (PTP-1B), inhibidores de GSK3 (glucógeno sintasa quinasa-3), GLP-1 (péptido-1 tipo glucagon), análogos de GLP-1, inhibidores de DPPIV (dipeptidilpeptidasa IV), ligandos RXR inhibidores del co-transportador de glucosa dependiente de sodio, inhibidores de la glucógeno fosforilasa A, un interruptor AGE, moduladores de PPAR, moduladores de LXR y FXR, agonista de PPARS de tipo no glitazona, antagonistas selectivos de glucocorticoides, metformina, Glipizida, gliburide, Amarilo, meglitinidas, nateglinida, repaglinida, PT-112, SB-517955, SB4195052, SB-216763, NN-57-05441, NN-57-05445, GW-0791,

646

AGN-[194,204], T-1095, BAY R3401, acarbosa Exendina-4, DPP728, LAF237, vildagliptina, MK-0431, saxagliptina, GSK23A, pioglitazona, rosiglitazona, ácido (R)-1-{4-[5-metil-2-(4-trifluorometil-fenil)-oxazol-4-ilmetoxi]-bencensulfonil}2,3-dihidro-1H-indol-2-carboxílico descrito en la Solicitud de Patente WO 03/043985, como el compuesto 19 del Ejemplo 4, y GI-262570.

*Enfermedades*

En la presente se describen métodos de tratamiento de una enfermedad en un individuo que sufre de dicha enfermedad que comprende administrarle a dicho individuo una cantidad eficaz de un compuesto de la fórmula I o una sal, solvato, polimorfo, éster, amida, tautómero, prodroga, hidrato o derivado farmacéuticamente aceptable del mismo.

En la presente también se describen métodos de tratamiento de una enfermedad o trastorno en un individuo que sufre de dicha enfermedad o trastorno que comprende administrarle a dicho individuo una cantidad eficaz de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida (Forma A). La invención se extiende al uso de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida (Forma A) en la elaboración de un medicamento para tratar una enfermedad o trastorno.

647

En algunas formas de realización, la invención se relaciona con la profilaxis o el tratamiento de cualquier enfermedad o trastorno en donde la MEK quinasa cumple un rol, incluyendo, en un sentido no limitativo: enfermedades oncológicas, hematológicas, inflamatorias, oftalmológicas, neurológicas, inmunológicas, cardiovasculares y dermatológicas, así como enfermedades causadas por una producción de citoquinas pro-inflamatorias excesiva o no regulada, incluyendo por ejemplo una producción excesiva o no regulada de TNF, IL-1, IL-6 e IL-8 en un ser humano u otro mamífero. La invención se extiende a dicho uso y al uso de los compuestos para la elaboración de un medicamento para el tratamiento de enfermedades o trastornos mediados por citoquinas. Además, la invención se extiende a la administración a un ser humano de una cantidad eficaz de un inhibidor de MEK para el tratamiento de cualquiera de dichas enfermedades o trastornos.

Las enfermedades o trastornos en los cuales la MEK quinasa cumple un rol, ya sea directamente o a través de citoquinas pro-inflamatorias incluyendo las citoquinas TNF, IL-1, IL-6 e IL-8, incluyen, en un sentido no limitativo: síndrome de ojo seco, glaucoma, enfermedades autoinmunes, enfermedades inflamatorias, trastornos destructivos de huesos, trastornos proliferativos, trastornos neurodegenerativos, enfermedades virales, alergias,

648

enfermedades infecciosas, ataque cardíaco, trastornos angiogénicos, reperfusión/isquemia en un accidente cerebrovascular, hiperplasia vascular, hipoxia de órganos, hipertrofia cardíaca, agregación plaquetaria inducida por trombina y condiciones asociadas con la prostaglandina endoperoxidasa sintetasa-2 (COX-2).

En determinados aspectos de la invención, la enfermedad es una condición hiperproliferativa del cuerpo humano o de un animal, incluyendo, pero en un sentido no limitativo, cáncer, hiperplasias, restenosis, inflamación, trastornos inmunes, hipertrofia cardíaca, aterosclerosis, dolor, migraña, condiciones o trastornos relacionado con la angiogénesis, proliferación inducida después de condiciones médicas incluyendo, pero en un sentido no limitativo, cirugía, angioplastia u otras condiciones.

En otras formas de realización, dicha condición hiperproliferativa se selecciona del grupo que consiste de distintos tipos de cáncer hematológico y no hematológico. En aún otras formas de realización, dicho cáncer hematológico se selecciona del grupo que consiste de múltiples mielomas, leucemias y linfomas. En aún otras formas de realización, dicha leucemia se selecciona del grupo que consiste de leucemias agudas y crónicas. En aún otras formas de realización, dicha leucemia aguda se selecciona del grupo que consiste de leucemia linfocítica aguda (ALL) y leucemia

649

no linfocítica aguda (ANLL). En aún otras formas de realización, dicha leucemia crónica se selecciona del grupo que consiste de leucemia crónica linfocítica (CLL) y leucemia mielogenosa crónica (CML). En otras formas de realización, dicho linfoma se selecciona del grupo que consiste de linfoma de Hodgkin y linfoma no Hodgkin. En otras formas de realización, dicho cáncer hematológico es mieloma múltiple. En otras formas de realización, dicho cáncer hematológico es de grado bajo, intermedio o alto. En otras formas de realización, dicho cáncer no hematológico se selecciona del grupo que consiste de: cáncer de cerebro, distintos tipos de cáncer de cabeza y cuello, cáncer de pulmón, cáncer de mama, distintos tipos de cáncer del sistema reproductor, distintos tipos de cáncer del sistema digestivo, cáncer pancreático y distintos tipos de cáncer del sistema urinario. En otras formas de realización, dicho cáncer del sistema digestivo es un cáncer del tracto digestivo superior o cáncer colorrectal. En otras formas de realización, dicho cáncer del sistema urinario es cáncer de vejiga o carcinoma de células renales. En otras formas de realización, dicho cáncer del sistema reproductor es cáncer de próstata.

Otros tipos de cáncer que se pueden tratar usando los compuestos y métodos que se describen en la presente incluyen: distintos tipos de cáncer de la cavidad oral y

650

faringe, distintos tipos de cáncer del sistema respiratorio, distintos tipos de cáncer de huesos y articulaciones, distintos tipos de cáncer de tejidos blandos, distintos tipos de cáncer de piel, distintos tipos de cáncer del sistema genital, distintos tipos de cáncer del ojo y la órbita, distintos tipos de cáncer del sistema nervioso, distintos tipos de cáncer del sistema linfático y distintos tipos de cáncer del sistema endócrino. En determinadas formas de realización, estos tipos de cáncer se pueden seleccionar del grupo que consiste de: cáncer de la lengua, boca, faringe u otra cavidad oral; cáncer de esófago, cáncer de estómago o cáncer del intestino delgado; cáncer de colon o cáncer rectal, anal o anorrectal; cáncer de hígado, ductos biliares intrahepáticos, vesícula biliar, páncreas u otros órganos biliares o digestivos; laringe, bronquial y otros tipos de cáncer de los órganos respiratorios; cáncer del corazón, melanoma, carcinoma de células basales, carcinoma de células escamosas, otro cáncer de piel no epitelial; cáncer uterino o cervical; cáncer del cuerpo uterino; de ovario, vulvar, vaginal o otro cáncer de los genitales femeninos; de próstata, testicular, de pene u otro cáncer de los genitales masculinos; cáncer de vejiga urinaria; cáncer de riñón; cáncer renal, pélvico o uretral u otro cáncer de los órganos genito-urinarios; cáncer de tiroides u otro cáncer endócrino; leucemia crónica linfocítica; y linfoma

651

cutánea de células T, tanto granulocítica como monocítica.

Aún otros tipos de cáncer que se pueden tratar usando los compuestos y métodos que se describen en la presente incluyen: adenocarcinoma, angiosarcoma, astrocitoma, neuroma acústico, astrocitoma anaplásico, carcinoma de células basales, blastoglioma, condrosarcoma, coriocarcinoma, cordoma, craneofaringioma, melanoma cutánea, cistadenocarcinoma, endoteliosarcoma, carcinoma embrionario, ependimoma, tumor de Ewing, carcinoma epitelial, fibrosarcoma, cáncer gástrico, distintos tipos de cáncer del tracto genitourinario, glioblastoma multiforme, hemangioblastoma, carcinoma hepatocelular, hepatoma, sarcoma de Kaposi, carcinoma de células grandes, leiomiosarcoma, liposarcoma, linfangiosarcoma, linfangioendoteliosarcoma, carcinoma de médula de tiroides, meduloblastoma, meningioma, mesotelioma, mielomas, mixosarcoma neuroblastoma, neurofibrosarcoma, oligodendroglioma, sarcoma osteogénico, cáncer epitelial de ovario, carcinoma papilar, adenocarcinomas papilares, tumores de paratiroides, feocromocitoma, pinealoma, plasmacitomas, retinoblastoma, rabdomiosarcoma, carcinoma de glándulas sebáceas, seminoma, distintos tipos de cáncer de piel, melanoma, carcinoma de pulmón de células pequeñas, carcinoma de células escamosas, carcinoma de glándulas sudoríparas, sinovioma, cáncer de tiroides, melanoma de úvea y tumor de Wilm.

652

También se describen métodos para el tratamiento de un trastorno hiperproliferativo en un mamífero que comprenden administrarle a dicho mamífero una cantidad terapéuticamente eficaz de un compuesto de la fórmula I, o una sal, solvato, polimorfo, éster, amida, tautómero, prodroga, hidrato o derivado farmacéuticamente aceptable del mismo, en combinación con un agente anti-tumoral. En algunas formas de realización, el agente anti-tumoral se selecciona del grupo que consiste de inhibidores mitóticos, agentes alquilantes, anti- metabolitos, antibióticos intercalantes, inhibidores de factores de crecimiento, inhibidores del ciclo celular, enzima inhibidores, inhibidores de topoisomerasa, modificadores de la respuesta biológica, anti-hormonas, inhibidores de la angiogénesis, anti-andrógenos, activadores de SHIP - AQX-MN100, Humax-CD20 (ofatumumab), antagonistas de CD20, fusiones de toxina de difteria-IL2.

La enfermedad que será tratada usando los compuestos, las composiciones y los métodos que se describen en la presente puede ser un trastorno hematológico. En determinadas formas de realización, dicho trastorno hematológico se selecciona del grupo que consiste de anemia de células falsiformes, trastornos mielodisplásicos (MDS) y trastornos mieloproliferativos. En otras formas de realización, dicho trastorno mieloproliferativo se selecciona del grupo que consiste de policitemia vera,

653

mielofibrosis y trombocitemia esencial.

Los compuestos, las composiciones y los métodos que se describen en la presente pueden ser de utilidad como agentes anti-inflamatorios con el beneficio adicional de tener efectos secundarios significativamente menos perjudiciales. Los compuestos, las composiciones y los métodos que se describen en la presente son de utilidad para tratar una artritis, incluyendo pero en un sentido no limitativo artritis reumatoide, espondiloartropatías, espondilitis anquilosante, gota, artritis gotosa, osteoartritis, lupus sistémica eritematosa, artritis juvenil, artritis reumática aguda, artritis enteropática, artritis neuropática, artritis psoriática y artritis piogénica. Los compuestos, las composiciones y los métodos que se describen en la presente también son de utilidad en el tratamiento de osteoporosis y otros trastornos relacionados con los huesos. Estos compuestos, composiciones y métodos que se describen en la presente también son de utilidad para tratar condiciones gastrointestinales tales como esofagitis por reflujo, diarrea, enfermedad de intestino inflamatorio, enfermedad de Crohn, gastritis, síndrome de intestino irritable y colitis ulcerosa. Los compuestos, las composiciones y los métodos que se describen en la presente también se pueden usar en el tratamiento de inflamación pulmonar, tal como la que está asociada con infecciones virales y fibrosis quística.

654

Además, los compuestos, las composiciones y los métodos que se describen en la presente también son de utilidad en pacientes con transplantes de órganos ya sea solos o en combinación con inmunomoduladores convencionales. Aún más, los compuestos, las composiciones y los métodos que se describen en la presente son de utilidad en el tratamiento de pruritis y vitaligo. En particular, los compuestos, las composiciones y los métodos que se describen en la presente son de utilidad en el tratamiento de la enfermedad inflamatoria particular, artritis reumatoide.

Otras enfermedades inflamatorias que se pueden prevenir o tratar incluyen, en un sentido no limitativo: asma, alergias, síndrome de dificultad respiratoria o pancreatitis aguda o crónica. Aún más, se pueden prevenir o tratar enfermedades del sistema respiratorio incluyendo, pero en un sentido no limitativo, la enfermedad pulmonar obstructiva crónica y fibrosis pulmonar. Además, los inhibidores de MEK quinasa que se describen en la presente también se asocian con la producción de prostaglandina endoperoxidase sintetasa-2 (COX-2). Los mediadores pro-inflamatorios de la vía de la ciclooxigenasa derivados del ácido araquidónico, tales como prostaglandinas, son producidos por la enzima COX-2 inducible. La regulación de COX-2 regularía estos mediadores pro-inflamatorios, que afectan una amplia variedad de células y son mediadores inflamatorios

655

importantes y críticos de una amplia variedad de estos de enfermedad y condiciones. En particular, estos mediadores inflamatorios se han relacionado con el dolor, tal como en la sensizibilización de los receptores del dolor, y edemas. Por lo tanto, las condiciones adicionales mediadas por MEK quinasa que se pueden prevenir o tratar incluyen edema, analgesia, fiebre y dolor, tal como dolor neuromuscular, cefalea, dolor dental, dolor por artritis y dolor causado por cáncer.

Además, la enfermedad a tratar mediante los compuestos, las composiciones y los métodos que se describen en la presente puede ser un trastorno oftalmológico. Las enfermedades oftalmológicas y otras enfermedades en las cuales la angiogénesis cumple un rol en la patogénesis, que se pueden tratar o prevenir incluyen, en un sentido no limitativo, síndrome de ojo seco (incluyendo el síndrome de Sjogren), degeneración macular, glaucoma de ángulo cerrado y amplio, degeneración del ganglio retinal, isquemia ocular, retinitis, retinopatías, uveítis, fotofobia ocular e inflamación y dolor asociados con lesiones agudos del tejido ocular. Los compuestos, las composiciones y los métodos que se describen en la presente son de utilidad para tratar una retinopatía glaucomatosa y/o una retinopatía diabética. Los compuestos, las composiciones y los métodos que se describen en la presente también son de utilidad para tratar una

656

inflamación post-operatoria o dolor debido a una cirugía oftálmica, tal como una cirugía de cataratas y una cirugía refractaria. En otras formas de realización, dicho trastorno oftalmológico se selecciona del grupo que consiste de síndrome de ojo seco, glaucoma de ángulo cerrado y glaucoma de ángulo amplio.

Además, la enfermedad a tratar mediante los compuestos, las composiciones y los métodos que se describen en la presente puede ser una enfermedad autoinmune. Las enfermedades autoinmunes que se pueden prevenir o tratar incluyen, pero en un sentido no limitativo: artritis reumatoide, enfermedad de intestino inflamatorio, dolor inflamatorio, colitis ulcerosa, enfermedad de Crohn, enfermedad periodontal, enfermedad de la articulación temporomandibular, esclerosis múltiple, diabetes, glomerulonefritis, lupus sistémica eritematosa, escleroderma, tiroiditis crónica, enfermedad de Grave, anemia hemolítica, gastritis autoinmune, neutropenia autoinmune, trombocitopenia, hepatitis crónica activa, miastenia grave, dermatitis atópica, enfermedad de injerto versus huésped y psoriasis. Las enfermedades inflamatorias que se pueden prevenir o tratar incluyen, pero en un sentido no limitativo: asma, alergias, síndrome de dificultad respiratoria o pancreatitis aguda o crónica. En particular, los compuestos, las composiciones y los métodos que se

657

describen en la presente que son de utilidad en el tratamiento de las enfermedades autoinmunes particulares, artritis reumatoide y esclerosis múltiple.

Además, la enfermedad a tratar mediante los compuestos, las composiciones y los métodos que se describen en la presente puede ser un trastorno dermatológico. En determinadas formas de realización, dicho trastorno dermatológico se selecciona del grupo que incluye, en un sentido no limitativo, melanoma, carcinoma de células basales , carcinoma de células escamosas y otro cáncer de piel no epitelial, así como psoriasis y picazón persistente, y otras enfermedades relacionadas con la piel y estructuras de la piel, y se pueden tratar o prevenir con los inhibidores de MEK quinasa de esta invención.

Las enfermedades metabólicas que se pueden tratar o prevenir incluyen, en un sentido no limitativo, síndrome metabólico, resistencia a insulina y diabetes Tipo 1 y Tipo 2. Además, las composiciones que se describen en la presente pueden ser de utilidad para tratar resistencia a insulina y otros trastornos metabólicos, tal como aterosclerosis, que típicamente están asociados con una señalización inflamatoria exagerada.

Los compuestos, las composiciones y los métodos que se describen en la presente también son de utilidad en el tratamiento de daños en tejidos en enfermedades tales como

638

las enfermedades vasculares, migraña, cefaleas, periarteritis nodosa, tiroiditis, anemia aplásica, enfermedad de Hodgkin, esclerodoma, fiebre reumática, diabetes tipo I, enfermedad de la unión neuromuscular incluyendo miastenia grave, enfermedad de la sustancia blanca incluyendo esclerosis múltiple, sarcoidosis, nefritis, síndrome nefrótico, síndrome de Behcet, polimiositis, gingivitis, periodontis, hipersensibilidad, hinchazón que tiene lugar después de una lesión, isquemias incluyendo isquemia de miocardio, isquemia cardiovascular e isquemia secundaria a un arresto cardíaco y semejantes. Los compuestos, las composiciones y los métodos que se describen en la presente también pueden ser de utilidad para tratar rinitis alérgica, síndrome de dificultad respiratoria, síndrome de shock por endotoxinas y aterosclerosis.

Además, la enfermedad a tratar mediante los compuestos, las composiciones y los métodos que se describen en la presente puede ser una condición cardiovascular. En determinadas formas de realización, dicha condición cardiovascular se selecciona del grupo que consiste de aterosclerosis, hipertrofia cardíaca, cardiomiopatías idiopáticas, insuficiencia cardíaca, condiciones o trastornos relacionados con la angiogénesis, y proliferación inducida después de condiciones médicas, incluyendo, pero en un sentido no limitativo, una restenosis debida a cirugía y

6-SG

angioplastia.

Además, la enfermedad a tratar mediante los compuestos, las composiciones y los métodos que se describen en la presente puede ser un trastorno neurológico. En determinadas formas de realización, dicho trastorno neurológico se selecciona del grupo que consiste de mal de Parkinson, mal de Alzheimer, demencia de Alzheimer, y daños al sistema nervioso central debidos a un accidente cerebrovascular, isquemia y traumatismo. En otras formas de realización, dicho trastorno neurológico se selecciona del grupo que consiste de epilepsia, dolor neuropático, depresión y trastornos bipolares.

Además, la enfermedad a tratar mediante los compuestos, las composiciones y los métodos que se describen en la presente puede ser cáncer, tal como leucemia mieloide aguda, cáncer de timo, de cerebro, de pulmón, de células escamosas, de piel, de ojos, retinoblastoma, melanoma intraocular, cáncer de la cavidad oral y orofaringea, de vejiga, gástrico, de estómago, pancreático, de vejiga, de mama, cervical, de cabeza y cuello, renal, de riñón, de hígado, de ovario, de próstata, colorrectal, de esófago, testicular, ginecológico, de tiroides, del CNS, PNS, relacionado con SIDA (por ejemplo linfoma y sarcoma de Kaposi) o cáncer inducido por virus. En algunas formas de realización, los compuestos y las composiciones son para el tratamiento de un

660

trastorno hiperproliferativo no canceroso, tal como hiperplasia benigna de la piel (por ejemplo, psoriasis), restenosis o próstata (por ejemplo, hipertrofia prostática benigna (BPH)).

Además, la enfermedad a tratar mediante los compuestos, las composiciones y los métodos que se describen en la presente puede ser pancreatitis, enfermedad de riñón (incluyendo glomerulonefritis proliferativa y enfermedad renal inducida por diabetes), dolor, una enfermedad relacionada con vasculogénesis o angiogénesis, angiogénesis de tumores, enfermedad inflamatoria crónica tal como artritis reumatoide, enfermedad de intestino inflamatorio, aterosclerosis, enfermedades de la piel tal como psoriasis, eczema y escleroderma, diabetes, retinopatía diabética, retinopatía del prematuro, degeneración macular relacionada con la edad, hemangioma, tendonitis, bursitis, ciática, glioma, melanoma, sarcoma de Kaposi y cáncer de ovario, de mama, de pulmón, pancreático, de próstata, de colon y epidermoide en un mamífero.

Además, la enfermedad a tratar mediante los compuestos, las composiciones y los métodos que se describen en la presente puede ser la prevención del implante de blastocitos en un mamífero.

Los pacientes que se pueden tratar con los compuestos que se describen en la presente, o sus sales, solvatos,

661

polimorfos, ésteres, amidas, tautómeros, prodrogas, hidratos o derivados farmacéuticamente aceptables de acuerdo con los métodos de esta invención incluyen, por ejemplo, pacientes que han sido diagnosticados con psoriasis; restenosis; aterosclerosis; BPH; cáncer de mama tal como carcinoma de ductos en el tejido de ductos en una glándula mamaria, carcinomas medulares, carcinomas coloides, carcinomas tubulares y cáncer de mama inflamatorio; cáncer de ovario, incluyendo tumores del epitelio de ovario tal como adenocarcinoma en el ovario y un adenocarcinoma que ha migrado del ovario hacia la cavidad abdominal; cáncer uterino; cáncer cervical tal como adenocarcinoma en el epitelio del cuello incluyendo carcinoma de células escamosas y adenocarcinomas; cáncer de próstata, tal como un cáncer de próstata seleccionado entre los siguientes: un adenocarcinoma o un adenocarinoma que ha migrado al hueso; cáncer pancreático tal como carcinoma epiteliode en el tejido de los ductos pancreáticos y un adenocarcinoma en un ducto pancreático; cáncer de vejiga tal como un carcinoma de células de transición en la vejiga urinaria, carcinomas uroteliales (carcinomas de células de transición), tumores en las células uroteliales que revisten la vejiga, carcinomas de células escamosas, adenocarcinomas, y distintos tipos de cáncer de células pequeñas; leucemia tal como leucemia mieloide aguda (AML), leucemia linfocítica

667

aguda, leucemia linfocítica crónica, leucemia mieloide crónica, leucemia de células pilosas, mielodisplasia, y trastornos mieloproliferativos; cáncer de hueso; cáncer de pulmón tal como cáncer de pulmón de células no pequeñas (NSCLC), que se divide en carcinoma de células escamosas, adenocarcinomas y carcinomas de células grandes no diferenciadas y cáncer de pulmón de células pequeñas; cáncer de piel tal como carcinoma de células basales, melanoma, carcinoma de células escamosas y queratosis actínica, que es una condición de la piel que a veces se desarrolla en carcinoma de células escamosas; retinoblastoma ocular; melanoma cutáneo o intraocular (ojo); cáncer de hígado primario (cáncer que comienza en el hígado); cáncer de riñón; cáncer de tiroides tal como papilar, folicular, medular y anaplásico; linfoma relacionado con el SIDA tal como linfoma de células B difuso grande, linfoma inmunoblástica de células B y linfoma de células pequeñas no clivadas; sarcoma de Kaposi; distintos tipos de cáncer inducidos por virus incluyendo virus de la hepatitis B (HBV), virus de la hepatitis C (HCV) y carcinoma hepatocelular; virus linfotrópico humano-tipo 1 (HTLV-1) y leucemia/linfoma de células T de adultos; y virus del papiloma humano (HPV) y cáncer del cuello uterino; distintos tipos de cáncer del sistema nervioso central (CNS) tal como tumor de cerebro primario, que incluye gliomas (astrocitoma,

astrocitoma anaplásico o glioblastoma multiforme), oligodendroglioma, ependimoma, meningioma, linfoma, Schwannoma y meduloblastoma; distintos tipos de cáncer del sistema nervioso periférico (PNS) tal como neuromas acústicos y tumor maligno de la envoltura de nervios periféricos (MPNST) incluyendo neurofibromas y schwannomas, citoma fibroso maligno, histiocitoma fibroso maligno, meningioma maligno, mesotelioma maligno y tumor Mülleriano maligno mixto; cáncer de la cavidad oral y orofaríngea tal como, cáncer hipofaríngeo, cáncer de laringe, cáncer nasofaringeo y cáncer orofaringeo; cáncer de estómago tal como linfomas, tumores del estroma gástrico y tumores carcinoides; cáncer testicular tal como tumores de células germinales (GCT), que incluyen seminomas y no seminomas, y tumores del estroma gonadal, que incluyen tumores de las células de Leydig y tumores de las células de Sertoli; cáncer de timo tales como timomas, carcinomas tímicos, enfermedad de Hodgkin, linfomas carcinoides no Hodgkin o tumores carcinoides; cáncer rectal; y cáncer de colon.

*Conjuntos de elementos (kits)*

Los compuestos, las composiciones y los métodos que se describen en la presente suministran conjuntos de elementos para el tratamiento de trastornos, tales como los que se describen en la presente. Estos conjuntos de elementos comprenden un compuesto, los compuestos o las composiciones

que se describen en la presente en un recipiente y, opcionalmente, instrucciones que explican el uso del conjunto de elementos de acuerdo con los diversos métodos y enfoques descritos en la presente. Dichos conjuntos de elementos también incluyen información, tal como referencias a literatura científica, prospectos, resultados de ensayos clínicos y/o resúmenes de los mismos y semejantes, que indican o establecen las actividades y/o ventajas de la composición, y/o que describen la dosificación, administración, efectos secundarios, interacciones con drogas u otra información de utilidad para el proveedor de servicio de salud. Dicha información se puede basar en los resultados de diversos estudios, por ejemplo, estudios usando animales experimentales que constituyen modelos in vivo y estudios basados en ensayos clínicos en humanos. Los conjuntos de elementos que se describen en la presente se pueden suministrar, comercializar y/o promover entre los profesionales de la salud, incluyendo médicos, enfermeras, farmacéuticos, profesionales en formulación y semejantes. Los conjuntos de elementos también se pueden comercializar, en algunas formas de realización, directamente al consumidor.

Los compuestos que se describen en la presente se pueden utilizar como reactivos de diagnóstico y de investigación. Por ejemplo, los compuestos que se describen

665

en la presente, ya sea solos o en combinación con otros compuestos, se pueden usar como herramientas en análisis diferenciales y/o combinatorios para dilucidar los patrones de expresión de genes que se expresan en las células y tejidos. A modo de ejemplo no limitativo, se comparan los patrones de expresión en las células o tejidos tratados con uno o más compuestos con células o tejidos control que no fueron tratados con los compuestos y los patrones producidos son analizados por niveles diferenciales de expresión de genes según si pertenecen, por ejemplo, a asociación con enfermedades, vías de señalización, localización celular, nivel de expresión, tamaño, estructura o función de los genes examinados. Estos análisis se pueden realizar con células estimuladas o no estimuladas y en la presencia o ausencia de otros compuestos que afectan a los patrones de expresión.

Además de su utilidad en el tratamiento de humanos, los compuestos y las formulaciones de la presente invención también son de utilidad para el tratamiento veterinario de animales de compañía (por ejemplo perros, gatos), animales exóticos y animales de granja (por ejemplo, caballos), incluyendo mamíferos, roedores y semejantes.

Los ejemplos y las preparaciones que se proveen más adelante ilustran y ejemplifican aún más los compuestos de la presente invención y los métodos para preparar dichos

666

compuestos. Se comprenderá que el alcance de la presente invención no es limitado en modo alguno por el alcance de los siguientes ejemplos y preparaciones.

**EJEMPLOS**

**Procedimientos ejemplares generales para la síntesis de Sulfonamidas**

**Procedimiento A**: a una solución de la amina (1 eq) en diclorometano anhidro (3 ml/ mmol) se agregó trietilamina anhidra (5 eq). A esta solución se agregó el cloruro de sulfonilo (1 eq) y la solución se agitó a temperatura ambiente por 16 h. El solvente se evaporó y el residuo se purificó mediante cromatografía flash de columna sobre sílice.

**Procedimiento B**: A una solución agitada de la amina (1 eq) en piridina anhidra (5ml/mmol) se agregó el cloruro de sulfonilo (1 - 5 eq). La mezcla de la reacción se agitó a 40 $^{oC}$ por 48 horas. La mezcla de la reacción se particionó con agua y EtOAc. La capa orgánica se lavó con salmuera, se secó ($MGSO_4$) y se concentró bajo presión reducida. El residuo se purificó mediante cromatografía flash de columna sobre sílice.

**Procedimiento C**: Sustitución del átomo de yodo:

Una suspensión que contenía 1 eq. de yoduro de arilo, 1,5 equiv. del ácido borónico o éster borónico, 0,25 eq. $PdCl_2$(dppf) x DCM y 10 eq. de $K_2CO_3$ anhidro en polvo en una

mezcla desoxigenada de dioxano y agua (3:1) se calentó en un reactor de microondas por 60 min a 115 $^{0}$C. Se extrajo usando $NH_4Cl$ acuoso/ THF, y la fracción orgánica se secó usando $Na_2SO_4$. Los productos de la reacción crudos se purificaron usando cromatografía flash de columna (Si, EtOAc / Hexanos, o $CHCl_3$ / MeOH). Rendimiento: 20-40%.

**Procedimiento D**: Síntesis de N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-2-(alquilamino)etansulfonamida:

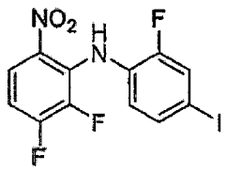
Se agregó cloruro de 2-cloro-etansulfonilo (0,1 ml, 1 mmol) a una solución de 5,6-difluoro-$N^1$-(2-fluoro-4-yodofenil)bencen-1,2-diamina (0,364 g, 1 mmol) y trietilamina (0,28 ml, 2 mmol) en $CH_2Cl_2$ (5 ml) y la mezcla de la reacción se agitó a temperatura ambiente por 16h. Luego se trató con un exceso de amina (10 eq) tanto en solución como en forma de un líquido límpido. La mezcla de la reacción se agitó a temperatura ambiente por otras 6h. La mezcla de la reacción se diluyó con $CH_2Cl_2$ (10 ml) y agua (10 ml). La capa orgánica se lavó en forma secuencial con HCl diluido (2x20 ml, 2N) y solución saturada de $NaHCO_3$ (2x10 ml). Luego la capa de $CH_2Cl_2$ se secó ($MgSO_4$) y se evaporó para obtener el producto crudo. El producto impuro se purificó bajo condiciones de HPLC preparativa para obtener los productos puros en 50-60 % de rendimiento.

Ejemplo 1

668

**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)metansulfonamida:**

**Paso A:** 2,3-Difluoro-N-(2-fluoro-4-yodofenil)-6-nitroanilina:

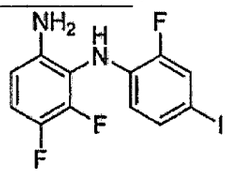



A una solución de 2-fluoro-4-yodoanilina (11,40 g, 47 mmol) en 100 ml de THF anhidro a 0°C, se agregó 47 ml de una solución 1M de LHMDS en THF (47 mmol) por goteo. El color de la solución se volvió morado oscuro. La solución se transfirió mediante cánulas a un embudo de vertido, y la solución (que contenía la base libre de amina) se agregó en pequeñas porciones a una solución de 2,3,4-trifluoronitrobenceno (8,321 g, 47,0 mmol) en THF anhidro (50 ml) a 0°C. luego de completarse la adición la mezcla se agitó bajo argón a temperatura ambiente por 15 horas. El volumen del solvente se redujo, seguido por extracción usando acetato de etilo y salmuera. La capa orgánica se secó sobre sulfato de sodio, el solvente se eliminó, y el aceite oscuro obtenido se purificó mediante cromatografía flash (EtOAc / hexano 1:5, $R_f$ = 0,58) para dar el producto crudo, el cual se volvió un sólido marrón luego de secar al vacío (rendimiento: 6,23 g, 33,6%): $m/z$ = 393 $[M-1]^-$.

**Paso B:** 5,6-Difluoro-N1-(2-fluoro-4-

669

yodofenil)bencen-1,2-diamina:

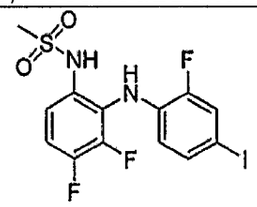


A una solución de nitro-diarilamina (6,23 g, 15,8 mmol) en 300 ml de etanol se agregó polvo de hierro (13,74 g, 246 mmol) y cloruro de amonio (13,59 g, 254 mmol) y la mezcla se calentó con agitación a una temperatura de baño de aceite de 100°C por 14 horas. Se filtró y el residuo se lavó dos veces con etanol. El etanol se retiró al vacío, y el residuo se extrajo usando una solución 1M de acetato de etilo / NaOH 1M. Durante la extracción, se formó más precipitado el cual se filtró y se descartó. Las capas orgánicas combinadas se lavaron con salmuera y se secó sobre sulfato de sodio. El solvente se eliminó, y el producto crudo se recristalizó a partir de $CHCl_3$ / hexano (1:50). El producto se obtuvo como agujas marrones (2,094 g, 66%,), $R_f$ = 0,44 (EtOAc / Hex 1:3), $^1$H-RMN (500 MHz, $CDCl_3$), $\delta$ = 7,40-7,38 (dd, 1H, $J$ = 11,3 Hz, $J$ = 1,5 Hz), 7,25-7,23 (d, 1H, $J$ = 8,5 Hz), 6,97-6,92 (q, 1H, $J$ = 9 Hz), 6,51-6,48 (m, 1H), 6,24-6,21 (t, 1H, $J$ = 9 Hz), 5,3 (s, 1H, NH, br), 3,80 (s, 2H, $NH_2$, br), LRMS (ESI): $m/z$ = 365 $[M+H]^-$.

**Paso C:** N-(3,4-difluoro-2-(2-fluoro-4-

676

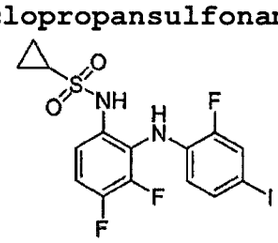
yodofenilamino)fenil)metansulfonamida:



De acuerdo con el procedimiento general A, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)bencen-1,2-diamina con cloruro de metansulfonilo para obtener el producto deseado. $^1$H RMN: (500 MHz, $CDCl_3$): δ = 7,38-7,37 (d, 1H), 7,35-7,34 (m, 1H), 7,27-7,26 (m, 1H), 7,20-7,0 (q, 1H), 6,68 (s, 1H, br), 6,15-6,12 (q, 1H), 5,65 (s, 1H, br), 2,95 (s, 3H); *m/z* = 441 $[M-1]^-$.

Ejemplo 2

**2 N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)ciclopropansulfonamida:**



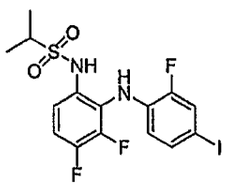
De acuerdo con el procedimiento general A, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)bencen-1,2-diamina con cloruro de ciclopropansulfonilo para obtener el producto deseado. $^1$H RMN: (500 MHz, $CDCl_3$): δ = 7,38-7,37 (d, 1H), 7,35-7,34 (m, 1H), 121-1 Id (m, 1H), 7,20-7,0 (q, 1H), 6,68 (s, 1H, br), 6,15-6,12 (q, 1H), 5,65 (s, 1H, br), 3,25-3,20 (m, 1H), 2,4-2,3 (m, 2H), 2,0-1,8 (m, 2H); *m/z* =

671

467 $[M-1]^-$.

Ejemplo 3

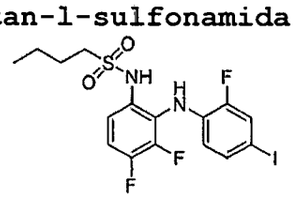
**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)propan-2-sulfonamida:**



De acuerdo con el procedimiento general A, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)bencen-1,2-diamina con cloruro de isopropilsulfonilo para obtener el producto deseado. Rendimiento: 39%. $^1$H-RMN (500 MHz, $CDCl_3$): $\delta$ = 7,50-7,43 (m, 1H), 7,35-7,34 (m, 1H), 7,27-7,26 (m, 1H), 7,15-7,09 (q, 1H, $J$ = 1,6 Hz), 6,62 (s, 1H, br), 6,22-6,18 (q, 1H, $J$ = 1,5 Hz), 5,65 (s, 1H, br), 3,30-3,28 (m, 1H), 1,38-1,37 (d, 6H, $J$ = 1,2 Hz); $m/z$ = 469 $[M- I]^-$.

Ejemplo 4

**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)butan-1-sulfonamida:**

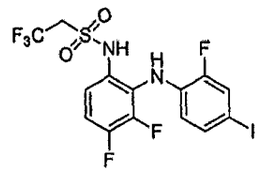


De acuerdo con el procedimiento general A, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)bencen-1,2-diamina con cloruro de n-butilsulfonilo para obtener el producto deseado. Rendimiento: 55%. $^1$H-RMN (500 MHz, $CDCl_3$):

δ = 7,50-7,43 (m, 1H), 7,35-7,34 (m, 1H), 7,27-7,26 (m, 1H), 7,15-7,09 (q, 1H, *J* = 1,6 Hz), 6,62 (s, 1H, br), 6,22-6,18 (q, 1H, *J* = 1,5 Hz)$_5$ 5,65 (s, 1H, br), 3,06-3,031 (t, 2H, *J* = 1,4 Hz), 1,75-1,71 (m, 2H), 1,38-1,36 (m, 2H), 0,87-0,86 (t, 3H, *J* = 1,3 Hz); *m/z* = 483 $[M-1]^-$.

Ejemplo 5

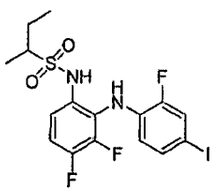
**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-2,2,2-trifluoroetansulfonamida:**



De acuerdo con el procedimiento general A, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)bencen-1,2-diamina con cloruro de 1,1,1-trifluoroetilsulfonilo para obtener el producto deseado. Rendimiento: 28%. *m/z* = 509 $[M-1]^-$.

Ejemplo 6

**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)butan-2-sulfonamida:**

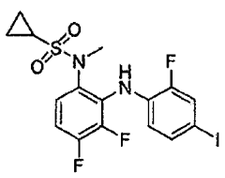


De acuerdo con el procedimiento general A, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)bencen-1,2-diamina con cloruro de sec-butilsulfonilo para obtener el

producto deseado. Rendimiento: 22%. $^1$H-RMN (500 MHz, MeOH[d4]): δ = 7,60-7,40 (m, 3H), 7,18-7,00 (q, 1H), 6,55-6,45 (m, 1H), 3,55-3,50 (m, 1H), 2,20-2,00 (m, 1H), 1,80-1,60 (m, 1H), 1,43-1,40 (d, 3H), 1,06-1,04 (t, 3H); *m/z* = 483 $[M-1]^-$.

Ejemplo 7

**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-N-metilo ciclopropano sulfonamida:**

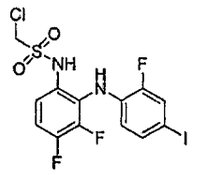


A una solución de N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)ciclopropan-sulfonamida (ver Ejemplo 2) (283,9 mg, 0,61 mmol) en 3 ml de THF anhidro se agregó a -78°C una solución 1M de LHMDS (0,6 ml, 0,6 mol) y la solución se agitó por 10 min a esta temperatura. Luego, se agregó yoduro de metilo (0,8 ml, 1,824 g, 12,9 mmol) y la mezcla se calentó a temperatura ambiente y se agitó por 7 h. El solvente se eliminó y el residuo se extrajo usando EtOAc y salmuera. Las fracciones orgánicas se secaron usando $Na_2SO_4$ y el solvente se eliminó. El producto crudo obtenido se purificó usando cromatografía flash de columna (Si, EtOAc/Hexanos 1:2, $R_f$ = 0,45). Rendimiento: 205 mg, 70%). $^1$H-RMN (500 MHz, $CDCl_3$): δ = 7,41-7,39 (d, 1H, *J* = 10 Hz), 7,30-7,29 (d, 1H, *J* = 8,0 Hz), 7,23-7,20 (m, 1H), 6,98-6,93

(q, 1H, $J$ = 8,5 Hz), 6,60 (s, 1H, br), 6,51-6,47 (m, 1H), 3,23 (s, 3H), 2,46-2,42 (m, 1H), 1,19-1,16 (m, 2H), 1,04-1,02 (m, 2H); $m/z$ = 481 $[M-1]^-$.

Ejemplo 8

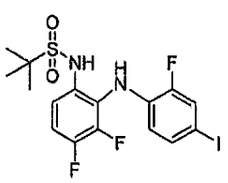
**1-Cloro-N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)metansulfonamida:**



De acuerdo con el procedimiento general A, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)bencen-1,2-diamina con cloruro de clorometansulfonilo para obtener el producto deseado, $m/z$ = 475 $[M-1]^-$.

Ejemplo 9

**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-2-metilpropan-2-sulfonamida:**

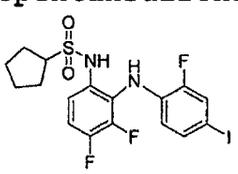


De acuerdo con el procedimiento general B, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)bencen-1,2-diamina con cloruro de 2-metilpropan-2-sulfonilo (sintetizado de acuerdo con el procedimiento de la literatura) para obtener el producto deseado. $^1$H RMN (300 MHz, $CDCl_3$): δ 7,50 (m, 1H), 7,43 (dd, $J$ = 1,8 & 10,5 Hz,

1H), 7,28 (br s, 1H), 7,10 (dd, $J$ = 9,0 & 17,7 Hz, 1H), 6,48 (br s, $D_2O$ intercambiable, 1H), 6,19 (t, $J$ = 7,8 & 9,6 Hz, 1H), 5,58 (br s, $D_2O$ intercambiable, 1H), 1,39 (s, 9H); $m/z$ = 383 $[M-1]^-$.

Ejemplo 10

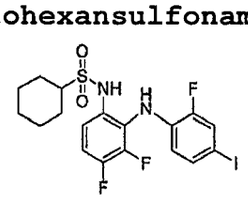
**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)ciclopentansulfonamida:**



De acuerdo con el procedimiento general B, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)bencen-1,2-diamina con cloruro de ciclopentansulfonilo para obtener el producto deseado $^1H$ RMN (300 MHz, $CDCl_3$): δ 7,42 (dd, $J$ = 2,1 & 10,5 Hz, 1H), 7,36 (ddd, $J$ = 2,4, 4,8, & 9,3 Hz, 1H), 7,25 (m, 2H), 7,10 (dd, $J$ = 9,6 & 17,7 Hz, 1H), 6,67 (br s, $D_2O$ intercambiable, 1H), 6,20 (dt, $J$ = 1,5, 8,4 & 17,4 Hz, 1H), 3,53 (p, 1H), 1,80 (m, 8H); $m/z$ = 495 $[M-1]^-$.

Ejemplo 11

**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)ciclohexansulfonamida:**



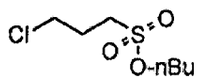
De acuerdo con el procedimiento general B, se hizo

reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)bencen-1,2-diamina con cloruro de ciclohexansulfonilo para obtener el producto deseado. $^1$H RMN (300 MHz, $CDCl_3$): δ 7,43 (dd, *J* = 1,5 & 10,2 Hz, 1H), 7,37 (ddd, *J* = 2,4, 4,8 & 9,6 Hz, 1H), 7,27 (m, 1H), 7,11 (dd, *J* = 9,3 & 18,0 Hz, 1H), 6,64 (br s, 1H), 6,18 (dt, *J* = 1,5, 9,0 & 17,4 Hz, 1H), 5,63 (br s, 1H), 2,95 (triplete de triplete, 2,10-1,16 (m, 10H); *m/z* = 509 $[M-1]^-$.

Ejemplo 12

**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-1-metilciclopropan-1-sulfonamida:**

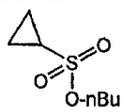
**Paso A:** 3-cloro-1-propansulfonato de n-butilo:




Se agregó trietilamina (28 ml, 200 mmol) en $CH_2Cl_2$ (50 ml) lentamente a una solución enfriada con hielo de cloruro de 3-cloro-1-propansulfonilo (36,6g, 200 mmol) y 1-butanol (18,4 g, 240 m mol) en $CH_2Cl_2$ (250 ml) y la agitación se continuó por 16h. La mezcla se diluyó con $CH_2Cl_2$ (200 ml), se lavó (HCl acuoso) y se secó ($MgSO_4$) y el solvente se evaporó para obtener el producto del título **1** (40,85 g, 95%) en forma cruda como un aceite ligeramente amarillo el cual se usó para la siguiente reacción sin purificación adicional. $^1$H RMN ($CDCl_3$) δ 0,94 (t, *J* = 7,5 Hz, 3H), 1,44 (sextuplete, 2H), 1,72 (quintuplete, 2H), 2,31 (quintuplete,

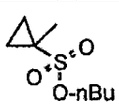
2H), 3,27(t, $J$ = 6,9 Hz, 2H), 3,68 (t, $J$ = 6,3 Hz), 4,23 (t, $J$ = 6,6 Hz, 2H).

**Paso B**: ciclopropansulfonato de 1-butilo:




Se agregaron simultáneamente soluciones de 3-cloro-1-propansulfonato de 1-butilo (4,6 g, 21,39 mmol en 25 ml THF) y de butillitio (14,7 ml, 23,53 mmol, 1,6M, THF) a THF (150 ml) a -78°C bajo una atmósfera de nitrógeno. La solución se dejó calentar a 0°C y luego se detuvo con agua (2 ml). Los volátiles se evaporaron bajo presión reducida y el residuo se extrajo con $CH_2Cl_2$ (150 ml). El extracto se lavó con agua y se secó ($MgSO_4$) y se evaporó para dar producto deseado crudo (3,23 g, 78,22%) en forma casi pura como un aceite amarillo pálido el cual se usó para el siguiente paso sin purificación adicional. $^1$H RMN (300 MHz, $CDCl_3$) δ 0,94 (t, J = 7,5 Hz, 3H), 1,07 (m, 2H), 1,25 (m, 2H), 1,45(sextuplete, 2H), 1,74(quintuplete, 2H), 2,45 (hepteto, 1H), 4,23 (t, J = 6,6 Hz, 2H).

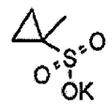
**Paso C**: 1-Metil-ciclopropansulfonato de butilo:




A una solución de ciclopropansulfonato de 1-butilo (1 g, 5,58 mmol) en THF (15 ml) se agregó lentamente una solución de butillitio ( 3,84 ml, 6,14 mmol, 1,6M, THF) a -78°C bajo

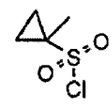
una atmósfera de nitrógeno. Luego de 15 minutos se agregó MeI (0,72 ml, 11,16 mmol) y la solución se dejó calentar a 0°C y se detuvo con agua (1 ml). Los volátiles se evaporaron bajo presión reducida y el residuo se extrajo con $CH_2Cl_2$ (100 ml). El extracto se lavó con agua, se secó ($MgSO_4$) y se evaporó. El residuo se purificó sobre cromatografía sobre gel de sílice (eluyentes: hexano/ $CH_2Cl_2$) para obtener el producto del título (0,59 g, 55,0%) como un aceite incoloro. $^1H$ RMN (300 MHz, $CDCl_3$) δ 0,84 (m, 2H), 0,95 (t, J = 7,2 Hz, 3H), 1,43 (m, 4H), 1,53 (s, 3H), 1,74(m, 2H), 4,21 ((t, J = 6,6 Hz, 2H).

**Paso D:** 1-metil-ciclopropansulfonato de 1-potasio:



Una mezcla de 1-Metil-ciclopropansulfonato de 1-butilo (0,386 g, 2 mmol) y tiocianato de potasio (0,194 g, 2 mmol) en DME (5 ml) y agua (5 ml) se sometió a reflujo por 16h. Los volátiles se evaporaron para obtener el sulfonato crudo (0,348g, cuantitativo) el cual se secó bajo vacío a 50°C por 16h. El producto crudo se usó en la siguiente reacción sin purificación adicional. $^1H$ RMN (300 MHz, $D_2O$) δ 0,56 (t, *J* = 6,3 Hz, 2H), 0,96 (t, *J* = 6,3 Hz, 2H), 1,26 (s, 3H).

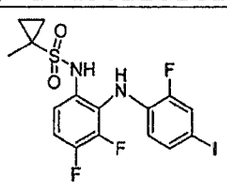
**Paso E:** cloruro de 1-metil-ciclopropansulfonilo:



679

Una solución de 1-metil-ciclopropansulfonato de 1-potasio (0,348 g, 2 mmol), cloruro de tionilo (5 ml) y DMF (5 gotas) se sometió a reflujo a 60°C por 16h. Los volátiles se evaporaron bajo presión reducida y el residuo se extrajo con $CH_2Cl_2$ (50 ml). El extracto se lavó con agua, se secó ($MgSO_4$) y se evaporó para obtener el producto crudo como un aceite gomoso amarillo el cual se usó en la siguiente reacción sin purificación adicional.

**Paso F:** N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-1-metilciclopropan-1-sulfonamida:

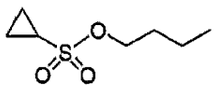


De acuerdo con el procedimiento general B, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)bencen-1,2-diamina con cloruro de 1-metil-ciclopropansulfonilo para obtener el producto deseado. $^1$H RMN (300 MHz, $CDCl_3$): δ 7,42 (dd, *J* = 1,8 & 10,5 Hz, 1H), 7,36 (ddd, *J* = 2,4, 4,5 & 9,0 Hz, 1H), 7,27 (d, *J* = 6,0 Hz, 1H), 7,07 (dd, *J* = 9,3 & 17,7 Hz, 1H), 6,24 (dt, *J* = 2,1, 8,7 & 17,4 Hz, 1H), 5,86 (br s, 1H), 1,43 (s, 3H), 1,33 (t, *J* = 5,4 Hz, 2H), 0,75 (dd, *J* = 5,1 & 6,3 Hz, 2H); *m/z* = 481 $[M-1]^-$.

Ejemplo 13

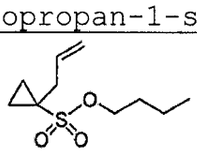
**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida:**

**Paso A**: Ciclopropansulfonato de butilo:



Se disolvió cloruro de ciclopropansulfonilo (5 g, 35 mmol, 1 eq) en un exceso de BuOH (20 ml), la mezcla de la reacción se enfrió a -10°C y se agregó piridina (5,8 ml, 70 mmol, 2 eq) lentamente por goteo. La mezcla se calentó lentamente a temperatura ambiente y se agitó durante la noche. El solvente se eliminó bajo presión reducida y el sólido blanco resultante se disolvió en $CHCl_3$. La fase orgánica se lavó con agua, salmuera y se secó (MgSO4) y se concentró para dar un aceite (4,8 g, 24,9 mmol, 71%). $^1H$ RMN (300 MHz, $CDCl_3$): δ 4,25 (t, 2H), 2,46 (m, 1H), 1,74 (m, 2H), 1,45 (m, 2H), 1,25 (dd, 2H), 1,09 (dd, 2H), ,93 (t, 3H).

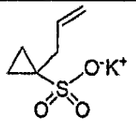
**Paso B**: 1-alilciclopropan-1-sulfonato de butilo:



A una solución de 1-ciclopropansulfonato de butilo (4,8 g, 24,9 mmol) en THF a -78°C se agregó simultáneamente solución de butillitio (15,6 ml, 24,9 mmol, 1,6M, THF) y yoduro de alilo (24,9 mmol) bajo una atmósfera de nitrógeno. La mezcla de la reacción se agitó 2 horas a -78°C y 3 horas a temperatura ambiente. Los volátiles se evaporaron bajo presión reducida y el residuo se extrajo con $CH_2Cl_2$ (100

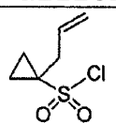
ml). El extracto se lavó con agua, se secó ($MgSO_4$) y se evaporó. El residuo se purificó sobre cromatografía sobre gel de sílice (eluyentes: hexano/ $CH_2Cl_2$) para obtener el producto del título (3,75 g, 69,0%) como un aceite incoloro. $^1H$ RMN (300 MHz, $CDCl_3$): δ 5,6 (m, 1H), 5,13-5,08 (t, 2H), 4,21 (t, 2H), 2,65 (d, 2H), 1,7 (m, 2H), 1,4 (m, 4H), ,93 (m, 5H).

**Paso C**: 1-alilciclopropan-1-sulfonato de potasio:




Una mezcla de 1-metil-ciclopropansulfonato de 1-butilo (3,75 g, 17,2 mmol) y tiocianato de potasio (1,7 g, 17,2 mmol) en DME (20 ml) y agua (20 ml) se sometió a reflujo por 16h. Los volátiles se evaporaron para obtener el sulfonato crudo (3,44g, cuantitativo) el cual se secó bajo vacío a 50°C por 16h. El producto crudo se usó en la siguiente reacción sin purificación adicional. $^1H$ RMN ($CDCl_3$): δ 5,6 (m, 1H), 4,91-4,85 (dd, 2H), 2,471-2,397 (d, 2H), 0,756 (m, 2H), 0,322 (m, 2H).

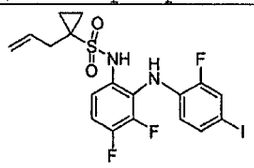
**Paso D**: cloruro de 1-alilciclopropan-1-sulfonilo:




Una solución de 1-alilciclopropan-1-sulfonato de potasio (3,44 g, 17,2 mmol), cloruro de tionilo (10 ml) y DMF (5 gotas) se sometió a reflujo a 60°C por 16h. Los volátiles

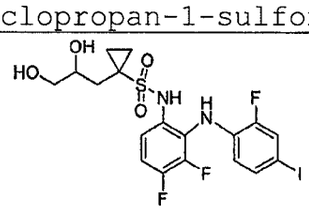
se evaporaron bajo presión reducida y el residuo se extrajo con $CH_2Cl_2$ (50 ml). El extracto se lavó con agua, se secó ($MgSO_4$) y se evaporó para obtener el producto crudo como un aceite gomoso amarillo el cual se lavó con hexano y se usó en la siguiente reacción sin purificación adicional (2,7 g, 15 mmol, 87%). $^1$HRMN (300 MHz, $CDCl_3$): δ 5,728 (m, 1H), 5,191 (t, 2H), 2,9 (d, 2H), 0,756 (m, 2H), 0,322 (m, 2H).

**Paso E**: 1-alil-N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)ciclopropan-1-sulfonamida:



De acuerdo con el procedimiento general B, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)bencen-1,2-diamina con cloruro de 1-alilciclopropan-1-sulfonilo para obtener el producto deseado. *m/z* = 507 $[M-1]^-$.

**Paso F**: N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida:



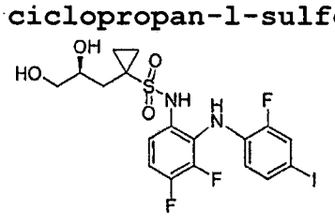
Se disolvió 1-alil-N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)ciclopropan-1-sulfonamida (0,77 g, 1,52 mmol) y N-óxido de 4-metilmorfolina (0,18 g, 1,52 mmol) en

683

THF (50 ml). Se agregó tetróxido de osmio a temperatura ambiente (0,152 mmol, 0,965 ml, 4% en $H_2O$) y la mezcla de la reacción se agitó a temperatura ambiente por 16 horas. Se agregó EtOAc, la fase orgánica se lavó con agua, se secó ($MgSO_4$) y se concentró bajo presión reducida. El residuo se purificó sobre cromatografía sobre gel de sílice (eluyentes: EtOAc/ MeOH) para obtener el producto del título (0,65 g, 79%). $^1$H RMN (300 MHz, $CDCl_3$ + $D_2O$): δ 7,38 (dd, *J* = 1,8 & 10,5 Hz, 1H), 7,36 (ddd, *J* = 2,4, 5,1 & 9,3 Hz, 1H), 7,25 (d, *J* = 8,7 Hz, 1H), 7,02 (dd, *J* = 9,0 & 17,7 Hz, 1H), 6,27 (dt, *J* = 3,0, 8,7 & 17,4 Hz, 1H), 3,92 (m, 1H), 3,54 (dd, *J* = 3,9 & 11,1 Hz, 1H), 3,39 (dd, *J* = 6,6 & 11,1 Hz, 1H), 2,16 (dd, *J* = 9,6 & 15,9 Hz, 1H), 1,59 (d, *J* = 14,1 Hz, 1H), 1,41 (m, 1H), 1,26 (m, 1H), 0,83 (m, 2H); *m/z* = 542 $[M-1]^-$.

Ejemplo 14

**(S)-N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida:**

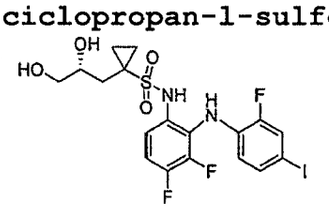



El isómero S puro se obtuvo mediante separación HPLC quiral de la mezcla racémica (ejemplo 13). $^1$H RMN (300 MHz, $CDCl_3$ + $D_2O$): δ 7,38 (dd, *J* = 1,8 & 10,5 Hz, 1H), 7,36 (ddd, *J* = 2,4, 5,1 & 9,3 Hz, 1H), 7,25 (d, *J* = 8,7 Hz, 1H), 7,02 (dd, *J* = 9,0 & 17,7 Hz, 1H), 6,27 (dt, *J* = 3,0, 8,7 & 17,4

Hz, 1H), 3,92 (m, 1H), 3,54 (dd, *J* = 3,9 & 11,1 Hz, 1H), 3,39 (dd, *J* = 6,6 & 11,1 Hz, 1H), 2,16 (dd, *J* = 9,6 & 15,9 Hz, 1H), 1,59 (d, *J* = 14,1 Hz, 1H), 1,41 (m, 1H), 1,26 (m, 1H), 0,83 (m, 2H); *m/z* = 542 $[M-1]^-$.

Ejemplo 15

**(R)-N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida:**

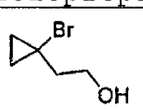



El isómero R puro se obtuvo mediante separación HPLC quiral de la mezcla racémica (ejemplo 13). $^1$H RMN (300 MHz, $CDCl_3$ + $D_2O$): δ 7,38 (dd, *J* = 1,8 & 10,5 Hz, 1H), 7,36 (ddd, *J* = 2,4, 5,1 & 9,3 Hz, 1H), 7,25 (d, *J* = 8,7 Hz, 1H), 7,02 (dd, *J* = 9,0 & 17,7 Hz, 1H), 6,27 (dt, *J* = 3,0, 8,7 & 17,4 Hz, 1H), 3,92 (m, 1H), 3,54 (dd, *J* = 3,9 & 11,1 Hz, 1H), 3,39 (dd, *J* = 6,6 & 11,1 Hz, 1H), 2,16 (dd, *J* = 9,6 & 15,9 Hz, 1H), 1,59 (d, *J* = 14,1 Hz, 1H), 1,41 (m, 1H), 1,26 (m, 1H), 0,83 (m, 2H); *m/z* = 542 $[M-1]^-$.

Ejemplo 16

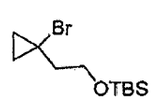
**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-1-(2-hidroxietil)ciclopropan-1-sulfonamida:**

**Paso A:** 2-d -bromociclopropil)etanol:



A una solución de dietilcinc puro (3,3 ml, 3,977 g, 30 mmol) en 100 ml de DCM anhidro se agregó muy lentamente ácido trifluoroacético (2,31 ml, 3,4188 g, 30 mmol) por goteo a 0°C. (Precaución: evolución violenta de gas, exotérmica!). Luego de completar la adición del TFA, la suspensión se agitó por 20 min a la misma temperatura, seguido por la adición de diyodometano (2,45 ml, 8,134 g, 30,4 mmol). Se agitó adicionalmente a 0°C por 20 min, y luego se agregó una solución de 3-bromobut-3-en-1-ol (1 ml, 1,523 g, 10,1 mmol) en 10 ml de DCM a la misma temperatura. Luego de completarse la adición, la mezcla se calentó a temperatura ambiente y se agitó por 4 horas. La mezcla se detuvo con 100 ml de MeOH y 40 ml de salmuera, y se agitó adicionalmente por 30 min. Los solventes se redujeron, y el residuo se extrajo usando $CHCl_3$ / ac. $NH_4Cl$. Las capas orgánicas se recogieron, se lavó con salmuera y agua, y el solvente se eliminó para dar 2-(1-bromociclopropil)-etanol en pureza suficiente (1,6564 g, 100%). $^1$H-RMN (500 MHz, $CDCl_3$): δ = 3,90-3,83 (t, 2H), 1,91-1,87 (t, 2H), 1,71 (s, 1H, br), 1,14-1,09 (m, 2H), 0,83-0,79 (m, 2H).

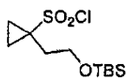
**Paso B**: 2-(1-bromociclopropil)etanol protegido con TBS:




A una solución del alcohol ciclopropílico (Paso A)

(1,303 g, 7,95 mmol) en 30 ml de DCM anhidro se agregó piridina anhidra (1,2 ml, 1,1736 g, 14,8 mmol) y TBSOTf (2,7 ml, 3,1077 g, 11,76 mol) y la solución se agitó a temperatura ambiente por 16h. Se extrajo con $CHCl_3$ / salmuera y la fracción orgánica se secó con $MgSO_4$. El solvente se redujo y el producto crudo se purificó usando cromatografía flash de columna (Si, $CHCl_3$ / hexanos 1:10, $R_f$ = 0,4). Rendimiento: 0,796 g, 36%. $^1$H-RMN (500 MHz, $CDCl_3$): $\delta$ = 3,95-3,75 (t, 2H), 1,95-1,85 (t, 2H), 1,15-1,05 (m, 2H), 0,95-0,80 (m, HH), 0,15-0,05 (s, 6H).

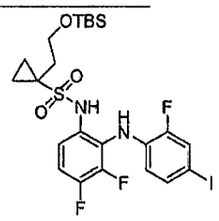
**Paso C:** 2-(1-clorosulfonilciclopropil)etanol protegido con TBS:




A una solución del bromuro de ciclopropilo preparado en paso B (1,1227 g, 4,04 mmol) en 15 ml de éter dietílico anhidro se agregó una solución 1,7 M de t-BuLi en pentano (4,8 ml, 8,16 mmol) a -78°C. La solución se agitó por 30 min a esta temperatura, y luego se transfirió por medio de un cánulo de transferencia a una solución de cloruro de sulfurilo recién destilado (0,65 ml, 1,029 g, 8,1 mmol) en 8 ml de éter dietílico a -78°C. La suspensión amarilla se calentó a temperatura ambiente. El solvente se eliminó, y el residuo se secó al vacío para eliminar el exceso de cloruro de sulfurilo. Luego, el residuo se extrajo dos veces con

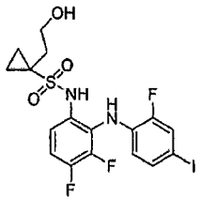
hexano, y luego de la filtración el solvente se evaporó al vacío para dar el cloruro de sulfonilo en pureza suficiente como un aceite incoloro. Rendimiento: 870 mg (72%). $^1$H-RMN (300 MHz, $CDCl_3$): δ = 3,95-3,85 (t, 2H), 2,35-2,25 (t, 2H), 1,80-1,70 (m, 2H), 1,45-1,38 (m, 2H), 0,90 (s, 9H), 0,10 (s, 6H).

**Paso D:** N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-1-(2-hidroxietil)ciclopropan-1-sulfonamida protegida con TBS:




De acuerdo con el procedimiento general B, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)bencen-1,2-diamina con el cloruro de ciclpropilsulfonilo preparado en paso C para obtener el producto deseado. $^1$H-RMN (300 MHz, $CDCl_3$): δ = 7,44-7,39 (dd, 1H), 7,32-7,24 (m, 2H), 7,1-6,98 (q, 1H), 6,34-6,24 (m, 1H), 6,16 (s, 1H, br), 3,85-3,75 (t, 2H), 2,15-2,00 (t, 2H), 1,35-1,20 (m, 2H), 0,95-0,75 (m, 1 1H), 0,10 (s, 6H); *m/z* = 625 $[M-1]^-$.

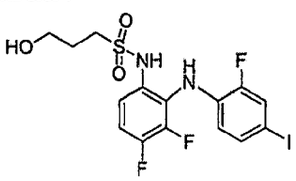
**Paso E:** N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-1-(2-hidroxietil)ciclopropan-1-sulfonamida:



A una solución de la sulfonamida protegida con TBS preparada en paso D (21 mg, 0,033 mmol) en 1 ml de THF se agregó 0,1 ml de solución acuosa 2N de HCl a 0°C y la solución se agitó por 2 h. Los solventes se redujeron y el residuo se extrajo usando solución acuosa de $NaHCO_3$ y EtOAc. Las fracciones orgánicas se secaron con $MgSO_4$ y los volátiles se eliminaron. El producto crudo se purificó usando cromatografía flash de columna (Si, $CHCl_3$ / MeOH 10:1, $R_f$ = 0,45) para dar el producto puro. Rendimiento: 16,9 mg (100%). $^1$H-RMN (300 MHz, $CDCl_3$): δ = 7,44-7,39 (dd, 1H), 7,32-7,24 (m, 2H), 7,1-6,98 (q, 1H), 6,34-6,24 (m, 1H), 6,16 (s, 1H, br), 3,85-3,75 (t, 2H), 2,15-2,00 (t, 2H), 1,35-1,20 (m, 2H), 0,95-0,85 (m, 2H); *m/z* = 511 $[M-1]^-$.

Ejemplo 17

**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-3-hidroxipropan-1-sulfonamida:**

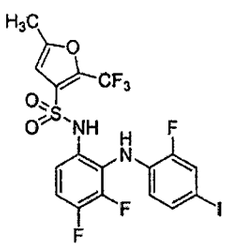


A una solución de 3-cloro-N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-propan- 1-sulfonamida (69,4 mg, 0,138 mmol) en una mezcla de 8 ml de 1,4-dioxano y 2 ml de $H_2O$ se

agregó KOH en polvo (0,674 g, 12,0 mmol) y la mezcla se calentó a temperatura de reflujo por 3 días. Se extrajo usando EtOAc / salmuera, la fracción orgánica se secó con $Na_2SO_4$ y los volátiles se eliminaron. El residuo se purificó usando cromatografía flash de columna (Si, DCM / MeOH 5:1, $R_f$ = 0,3). Rendimiento: 41 mg (62%). $^1$H-RMN (500 MHz, MeOH [d4]): δ = 7,38- 7,21 (d, 1H), 7,23-7,21 (d, 1H), 7,06-7,00 (q, 1H), 6,52-6,50 (m, 1H), 6,17-6,13 (t, 1H), 3,30-3,27 (t, 2H), 2,86-2,83 (t, 2H), 2,05-2,00 (m, 2H); *m/z* = 485 $[M-1]^-$.

Ejemplo 18

**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-2-metil-5- (trifluorometil)furan-3-sulfonamida:**

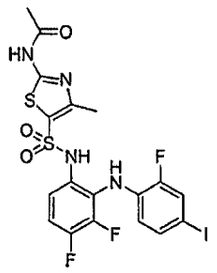



De acuerdo con el procedimiento general B, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)bencen-1,2-diamina (0,182 mmol) con cloruro de 2-metil-5-(trifluorometil)furan-3-sulfonilo (0,5 mmol) para formar N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-2-metil-5-(trifluorometil)furan-3-sulfonamida. $^1$H RMN ($CDCl_3$) δ 2,2 (s, 3H), 5,3 (s, 1H), 6,0 (dt, 1H), 6,8 (s, 1H), 6,95 (s, 1H), 7,0-7,3 (m, 3H), 7,4 (dd, 1H).

Ejemplo 19

670

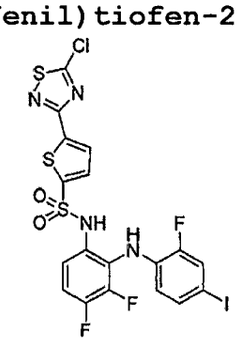
**N-(5-(N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)sulfamoil)-metiltiazol-2-il)acetamida:**



De acuerdo con el procedimiento general B, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)bencen-1,2-diamina (0,182 mmol) con cloruro de 2-acetamido-4-metiltiazol-5-sulfonilo (0,5 mmol) para obtener N-(5-(N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)sulfamoil)-4-metiltiazol-2-il)acetamida . $^1$H RMN ($CDCl_3$) δ 2,1 (s, 3H), 2,2 (s, 3H), 5,9 (dt, 1H), 6,05 (s, 1H), 7,0-7,6 (m, 3H), 7,4 (dd, 1H), 8,0 (s, 1H).

Ejemplo 20

**5-(5-Cloro-1,2,4-tiadiazol-3-il)-N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)tiofen-2-sulfonamida:**

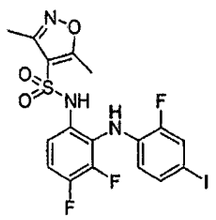


De acuerdo con el procedimiento general B, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)bencen-1,2-diamina (0,182 mmol) con cloruro de 5-(5-cloro-1,2,4-

tiadiazol-3-il)tiofen-2-sulfonilo (0,5 mmol) para obtener 5-(5-cloro-1,2,4-tiadiazol-3-il)-N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)tiofen-2-sulfonamida. $^1$H RMN (300 MHz, $CDCl_3$) δ 5,8 (dt, 1H), 5,95 (s, 1H), 6,95 (d, 1H),7,4 (m, 2H), 7,6 (d, 1H), 7,8 (s, 1H).

Ejemplo 21

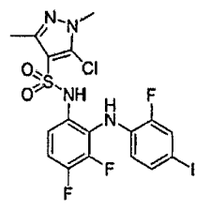
**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-3,5dimetilisoxazol-4-sulfonamida:**



De acuerdo con el procedimiento general B, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenilo) bencen-1,2-diamina (0,182 mmol) con cloruro de 3,5-dimetilisoxazol-4-sulfonilo (0,5 mmol) para obtener N-(3,4-difluoro-2-(2-fluoro-4-yodofenilo amino)fenil)-3,5dimetilisoxazol-4-sulfonamida. $^1$H RMN (300 MHz, $CDCl_3$)) δ 2,2 (s, 3H), 2,4 (s, 3H), 5,8 (s, 1H), 6,0 (dt, 1H), 5,95 (s, 1H), 6,9 (s, 1H),7,0 (q, 1H), 7,2 (m, 3H), 7,4 (dd, 1H).

Ejemplo 22

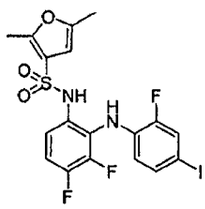
**5-Cloro-N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-1,3-dimetil- lH-pirazol-4-sulfonamida:**



De acuerdo con el procedimiento general B, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenilo) bencen-1,2-diamina (0,182 mmol) con cloruro de 5-cloro-1,3-dimetil-1H-pirazol-4-sulfonilo (0,5 mmol) para obtener 5-cloro-N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino) fenil)-1,3-dimetil-1H-pirazol-4-sulfonamida. $^1$H RMN (300 MHz, $CDCl_3$) δ 2,1 (s, 3H), 3,6 (s, 3H), 5,8 (s, 1H), 5,95 (dt, 1H), 7,0 (q, 1H), 7,2 (d, 1H), 7,3 (m, 2H), 7,4 (dd, 1H).

Ejemplo 23

**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-2,5-dimetilfuran-3-sulfonamida:**

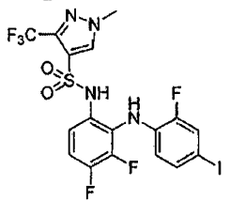


De acuerdo con el procedimiento general B, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenilo) bencen-1,2-diamina (0,182 mmol) con cloruro de 2,5-dimetilfuran-3-sulfonilo (0,5 mmol) para obtener N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino) fenil)-2,5-dimetilfuran-3-sulfonamida. $^1$H RMN (300 MHz, $CDCl_3$)) δ 2,2 (s, 3H), 2,3 (s, 3H), 5,8 (s, 1H), 6,0 (dt, 1H), 6,8 (s, 1H), 7,0 (q, 1H), 7,2 (d, 1H), 7,3 (m, 2H), 7,4 (dd, 1H).

673

Ejemplo 24

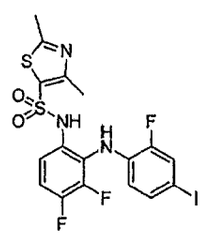
**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-1-metil-3-(trifluorometil)-1H-pirazol-4-sulfonamida:**



De acuerdo con el procedimiento general B, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)bencen-1,2-diamina (0,182 mmol) con cloruro de 1-metil-3-(trifluorometil)-1H-pirazol-4-sulfonilo (0,5 mmol) para obtener N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-1-metil-3-(trifluorometil)-1H-pirazol-4-sulfonamida. $^1$H RMN (300 MHz, $CDCl_3$) δ 3,8 (s, 3H), 5,7 (s, 1H), 6,0 (dt, 1H), 7,0 (q, 1H), 7,2 (m, 2H), 7,4 (dd, 1H), 7,8 (s, 1H).

Ejemplo 25

**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-2,4-dimetiltiazol-5-sulfonamida:**

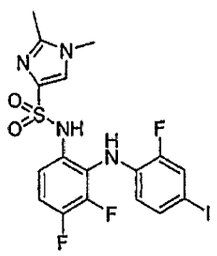


De acuerdo con el procedimiento general B, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenilo) bencen-1,2-diamina (0,182 mmol) con cloruro de 2,4-dimetiltiazol-5-sulfonilo (0,5 mmol) para obtener N-(3,4-difluoro-2-(2-

fluoro-4-yodofenilamino)fenil)-2,4-dimetiltiazol-5-sulfonamida. $^1$H RMN (300 MHz, $CDCl_3$)) δ 2,3 (s, 3H), 2,6 (s, 3H), 5,7 (s, 1H), 5,9 (dt, 1H), 7,1 (q, 1H), 7,2 (d, 1H), 7,3 (m, 1H), 7,4 (d, 1H), 7,4 (s, 1H).

Ejemplo 26

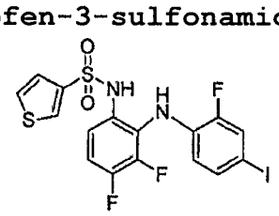
**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-1,2-dimetil-1H-imidazol-4-sulfonamida:**



De acuerdo con el procedimiento general B, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)bencen-1,2-diamina con cloruro de 1,2-dimetil-1H-imidazol-4-sulfonilo para obtener el compuesto del título. $^1$H RMN (300 MHz, $CDCl_3$): δ 7,95 (br s, 1H), 7,37 (dd, $J$ = 1,8 & 10,8 Hz, 1H), 7,32-7,14 (m, 3H), 6,98 (dd, $J$ = 9,6 & 17,7 Hz, 1H), 5,87 (dt, $J$ = 4,2, 9,0 & 17,4 Hz, 1H), 5,55 (br s, 1H), 3,49 (s, 3H), 2,31 (s, 3H).

Ejemplo 27

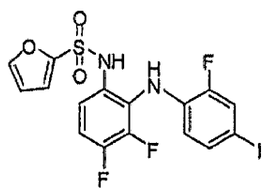
**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)tiofen-3-sulfonamida:**



De acuerdo con el procedimiento general B, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)bencen-1,2-diamina con cloruro de tiofen-3-sulfonilo para obtener el compuesto del título. $^1$H RMN (300 MHz, $CDCl_3$): δ 8,00 (dd, *J* = 1,2 & 3,3 Hz, 1H), 7,45 (dd, *J* = 0,9 & 5,1 Hz, 1H), 7,35 (m, 2H), 7,27 (m, 2H), 6,91 (dd, *J* = 9,3 & 17,1 Hz, 1H), 6,64 (ddd, *J* = 2,1, 4,8 & 8,7 Hz, 1H), 6,34 (dt, *J* = 5,4, 8,7 & 14,1 Hz, 1H), 5,98 (br d, *J* = 2,1 Hz, $D_2O$ intercambiable, 1H).

Ejemplo 28

**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)furan-2-sulfonamida:**

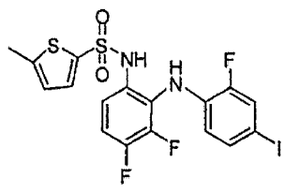



De acuerdo con el procedimiento general B, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)bencen-1,2-diamina con cloruro de furan-2-sulfonilo para obtener el compuesto del título. $^1$H RMN (300 MHz, $CDCl_3$): δ 7,53 (br s, $D_2O$ intercambiable, 1H), 7,38 (dd, *J* = 1,8 & 10,5 Hz, 1H), 7,30 (d, *J* = 8,4 Hz, 1H), 7,21 (d, *J* = 3,0 Hz, 1H), 6,96 (dd, *J* = 8,7 & 16,5 Hz, 1H), 6,87 (ddd, *J* = 1,8, 5,1 & 9,0 Hz, 1H), 6,53 (dd, *J* = 1,8 & 3,6 Hz, 1H), 6,44 (dt, *J* = 5,1, 8,7 & 13,8 Hz, 1H), 6,22 (br s, $D_2O$ intercambiable, 1H).

Ejemplo 29

676

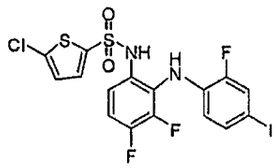
**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-5-metiltiofen-2- sulfonamida:**



De acuerdo con el procedimiento general B, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)bencen-1,2-diamina con cloruro de 5-metiltiofen-2-sulfonilo para obtener el compuesto del título. $^1$H RMN (300 MHz, $CDCl_3$): δ 7,34 (dd, *J* = 0,9 & 10,2 Hz, 1H), 7,30 (ddd, *J* = 2,1, 4,8 & 9,0 Hz, 1H), 7,25 (d, *J* = 3,9 Hz, 1H), 7,07 (m, 2H), 6,65 (dd, *J* = 1,2 & 3,9 Hz, 1H), 5,89 (dt, *J* = 2,4, 8,7 & 17,4 Hz, 1H), 5,54 (br s, $D_2O$ intercambiable, 1H), 2,46 (s, 3H).

Ejemplo 30

**5-Cloro-N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)tiofen-2-sulfonamida:**

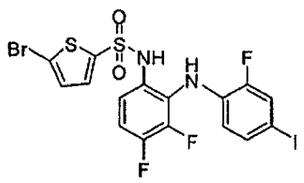


De acuerdo con el procedimiento general B, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)bencenol,2-diamina con cloruro de 5-clorotiofen-2-sulfonilo para obtener el compuesto del título. $^1$H RMN (300 MHz, $CDCl_3$): δ 7,38 (dd, *J* = 1,5 & 10,2 Hz, 1H), 7,32 (ddd, *J* = 2,1, 5,1 & 9,3 Hz, 1H), 7,25 (d, *J* = 3,9 Hz, 1H), 7,10 (dd, *J* = 9,0 &

18,6 Hz, 3H), 6,84 (d, $J$ = 4,2 Hz, 1H), 5,86 (dt, $J$ = 1,8, 8,7 & 17,4 Hz, 1H), 5,49 (br s, $D_2O$ intercambiable, 1H).

Ejemplo 31

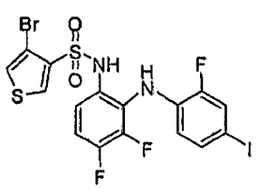
**5-Bromo-N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)tiofen-2-sulfonamida:**



De acuerdo con el procedimiento general B, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)benceno1,2-diamina con cloruro de 5-bromotiofen-2-sulfonilo para obtener el compuesto del título. $^1$H RMN (300 MHz, $CDCl_3$): δ 7,39-7,29 (m, 2H), 7,20-7,05 (m, 3H), 6,96 (d, $J$ = 3,6 Hz, 1H), 5,85(dt, $J$ = 2,1, 9,0 & 17,4 Hz, 1H), 5,54 (br s, 1H).

Ejemplo 32

**4-Bromo-N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)tiofen-3-sulfonamida:**



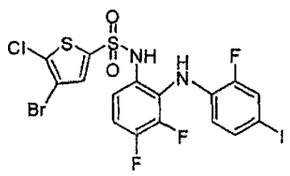
De acuerdo con el procedimiento general B, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)benceno1,2-diamina con cloruro de 4-bromotiofen-3-sulfonilo para obtener el compuesto del título. $^1$H RMN (300 MHz, $CDCl_3$): δ 7,48 (br m, 2H), 7,39 (dd, $J$ = 1,8 & 10,5 Hz, 1H), 7,28

678

(ddd, $J$ = 2,4, 4,8 & 9,0 Hz, 1H), 7,17 (d, $J$ = 8,4 Hz, 1H), 7,02 (m, 1H), 6,02 (dt, $J$ = 2,4, 8,7 & 17,4 Hz, 1H), 5,68 (br s, 1H).

Ejemplo 33

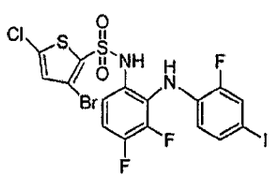
**4-Bromo-5-cloro-N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)tiofen-2- sulfonamida:**



De acuerdo con el procedimiento general B, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)benceno1,2-diamina con cloruro de 4-bromo-5-clorotiofen-2-sulfonilo para obtener el compuesto del título. $^1$H RMN (300 MHz, $CDCl_3$): δ 7,42-7,34 (m, 2H), 7,25 (br m, 3H), 7,13 (dd, $J$ = 9,0 & 17,1 Hz, 1H), 6,02 (dt, $J$ = 2,4, 6,6 & 17,4 Hz, 1H), 5,52 (br s, 1H).

Ejemplo 34

**3-Bromo-5-cloro-N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino) fenil)tiofen-2- sulfonamida:**



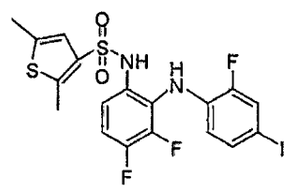
De acuerdo con el procedimiento general B, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)benceno1,2-diamina con cloruro de 3-bromo-5-clorotiofen-2-sulfonilo

679

para obtener el compuesto del título. $^1$H RMN (300 MHz, $CDCl_3$): δ 7,41 (dd, *J* = 2,1 & 10,5 Hz, 1H), 7,35 (br m, 2H), 7,31 (dd, *J* = 2,1 & 4,2 Hz, 1H), 7,19 (d, *J* = 8,7 Hz, 1H), 7,08 (dd, *J* = 9,0 & 17,4 Hz, 1H), 6,02(dt, *J* = 2,1, 8,4 & 17,1 Hz, 1H), 5,59 (br s, 1H).

Ejemplo 35

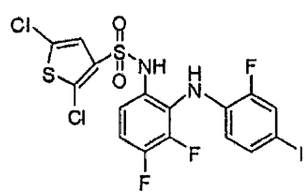
**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-2,5-dimetiltiofen-3-sulfonamida:**



De acuerdo con el procedimiento general B, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)benceno1,2-diamina con cloruro de 2,5-dimetiltiofen-3-sulfonilo para obtener el compuesto del título. $^1$H RMN (300 MHz, $CDCl_3$): δ 7,39 (dd, *J* = 1,8 & 10,2 Hz, 1H), 7,24-7,16 (br m, 2H), 7,13 (dd, *J* = 9,0 & 17,4 Hz, 1H), 6,77 (d, *J* = 9,6 Hz, 1H), 5,98 (dt, *J* = 2,4, 8,7 & 17,4 Hz, 1H), 5,55 (br s, 1H), 2,33 (s, 6H).

Ejemplo 36

**2,5-Dicloro-N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)tiofen-3-sulfonamida:**

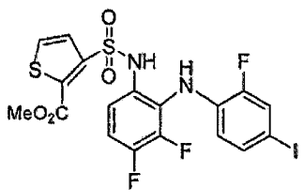


680

De acuerdo con el procedimiento general B, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)benceno1,2-diamina con cloruro de 2,5-diclorotiofen-3-sulfonilo para obtener el compuesto del título. $^1$H RMN (300 MHz, $CDCl_3$): δ 7,41(dd, *J* = 1,5 & 10,5 Hz, 1H), 7,28-7,20 (m, 2H), 7,08 (dd, *J* = 9,0 & 17,4 Hz, 2H), 6,99 (s, 1H), 6,03 (dt, *J* = 2,1, 8,7 & 17,4 Hz, 1H), 5,56 (br s, 1H).

Ejemplo 37

**3-(N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenilo) sulfamoil)tiofen-2-carboxilato de metilo:**

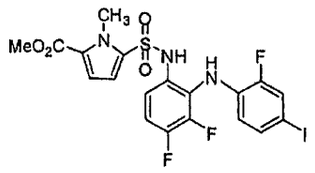



De acuerdo con el procedimiento general B, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)benceno 1,2-diamina con 3-(clorosulfonil)tiofen-2-carboxilato de metilo para obtener el compuesto del título. $^1$H RMN (300 MHz, $CDCl_3$): δ 8,58 (s, 1H), 7,43 (dd, *J* = 5,1 & 10,8 Hz, 2H), 7,35 (dd, *J* = 1,8 & 10,2 Hz, 1H), 7,31 (ddd, *J* = 2,1, 4,2 & 9,3 Hz, 1H), 7,04 (m, 2H), 5,88 (dt, *J* = 2,7, 8,7 & 17,4 Hz, 1H), 5,65 (br s, 1H), 3,85 (s, 3H).

Ejemplo 38

**5-(N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)sulfamoil)-1-metil- 1H-pirrol-2-carboxilato de metilo:**

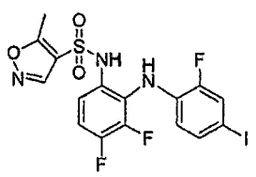
681



De acuerdo con el procedimiento general B, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)benceno1,2-diamina con 5-(clorosulfonil)-1-metil-1H-pirrol-2-carboxilato de metilo para obtener el compuesto del título. $^1$H RMN (300 MHz, $CDCl_3$): δ 7,37 (dd, *J* = 1,8 & 10,5 Hz, 1H), 7,29 (m, 2H), 7,12-6,94 (m, 4H), 5,87 (dt, *J* = 1,8, 8,4 & 17,4 Hz, 1H), 5,56 (br s, 1H), 3,65 (s, 3H), 3,75 (s, 3H).

Ejemplo 39

**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-5-metilisoxazol-4-sulfonamida:**

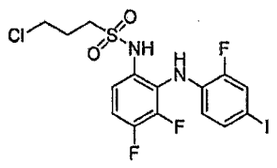


De acuerdo con el procedimiento general A, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)benceno1,2-diamina con el cloruro de sulfonilo correspondiente para obtener el compuesto del título. Rendimiento: 22%. *m/z*= 508 $[M-1]^-$.

Ejemplo 40

**3-Cloro-N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)propan-1-sulfonamida:**

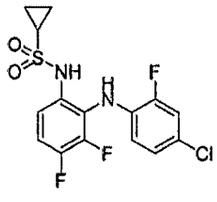
682



De acuerdo con el procedimiento general A, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)bencen-1,2-diamina con cloruro de 3-cloropropan-1-sulfonilo para obtener el producto deseado. $^1$H RMN (500 MHz, $CDCl_3$): δ = 7,39-7,38 (d, 1H), 7,35-7,34 (m, 1H), 7,27-7,26 (m, 1H), 7,10-7,0 (q, 1H), 6,63 (s, 1H, br), 6,15-6,11 (q, 1H), 5,60 (s, 1H, br), 3,60-3,56 (t, 2H), 3,22-3,20 (m, 2H), 2,22-2,16 (m, 2H).

Ejemplo 41

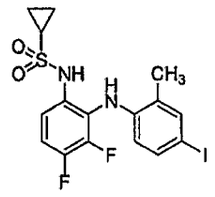
**N-(2-(4-cloro-2-fluorofenilamino)-3,4-difluorofenilo) ciclopropansulfonamida:**



Véase el ejemplo 1. $^1$H RMN (300 MHz, $CDCl_3$) δ 0,85-0,95 (m, 2H), 1,05-1,15 (ra, 2H), 2,2-2,4 (m, 1H), 5,8 (s, 1H), 6,3 (t, 1H), 6,6-7,4 (m, 5H); *m/z* = 375 $[M-1]^-$.

Ejemplo 42

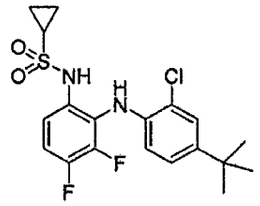
**N-(3,4-difluoro-2-(4-yodo-2-metilfenilamino)fenil)ciclopropansulfonamida:**



Véase el ejemplo 1. $^1$H RMN ($CDCl_3$) δ 0,80-1,0 (m, 2H), 1,05-1,20 (m, 2H), 1,55 (s, 3H), 2,4-2,5 (m, 1H), 5,6 (s, 1H), 6,2 (dd, 1H), 6,4 (s, 1H), 7,1 (q, 1H), 7,3-7,4 (m, 2H), 7,5 (s, 1H); *m/z* = 463 $[M-1]^-$.

Ejemplo 43

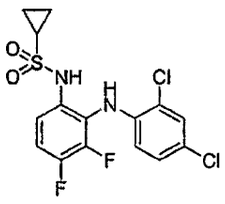
**N-(2-(4-tert-butil-2-clorofenilamino)-3,4-difluorofenilo) ciclopropansulfonamida:**



Véase el ejemplo 1. $^1$H RMN (300 MHz, $CDCl_3$) δ 0,9-1,0 (m, 2H), 1,05-1,20 (m, 2H), 1,3 (s, 9H), 2,4-2,5 (m, 1H), 5,8 (s, 1H), 6,3 (dd, 1H), 6,6 (s, 1H), 7,0-7,2 (m, 2H), 7,3-7,4 (m, 2H); *m/z* = 413 $[M-1]^-$.

Ejemplo 44

**N-(2-(2,4-diclorofenilamino)-3,4-difluorofenil)ciclopropansulfonamida:**



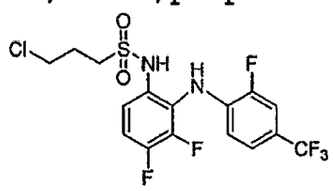
Véase el ejemplo 1. $^1$H RMN (300 MHz, $CDCl_3$) δ 0,9-1,0 (m,

683

2H), 1,05-1,20 (m, 2H), 2,4-2,5 (m, 1H), 6,0 (s, 1H), 6,3 (dd, 1H), 6,6 (s, 1H), 7,0-7,2 (m, 2H), 7,3-7,4 (m, 2H); *m/z* = 392 $[M-1]^-$.

Ejemplo 45

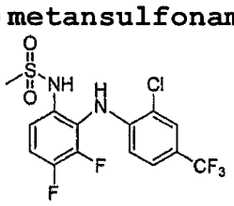
**3-Cloro-N-(3,4-difluoro-2-(2-fluoro-4-trifluorometil)fenilamino)fenil)propan- 1-sulfonamida:**



Véase el ejemplo 1. $^1$H RMN (300 MHz, $CDCl_3$): δ 7,39-7,26 (m, 2H), 7,25 (m, 1H), 7,18 (dd, *J* = 9,0 & 17,7 Hz, 1H), 6,78 (br s, $D_2O$ intercambiable, 1H), 6,50 (t, *J* = 8,1 Hz, 1H), 6,00 (br d, $D_2O$ intercambiable, *J* = 1,5 Hz, 1H), 3,63 (t, *J* = 6,0 & 6,3 Hz, 2H), 3,29 (t, *J* = 7,2 & 7,8 Hz, 2H), 2,26 (quintuplete, 2H); *m/z* = 445 $[M-1]^-$.

Ejemplo 46

**N-(3,4-difluoro-2-(2-cloro-4-trifluorometil)fenilamino)metansulfonamida:**



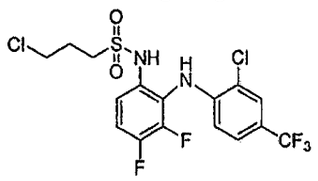
Véase el ejemplo 1. $^1$H RMN (300 MHz, $CDCl_3$): δ 7,65 (d, *J* =7,8 Hz, 1H), 7,33 (m, 2H), 7,19 (dd, *J* = 9,3 & 17,4 Hz, 1H), 6,90 (br s, $D_2O$ intercambiable, 1H), 6,45 (dd, *J* = 1,5 & 8,4 Hz, 1H), 6,39 (br s, $D_2O$ intercambiable, 1H), 3,02 (s,

684

3H); *m/z* = 399 $[M-1]^-$.

Ejemplo 47

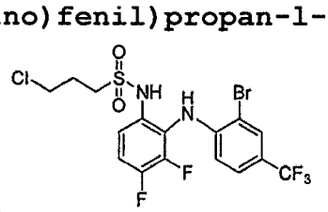
**3-Cloro-N-(3,4-difluoro-2-(2-cloro-4-trifluorometil)fenilamino)fenil)propan-1-sulfonamida:**



Véase el ejemplo 1. $^1$H RMN (300 MHz, $CDCl_3$): δ 7,66 (d, *J* = 1,5 Hz, 1H), 7,36 (m, 2H), 7,19 (dd, *J* = 9,0 & 17,4 Hz, 1H), 6,91 (br s, $D_2O$ intercambiable, 1H), 6,50 (dd, *J* = 8,4 & 1,5 Hz, 1H), 6,37 (s, $D_2O$ intercambiable, 1H), 3,62 (t, *J* = 6,0 Hz, 2H), 3,29 (t, *J* = 7,5 & 7,8 Hz, 2H), 2,27 (quintuplete, 2H); *m/z* = 462 $[M-1]^-$.

Ejemplo 48

**3-Cloro-N-(3,4-difluoro-2-(2-bromo-4-trifluorometil)fenilamino)fenil)propan-1-sulfonamida:**



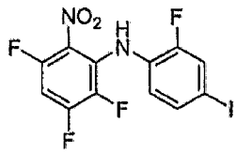
Véase el ejemplo 1. $^1$H RMN (300 MHz, $CDCl_3$): δ 7,82 (s, 1H), 7,38 (m, 2H), 7,20 (dd, *J* = 9,0 & 17,7 Hz, 1H), 6,62 (br s, $D_2O$ intercambiable, 1H), 6,43 (d, *J* = 8,4 Hz, 1H), 6,23 (s, $D_2O$ intercambiable, 1H), 3,65 (t, *J* = 6,0 Hz, 2H), 3,30 (t, *J* = 7,5 Hz, 2H), 2,28 (quintuplete, 2H); *m/z* = 506 $[M-1]^-$.

685

Ejemplo 49

**(3,4,6-trifluoro-2-(2-fluoro-4-yodo-fenilamino)-fenil)-amida del ácido ciclopropansulfónico:**

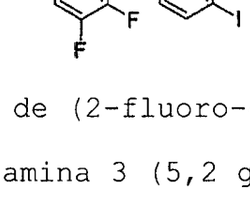
**Paso A:** (2-Fluoro-4-yodo-fenil)-(2,3,5-trifluoro-6-nitro-fenil)-amina:



Una solución agitada de 2-fluoro-4-yodoanilina (3,64 gm, 15,37 mmol) en THF seco (100 ml) bajo nitrógeno se enfrió a -78°C y se agregó una solución 1,0 M de hexametildisilazida de litio ($LiN(SiMe_3)_2$) "LHMDS" (15,37 ml, 15,37 mmol) lentamente. Esta mezcla de reacción se mantuvo en agitación a -78°C por otra hora y luego se agregó 2,3,4,6-tetrafluoronitrobenceno. La mezcla de la reacción se dejó calentar a temperatura ambiente y la agitación se continuó por otras 16 horas. Se agregó acetato de etilo (200 ml) a la mezcla de la reacción y se lavó con agua. La capa orgánica se secó sobre sulfato de sodio y se purificó adicionalmente mediante cromatografía de columna para dar sólido amarillo (3,75 gm, rendimiento: 59,24%). $M-H^+$: 410,9. $^1H$ RMN (DMSO, 300 MHz): 6,85 (t, 1H); 7,38 (d, 1H); 7,62 (m, 2H); 8,78 (s, 1H).

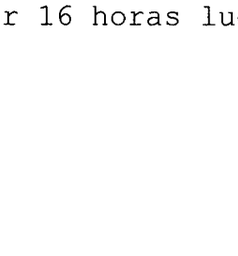
**Paso B:** 3,4,6-Trifluoro-$N^2$-(2-Fluoro-4-yodo-fenil)-bencen-1,2-diamina:

685



A la solución agitada de (2-fluoro-4-yodo-fenil)-(2,3,5-trifluoro-6-nitro-fenil)-amina 3 (5,2 gm, 12,62 mmol) en EtOH (200 ml), se agregó cloruro de amonio (10,12 gm, 189,3 mmol) y polvo de hierro (10,57 gm, 189,3 mmol). Esta mezcla de reacción se mantuvo en agitación a reflujo por 16 horas. La mezcla de la reacción se dejó enfriar y se filtró sobre celite y se concentró hasta secar. El residuo obtenido se colocó en EtOAc y se lavó con agua. La capa de EtOAc se secó sobre sulfato de sodio y se purificó adicionalmente mediante cristalización a partir de EtOH para dar un sólido blanco opaco (3,2 gm, rendimiento: 66,39%). $M-H^+$: 381,1. $^1H$ RMN (DMSO, 300 MHz): 5,0 (s, 2H); 6,2 (t, 1H); 7,2 - 7,3 (m, 2H); 7,45 (s, 1H); 7,5 (d, 1H).

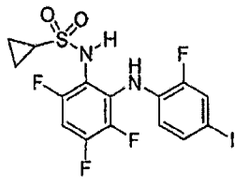
**Paso C:** 4,6,7-Trifluoro-1-('2-Fluoro-4-yodo-fenil)-1,3,-dihidrobenzoimidazol-2-ona:



A la solución agitada de 3,4,6-trifluoro-N2-(2-Fluoro-4-yodo-fenil)-bencen-1,2- diamina 3 (0,285 gm, 0,74 mmol) en $CH_2Cl_2$ (2 ml), se agregó 1,1'-carbonildiimidazol (0,125 gm, 0,75 mmol). Esta mezcla de reacción se mantuvo en agitación a temperatura ambiente por 16 horas luego de las cuales el

producto precipitó. El sólido blanco se filtró y se usó sin realizar purificación. (0,2 gm, rendimiento: 65,85%): *m/z* = 407 $[M-1]^-$.

**Paso D/E:** (3,4,6-trifluoro-2-(2-fluoro-4-yodo-fenilamino)-fenil)-amida del ácido ciclopropansulfónico:



Una solución agitada de 4,6,7-trifluoro-1-(2-fluoro-4-yodo-fenil)-1,3,- dihidrobencimidazol-2-ona (0,2 gm, 0,41 mmol) en THF seco (4 ml) bajo nitrógeno se enfrió a -78°C y se agregó una solución 1,0 M de LiHMDS (0,41 ml, 0,41 mmol) lentamente. (2 ml) seguido por la adición de cloruro de ciclopropansulfonilo (0,050 ml, 0,49 mmol). Esta mezcla de reacción se mantuvo en agitación a temperatura ambiente por 16 horas, se concentró hasta secar y se colocó en EtOAc. El EtOAc se lavó con agua, se secó sobre sulfato de sodio y se concentró hasta secar. El residuo obtenido, 1-ciclopropansulfonil-4,5,7-trifluoro-3-(2- fluoro-4-yodo-fenil)-1,3-dihidro-bencimidazol-2-ona **5**, se colocó en dioxano (2 ml) y a esto se agregó NaOH 1,0 N (0,5ml) y se mantuvo en agitación a 50°C por 16 horas. La TLC indicó reacción incompleta, el producto se purificó mediante HPLC para dar un sólido blanco opaco (4,4 mg) $M+H^+$: 484,7, $M-H^+$:

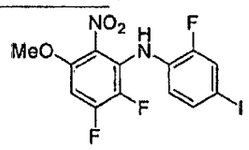
687

486,7. $^1$H RMN ($CDCl_3$, 300 MHZ): 0,9 - 1,1 - (m, 2H); 1,1 - 1,2 (m, 2H); 2,45 - 2,55 (m, 1H); 6,05 (s, 1H); 6,44 - 6,54 (m, 1 H); 7,1 (s, 1H); 7,4 - 7,7 (d, 1H); 7,38 - 7,44 (dd, 1H); *m/z* = 485 $[M-1]^-$.

Ejemplo 50

**N-(3,4-difluoro-2-(4-fluoro-2-yodofenilamino)-6-etoxifenil)ciclopropansulfonamida:**

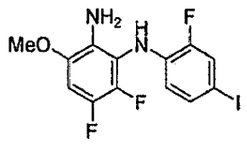
**Paso A:** (2J-Difluoro-5-metoxi-6-nitro-fenil)-(2-fluoro-4-yodo-fenil)-amina:




Una solución agitada de (2-fluoro-4-yodo-fenil)-(2,3,5-trifluoro-6-nitro-fenil)-amina (1,23 gm, 3 mmol) en THF seco (25 ml) bajo nitrógeno se enfrió a -78°C y se agregó una solución al 25% de NaOMe (0,68 ml, 0,3 mmol) lentamente. La mezcla de reacción se dejó calentar a temperatura ambiente y la agitación se continuó por otras 16 horas. La TLC indicó reacción incompleta. Se agregó acetato de etilo (100 ml) a la mezcla de la reacción y se lavó con agua. La capa orgánica se secó sobre sulfato de sodio y se purificó adicionalmente mediante cromatografía de columna para dar sólido amarillo (0,6 gm, rendimiento: 47,6%). *m/z* = 424 $[M=H]^+$.

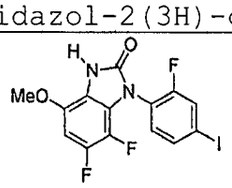
**Paso B:** 5,6-Difluoro-N1-(4-fluoro-2-yodofenil)-3-metoxibencen-1,2-diamina:

688




A la solución agitada de (2,3-difluoro-5-metoxi-6-nitro-fenil)-(2-fluoro-4-yodo-fenil)-amina (0,57 gm, 1,34 mmol) en EtOH (20 ml), se agregó cloruro de amonio (1,18 gm, 20,16 mmol) y polvo de hierro (1,15 gm, 21,44 mmol). Esta mezcla de reacción se mantuvo en agitación a reflujo por 16 horas. La mezcla de reacción se dejó enfriar y se filtró sobre celite y se concentró hasta secar. El residuo obtenido se colocó en EtOAc y se lavó con agua. La capa de EtOAc se secó sobre sulfato de sodio y se purificó adicionalmente mediante cristalización a partir de EtOH para dar un sólido blanco opaco (0,47 gm, rendimiento: 90,3%). $M-H^+$: 393,2. $^1H$ RMN (DMSO, 300 MHz): 3,76 (s, 3H); 6,1 (t, 1H); 6,8 - 7,0 (m, 1H); 7,2 (d, 1H); 7,35 (s, 1H); 7,42 (d, 1H).

**Paso C**: 6,7-Difluoro-1-(4-fluoro-2-yodofenil)-4-metoxi-1H-benzo[d]imidazol-2(3H)-ona:

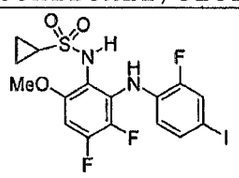



A la solución agitada de 5,6-difluoro-N1-(4-fluoro-2-yodofenil)-3-metoxibencen-1,2-diamina (0,17 gm, 0,43 mmol) en $CH_2Cl_2$ (2 ml), se agregó 1,1'-Carbonildiimidazol (0,085 gm, 0,53 mmol). Esta mezcla de reacción se mantuvo en agitación a temperatura ambiente por 16 horas luego de las

689

cuales el producto precipitó. El sólido blanco se filtró y se usó más adelante sin realizar purificación. (0,089 gm); *m/z* = 419 $[M-1]^-$.

**Paso D/F:** N-(3,4-difluoro-2-(4-fluoro-2-yodofenilamino)-6-metoxifenil)ciclopropansulfonamida:



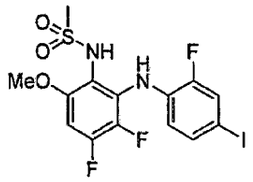

Una solución agitada de 1-(ciclopropilsulfonil)-4,5-difluoro-3-(2-fluoro-4-yodofenil)-7-metoxi-1H-benzo[d]imidazol-2(3H)-ona (0,89 gm, 0,17 mmol) en THF seco (4 ml) bajo nitrógeno se enfrió a -78°C y se agregó una solución 1,0 M de LiHMDS (0,17 ml, 0,17 mmol) lentamente. (2 ml) seguido por la adición de cloruro de ciclopropansulfonilo (0,021 ml, 0,21 mmol). Esta mezcla de reacción se mantuvo en agitación a temperatura ambiente por 16 horas, se concentró hasta secar y se colocó en EtOAc. El EtOAc se lavó con agua, se secó sobre sulfato de sodio y se concentró hasta secar. La 1-(ciclopropilsulfonil)-4,5-difluoro-3-(2-fluoro-4-yodofenil)-7-metoxi-1H-benzo[d]imidazol-2(3H)-ona se colocó en dioxano (2 ml) y a esto se agregó NaOH 1,0 N (0,5ml) y se mantuvo en agitación a 50°C por 16 horas. La TLC indicó reacción incompleta, el producto se purificó mediante HPLC para dar sólido blanco opaco (2,5 mg) $M+H^+$: 484,7, $M-H^+$: 497,3. $^1H$ RMN ($CDCl_3$, 300

690

MHz): 0,85 - 0,95 (m, 2H); 1,05 - 1,15 (m, 2H); 2,4 - 2,5 (m, 1H); 3,9 (s, 3H); 6,1 (s, 1H); 6,4 - 6,6 (m, 2 H); 7,3 (m, 1H); 7,35 - 7,4 (dd, 1H); *m/z* = 497 $[M-1]^-$.

Ejemplo 51

**(3,4-difluoro-2-(2-fluoro-4-yodo-fenilamino)-6-metoxi-fenil)-amida del ácido metilsulfónico:**




Una solución agitada de 5,6-difluoro-N1-(4-fluoro-2-yodofenil)-3-metoxibencen-1,2-diamina (0,150 gm, 0,38 mmol) en $CH_2Cl_2$ seco (4 ml), se agregó TEA (,264 ml, 1,9 mmol) y cloruro de metansulfonilo lentamente. Esta mezcla de reacción se mantuvo en agitación a temperatura ambiente por 16 horas, la TLC indicó reacción incompleta, junto con el material de partida se observaron dos productos. La mezcla de la reacción se lavó con agua, la capa orgánica se secó sobre sulfato de sodio y se concentró hasta secar, el producto se purificó mediante cromatografía de columna. El producto minoritario resultó ser el compuesto esperado (6,4 mg). $M-H^+$: 471,5. $^1H$ RMN ($CDCl_3$, 300 MHz): 3,9 (s, 3H); 6,05 (s, 1H); 6,4 - 6,5 (m, 1H); 6,5 - 6,6 (m, 1H); 7,2 (s, 1H); 7,28 (d, 1H); 7,35 - 7,4 (d, 1H); *m/z* = 471 $[M-1]^-$.

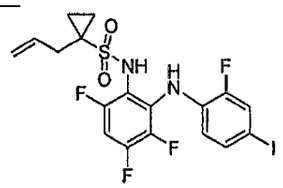
Ejemplo 52

**[3,4,6-trifluoro-2-(4-fluoro-2-yodo-fenilamino)-fenil]-**

691

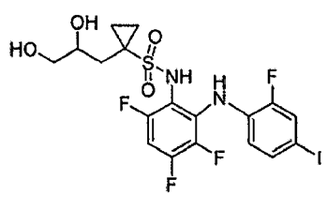
**amida del ácido 1-(2,3-Dihidroxi-propil)-ciclopropansulfónico:**

**Paso A:** [3,4,6-trifluoro-2-(2-fluoro-4-yodo-fenilamino)fenil]-amida del ácido 1-alil-ciclopropansulfónico:



De acuerdo con el procedimiento general B, se hizo reaccionar cloruro de 1-alil-ciclopropansulfonilo con 3,5,6-trifluoro-$N^1$-(2-fluoro-4-yodofenil)bencen-1,2-diamina para obtener el producto del título. $^1$H RMN ($CDCl_3$, 300 MHz): δ 7,41 (dd, 1H), 7,38 (dd, 1H), 7,09 (s, 1H), 6,78 (m, 1H), 6,49 (m, 1H), 5,96 (s, 1H), 5,86 (m, 1H), 5,18 (d, 2H), 2,76 (d, 2H), 1,23 (m, 2H), 0,872 (m, 2H).

**Paso B:** 1-(2,3-Dihidroxipropil)-N-(3,4,6-trifluoro-2-(2-fluoro-4-yodofenilamino)fenil)ciclopropan-1-sulfonamida:



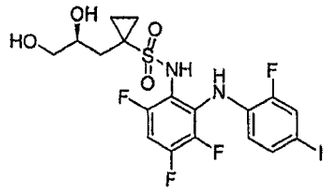
Se disolvió [3,4,6-trifluoro-2-(2-fluoro-4-yodo-fenilo amino)-fenil]-amida del ácido 1-alil-ciclopropansulfónico (110 mg, 0,21 mmol) y N-óxido de 4-metilmorfolina (24,6 mg, 0,21 mmol) en THF (8 ml). Se agregó tetróxido de osmio a

692

temperatura ambiente (0,021 mmol, 0,153 ml, 4% en $H_2O$) y la mezcla de la reacción se agitó a temperatura ambiente por 16 horas. Se agregó EtOAc, la fase orgánica se lavó con agua, se secó ($MgSO_4$) y se concentró bajo presión reducida. El residuo se purificó sobre cromatografía sobre gel de sílice (eluyentes: EtOAc/ MeOH) para obtener el producto del título (0,89 g, 75 %). $^1H$ RMN ($CDCl_3$, 300 MHz): δ 7,39 (dd, J = 1,5 & 10,6 Hz, 1H), 7,29 (d, J = 8,8 Hz, IH), 7,28 (s, 1H), 6,97 (s, 1H), 6,76 (m, 1H), 6,49 (m, 1H), 4,13 (m, 1H), 3,66 (dd, J = 3,7 & 11,4 Hz, 1H), 3,53 (dd. J = 6,7 & 11,2 Hz, 1H), 2,50(dd, J = 10,0 & 16,1 Hz, 1H), 1,6 (m,lH), 1,46 (m, 1H), 1,28 (m, 1H), 1,20 (m, 2H), 0,92 (m, 2H); *m/z* = 559 $[M-1]^-$.

Ejemplo 53

**(S)-1-(2,3-dihidroxipropil)-N-(3,4,6-trifluoro-2-(2-fluoro-4-yodofenilamino)fenil)ciclopropan-1-sulfonamida:**



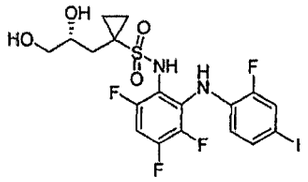

El isómero S puro se obtuvo mediante separación HPLC quiral de la mezcla racémica (ejemplo 52). $^1H$ RMN ($CDCl_3$, 300 MHz): δ 7,39 (dd, J = 1,5 & 10,6 $Hz_5$ 1H), 7,29 (d, J = 8,8 Hz, 1H), 7,28 (s, 1H), 6,97 (s, 1H), 6,76 (m, 1H), 6,49 (m, 1H), 4,13 (m, 1H), 3,66 (dd, J = 3,7 & 11,4 $Hz_5$ 1H), 3,53 (dd, J = 6,7 & 11,2 Hz, 1H), 2,50(dd, J = 10,0 & 16,1 Hz, 1H), 1,6 (m,lH), 1,46 (m, 1H), 1,28 (m, 1H), 1,20 (m,

693

2H), 0,92 (m, 2H); *m/z* = 559 $[M-1]^-$.

Ejemplo 54

**(R)-1-(2,3-dihidroxipropil)-N-(3,4,6-trifluoro-2-(2-fluoro-4-yodofenilamino)fenil)ciclopropan-1-sulfonamida:**

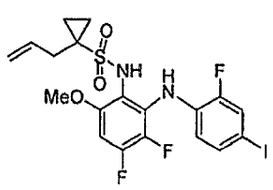


El isómero R puro se obtuvo mediante separación HPLC quiral de la mezcla racémica (ejemplo 52). $^1$H RMN ($CDCl_3$, 300 MHz): δ 7,39 (dd, J = 1,5 & 10,6 Hz, 1H), 7,29 (d, J = 8,8 Hz, 1H), 7,28 (s, 1H), 6,97 (s, 1H), 6,76 (m, 1H), 6,49 (m, 1H), 4,13 (m, 1H), 3,66 (dd, J = 3,7 & 11,4 Hz, 1H), 3,53 (dd, J = 6,7 & 11,2 Hz, 1H), 2,50(dd, J = 10,0 & 16,1 Hz, 1H), 1,6 (m, 1H), 1,46 (m, 1H), 1,28 (m, 1H), 1,20 (m, 2H), 0,92 (m, 2H); *m/z* = 559 $[M-1]^-$.

Ejemplo 55

**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida:**

**Paso A:** 1-alil-N-3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)ciclopropan-1-sulfonamida:

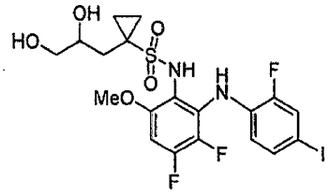


De acuerdo con el procedimiento general B, se hizo

694

reaccionar cloruro de 1-alil-ciclopropansulfonilo con 5,6-difluoro-N1-(2-fluoro-4-yodofenil)-3-metoxibencen-1,2-diamina para obtener el producto del título. $^1$H RMN ($CDCl_3$, 300 MHz): δ 7,417 (dd, 1H), 7,309(s, 1H), 7,25 (m, 1H), 6,89 (m, 1H), 6,52(m, 1H), 6,427 (m, 1H), 6,03 (s, 1H), 5,668 (m, 1H), 5,11 (t, 1H), 3,9 (s, 3H), 2,75 (d, 2H), 1,21 (m, 2H), 0,767 (m, 2H).

**Paso B:** N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida:



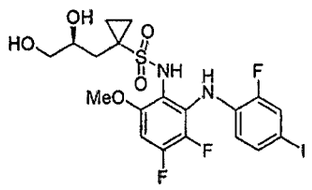

Se disolvió 1-alil-N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)ciclopropan-1-sulfonamida (97 mg, 0,18 mmol) y N-óxido de 4-metilmorfolina (21 mg, 0,18 mmol) en THF (8 ml). Se agregó tetróxido de osmio a temperatura ambiente (0,018 mmol, 0,13 ml, 4% en $H_2O$) y la mezcla de la reacción se agitó a temperatura ambiente por 16 horas. Se agregó EtOAc, la fase orgánica se lavó con agua, se secó ($MgSO_4$) y se concentró bajo presión reducida. El residuo se purificó sobre cromatografía sobre gel de sílice (eluyentes: EtOAc/ MeOH) para obtener el producto del título (0,80 g, 78 %). $^1$H RMN ($CDCl_3$, 300 MHz): δ 7,38 (dd, J = 1,7 & 10,3 Hz,1H), 7,26 (m, 1H), 7,14 (s, 1H), 6,87 (s, 1H),

695

6,53 (dd, J = 6,8 & 11,4 Hz, 1H), 6,43 (m, 1H), 4,06 (m, 1H), 3,89 (s, 3H), 3,63 (dd, J = 3,7 & 11,1 Hz, 1H), 3,49 (dd, J = 6,4 & 11,1 Hz, 1H), 2,3 (dd, J = 9,7 & 16,1 Hz, 1H), 1,77 (dd, J = 1,9 & 16,0 Hz, 1H), 1,37 (m, 1H), 1,25 (m, 1H), 1,21 (m, 2H), 0,86 (m, 2H); *m/z* = 571 $[M-1]^-$.

Ejemplo 56

**(S)-N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida:**

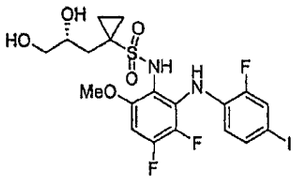



El isómero S puro se obtuvo mediante separación HPLC quiral de la mezcla racémica (ejemplo 55). $^1$H RMN ($CDCl_3$, 300 MHz): δ 7,38 (dd, J = 1,7 & 10,3 Hz,1H), 7,26 (m, 1H), 7,14 (s, 1H), 6,87 (s, 1H), 6,53 (dd, J = 6,8 & 11,4 Hz, 1H), 6,43 (m, 1H), 4,06 (m, 1H), 3,89 (s, 3H), 3,63 (dd, J = 3,7 & 11,1 Hz, 1H), 3,49 (dd, J = 6,4 & 11,1 Hz, 1H), 2,3 (dd, J = 9,7 & 16,1 Hz, 1H), 1,77 (dd, J = 1,9 & 16,0 Hz, 1H), 1,37 (m, 1H), 1,25 (m, 1H), 1,21 (m, 2H), 0,86 (m, 2H); *m/z* = 571 $[M-1]^-$.

Ejemplo 57

**(R)-N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida:**

696

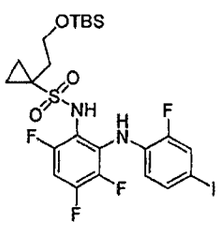


El isómero R puro se obtuvo mediante separación HPLC quiral de la mezcla racémica (ejemplo 55). $^1$H RMN ($CDCl_3$, 300 MHz): δ 7,38 (dd, J = 1,7 & 10,3 Hz,1H), 7,26 (m, 1H), 7,14 (s, 1H), 6,87 (s, 1H), 6,53 (dd, J = 6,8 & 11,4 Hz, 1H), 6,43 (m, 1H), 4,06 (m, 1H), 3,89 (s, 3H), 3,63 (dd, J = 3,7 & 11,1 Hz, 1H), 3,49 (dd, J = 6,4 & 11,1 Hz, 1H), 2,3 (dd, J = 9,7 & 16,1 Hz, 1H), 1,77 (dd, J = 1,9 & 16,0 Hz, 1H), 1,37 (m, 1H), 1,25 (m, 1H), 1,21 (m, 2H), 0,86 (m, 2H); *m/z* = 571 $[M-1]^-$.

Ejemplo 58

**1-(2-hidroxietil)-N-(3,4,6-trifluoro-2-(2-fluoro-4-yodofenilamino)fenil)ciclopropan-1-sulfonamida:**

**Paso A:** 1-(2-hidroxietil)-N-(3,4,6-trifluoro-2-('2-fluoro-4-yodofenilamino)fenil)ciclopropan-1-sulfonamida protegida con TBS:

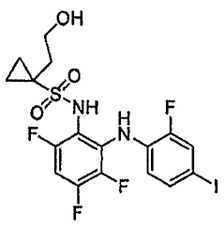


De acuerdo con el procedimiento general B, el cloruro de sulfonilo preparado en paso C de ejemplo 16 se hizo reaccionar con 5,6-difluoro-N1-(2-fluoro-4-yodofenil)-3-fluorobencen-1,2- diamina para obtener el producto del

697

título. Rendimiento: 13%. $^1$H-RMN (300 MHz, $CDCl_3$): δ = 7,51 (s, 1H, br), 7,37-7,35 (d, 1H), 7,27-7,25 (d, 1H), 6,94 (s, 1H, br), 6,78-6,68 (m, 1H), 6,46-6,44 (m, 1H), 3,90-3,88 (t, 2H), 2,12-2,10 (t, 2H), 1,31-1,28 (m, 2H), 0,91-0,89 (m, 2H), 0,86 (s, 9H), 0,05 (s, 6H); *m/z* = 643 $[M-1]^-$

**Paso B:** 1-(2-hidroxietil)-N-(3,4,6-trifluoro-2-(2-fluoro-4-yodofenilamino)-fenilo) ciclopropan-1-sulfonamida:



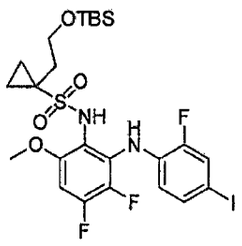

Mismo procedimiento que en paso E, ejemplo 16. Rendimiento: 100%. $^1$H-RMN (300 MHz, $CDCl_3$): δ = 7,51 (s, 1H, br), 7,37-7,35 (d, 1H), 7,27-7,25 (d, 1H), 6,94 (s, 1H, br), 6,78-6,68 (m, 1H), 6,46-6,44 (m, 1H), 3,90-3,88 (t, 2H), 2,12-2,10 (t, 2H), 1,31-1,28 (m, 2H), 0,91-0,89 (m, 2H); *m/z* = 529 $[M-1]^-$.

Ejemplo 59

**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(2-hidroxietil)ciclopropan-1-sulfonamida:**

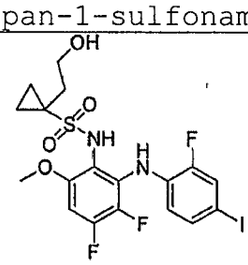
**Paso A:** N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino')-6-metoxifenil)-1-(2-hidroxietil)ciclopropan-1-sulfonamida protegida con TBS:

648




De acuerdo con el procedimiento general B, el cloruro de sulfonilo preparado en paso C de ejemplo 16 se hizo reaccionar con 5,6-difluoro-N1-(2-fluoro-4-yodofenil)-3-metoxi-bencen- 1,2-diamina para obtener el producto del título. Rendimiento: 37%. $^1$H-RMN (300 MHz, $CDCl_3$): δ = 7,40-7,34 (dd, 1H), 7,23-7,21 (m, 1H), 6,61 (s, 1H, br), 6,57-6,49 (dd, 1H), 6,48-6,39 (m, 1H), 3,9-3,7 (m, 5H), 2,15-2,05 (t, 2H), 1,30-1,20 (m, 2H), 0,95-0,80 (m, 11H), 0,05 (s, 6H); *m/z* = 655 $[M-1]^-$.

**Paso B:** N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(2-hidroxietil)ciclopropan-1-sulfonamida:



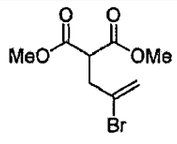

Mismo procedimiento que en paso E, ejemplo 16. Rendimiento: 100%. $^1$H-RMN (300 MHz, $CDCl_3$): δ = 7,40-7,34 (dd, 1H), 7,23-7,21 (m, 1H), 6,61 (s, 1H, br), 6,57-6,49 (dd, 1H), 6,48-6,39 (m, 1H), 3,9-3,7 (m, 5H), 2,15-2,05 (t, 2H), 1,30-1,20 (m, 2H), 0,95-0,80 (m, 2H); *m/z*= 541 $[M-1]^-$.

694

Ejemplo 60

**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(3-hidroxi-2-(hidroximetil)propil)ciclopropan-1-sulfonamida:**

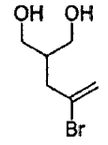
**Paso A:** 2-(2-bromoalil)malonato de dimetilo:




A una suspensión de hidruro de sodio (5,0 g, 125 mmol) en HMPA (50 ml, destilado a partir de hidruro de calcio) se agregó una solución de malonato de dimetilo (11,7 ml, 100 mmol) en HMPA (5 ml) a 0°C bajo argón. La mezcla se calentó a 50°C y se agitó 1 hora. Luego la solución se enfrió nuevamente a 0°C, y se agregó una solución de 2,3-dibromopropeno (12,2 ml, 100 mmol) en HMPA (5 ml) a la mezcla de la reacción. Luego, la solución se calentó a 40°C y se agitó por 1 hora. La mezcla de la reacción se detuvo con HCl acuoso (10%, 88 ml) y se extrajo con éter (3 x 45 ml). Las fracciones orgánicas se recogieron, se secó sobre $MgSO_4$, y el solvente se eliminó al vacío. El aceite crudo se purificó vía cromatografía sobre gel de sílice (eluyentes: cloroformo/hexano) para obtener el producto del título como un sólido incoloro (16,3 g, 65%). $^1$H-RMN (300 MHz, $CDCl_3$) δ 5,70 (d, J = 1,8 Hz, 1 H), 5,48 (d, J = 1,8 Hz, 1H), 3,63 (t, J = 7,5 Hz, 1 H), 3,76 (s, 6 H), 3,04 (d, J = 7,5 Hz, 2 H).

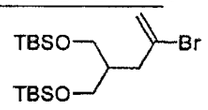
760

**Paso B:** 2-(2-Bromoalil)propan-1,3-diol:




Se formó una lechada de hidruro de litio y aluminio (1,9 g, 7,65 mmol) en éter dietílico anhidro (50 ml) y se enfrió a -78°C en un baño de hielo seco/acetona. Luego se agregó una solución del producto del paso A (0,639 g, 16,84 mmol) en éter seco (26 ml) por goteo. Luego de agregar el malonato, la solución se dejó calentar a temperatura ambiente y la agitación se continuó por 3 horas. La reacción se detuvo con salmuera (50 ml), se extrajo con acetato de etilo (3 x 25 ml) y se secó sobre $MgSO_4$. El solvente se eliminó al vacío para dar el producto deseado (1,3 g, 86%) el cual se usó para el siguiente paso sin purificación adicional. $^1$H-RMN (300 MHz, $CDCl_3$) δ 5,66 (d, J = 1,2 Hz, 1 H), 5,48 (d, J = 1,5 Hz, 1H), 3,86 (m, 2 H), 3,73 (m, 2 H), 2,51 (d, J = 7,5 Hz, 2 H), 2,40 (br s, 2 H), 2,15 (m, 1 H).

**Paso C:** 2-(2-bromoalil)propan-1,3-diol protegido con di-tert-butildimetilsililo:

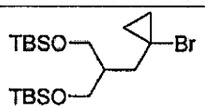



El producto del paso B (2,8 g, 14,20 mmol) se disolvió en THF anhidro (140 ml). Se agregó piridina anhidra (2,5 ml, 31,24 mmol), y la solución se enfrió a 0°C. Se agregó dimetilsililtriflato de tert-butilo (7,2 ml, 31,24 mmol) por

701

goteo, y al completarse, la solución de la reacción se calentó a 35°C. Luego de agitar por 6 días, la reacción se detuvo con 100 ml de salmuera, se extrajo con acetato de etilo (3 x 50 ml) y se secó sobre $MgSO_4$. Las fases orgánicas combinadas se evaporaron para obtener el producto crudo (5,5 g, 91%) como un aceite amarillo el cual se usó en el siguiente paso sin purificación adicional. $^1$H-RMN (300 MHz, $CDCl_3$) δ 5,54 (d, J = 0,9 Hz, 1 H), 5,40 (d, J = 1,2 Hz, 1H), 3,55 (d, J = 5,4, 4 H), 2,40 (d, J = 6,9 Hz, 2 H), 1,97 (m, 1 H), 0,85 (s, 18 H), 0,02 (s, 9 H).

**Paso D:** 2-((1-bromociclopropil)metilo) propan-1,3-diol protegido con di-tert-butildimetilsililo:

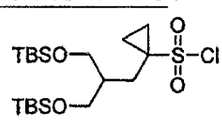



Un recipiente de reacción se cargó con $CH_2Cl_2$ anhidro (10 ml) y dietilcinc (1,0 M en hexanos, 4,65 ml, 4,65 mmol) a 0°C. Se agregó ácido trifluoroacético (0,358 ml, 4,65 mmol) por goteo y la solución se dejó agitar por 20 minutos. Luego se agregó diiodometano (0,375 ml, 4,65 mmol) y la solución se agitó por otros 20 minutos. Finalmente, se agregó el producto del paso **C** (0,492 g, 1,16 mmol) y la solución se dejó calentar a temperatura ambiente, agitando por 16 horas. La reacción se detuvo con $NH_4Cl$ acuoso saturado. Las capas se particionaron y la fase acuosa se extrajo con cloroformo (3 x 5 ml). Las fases orgánicas combinadas se lavaron con

762

salmuera (10 ml), se secó sobre $MgSO_4$, y los volátiles se eliminaron al vacío. El crudo resultante se purificó vía cromatografía sobre gel de sílice (eluyentes: cloroformo/hexanos) para dar el producto como un aceite traslúcido (0,280 g, 64%). $^1$H-RMN (300 MHz, $CDCl_3$) δ 3,66 (d, J = 5,4, 4 H), 2,08 (m, 1 H), 1,64 (d, J = 6,9, 2 H), 1,13 (m, 2 H), 0,88 (s, 18 H), 0,81 (m, 2 H), 0,04 (s, 9 H).

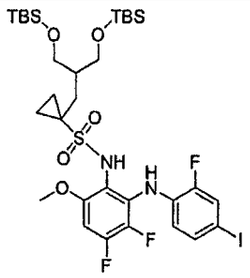
**Paso E**: cloruro de 1-(3-hidroxi-2-(hidroximetil)propil)ciclopropan-1-sulfonilo protegido con di-tert-butildimetilsililo:




El producto del paso D (0,507 g, 1,16 mmol) se disolvió en éter anhidro (6 ml) y la solución de la reacción se enfrió a -78°C. Luego, se agregó tert-butillitio (1,7 M en pentano, 1,50 ml, 2,55 mmol) por goteo durante 5 minutos. Luego de agitar por 0,5 horas, el producto litiado se transfirió mediante cánulos a una solución agitada de cloruro de sulfurilo (0,206 ml, 2,55 mmol) en éter seco (6 ml) a -78°C. Luego de completarse la transferencia, la solución se dejó calentar a temperatura ambiente, el solvente se evaporó y se formó una lechada del sólido blanco resultante en hexanos secos. Esta lechada se filtró inmediatamente a través de celite, y todos los volátiles se eliminaron al vacío. El producto resultante crudo (0,376 g,

71%) se aisló como un aceite amarillo y se usó en el paso siguiente sin purificación adicional. $^1$H-RMN (300 MHz, $CDCl_3$) δ 3,60 (m, 4 H), 2,16 (m, 1 H), 2,03 (d, 2 H), 0,88 (s, 18 H), 0,04 (s, 9 H).

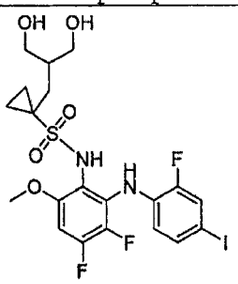
**Paso F:** N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(3-hidroxi-2-(hidroximetil)propil)ciclopropan-1-sulfonamida protegida con di-tert-butildimetilsililo:




Se disolvió 5,6-difluoro-N1-(2-fluoro-4-yodofenil)-3-metoxibencen-1,2-diamina (8,8 mg, 0,022 mmol) en piridina anhidra (0,5 ml) bajo una atmósfera de argón. El producto del paso E (20,5 mg, 0,045 mmol), disuelto en piridina seca (0,5 ml), se agregó al recipiente de la reacción y la mezcla se calentó a 80°C por 21 horas. El solvente se eliminó al vacío y el crudo resultante se purificó vía cromatografía sobre gel de sílice (eluyentes: acetato de etilo/hexanos) para dar el compuesto del título (2,75 mg, 15%). *m/z* 813,5 (M-1).

**Paso G:** N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(3-hidroxi-2-

(hidroximetil)propil)ciclopropan-1-sulfonamida:

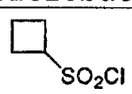


El producto del paso F (27,9 mg, 0,0342 mmol) se disolvió en THF (1 ml) y se trató con HCl acuoso (1,2 N, 0,2 ml) a 0°C. La solución resultante se agitó por 4 horas. Luego, la reacción se detuvo con $NaHCO_3$ acuoso saturado, se extrajo con acetato de etilo, se secó sobre $MgSO_4$ y los volátiles se eliminaron al vacío. El crudo resultante se purificó mediante cromatografía sobre gel de sílice (eluyentes: metanol/cloroformo) seguido por Purificación LC-MS para dar el compuesto del título (11,8 mg, 59%). $^1$H-RMN (300 MHz, $CD_3OD$) δ 7,32 (dd, 1 H), 7,21 (d, 1 H), 6,76 (dd, 1 H), 6,33 (m, 1 H), 3,82 (s, 3 H), 3,52 (d, 4 H), 2,01 (m, 1 H), 1,88 (d, 2 H), 1,07 (m, 2 H), 0,75 (m, 2 H), *m/z* 585,3 $(M-1)^-$.

Ejemplo 61

**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)ciclobutansulfonamida:**

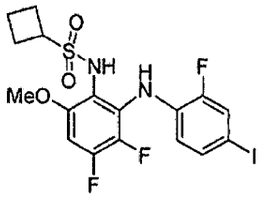
**Paso A:** cloruro de ciclobutansulfonilo:



A una suspensión de torneados de Mg (0,790 g, 32,5 mmol)

en 20 ml de éter dietílico anhidro se agregó una solución de bromuro de ciclobutilo (1,8 ml, 2,5722 g, 19,1 mmol) en 20 ml de éter dietílico en pequeñas porciones con agitación fuerte. Luego de que la reacción exotérmica inicial hubiese cesado, la mezcla se calentó adicionalmente a temperatura de reflujo por 30 min. La suspensión se enfrió hasta temperatura ambiente y el sobrenadante se agregó en pequeñas porciones a una solución helada de cloruro de sulfurilo (4,6 ml, 7,728 g, 57,2 mmol) en 30 ml de DCM anhidro. Luego de completarse la adición, la suspensión se calentó a temperatura ambiente y los volátiles se eliminaron al vacío. El residuo se secó en vacío de bomba de aceite por 15 min, luego se extrajo con hexano (150 ml). La suspensión de hexano se filtró y el hexano se retiró al vacío para dar el producto crudo como un aceite morado oscuro el cual se usó para el siguiente paso sin purificación adicional. Se encontró algo de bromuro de ciclopropilo sin reaccionar. Rendimiento crudo: 1,1 g (38%).

**Paso B:** N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)ciclobutansulfonamida:




De acuerdo con el procedimiento general B, el cloruro de ciclobutilsulfonilo preparado en el paso precedente se hizo

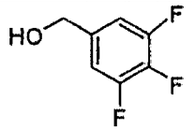
706

reaccionar con 5,6-difluoro-N1-(2-fluoro-4-yodofenil)-3-metoxi-bencen- 1,2-diamina para obtener el producto del título. Rendimiento: 75%. $^1$H-RMN (300 MHz, $CDCl_3$): $\delta$ = 7,44 (s, 1H, br), 7,41-7,36 (dd, 1H), 7,24-7,23 (m, 1H), 6,54-6,38 (m, 2H), 5,90 (s, 1H, br), 3,85-3,75 (m, 5H), 2,60-2,40 (m, 2H), 2,25-2,15 (m, 1H), 2,15-1,95 (m, 2H); *m/z* = 511 $[M-1]^-$.

Ejemplo 62

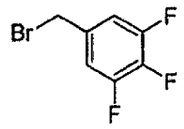
**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metilfenil)-1-(2,3- dihidroxipropil)ciclopropan-1-sulfonamida:**

**Paso A:** (3,4,5-Trifluorofenil)metanol:



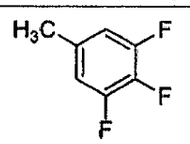

A una solución fría (-5° C) de 3,4,5 - trifluorobenzaldehido (7,0 g, 43,75 mmol) en una mezcla ( 50 ml, 9:1) de THF y agua se agregó $NaBH_4$ (1,662 g, 43,75 mmol) lentamente en porciones durante un periodo de 30 min. La mezcla de la reacción se dejó alcanzar temperatura ambiente durante un periodo de 2h y se vertió cuidadosamente en HCl diluido helado (200 ml, 1N). La capa oleosa se extrajo en $CH_2Cl_2$ (250 ml) y la capa orgánica se lavó con agua (200 ml), se secó ($MgSO_4$) y se evaporó. El producto crudo (7,08 g, cuantitativo) obtenido se llevó adelante sin purificación adicional.

**Paso B:** 5-(Bromometil)-1,2,3-trifluorobenceno:




A una solución del (3,4,5-Trifluorofenil)metanol (40 mmol) en $CH_2Cl_2$ (150 ml), se agregó una solución de bromuro de tionilo (6,16 ml, 80 mmol) en $CH_2Cl_2$ (50 ml) lentamente. La mezcla de la reacción se agitó a temperatura ambiente por 16h y se vertió en hielo-agua (200 ml). La capa orgánica se separó y se lavó con $NaHCO_3$ saturado (2x200 ml), agua (200 ml), se secó ($MgSO_4$) y se evaporó para obtener el compuesto de bromo correspondiente como un aceite amarillo pálido en rendimiento cuantitativo. El producto crudo se llevó adelante hacia la siguiente reacción sin purificación adicional.

**Paso C:** 1,2,3-Trifluoro-5-metilbenceno:

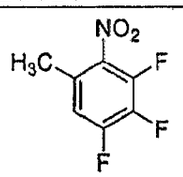



El compuesto de bromo precedente (40 mmol) se mezcló con trietilsilano (48 mmol) y la mezcla de la reacción se trató con $PdCl_2$ sólido (4 mmol) en pequeñas porciones. Luego de unos pocos minutos siguió una reacción exotérmica enérgica y se llevó cuidadosamente a reflujo los contenidos del recipiente colocando un condensador de reflujo. La mezcla de la reacción se agitó a temperatura ambiente por otras 6h y

708

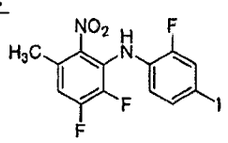
los contenidos se dejaron reposar 16h. Luego el producto líquido crudo se decantó cuidadosamente y se llevó adelante hacia la siguiente reacción sin purificación adicional. Se asumió que la reacción procedió en rendimiento cuantitativo.

**Paso D:** 1,2,3-Trifluoro-5-metil-4-nitrobenceno:



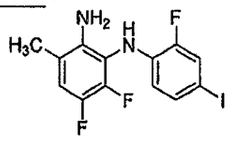
Se agregó 1,2,3-trifluoro-5-metilbenceno (40 mmol) a $H_2SO_4$ concentrado (50 ml) a 0-5° C. Luego la mezcla de la reacción se trató lentamente con $HNO_3$ concentrado (3,39 ml, 48,44 mmol, 90%) manteniendo la temperatura interna por debajo de 20° C. La mezcla de la reacción se agitó a temperatura ambiente por 16h y se vertió sobre hielo (300 g) y la capa oleosa se extrajo con $CH_2Cl_2$ (2x125 ml). La capa orgánica se lavó con agua (2x200 ml), salmuera (200 ml) y se secó ($MgSO_4$) y se evaporó para obtener el producto crudo el cual se purificó mediante cromatografía flash sobre gel de sílice para obtener el producto del título (6,5 g, 85%). $^1$H-RMN (300 MHz, $CDCl_3$): δ 6,96 (septuplete, 1H), 2,39 (s, 3H). $^{19}$FRMN ($CDCl_3$): δ -128,18, - 141,50, -159,05.

**Paso E:** 2,3-Difluoro-N-(2-fluoro-4-yodofenil)-5-metil-6-nitroanilina:



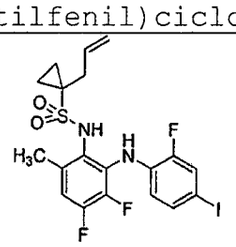
Se hizo reaccionar 2-fluoro-4-yodoanilina y 1,2,3-trifluoro-5-metil-4-nitrobenceno usando las condiciones descritas en Ejemplo 1 (Paso A) para formar el compuesto del título. $M-H^+$: 407,9

**Paso F**: 5,6-Difluoro-N1-(2-fluoro-4-yodofenil)-3-metilbencen-1,2-diamina:



Se redujo 2,3-difluoro-N-(2-fluoro-4-yodofenil)-5-metil-6-nitroanilina usando las condiciones descritas en Ejemplo 1 (paso B) para formar el compuesto del título. $M-H^+$: 377,4

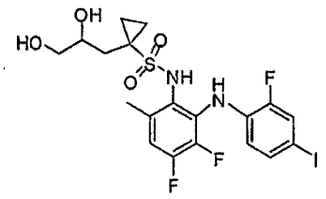
**Paso G**: 1-alil-N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metilfenil)ciclopropan-1-sulfonamida:



De acuerdo con el procedimiento general B, se hizo reaccionar cloruro de 1-alil-ciclopropansulfonilo (142 mg, 142 mg) con 5,6-difluoro-N1-(2-fluoro-4-yodofenil)-3-metilbencen-1,2- diamina (150 mg, 0,4 mmol) para obtener el producto del título (100 mg, 47%); *m/z* = 521 $[M-1]^-$.

**Paso H**: N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metilfenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida:

710

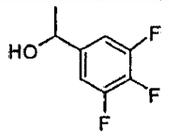


Se disolvió 1-alil-N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metilfenilo) ciclopropan-1-sulfonamida ( 150 mg, 0,29 mmol) y N-óxido de 4-metilmorfolina (33 mg, 0,29 mmol) en THF (5 ml). Se agregó tetróxido de osmio a temperatura ambiente (0,029 mmol, 0,18 ml, 4% en $H_2O$) y la mezcla de la reacción se agitó a temperatura ambiente por 16 horas. Se agregó EtOAc, la fase orgánica se lavó con agua, se secó ($MgSO_4$) y se concentró bajo presión reducida. El residuo se purificó sobre cromatografía sobre gel de sílice (eluyentes: EtOAc/ MeOH) para obtener el producto del título (0,110 g, 68 %). $^1$H-RMN (300 MHz, $CDCl_3$): δ 7,07 (m, 1H), 6,97 (br m, 2H), 6,84 (m, 2H), 6,60 (br m, 2H), 3,98 (br m, 1H), 3,58 (m, 1H), 3,43 (m, 1H), 3,20 (d, *J* = 3,9 Hz, 1H), 2,42 (s, 3H), 2,31 (dd, *J* = 9,9 & 15,6 Hz, 1H), 2,01 (br t, 1H), 2,31 (dd, *J* = 9,9 & 15,6 Hz, 1H), 1,66 (dd, *J* = 2,1 & 15,9 Hz, 1H), 1,52 (m, 1H), 1,40 (m, 1H), 0,91 (m, 2H).

Ejemplo 63

**1-(2,3-Dihidroxipropil)-N-(6-etil-3,4-difluoro-2-(2-fluoro-4-yodofenilamino) fenilo) ciclopropan-1-sulfonamida:**

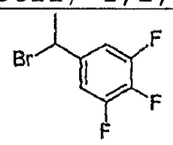
**Paso A:** 1-(3,4,5-Trifluorofenil)etanol:



711

Una solución en éter (17,41 ml, 52,24 mmol, 3M) de MeMgBr se agregó lentamente a - 78° C a una solución de 3,4,5-trifluorobenzaldehido (6,96 g, 43,53 mmol) en THF (125 ml). La mezcla de la reacción se agitó a temperatura ambiente por 16h y se enfrió (0° C) y se detuvo, en forma secuencial, con exceso de acetato de etilo (10 ml) y agua (5 ml). Se agregó exceso de $MgSO_4$ anhidro (5 g) y se agitó por 30 minutos a temperatura ambiente. La suspensión se filtró sobre celite y los sólidos se lavaron con acetato de etilo (2x25 ml). El material filtrado combinado se evaporó para obtener el producto en rendimiento cuantitativo (7,65 g).

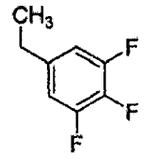
**Paso B:** 5-(1-Bromoetil)-1,2,3-trifluorobenceno:




A una solución del 1-(3,4,5-Trifluorofenil)etanol (7,65 g, 43,5 mmol) en $CH_2Cl_2$ (250 ml), se agregó una solución de bromuro de tionilo (18,1 g , 87 mmol) en $CH_2Cl_2$ (50 ml) lentamente. La mezcla de la reacción se agitó a temperatura ambiente por 16h y se vertió en hielo-agua (200 ml). La capa orgánica se separó y se lavó con $NaHCO_3$ saturado (2x200 ml), agua (200 ml), se secó ($MgSO_4$) y se evaporó para obtener el compuesto de bromo correspondiente como un aceite amarillo pálido en rendimiento cuantitativo (10,4 g). El producto crudo se llevó adelante hacia la siguiente reacción sin purificación adicional.

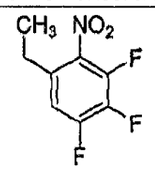
712

**Paso C:** 5-Etil- 1,2,3 -trifluorobenceno:




El compuesto de bromo precedente (9,65 g, 40,4 mmol) se mezcló con trietilsilano (41 mmol) y la mezcla de la reacción se trató con $PdCl_2$ sólido (177 mg, 4 mmol) en pequeñas porciones. Luego de unos pocos minutos siguió una reacción exotérmica enérgica y se llevó cuidadosamente a reflujo los contenidos del recipiente colocando un condensador de reflujo. La mezcla de la reacción se agitó a temperatura ambiente por otras 6h y los contenidos se dejaron reposar 16h. Luego el producto líquido crudo se decantó cuidadosamente y se llevó adelante hacia la siguiente reacción sin purificación adicional. Se asumió que la reacción procedió en rendimiento cuantitativo.

**Paso D:** 1-Etil-3,4,5-trifluoro-2-nitrobenceno:

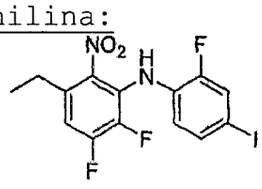



Se agregó 1,2,3-trifluoro-5-metilbenceno (6,46 g, 40,4 mmol) a $H_2SO_4$ concentrado (50 ml) a 0-5° C. Luego la mezcla de la reacción se trató lentamente con $HNO_3$ concentrado (3,39 ml, 48,44 mmol, 90%) manteniendo la temperatura interna por debajo de 20° C. La mezcla de la reacción se agitó a temperatura ambiente por 16h y se vertió sobre hielo

713

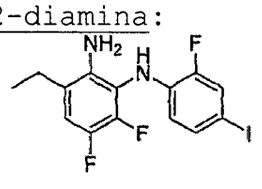
(300 g) y la capa oleosa se extrajo con $CH_2Cl_2$ (2x125 ml). La capa orgánica se lavó con agua (2x200 ml), salmuera (200 ml) y se secó ($MgSO_4$) y se evaporó para obtener el producto crudo el cual se purificó mediante cromatografía flash sobre gel de sílice para obtener el producto del título (6,6 g, 79%). $^1H$ RMN ($CDCl_3$): δ 6,98 (septuplete, 1H), 2,68 (q, 2H), 1,26 (t, $J$ = 7,8 & 7,2 Hz, 3H).

**Paso E**: 3-Etil-5,6-difluoro-N-(2-fluoro-4-yodofenil)-2 nitroanilina:




Se hizo reaccionar 2-fluoro-4-yodoanilina (2,05 g, 10 mmol) y 1-etil-3,4,5-trifluoro-2-nitrobenceno (2,37 g, 10 mmol) usando las condiciones descritas en ejemplo 1 (Paso A) para formar el compuesto del título (2,47 g, 60%); $m/z$ = 407 $[M-1]^-$.

**Paso F**: 3-Etil-5,6-difluoro-N1-(2-fluoro-4-yodofenil)bencen-1,2-diamina:

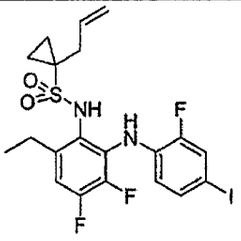



Se redujo 1,2,3-trifluoro-5-metil-4-nitrobenceno (2,47 g, 5,85 mmol) usando las condiciones descritas en ejemplo 1 (Paso B) para formar el compuesto del título. $M-H^+$: 393

**Paso G**: 1-alil-N-(6-etil-3,4-difluoro-2-(2-fluoro-

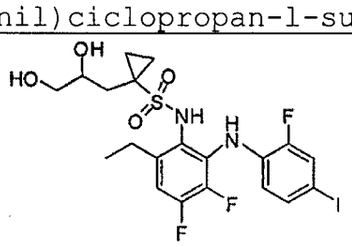
714

4-yodofenilamino)fenil)ciclopropan-1-sulfonamida:



De acuerdo con el procedimiento general B, se hizo reaccionar cloruro de 1-alil-ciclopropansulfonilo (230 mg, 1,27 mmol) con 5,6-difluoro-N1-(2-fluoro-4-yodofenil)-3-metilbencen-1,2-diamina (100 mg, 0,255 mmol) para obtener el producto del título (72 mg, 53%); *m/z* = 535 [M-1].

**Paso H:** 1-(2,3-Dihidroxipropil)-N-(6-etil-3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)ciclopropan-1-sulfonamida:



Se disolvió 1-alil-N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metilfenilo) ciclopropan-1-sulfonamida ( 70 mg, 0,13 mmol) y N-óxido de 4-metilmorfolina (15 mg, 0,13 mmol) en THF (2 ml). Se agregó tetróxido de osmio a temperatura ambiente (0,013 mmol) 0,075 ml, 4% en $H_2O$) y la mezcla de la reacción se agitó a temperatura ambiente por 16 horas. Se agregó EtOAc, la fase orgánica se lavó con agua, se secó ($MgSO_4$) y se concentró bajo presión reducida. El residuo se purificó sobre cromatografía sobre gel de sílice

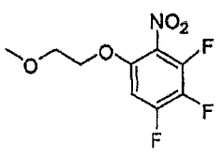
715

(eluyentes: EtOAc/MeOH) para obtener el producto del título. $^1$H RMN (300 MHz, $CDCl_3$): δ 7,38 (dd, *J* = 2,1 & 10,8 Hz, 1H), 7,27 (m, 2H), 7,12 (br s, 1H), 6,91 (dd, *J* = 8,1 & 10,8 Hz, 1H), 6,69 (br s, 1H), 6,36 (dt, *J* = 4,8, 8,7 & 13,5 Hz, 1H), 4,00 (m, 1H), 3,62 (dd, *J* = 3,6 & 10,5 Hz, 1H), 3,47 (br m, 2H), 2,81 (q, 2H), 2,40 (dd, *J* = 10,2 & 15,9 Hz, 1H), 1,73 (br m, 2H), 1,58 (m, 1H), 1,43 (m, 1H), 0,94 (m, 2H).

Ejemplo 64

**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-(2-metoxietoxi)fenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida:**

**Paso A:** 1,2,3-Trifluoro-5-(2-metoxietoxi)-4-nitrobenceno:

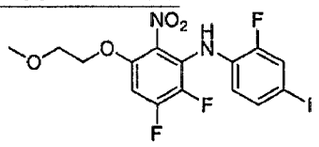



A una mezcla de 3,4,5-trifluoro-2-nitrofenol (1,93, 10 mmol), $Ph_3P$ (3,93 g, 15 mmol), y 2-metoxi-etanol (1,18 ml, 15 mmol) en THF anhidro (25 ml) se agregó una solución de azodicarboxilato de diisopropilo (2,91 ml, 15 mmol) en THF (5 ml) a 0° C y la mezcla de la reacción se agitó a temperatura ambiente por 16h. Los volátiles se evaporaron y el residuo se disolvió en $CH_2Cl_2$ (100 ml) y la capa orgánica se lavó con agua (100 ml), salmuera (100 ml), se secó ($MgSO_4$) y se evaporó. El residuo obtenido se purificó mediante cromatografía flash sobre gel de sílice para

716

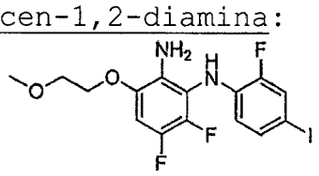
obtener el producto del título en 68% (1,70 g) rendimiento. $^1$H RMN (300 MHz, $CDCl_3$): δ 6,78 (ddd, *J* = 2,4, 6,0, 11,7 Hz, 1H), 4,19 (t, *J* = 4,5 Hz, 2H), 3,72 (t, *J* = 4,5 Hz, 2H), 3,39 (s, 3H).

**Paso B**: 2,3-Difluoro-N-(2-fluoro-4-yodofenil)-5-(2-metoxietoxi)-6-nitroanilina:



Se hizo reaccionar 2-fluoro-4-yodoanilina (1,6 g, 6,8 mmol) y 1,2,3-trifluoro-5-(2-metoxietoxi)-4-nitrobenceno (1,7 g, 6,8 mmol) usando las condiciones descritas en Ejemplo 1 (Paso A) para formar el compuesto del título (1,02 g, 32%); *m/z* = 467 [M-1].

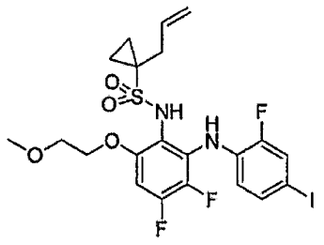
**Paso C**: 5,6-Difluoro-N1-(2-fluoro-4-yodofenil)-3-(2-metoxietoxi)bencen-1,2-diamina:



Se redujo 2,3-difluoro-N-(2-fluoro-4-yodofenil)-5-(2-metoxietoxi)-6-nitroanilina (1,017 g, 2,17 mmol) usando las condiciones descritas en Ejemplo 1 (Paso B) para formar el compuesto del título; *m/z* = 337 [M-1].

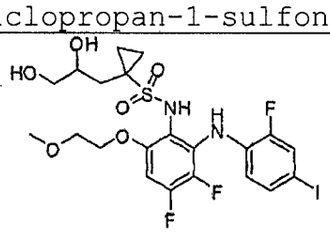
**Paso D**: 1-alil-N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-(2-metoxietoxi)fenil)ciclopropan-1-sulfonamida:

317



De acuerdo con el procedimiento general B, se hizo reaccionar cloruro de 1-alil-ciclopropansulfonilo (450 mg, 2,5 mmol) reaccionar con 5,6-difluoro-N1-(2-fluoro-4-yodofenil)-3-(2-metoxietoxi)bencen-1,2-diamina (219 mg, 2,5 mmol) para obtener el producto del título (230 mg, 78%); *m/z* = 581 [M-1].

**Paso E:** N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-(2-metoxietoxi)fenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida:



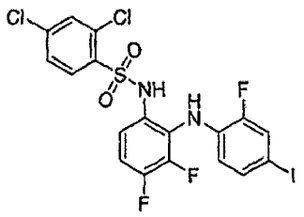
Se disolvió 1-alil-N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-(2-metoxietoxi)fenil)ciclopropan-1-sulfonamida (230 mg, 0,395 mmol) y N-óxido de 4-metilmorfolina (46 mg, 0,395 mmol) en THF (2 ml). Se agregó tetróxido de osmio a temperatura ambiente (0,039 mmol, 0,25 ml, 4% en $H_2O$) y la mezcla de la reacción se agitó a temperatura ambiente por 16 horas. Se agregó EtOAc, la fase orgánica se lavó con agua, se secó ($MgSO_4$) y se concentró bajo presión reducida. El residuo se purificó sobre

718

cromatografía sobre gel de sílice (eluyentes: EtOAc/MeOH) para obtener el producto del título. $^1$H RMN (300 MHz, $CDCl_3$): δ 7,36 (dd, *J* = 1,8 & 10,5 Hz, 1H), 7,27 (m, 2H), 6,56 (dd, *J* = 6,9 & 11,4 Hz, 1H), 6,40 (dt, *J* = 5,7, 7,5 & 12,9 Hz, 1H), 4,17 (m, 2H), 4,01 (m, 1H), 3,78 (m, 2H), 3,60 (dd, *J* = 3,6 & 11,1 Hz, 1H), 3,47 (m, 1H), 3,45 (s, 3H), 2,36 (dd, *J* = 9,6 & 15,9 Hz, 1H), 1,78 (dd, *J* = 2,4 & 15,6 Hz, 1H), 1,45-1,25 (m, 2H), 0,89 (m, 2H).

Ejemplo 65

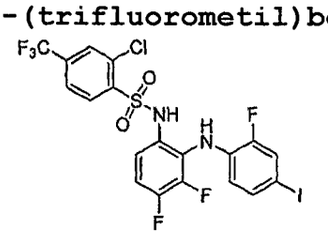
**2,4-dicloro-N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)bencensulfonamida:**



Se sintetizó mediante el método A usando el cloruro de sulfonilo apropiado, *m/z* = 571 [M-1].

Ejemplo 66

**2-cloro-N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-4-(trifluorometil)bencenosulfonamida:**

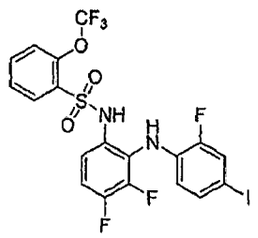


Se sintetizó mediante el método A usando el cloruro de sulfonilo apropiado, *m/z* = 605 [M-1].

719

Ejemplo 67

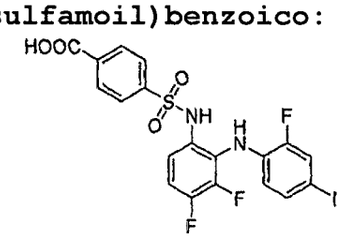
**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-2-(trifluorometoxi) bencensulfonamida:**



Se sintetizó mediante el método A usando el cloruro de sulfonilo apropiado, *m/z* = 587 [M-1].

Ejemplo 68

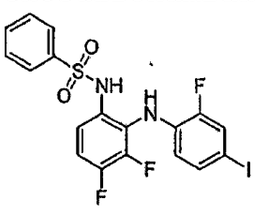
**ácido 4-(N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)sulfamoil)benzoico:**



Se sintetizó mediante el método A usando el cloruro de sulfonilo apropiado, *m/z* = 584 [M-1].

Ejemplo 69

**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)bencenosulfonamida:**

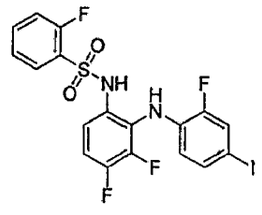


Se sintetizó mediante el método A usando el cloruro de sulfonilo apropiado, *m/z* = 503 [M-1].

720

Ejemplo 70

**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-2-fluorobencensulfonamida:**



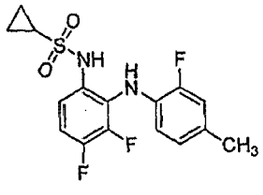
Se sintetizó mediante el método A usando el cloruro de sulfonilo apropiado, *m/z* = 521 [M-1].

**Procedimiento general D:** sustitución del átomo de yodo:

Una suspensión que contenía 1 eq. de yoduro de arilo, 1,5 equiv. del ácido borónico o éster borónico, 0,25 eq. $PdCl_2$(dppf) x DCM y 10 eq. de polvo de $K_2CO_3$ anhidro en una mezcla desoxigenada de dioxano y agua (3:1) se calentó en un reactor de microondas por 60 min a 115°C. Se extrajo usando $NH_4Cl$ acuoso/THF, y la fracción orgánica se secó usando $Na_2SO_4$. Los productos de la reacción crudos se purificaron usando cromatografía flash de columna (Si, EtOAc/Hexanos, o $CHCl_3$/MeOH). Rendimiento: 20-40%.

Ejemplo 71

**N-(3,4-difluoro-2-(2-fluoro-4-metilfenilamino)fenil)ciclopropansulfonamida;**



721

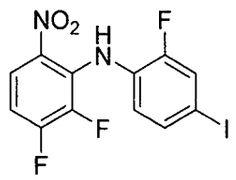
Procedimiento general D: $^1$H-RMN (500 MHz, $CDCl_3$): δ = 7,38-7,36 (m, 1H), 7,06-7,03 (q, 1H), 6,92-6,90 (1H), 6,73-6,72 (d, 1H), 6,63 (s, 1H, br), 6,37-6,33 (t, 1H), 5,54 (s, 1H, br), 2,42-2,39 (m, 1H), 2,25 (s, 3H), 1,14-1,11 (m, 2H), 0,94-0,90 (m, 2H); *m/z* = 355 [M-1].

Donde se resolvieron mezclas racémicas de compuestos quirales en enantiómeros separados, la frase "sustancialmente libre" del epímero, como se lo utiliza aquí, significa un exceso enantiomérico de al menos 90%.

Ejemplo 72

**N-(3,4-difluoro-2-(2-fluoro-4-(1H-pirazol-4-il)fenilamino)fenil)ciclopropansulfonamida**

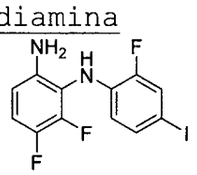
**Paso A:** 2,3-Difluoro-N-(2-fluoro-4-yodofenil)-6-nitroanilina:




A una solución de 2-fluoro-4-yodoanilina (11,40 g, 47 mmol) en 100 ml de THF anhidro a 0 °C, se agregó 47 ml de una solución 1M de LHMDS en THF (47 mmol) por goteo. El color de la solución se volvió morado oscuro. La solución se transfirió mediante cánulos a un embudo de vertido, y la solución (que contenía la base libre de amina) se agregó en pequeñas porciones a una solución de 2,3,4-trifluoronitrobenceno (8,321 g, 47,0

mmol) en THF anhidro (50 ml) a 0 °C. Luego de completarse la adición la mezcla se agitó bajo argón a temperatura ambiente por 15 horas. El volumen del solvente se redujo, seguido por extracción usando acetato de etilo y salmuera. La capa orgánica se secó sobre sulfato de sodio, el solvente se eliminó, y el aceite oscuro obtenido se purificó mediante cromatografía flash (EtOAc / hexano 1:5, $R_f$ = 0,58) para dar el producto crudo, el cual se volvió un sólido marrón luego de secar al vacío (rendimiento: 6,23 g, 33,6%). *m/z* = 393 $[M-1]^-$.

**Paso B:** 5,6-Difluoro-N1-(2-fluoro-4-yodofenil)bencen-1,2-diamina

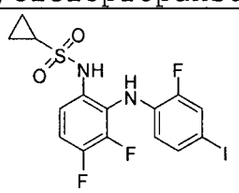



A una solución de nitro-diarilamina (6,23 g, 15,8 mmol) en 300 ml de etanol se agregó polvo de hierro (13,74 g, 246 mmol) y cloruro de amonio (13,59 g, 254 mmol) y la mezcla se calentó con agitación a una temperatura de baño de aceite de 100 °C por 14 horas. Se filtró y el residuo se lavó dos veces con etanol. El etanol se retiró al vacío, y el residuo se extrajo usando solución 1 M de acetato de etilo / NaOH. Durante la extracción, se formó más precipitado el cual se filtró y se descartó. Las capas orgánicas combinadas se

723

lavaron con salmuera y se secó sobre sulfato de sodio. El solvente se eliminó, y el producto crudo se recristalizó a partir de $CHCl_3$ / hexano (1:50). El producto se obtuvo como agujas marrones (2,094 g, 66%,). $R_f$ = 0,44 (EtOAc / Hex 1:3). $^1$H-RMN (500 MHz, $CDCl_3$): $\delta$ = 7,40-7,38 (dd, 1H, $J$ = 11,3 Hz, $J$ = 1,5 Hz). 7,25-7,23 (d, 1H, $J$ = 8,5 Hz), 6,97-6,92 (q, 1H, $J$ = 9 Hz), 6,51-6,48 (m, 1H), 6,24-6,21 (t, 1H, $J$ = 9 Hz), 5,3 (s, 1H, NH, br), 3,80 (s, 2H, $NH_2$, br); LRMS (ESI): $m/z$ = 365 $[M+H]^+$.

**Paso C:** N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)ciclopropansulfonamida:

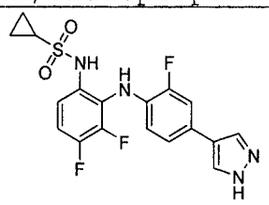



De acuerdo con el procedimiento general A, se hizo reaccionar 5,6-difluoro-N1-(2-fluoro-4-yodofenil)bencen-1,2-diamina con cloruro de ciclopropansulfonilo para obtener el producto deseado. (500 MHz, $CDCl_3$): $\delta$ = 7,38-7,37 (d, 1H), 7,35-7,34 (m, 1H), 7,27-7,26 (m, 1H), 7,20-7,0 (q, 1H), 6,68 (s, 1H, br), 6,15-6,12 (q, 1H), 5,65 (s, 1H, br), 3,25-3,20 (m, 1H), 2,4-2,3 (m, 2H), 2,0-1,8 (m, 2H); $m/z$ = 467 $[M-1]^-$ .

**Paso D:** N-(3,4-difluoro-2-(2-fluoro-4-(1H-pirazol-

724

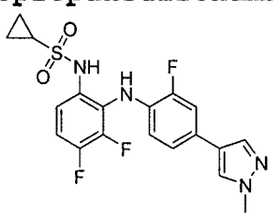
4-il)fenilamino)fenil)ciclopropansulfonamida:



Procedimiento general C : $^1$H-RMN (500 MHz, $CDCl_3$): δ = 8,00-7,90 (m, 2H), 7,30-7,20 (m, 2H), 7,15-7,10 (m, 1H), 7,05-7,00 (m, 1H), 6,70-6,60 (m, 1H), 2,40-2,35 (m, 1H), 1,05-1,0 (m, 2H), 0,95-0,85 (m, 2H); *m/z* = 407 $[M-1]^-$.

Ejemplo 73

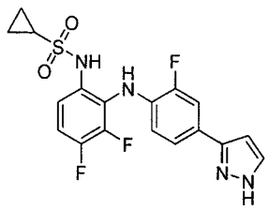
**N-(3,4-difluoro-2-(2-fluoro-4-(1-metil-1H-pirazol-4-il)fenilamino)fenil)ciclopropansulfonamida**



Procedimiento general C : $^1$H-RMN (500 MHz, $CDCl_3$): δ = 7,95 (s, 1H), 7,75 (s, 1H), 7,30-7,20 (m, 2H), 7,15-7,10 (m, 1H), 7,05-7,00 (m, 1H), 6,70-6,60 (m, 1H), 3,95 (s, 3H), 2,40-2,35 (m, 1H), 1,05-1,0 (m, 2H), 0,95-0,85 (m, 2H); *m/z* = 421 $[M-1]^-$

Ejemplo 74

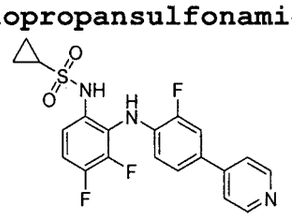
**N-(3,4-difluoro-2-(2-fluoro-4-(1H-pirazol-3-il)fenilamino)fenil)ciclopropansulfonamida**



Procedimiento general C : $^1$H-RMN (500 MHz, $CDCl_3$): δ = 7,90 (s, 1H), 7,80 (s, 1H), 7,30-7,20 (m, 2H), 7,15-7,10 (m, 1H), 7,05-7,00 (m, 1H), 6,70-6,60 (m, 1H), 3,95 (s, 3H), 2,40-2,35 (m, 1H), 1,05-1,0 (m, 2H), 0,95-0,85 (m, 2H); *m/z* = 407 $[M-1]^-$

Ejemplo 75

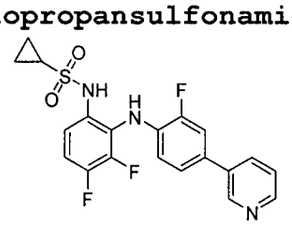
**N-(3,4-difluoro-2-(2-fluoro-4-(piridin-4-il)fenilamino)fenil)ciclopropansulfonamida**



Procedimiento general C : $^1$H-RMN (500 MHz, $CDCl_3$): δ = 8,62-8,61 (d, 2H), 7,43-7,41 (m, 4H), 7,23-7,22 (m, 1H), 7,16-7,11 (q, 1H), 6,61-6,58 (t, 1H), 6,11 (s, 1H, br), 2,53-2,50 (m, 1H), 1,21-1,10 (m, 2H), 1,02-0,99 (m, 2H); *m/z* = 418 $[M-1]^-$.

Ejemplo 76

**N-(3,4-difluoro-2-(2-fluoro-4-(piridin-3-il)fenilamino)fenil)ciclopropansulfonamida**

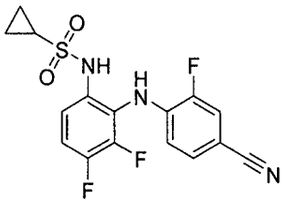


726

Procedimiento general C : $^1$H-RMN (500 MHz, [D6]-DMSO): δ = 9,45 (s, 1H), 8,91 (s, 1H), 8,54 (s, 1H), 8,07-8,06 (d, 1H), 7,76-7,70 (m, 2H), 7,46-7,34 (m, 2H), 7,34-7,33 (d, 2H), 6,80-6,78 (m, 1H), 0,86-0,79 (m, 4H); *m/z* = 418 $[M-1]^-$

Ejemplo 77

**N-(2-(4-ciano-2-fluorofenilamino)-3,4-difluorofenil)ciclopropansulfonamida**



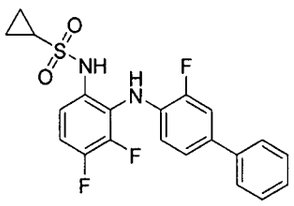
Una suspensión que contenía el yoduro de arilo (75,5 mg, 0,161 mmol), CuCN (46,6 mg, 0,520 mmol y $Pd(OAc)_2$ (0,47 mg) en 1 ml de DMF anhidro se calentó a 130 $^0$C por 60 min. en un reactor de microondas. La mezcla se extrajo usando salmuera / THF, y las fracciones orgánicas se secaron usando $Na_2SO_4$. La cromatografía flash de columna subsiguiente dio el producto como un semisólido rojo oscuro ($R_f$ = 0,42 (EtOAc/Hexanos 1:1). Rendimiento: 15 %.

*m/z* = 366 $[M-1]^-$.

Ejemplo 78

**N-(3,4-difluoro-2-(3-fluorobifenil-4-ilamino)fenil)ciclopropansulfonamida**

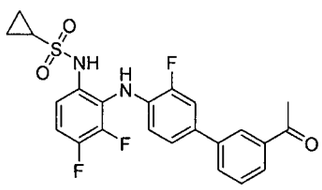
727



Procedimiento general C : $^1$H-RMN (500 MHz, $CDCl_3$): δ = 7,55-7,53 (m, 2H), 7,45-7,3 (m, 5H), 7,20-7,15 (d, 1H), 7,13-7,10 (q, 1H), 6,70 (s, 1H, br),6,60-6,55 (t, 1H), 5,75 (s, 1H, br), 2,53-2,50 (m, 1H), 1,21-1,10 (m, 2H), 1,02-0,99 (m, 2H); *m/z* = 417 $[M-1]^-$.

Ejemplo 79

**N-(2-(3'-acetil-3-fluorobifenil-4-ilamino)-3,4-difluorofenil)ciclopropansulfonamida**

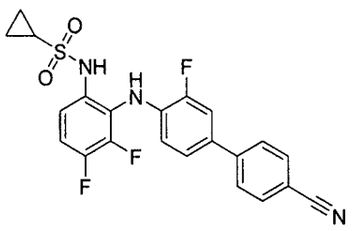


Procedimiento general C : $^1$H-RMN (500 MHz, $CDCl_3$): δ = 8,6 (s, 1H), 7,86-7,85 (d, 1H), 7,68-7,66 (d,1H), 7,49-7,46 (t, 1H), 7,38-7,33 (m, 2H), 7,20-7,18 (d, 1H), 7,09-7,03 (q, 1H), 6,90 (s, 1H, br), 6,57-6,54 (t, 1H), 5,90 (s, 1H), br), 2,61 (s, 3H), 2,46-2,43 (m, 1H), 1,15-1,13 (m, 2H), 0,94-0,91 (m, 2H); *m/z* = 459 $[M-1]^-$.

Ejemplo 80

**N-(2-(4'-ciano-3-fluorobifenil-4-ilamino)-3,4-difluorofenil)ciclopropansulfonamida**

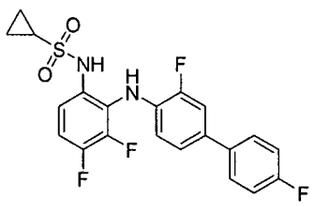
728



Procedimiento general C : $^1$H-RMN (500 MHz, $CDCl_3$): δ = 7,68-7,66 (m, 2H), 7,58-7,57 (m, 2H), 7,38-7,35 (m, 2H), 7,20-7,18 (d, 1H), 7,18-7,02 (q, 1H), 6,67 (s, 1H, br), 6,58-6,54 (t, 1H), 5,99 (s, 1H, br), 2,47-2,44 (m, 1H), 1,15-1,13 (m, 2H), 0,94-0,91 (m, 2H); *m/z* = 442 $[M-1]^-$.

Ejemplo 81

**N-(2-(3,4'-difluorobifenil-4-ilamino)-3,4-difluorofenil)ciclopropansulfonamida**

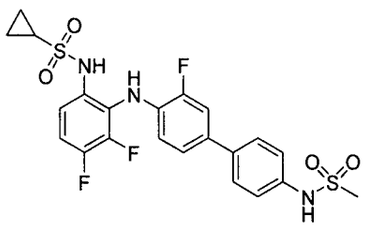


Procedimiento general C : $^1$H-RMN (500 MHz, $CDCl_3$): δ = 7,44-7,37 (m, 3H), 7,29-7,27 (d, 1H), 7,11-7,05 (m, 4H), 6,70 (s, 1H, br), 6,53-6,50 (t, 1H), 5,81 (s, 1H, br), 2,47-2,44 (m, 1H), 1,15-1,13 (m, 2H), 0,94-0,91 (m, 2H); *m/z* = 435 $[M-1]^-$.

Ejemplo 82

**N-(3,4-difluoro-2-(3-fluoro-4'-(metilsulfonamido)bifenil-4-ilamino)fenil)ciclopropansulfonamida**

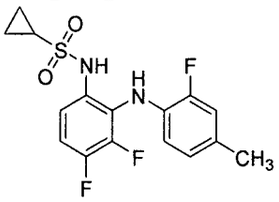
729.



Procedimiento general C : $^1$H-RMN (500 MHz, [D6]-DMSO): δ = 9,39 (s, 1H, br), 7,63-7,60 (m, 3H), 7,53-7,50 (d, 1H), 7,30-7,23 (m, 4H), 7,74-7,65 (m, 1H), 2,99 (s, 3H), 0,80-0,73 (m, 4H); *m/z* = 510 $[M-1]^-$.

Ejemplo 83

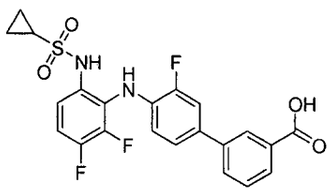
**N-(3,4-difluoro-2-(2-fluoro-4-metilfenilamino)fenil)ciclopropansulfonamida**



Procedimiento general C : $^1$H-RMN (500 MHz, $CDCl_3$): δ = 7,38-7,36 (m, 1H), 7,06-7,03 (q, 1H), 6,92-6,90 (1H), 6,73-6,72 (d, 1H), 6,63 (s, 1H, br), 6,37-6,33 (t, 1H), 5,54 (s, 1H, br), 2,42-2,39 (m, 1H), 2,25 (s, 3H), 1,14-1,11 (m, 2H), 0,94-0,90 (m, 2H); *m/z* = 355 $[M-1]^-$.

Ejemplo 84

**ácido 4'-(6-(ciclopropansulfonamido)-2,3-difluorofenilamino)-3'-fluorobifenil-3-carboxílico**

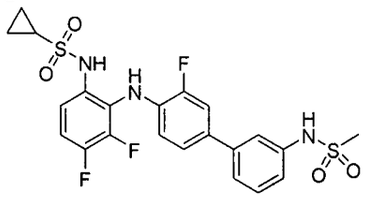


726

Procedimiento general C : $^1$H-RMN (500 MHz, [D4]-MeOH): δ = 8,21 (s, 1H), 7,93-7,91 (d, 1H), 7,73-7,72 (d, 1H), 7,47-7,43 (m, 2H), 7,33-7,31 (d, 2H), 7,15-7,12 (q, 1H), 6,71-6,68 (m, 1H), 2,51-2,46 (m, 1H), 0,94-0,93 (m, 2H), 0,88-0,87 (m, 2H); *m/z* = 499 $[M-1]^-$.

Ejemplo 85

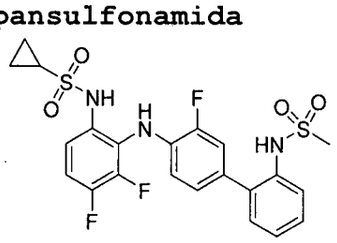
**N-(3,4-difluoro-2-(3-fluoro-3'-(metilsulfonamido)bifenil-4-ilamino)fenil)ciclopropansulfonamida**



Procedimiento general C : $^1$H-RMN (500 MHz, [D4]-MeOH): δ = 7,92 (s, 1H), 7,46-7,34 (m, 5H), 7,34-7,31 (d, 1H), 7,29-7,22 (m, 1H), 7,16-7,15 (q, 1H), 6,74-6,71 (m, 1H), 2,80 (s, 3H), 2,54-2,51 (m, 1H), 0,94-0,92 (m, 2H), 0,91-0,90 (m, 2H); *m/z* = 510 $[M-1]^-$.

Ejemplo 86

**N-(3,4-difluoro-2-(3-fluoro-2'-(metilsulfonamido)bifenil-4-ilamino)fenil)ciclopropansulfonamida**

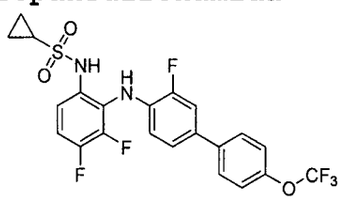


731

Procedimiento general C : $^1$H-RMN (500 MHz, [D4]-MeOH): δ = 7,50-7,49 (d, 1H), 7,40-7,32 (m, 4H), 7,29-7,28 (d, 1H), 7,26-7,10 (m, 2H), 6,73-6,71 (m, 1H), 2,80 (s, 3H), 2,51-2,49 (m, 1H), 0,94-0,92 (m, 2H), 0,91-0,90 (m, 2H); *m/z* = 510 $[M-1]^-$.

Ejemplo 87

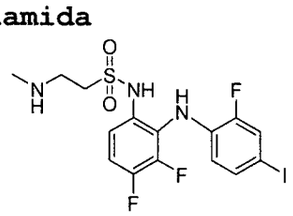
**N-(3,4-difluoro-2-(3-fluoro-4'-(trifluorometoxi)bifenil-4-ilamino)fenil)ciclopropansulfonamida**



Procedimiento general C : $^1$H-RMN (500 MHz, [D4]-MeOH): δ = 7,69-7,67 (d, 2H), 7,46-7,43 (d, 1H), 7,36-7,33 (m, 4H), 7,30-7,29 (q, 1H), 6,73-6,72 (m, 1H), 2,51-2,49 (m, 1H), 0,94-0,92 (m, 2H), 0,91-0,90 (m, 2H); *m/z* = 501 $[M-1]^-$.

Ejemplo 88

**N-(3,4-Difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-2-(metilamino) etansulfonamida**



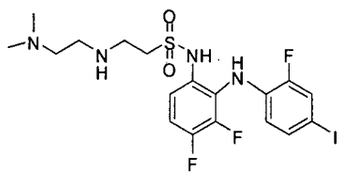
Procedimiento general D. $^1$H RMN (300 MHz, $CDCl_3$): δ 9,01 (br s, $D_2O$ intercambiable, 1H), 7,36 (dd, *J* = 2,1 & 10,5 Hz, 1H), 7,27 (m, 1H), 7,17 (m, 1H), 7,03 (dd, *J* = 9,0 & 16,8 Hz, 1H), 6,48 (s, $D_2O$ intercambiable, 1H), 6,31 (dt, *J* =

732

3,0, 8,7 & 17,4 Hz, 1H), 3,45 (br t. 2H). 3,31 (br s, 2H), 2,65 (s. 3H). 1,80(br s, $D_2O$ intercambiable, 1H).

Ejemplo 89

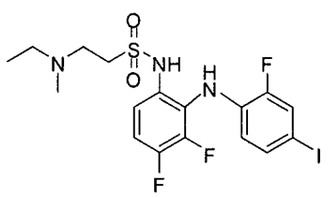
**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-2-(2-(dimetilamino)etilamino) etansulfonamida**



Procedimiento general D. $^1H$ RMN (300 MHz, $CDCl_3$): δ 7,35 (m, 1H), 7,25 (m, 1H), 7,18 (d, *J* = 8,7 Hz, 1H), 7,02 (dd, *J* = 8,7 & 18,0 Hz, 1H), 6,38 (m, 1H), 6,18 (dd, *J* = 8,7 & 17,1 Hz, 1H), 3,62 (t, *J* = 5,7 & 6,3 Hz, 2H), 3,35 (m, 2H), 3,26 (m, 2H), 3,26 (t, *J* = 5,7 & 6,6 Hz, 2H), 3,11 (t, *J* = 5,1 & 6,0 Hz, 2H), 2,85 (s, 6H).

Ejemplo 90

**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-2-(etil(metil)amino) etansulfonamida**

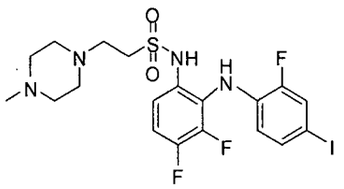


Procedimiento general D. $^1H$ RMN (300 MHz, ($CDCl_3$ + $D_2O$)): δ 7,39 (dd, *J* = 1,5 & 10,5 Hz, 1H), 7,31 (m, 2H), 7,07 (dd, *J* = 9,0 & 17,4 Hz, 1H), 6,30 (dt, *J* = 2,4, 9,0 & 17,4 Hz, 1H), 3,55 (t, *J* = 6,9 & 7,8 Hz, 2H), 3,38 (br t, *J* = 6,0 & 8,7 Hz, 2H), 3,05 (q, 2H), 2,69 (s, 3H), 1,31 (t, *J* = 7,2 Hz, 3H).

733

Ejemplo 91

**N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)-2-(4-metilpiperazin-1-il)etansulfonamida**



Procedimiento general D. $^1$H RMN (300 MHz, $CD_3OD$): δ 7,45 (dd, *J* = 2,1 & 10,8 Hz, 1H), 7,30 (m, 2H), 7,16 (dd, *J* = 9,6 & 17,7 Hz, 1H), 6,39 (dt, *J* = 3,3, 9,3 & 17,7 Hz, 1H), 3,26 (m, *J* = 7,5 Hz, 2H), 3,10 (br m, 6H), 2,87 (s, 3H), 2,82 (t, *J* = 7,5 Hz, 2H), 2,48 (br m, 4H).

**Actividad biológica *in vitro***

**Ejemplo 92**

Generación de los datos de IC50

Materiales y preparación de reactivos: Se subclonó el GST-MEK1 humano y el alelo constitutivamente activo GST-MEK1$^{CA}$ (que contiene las mutaciones Ser218Asp y Ser222Asp) en el vector de expresión de levadura pGEM4Z (Promega, Madison, WI) a partir del ADNc de MEK1 de tipo salvaje humano. GST-MEK1$^{CA}$ se expresó en *Escherichia coli* y se purificó parcialmente usando la resina de afinidad Glutatión-Sefarose 4B (Amersham Pharmacia Biotech, Piscataway, NJ). El alelo ERK2 se subclonó a partir del ADNc de MAPK2/Erk2 (de tipo salvaje) en el vector pUSEamp (Upstate Biotechnology, Inc., Waltham, MA) en el vector

734

pET21a (Novagen, Madison, WI) dando como resultado un alelo ERK2 marcado con histidina N-terminal de ratón. ERK2 se expresó y se purificó hasta homogeneidad [Zhang, 1993 N° 33]. La proteína básica de mielina (MBP) se obtuvo de Gibco BRL (Rockville, MD). La adenosina 5'-trifosfato (ATP) ([$\gamma$-$^{33}$P]) EasyTides (NEN Perkin Elmer, Wellesley, MA) era la fuente de la marca radioactiva para todas las reacciones con quinasas. El Raf-1 activado (truncado) y la MAPQuinasa 2/ERK2 activada se obtuvieron de Upstate, Inc. (Lake Placid, NY). Los geles premoldeados Criterion 4-20% se obtuvieron de Bio-Rad (Hercules, CA).

Determinación de la actividad enzimática: Los compuestos se diluyeron a partir de soluciones madre en dimetilsulfóxido (DMSO) en 1xHMNDE (HEPES 20 mM, pH 7,2, $MgCl_2$ 1 mM, NaCl 100 mM, DTT 1,25 mM, EDTA 0,2 mM). Un típico ensayo de 25 microlitros contenía 0,002 nanomoles de $MEK1^{CA}$, 0,02 nanomoles de ERK2, 0,25 de nanomoles MBP, 0,25 de nanomoles de no marcado ATP y 0,1 µCi de [$\gamma^{33}$P] ATP. El ensayo de selección comprendía esencialmente cuatro adiciones. Se dispensaron cinco µl de compuesto diluido en placas de ensayo de 96 cavidades. Luego se agregaron 10 µl de cóctel de enzimas 2,5x ($MEK1^{CA}$ y ERK2 solamente) a cada cavidad seguido por una preincubación durante 30 minutos a temperatura ambiente. A continuación se agregaron 10 µl de cóctel de sustrato 2,5x (ATP marcado y no marcado más MBP),

735

seguido por incubación durante 60 minutos a temperatura ambiente. Finalmente, se agregaron 100 µl de ácido tricloroacético 10% (TCA) y se incubaron durante 30 minutos a temperatura ambiente para detener la reacción y precipitar los productos proteicos marcados radioactivamente. Los productos de reacción se cosecharon sobre placas filtrantes de fibra de vidrio de 96 cavidades prehumedecidas con agua y pirofosfato 1%. La placa filtrante se lavó luego 5 veces con agua. El agua se desplazó con etanol absoluto y se dejó que la placa se secara al aire durante 30 minutos a temperatura ambiente. Se aplicó manualmente un sello de recubrimiento y se dispensaron 40 µl de cóctel de centelleo en cada cavidad. Se aplicó un sello superior y la placa se contó en el TopCount por dos segundos por cavidad.

En determinados experimentos se usó una versión truncada de MEK que requiere de activación por la Raf quinasa.

**Ejemplo 93**

Generación de los datos de EC50

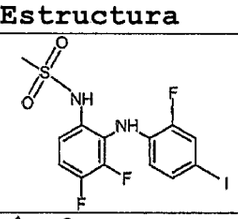
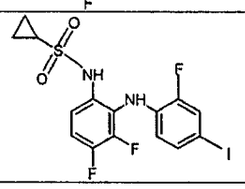
Los efectos de los compuestos en la célula se determinaron por transferencia Western para ERK fosforilada. Se plaquearon células de cáncer de mama MDA-MB-231 en una placa de 48 cavidades a 20.000 células por cavidad y se cultivaron en un incubador con $CO_2$ humidificado a 37°. Al día siguiente, el medio de crecimiento (DMEM + suero fetal

736

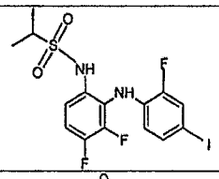
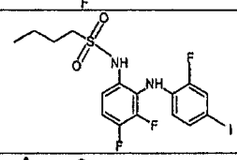
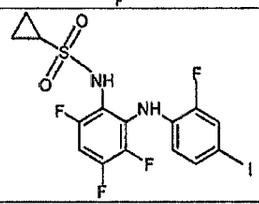
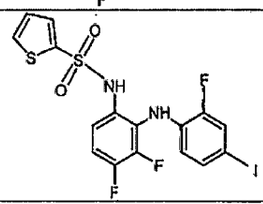
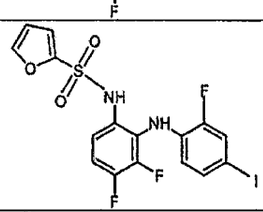
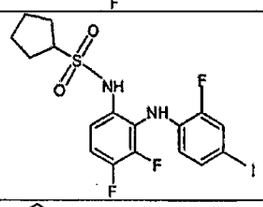
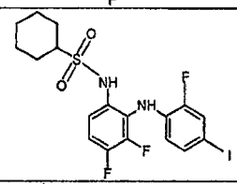
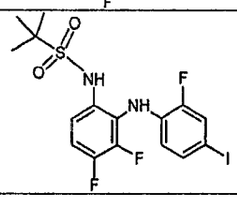
bovino 10%) se removió y se reemplazó por medio de deprivación (DMEM + suero fetal bovino 0,1%). Las células se incubaron en el medio de deprivación durante dieciséis horas y luego se trataron con un rango de concentraciones de compuesto por treinta minutos. Después de la incubación con el compuesto, las células fueron estimuladas con EGF 100 ng/ml durante cinco minutos. A continuación, las células se lisaron y analizaron mediante transferencia Western usando un anticuerpo monoclonal generado contra ERK fosforilada. La señal se amplificó usando un anticuerpo secundario conjugado con un colorante del IR-cercano y se detectó con un escáner Licor Odyssey. Se cuantificó la intensidad de la señal y este dato se usó para generar curvas de dosis-respuesta y efectuar los cálculos de EC50.

Leyenda: A, $EC_{50}$ = < 2,0 nM; B, $EC_{50}$ = 2,0-15 nM; C, $EC_{50}$ = 15 nM-100 nM;

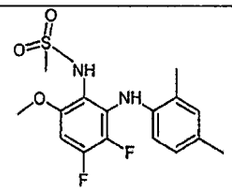
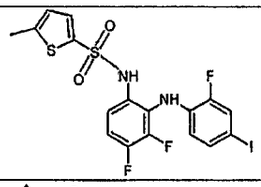
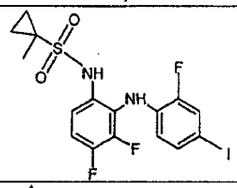
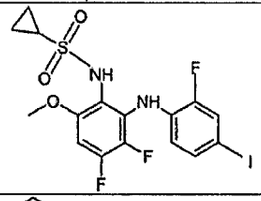
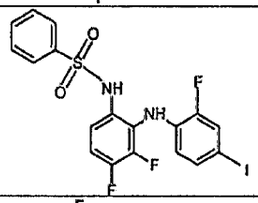
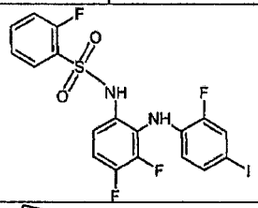
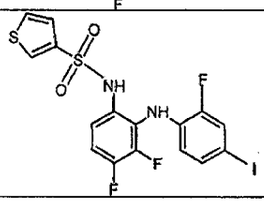
D, $EC_{50}$ > 100 nM, $IC_{50}$ < 20 µM; F, $EC_{50}$ > 100 nM, $IC_{50}$ > 20 µM

| **N° de compuesto** | **Estructura** | **Actividad, µM** |
|---|---|---|
| 1000 |  | A |
| 1001 |  | A |

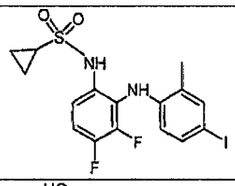
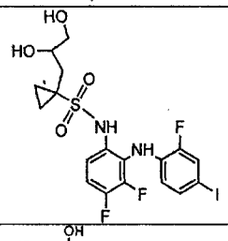
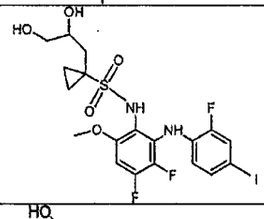
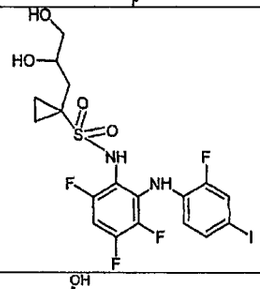
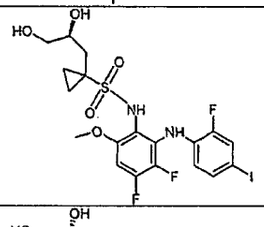
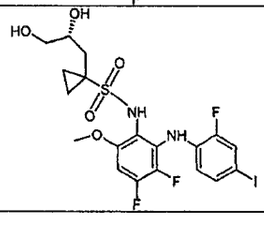
737

| N° de compuesto | Estructura | Actividad, µM |
|---|---|---|
| 1002 |  | B |
| 1003 |  | C |
| 1004 |  | C |
| 1005 |  | C |
| 1006 |  | C |
| 1007 |  | C |
| 1008 |  | C |
| 1009 |  | C |

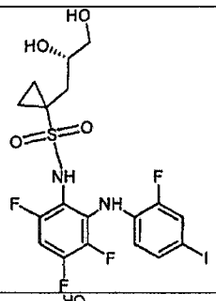
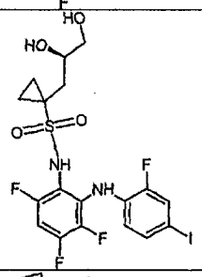
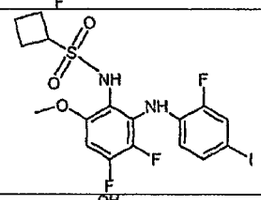
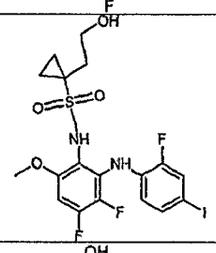
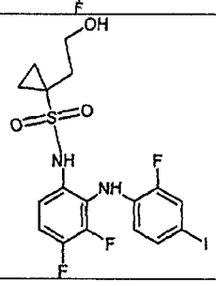
738

| N° de compuesto | Estructura | Actividad, µM |
|---|---|---|
| 1010 |  | A |
| 1011 |  | C |
| 1012 |  | B |
| 1013 |  | B |
| 1014 |  | C |
| 1015 |  | D |
| 1016 |  | C |

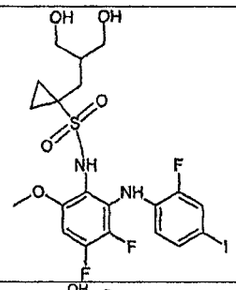
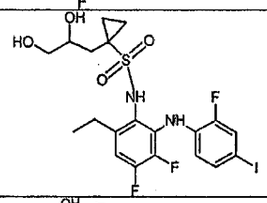
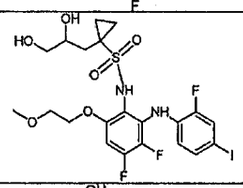
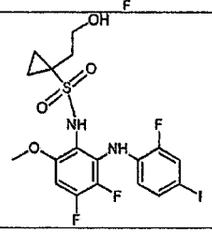
739

| N° de compuesto | Estructura | Actividad, µM |
|---|---|---|
| 1017 |  | B |
| 1018 (Racémico) |  | A |
| 1019 (Racémico) |  | A |
| 1020 (Racémico) |  | A |
| 1021 (isómero S) Compuesto A |  | A |
| 1022 (isómero R) Compuesto B |  | B |

740

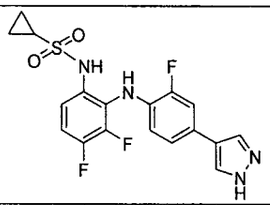
| N° de compuesto | Estructura | Actividad, µM |
|---|---|---|
| 1023 (isómero R) |  | B |
| 1024 (isómero S) |  | B |
| 1025 |  | B |
| 1026 |  | A |
| 1027 |  | A |

741

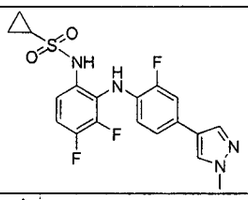
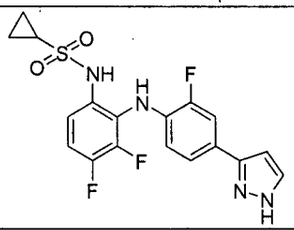
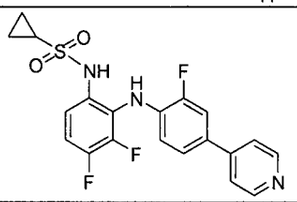
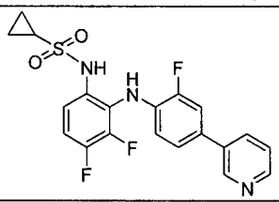
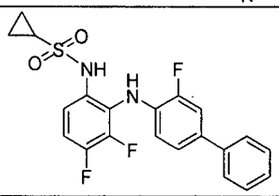
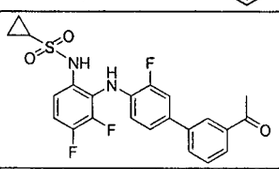
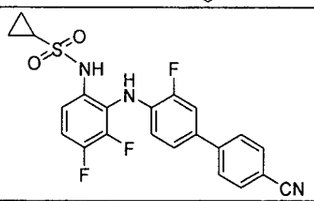
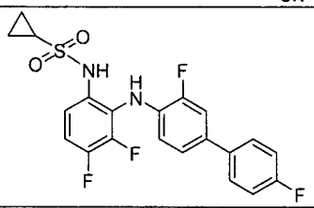
| N° de compuesto | Estructura | Actividad, µM |
|---|---|---|
| 1028 |  | A |
| 1029 |  | C |
| 1030 |  | C |
| 1031 |  | A |

Leyenda: A, $EC_{50}$ = < 2,0 nM; B, $EC_{50}$ = 2,0-15 nM; C, $EC_{50}$ = 15 nM-100 nM;

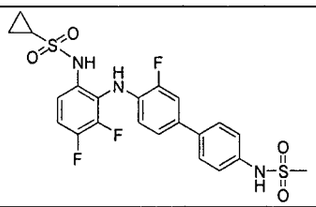
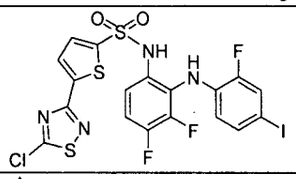
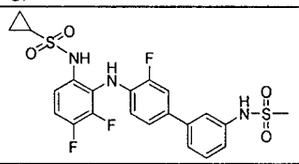
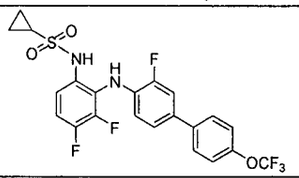
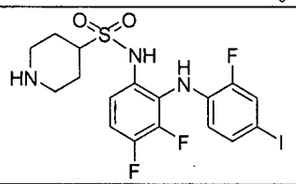
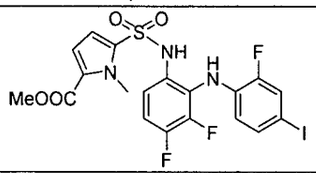
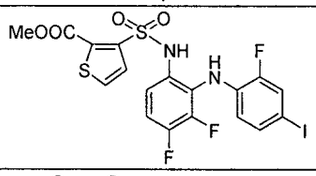
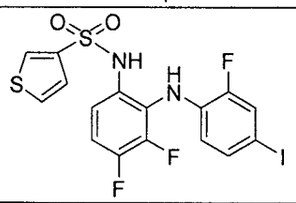
D, $EC_{50}$ =100 nM - 200 nM; E, $EC_{50}$ > 200 nM; ND = no determinado aún

| N° CPD | Estructura | $EC_{50}$ ELISA de MDA pERK |
|---|---|---|
| **0497618** |  | **E** |

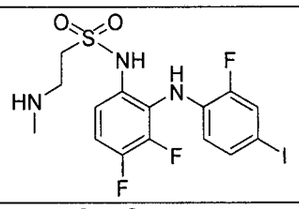
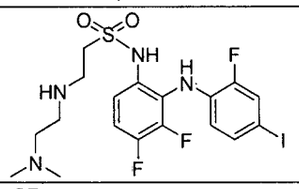
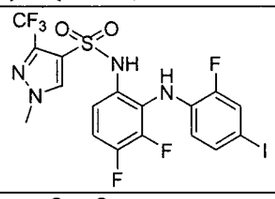
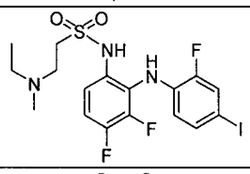
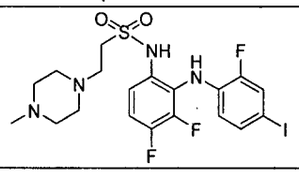
742

| N° CPD | Estructura | $EC_{50}$ ELISA de MDA pERK |
|---|---|---|
| 0497620 |  | E |
| 0497654 |  | D |
| 0497688 |  | E |
| 0497689 |  | E |
| 0497692 |  | E |
| 0499266 |  | E |
| 0499267 |  | ND |
| 0499268 |  | ND |

743

| N° CPD | Estructura | $EC_{50}$ ELISA de MDA pERK |
|---|---|---|
| 0499271 |  | E |
| 0530701 |  | D |
| 0530716 |  | ND |
| 0530717 |  | ND |
| 0561599 |  | C |
| 0561608 |  | C |
| 0620926 |  | E |
| 0620927 |  | C |

744

| N° CPD | Estructura | $EC_{50}$ ELISA de MDA pERK |
|---|---|---|
| 0621002 |  | C |
| 0621016 |  | C |
| 0621026 |  | D |
| 0621029 |  | D |
| 0621030 |  | ND |

**Actividad biológica *in vivo***

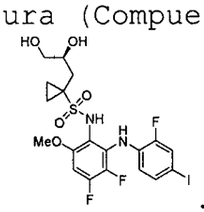
**Ejemplo 94**

Los compuestos y las composiciones que se describen en la presente son de utilidad para el tratamiento o la profilaxis de una o más enfermedades incluyendo, pero en un sentido no limitativo, cáncer, enfermedad de intestino inflamatorio (IBD), psoriasis y artritis reumatoide (RA). Los compuestos y las composiciones que se describen en la presente también son de utilidad para el tratamiento o la profilaxis de una vez o dos veces por día por vía oral de

745

una o más enfermedades incluyendo, pero en un sentido no limitativo, cáncer, IBD, psoriasis y RA.

En este ejemplo se describen pruebas *in vivo* del compuesto de la siguiente estructura (Compuesto A, preparado como se describe en la presente):




.

Se implantaron tumores humanos en ratones nu/nu. El compuesto A se administró por vía oral durante 14 días una vez que los tumores eran de un tamaño de 100 $mm^3$ aproximadamente. La inhibición del crecimiento tumoral (TGI) se determinó después de 14 días de tratamiento como la reducción en el tamaño de los tumores en los grupos tratados versus controles de vehículo. El tiempo hasta el punto final (TTE) se calculó como el tiempo para que el tumor alcanzara el volumen de punto final especificado o el último día del estudio, cualquiera que fuera el primero. El resultado del tratamiento se determinó a partir del porcentaje de retardo del crecimiento tumoral (%TGD), definido como el porcentaje de incremento en la mediana de TTE de ratones tratados versus control tratados con vehículo. Los animales también fueron monitoreados por las respuestas de regresión. Los niveles de pERK en tumores y cerebro se determinaron mediante transferencias Western y se correlacionaron con los niveles en plasma del Compuesto A

746

para el estudio farmacodinámico/farmacocinético. Se evaluaron numerosos modelos de tumores con diferentes dosis y regímenes de dosificación. El tratamiento con 25 ó 50 mg/kg una vez por día (QD) mostró un %TGD estadísticamente significativo en tumores de melanoma A375, tumores de cáncer de colon Colo205 y tumores epidermoides A431. Se observó un TGI estadísticamente significativo para la dosificación oral a 25 mg/kg QD para estos modelos de tumores, así como en tumores de cáncer de colon HT29. Se evaluó el efecto de diferentes regímenes de dosificación en xenoinjertos A375. Aunque 100 mg/kg de Compuesto A administrado por vía oral una vez cada dos días mostró un %TGD estadísticamente significativo (91%), no fue tan eficaz como los tratamientos QD a 25 mg/kg (143% TGD) o 50 mg/kg (233% TGD). La dosificación dos veces por día (BID) también fue más eficaz que la dosificación QD medido según el valor de %TGI. La dosificación a 12,5 mg/kg BID resultó en un 79,5% de TGI en comparación con un 51,7% para 25 mg/kg QD de Compuesto A. La dosificación a 25 mg/kg BID resultó en 110,1% de TGI en comparación con un 69,9% de TGI para 50 mg/kg QD. Un estudio farmacodinámico/farmacocinético en xenoinjertos Colo205 muestra inhibición de formación de pERK en los tumores, en tanto se observó una inhibición mínima en cerebro, lo cual sugiere una potente actividad anti-tumoral con una penetración limitada en el CNS.

747

El compuesto A es un potente inhibidor de MEK1/2 que suprime el crecimiento de células tumorales *in vitro* e *in vivo*. El estado BRAF determina la sensibilidad a la inhibición del crecimiento por el compuesto en un crecimiento dependiente del anclaje pero no en un crecimiento independiente del anclaje o en xenoinjertos. El mantenimiento de una inhibición de MEK adecuada en todo el intervalo de dosificación parece ser más importante que los niveles pico debido a la mayor eficacia con una dosificación más frecuente. El compuesto A tiene un perfil de pk favorable en humanos, con la dosis terapéutica proyectada, en base a los resultados para el xenoinjerto, de 20-40 mg/día en seres humanos.

**Ejemplo 94A**

Inhibición del crecimiento de células cancerosas ($GI_{50}$)

La inhibición del crecimiento dependiente del anclaje se midió usando el reactivo CellTiterGlo después de 48 hs de tratamiento con el Compuesto A de células cultivadas en placas de 384 cavidades. Los ensayos crecimiento independiente del anclaje empleaban el reactivo MTS (metantiosulfonato) después de 7 días de tratamiento de células cultivadas en un medio que contiene agarosa 0,15% o sobre placas a las que no se unen las células (A431). Los valores de inhibición del crecimiento ($GI_{50}$) se muestran en la siguiente tabla.

748

| Línea de células tumorales | Estado BRAF | $GI_{50}$ dependiente del anclaje (nM ± d.e.) | $GI_{50}$ independiente del anclaje (nM ± d.e.) |
|---|---|---|---|
| Melanoma A375 | V600E | 67 ± 12 | 68 ± 34 |
| Colon Colo205 | V600E | 74 ± 45 | 33 ± 16 |
| Colon HT29 | V600E | 70 ± 12 | No determinado |
| A431 epidermoide | Normal | >10.000 | 65 ± 19 |

**Ejemplo 94B**

Actividad anti-tumoral de xenoinjertos

Se implantaron en ratones nu/nu hembra células de melanoma A375, tumor de colon Colo205, tumor epidermoide A431 o tumor de colon HT-29, y se dejaron crecer hasta 100-200 $mm^3$. El compuesto A o vehículo se administró por vía oral (25 mg/kg, 50 mg/kg o 100 mg/kg), una vez por día, durante 14 días. Se graficaron los volúmenes tumorales promedio para los grupos de vehículo y tratados y se muestran en la FIG. 1.

**Ejemplo 94C**

Inhibición del crecimiento tumoral (TGI) 25 mg/kg QD

Se calculó la inhibición del crecimiento tumoral para los grupos tratados con 25 mg/kg de compuesto A para los

749

xenoinjertos de tumores indicados. La inhibición del crecimiento tumoral se midió al final de la dosificación una vez por día durante 14 días y se calculó de acuerdo con:

$$\%TGI = 100 \times 1 - \frac{\text{(volumen tumoral tratado}_{final} - \text{volumen tumoral}_{inicial})}{\text{(volumen tumoral tratado con vehículo}_{final} - \text{volumen tumoral}_{inicial})}$$

El rango para A375 y Colo205 representa valores de 2 estudios separados.

| Xenoinjerto tumoral | % TGI | Valor p |
|---|---|---|
| Melanoma A375 | 52-72** | <0,001 |
| Colon Colo205 | 70-123** | <0,001 |
| Colon HT29 | 56 | <0,001 |
| A431 epidermoide | 67 | <0,001 |

**Regresiones que se notaron durante el transcurso del experimento

**Ejemplo 94D**

$ED_{50}$ en xenoinjertos de Colo205

Se implantaron células tumorales Colo205 en ratones nu/nu macho. Después de 10 días, los animales fueron randomizados según el tamaño tumoral (rango 126-256 $mm^3$) y tratados con paclitaxel (IV, QODx5), vehículo o Compuesto A (PO, QDx14).

Los parámetros farmacocinética se obtuvieron a partir de la dosificación de ratones Balb/c con 25 mg/kg de Compuesto A y extrapolación de los valores para los grupos

750

de dosis inferior y se muestran en la siguiente tabla.

| Grupo | n | Régimen de tratamiento | | Volumen tumoral inicial ($mm^3$) | Volumen tumoral del día 15 ($mm^3$) | % TGI | $C_{máx}$ (µg/ml) | $C_{min}$ (µg/ml) | AUC (µg-hs/ml) |
|---|---|---|---|---|---|---|---|---|---|
| | | Agente | (mg/kg) | | | | | | |
| 1 | 10 | Vehículo | - | 185±11,1 | 2093±174 | - | - | - | - |
| 2 | 10 | Paclitaxel | 30 | 184±9,8 | 113±9,6 | 104* | - | - | - |
| 3 | 10 | Compuesto A | 2,5 | 184±9,8 | 1187±127 | 47* | 0,99 | 0,003 | 5,5 |
| 4 | 10 | | 5 | 183,8±9,8 | 1175±104 | 48* | 1,97 | 0,006 | 11,0 |
| 5 | 10 | | 10 | 185,1±11,7 | 1045±160 | 55* | 3,94 | 0,012 | 22,0 |
| 6 | 10 | | 25 | 185,1±11,7 | 762±81 | 70* | 9,85 | 0,029 | 55,0 |

*P<0,001

**Ejemplo 94E**

Inhibición del crecimiento tumoral con xenoinjertos de A375

Se administró el Compuesto A 50 mg/kg QD, 25 mg/kg BID, 50 mg/kg QD y 12,5 mg/kg BID a ratones con xenoinjerto de A375. Se calculó el %TGI y se graficó y se muestra en la FIG. 2.

**Ejemplo 94F**

Concentraciones plasmáticas en ratones

Se implantaron células tumorales A375 en ratones nu/nu hembra, y se dejaron crecer hasta 100-200 $mm^3$. Luego se administró el Compuesto A o vehículo por vía oral una vez por día (QD) o dos veces por día (BID) (50 mg/kg QD, 25 mg/kg BID, 50 mg/kg QD y 12,5 mg/kg BID). La inhibición del crecimiento tumoral se midió al final de la dosificación una vez por día durante 14 días y se calculó de acuerdo con:

$$\%TGI = 100 \times 1 - \frac{(\text{volumen tumoral tratado}_{final} - \text{volumen tumoral}_{inicial})}{(\text{volumen tumoral tratado con vehículo}_{final} - \text{volumen tumoral}_{inicial})}$$

751

| | | | | |
|---|---|---|---|---|
| AUC (µg·hs/ml) | 132,5 | 117,0 | 66,5 | 78,0 |
| Cmáx (µg/ml) | 23,8 | 10,2 | 11,9 | 7,8 |
| $C_{mín}$ (µg/ml) | 0,06 | 1,24 | 0,03 | 0,49 |
| $C_{min}$ de la fracción libre (ng/ml) | 0,117 | 2,48 | 0,059 | 0,986 |

Significancia estadística = Prueba Logrank

**Ejemplo 94G**

Tumores de xenoinjerto en ratón e inhibición de la actividad MEK en cerebro

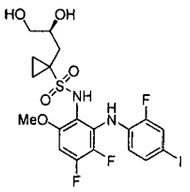
Los ratones nu/nu hembra implantados con células tumorales Colo205 recibieron una sola dosis de vehículo o Compuesto A a razón de 2,5, 5, 10 ó 25 mg/kg. Los niveles de compuesto se determinaron en muestras de plasma y los niveles de pERK se determinaron en muestras de tumor y de cerebro recolectadas a las 2, 6, 12 y 24 hs después de administrar la dosis. Los niveles de pERK de las transferencias Western se cuantificaron usando LI-COR Odyssey, normalizados para los niveles de ERK total y se compararon con los niveles tratados con vehículo para determinar el % de inhibición de MEK. Se graficó la inhibición de MEK en tumores o cerebro para cada ratón con la correspondiente concentración en plasma de Compuesto A en el animal. La regresión no lineal permitió obtener un valor de $EC_{50}$ de 73 nM para la inhibición de MEK en tumores. El valor de $EC_{50}$ en cerebro era >5000 nM.

En la FIG. 3 se muestra un gráfico de concentración en plasma (log nM) contra % de inhibición de pERK.

752

**Preparación de cápsulas**

**Ejemplo 95A**

Se prepararon cápsulas de gelatina dura de tamaño 1 azules que contienen una composición de una mezcla en polvo seco con cantidades de 1 mg y de 10 mg de Compuesto A (véase la tabla que se muestra en el ejemplo 93 anterior) de la siguiente estructura: 

.

El Compuesto A se preparó como se describe en la presente y luego se micronizó usando un molino de energía fluida (Spiral Jet Mill, molido electrónicamente, con un diámetro de la cámara de molienda de 50 mm; a 50°; tobera con anillo de 4 x 0,8 mm; un diámetro de tobera del inyector de 0,8 mm y una distancia de tobera del inyector de 3 mm). El Compuesto A y una porción de la celulosa microcristalina se mezclaron y se tamizaron a través de una malla N° 20 mesh y se agregaron a un mezclador por difusión rotatorio (mezclador V). La celulosa microcristalina remanente se tamizó a través de una malla N° 20 mesh, se agregó a los materiales en el mezclador y se mezcló. La croscarmellosa sódica y el laurilsulfato de sodio se tamizaron a través de una malla N° 20, se agregaron a los materiales en el mezclador y se mezclaron. La mezcla en polvo se hizo pasar a través de un molino de rodillos rotatorio (Quadro CoMil) y

753

se volvió a introducir en el mezclador y se continuó con el mezclado. El estearato de magnesio se tamizó a través de una malla N° 20 mesh y se mezcló con la mezcla de polvo molido. La mezcla de polvo se rellenó en cápsulas de tamaño 1. Las cápsulas de 10 mg se marcaron con bandas para su identificación.

La composición de las cápsulas se muestra en la siguiente tabla:

| **Componente** | **Cápsula de 1 mg** | | **Cápsula de 10 mg** | |
|---|---|---|---|---|
| | **mg/unidad** | **%** | **mg/unidad** | **%** |
| Compuesto A | 1,0 | 0,4 | 10,0 | 4,2 |
| Celulosa microcristalina, NF (Avicel PH302) | 222,2 | 92,6 | 213,2 | 88,8 |
| Croscarmellosa sódica, NF (Ac-Di-Sol) | 12,0 | 5,0 | 12,0 | 5,0 |
| Laurilsulfato de sodio, NF | 2,4 | 1,0 | 2,4 | 1,0 |
| Estearato de magnesio, NF | 2,4 | 1,0 | 2,4 | 1,0 |
| Total[a] | 240,0 | 100,0 | 240,0 | 100,0 |
| Recubrimiento de cápsula de gelatina dura de tamaño 1 azul | 1 | | 1 | |

[a]Peso del relleno blanco ajustado en base a la potencia real de la mezcla.

La fórmula para lote típica para un lote de 10.000 cápsulas de 1 mg era:

| **Componentes de la fórmula del lote** | **Cantidad por lote (g) (para 10.000 unidades)** |
|---|---|
| Compuesto A | 10,0 |
| Celulosa microcristalina, NF (Avicel PH302) | 2222 |
| Croscarmellosa sódica, NF (Ac-Di-Sol) | 120,0 |
| Laurilsulfato de sodio, NF | 24,0 |

754

| | |
|---|---|
| Estearato de magnesio, NF | 24,0 |
| Peso total del relleno[a] | 2400 |
| Recubrimiento de cápsula de gelatina dura de tamaño 1 azul | 10.000 |

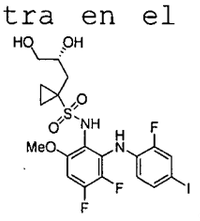
[a]Peso del relleno blanco ajustado en base a la potencia real de la mezcla.

La fórmula para lote típica para un lote de 10.000 cápsulas de 10 mg era:

| **Componentes de la fórmula del lote** | **Cantidad por lote (g) (para 10.000 unidades)** |
|---|---|
| Compuesto A | 100,0 |
| Celulosa microcristalina, NF (Avicel PH302) | 2132 |
| Croscarmellosa sódica, NF (Ac-Di-Sol) | 120,0 |
| Laurilsulfato de sodio, NF | 24,0 |
| Estearato de magnesio, NF | 24,0 |
| Peso total del relleno[a] | 2400 |
| Recubrimiento de cápsula de gelatina dura de tamaño 1 azul[b] | 10.000 |

[a]Peso del relleno blanco ajustado en base a la potencia real de la mezcla.

**Ejemplo 95B**

Se preparan cápsulas de gelatina dura de tamaño 1 azules que contienen una composición de una mezcla en polvo seco con cantidades de 1 mg y de 10 mg de Compuesto B (véase la tabla que se muestra en el ejemplo 93 anterior) de la siguiente estructura: 

.

El Compuesto B se prepara como se describe en la

755

presente y luego se micronizó usando un molino de energía fluida (Spiral Jet Mill, molido electrónicamente, con un diámetro de la cámara de molienda de 50 mm; a 50°; tobera con anillo de 4 x 0,8 mm; un diámetro de tobera del inyector de 0,8 mm y una distancia de tobera del inyector de 3 mm). El Compuesto B y una porción de la celulosa microcristalina se mezclan y se tamizan a través de una malla N° 20 mesh y se agregaron a un mezclador por difusión rotatorio (mezclador V). La celulosa microcristalina remanente se tamiza a través de una malla N° 20 mesh, se agrega a los materiales en el mezclador y se mezcla. La croscarmellosa sódica y el laurilsulfato de sodio se tamizan a través de una malla N° 20, se agregan a los materiales en el mezclador y se mezclan. La mezcla en polvo se hace pasar a través de un molino con impulsor rotatorio (Quadro CoMil) y se vuelve a introducir en el mezclador y se continúa con el mezclado. El estearato de magnesio se tamiza a través de una malla N° 20 mesh y se mezcla con la mezcla de polvo molido. La mezcla de polvo se rellena en cápsulas de tamaño 1. Las cápsulas de 10 mg se marcan con bandas para su identificación.

La composición de las cápsulas se muestra en la siguiente tabla:

| **Componente** | **Cápsula de 1 mg** | | **Cápsula de 10 mg** | |
|---|---|---|---|---|
| | **mg/unidad** | **%** | **mg/unidad** | **%** |
| Compuesto B | 1,0 | 0,4 | 10,0 | 4,2 |
| Celulosa microcristalina, | 222,2 | 92,6 | 213,2 | 88,8 |

756

| | | | | |
|---|---|---|---|---|
| NF (Avicel PH302) | | | | |
| Croscarmellosa sódica, NF (Ac-Di-Sol) | 12,0 | 5,0 | 12,0 | 5,0 |
| Laurilsulfato de sodio, NF | 2,4 | 1,0 | 2,4 | 1,0 |
| Estearato de magnesio, NF | 2,4 | 1,0 | 2,4 | 1,0 |
| Total[a] | 240,0 | 100,0 | 240,0 | 100,0 |
| Recubrimiento de cápsula de gelatina dura de tamaño 1 azul | 1 | | 1 | |

**Actividad en humanos *in vivo***

**Ejemplo 96**

Administración de las cápsulas descritas en el ejemplo 95A en pacientes humanos con cáncer

Se administra una sola dosis de la composición para cápsulas de 1 mg o 10 mg descrita anteriormente en el ejemplo 95A a pacientes humanos con cáncer. Para una dosis de 2 mg, los pacientes recibieron 2 cápsulas x 1 mg; para una dosis de 4 mg, los pacientes recibieron 4 cápsulas x 1 mg; para una dosis de 6 mg, los pacientes recibieron 6 cápsulas x 1 mg; para una dosis de 10 mg, los pacientes recibieron 1 cápsula x 10 mg; para una dosis de 20 mg, los pacientes recibieron 2 cápsulas x 10 mg.

Se monitorearon los perfiles de concentración-tiempo y se muestran en la FIG. 4 y en la siguiente tabla:

| **Dosis (mg)** | **Día** | **Tmáx (hs)** | **$C_{máx}$ (ng/ml)** | **$C_{12hs}$ (ng/ml)** | **$AUC_{0-12hs}$ (ng·hs/ml)** | **$AUC_\tau$ (ng*h/ml)** |
|---|---|---|---|---|---|---|
| 2 | 1 | 2,0 | 0,111 | 0,0378 | 0,700 | ND |
| | 35 | 2,0 | 0,202 | 0,0756 | ND | 2,07 |
| 4 | 1 | 1,5 | 0,292 | 0,134 | 2,26 | ND |
| | 35 | 1,0 | 0,544 | 0,310 | ND | 5,12 |
| 10 | 35 | ND | 1,57 | 1,01 | ND | 14,3 |
| 20 | 35 | ND | 3,28 | 2,19 | ND | 29,5 |

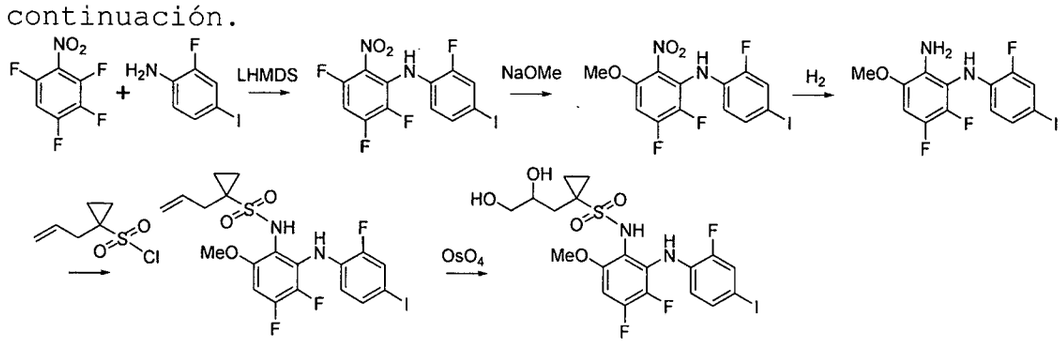
757

**Formas polimórficas cristalinas**

**Ejemplo 97:**

Preparación de N-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)fenil)-1-(2,3-dihidroxipropil) ciclopropan-1-sulfonamida

La N-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)fenil)-1-(2,3-dihidroxipropil) ciclopropan-1-sulfonamida se preparó de acuerdo con los procedimientos descritos previamente (véase la publicación de la Solicitud de Patente Internacional WO 2007/014011) y como se indica a continuación.




Paso A: 2-fluoro-N-(2,3,5-trifluoro-6-nitrofenil)-4-iodobencenamina

Se agregó lentamente una solución de hexametildisilazida de litio 1,0 M ($LiN(SiMe_3)_2$) "LHMDS" (15,37 ml, 15,37 mmol) a una solución agitada de 2-fluoro-4-iodoanilina (3,64 g, 15,37 mmol) en THF seco (100 ml) bajo nitrógeno a -78°C y se continuó agitando a -78°C durante otra hora. Se agregó 2,3,4,6-tetrafluoronitrobenceno y la se dejó que la mezcla de reacción se calentara hasta alcanzar

758

temperatura ambiente y se continuó agitando durante otras 16 horas. Se agregó acetato de etilo (200 ml) y la fase orgánica se lavó con agua, se secó sobre sulfato de sodio y se purificó adicionalmente por cromatografía en columna para proveer el producto como un sólido amarillo (3,75 g, 59,24%). $M-H^+$: 410,9. $^1H$ RMN (DMSO, 300 MHz): 6,85 (t, 1H); 7,38 (d, 1H); 7,62 (m, 2H); 8,78 (s, 1H).

Paso B: 2-fluoro-N-(2,3-difluoro-5-metoxi-6-nitrofenil)-4-iodobencenamina

Se enfrió una solución agitada de (2-fluoro-4-iodo-fenil)-(2,3,5-trifluoro-6-nitro-fenil)-amina (1,23 g, 3 mmol) en THF seco (25 ml) bajo nitrógeno a -78°C y se agregó lentamente una solución de metóxido de sodio 25% (0,68 ml, 0,3 mmol). Se dejó que la mezcla de reacción se calentara hasta alcanzar temperatura ambiente y se continuó agitando durante otras 16 horas. La TLC indicó una reacción incompleta. Se agregó acetato de etilo (100 ml) a la mezcla de reacción y la capa orgánica se lavó con agua, se secó sobre sulfato de sodio y se purificó también por cromatografía en columna para proveer el compuesto deseado como un sólido amarillo (0,6 g, 47,6%). $m/z$ = 424 $[M+H]^+$.

Paso C: 5,6-difluoro-$N^1$-(2-fluoro-4-iodofenil)-3-metoxibencen-1,2-diamina

Se agregó cloruro de amonio (1,18 g, 20,16 mmol) y hierro en polvo (1,15 g, 21,44 mmol) a una solución agitada

754

de (2,3-difluoro-5-metoxi-6-nitro-fenil)-(2-fluoro-4-iodo-fenil)-amina (0,57 g, 1,34 mmol) en etanol (20 ml). La mezcla se agitó a reflujo durante 16 horas, se enfrió a temperatura ambiente, se filtró sobre Celite y el filtrado se concentró hasta sequedad. El residuo resultante se tomó en acetato de etilo, se lavó con agua, se secó sobre sulfato de sodio y se purificó también por cristalización a partir de etanol para proveer el producto como un sólido blancuzco (0,47 g, 90,3%). $M-H^+$: 393,2. $^1H$ RMN (DMSO, 300 MHz): 3,76 (s, 3H); 6,1 (t, 1H); 6,8 - 7,0 (m, 1H); 7,2 (d, 1H); 7,35 (s, 1H); 7,42 (d, 1H).

Paso D: 1-alil-N-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)ciclopropan-1-sulfonamida

A una solución agitada de 5,6-difluoro-$N^1$-(2-fluoro-4-iodofenil)-3-metoxibenceno-1,2-diamina (1 eq) en piridina anhidra (5 ml/mmol) se agregó cloruro de 1-alil-ciclopropansulfonilo (1 - 5 eq). La mezcla de reacción se agitó a 40°C durante 48 horas. La mezcla de reacción se particionó con agua y acetato de etilo. La capa orgánica se lavó con salina, se secó ($MgSO_4$) y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna flash sobre sílice para obtener el producto del título. $^1H$-RMN ($CDCl_3$; 300 MHz): δ 7,417 (dd, 1H), 7,309 (s, 1H), 7,25 (m, 1H), 6,89 (m, 1H), 6,52(m, 1H), 6,427 (m, 1H), 6,03 (s, 1H), 5,668 (m, 1H), 5,11 (t, 1H), 3,9 (s, 3H),

760

2,75 (d, 2H), 1,21 (m, 2H), 0,767 (m, 2H).

Paso E: N-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil) ciclopropan-1-sulfonamida

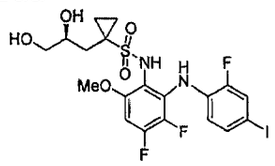
Se disolvieron los compuestos 1-alil-N-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)ciclopropan-1-sulfonamida (97 mg, 0,18 mmol) y N-óxido de 4-metilmorfolina (21 mg, 0,18 mmol) en THF (8 ml). Se agregó tetróxido de osmio a temperatura ambiente (0,018 mmol, 0,13 ml, 4% en $H_2O$) y la mezcla de reacción se agitó a temperatura ambiente durante 16 horas. Se agregó acetato de etilo y la fase orgánica se lavó con agua, se secó ($MgSO_4$) y se concentró bajo presión reducida. El residuo se purificó por cromatografía sobre gel de sílice (eluyentes: EtOAc/ MeOH) para obtener el producto del título (0,80 g, 78 %). $^1$H-RMN ($CDCl_3$; 300 MHz): δ 7,38 (dd, J = 1,7 y 10,3 Hz,1H), 7,26 (m, 1H), 7,14 (s, 1H), 6,87 (s, 1H), 6,53 (dd, J = 6,8 & 11,4 Hz, 1H), 6,43 (m, 1H), 4,06 (m, 1H), 3,89 (s, 3H), 3,63 (dd, J = 3,7 & 11,1 Hz, 1H), 3,49 (dd, J = 6,4 & 11,1 Hz, 1H), 2,3 (dd, J = 9,7 & 16,1 Hz, 1H), 1,77 (dd, J = 1,9 & 16,0 Hz, 1H), 1,37 (m, 1H), 1,25 (m, 1H), 1,21 (m, 2H), 0,86 (m, 2H); *m/z* = 571 $[M-1]^-$.

**Ejemplo 98:**

Preparación de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)

761

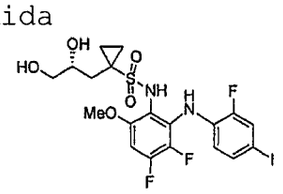
ciclopropan-1-sulfonamida



El isómero S puro se obtuvo mediante separación por HPLC quiral de la mezcla racémica. $^1$H-RMN ($CDCl_3$; 300 MHz): δ 7,38 (dd, J = 1,7 y 10,3 Hz,1H), 7,26 (m, 1H), 7,14 (s, 1H), 6,87 (s, 1H), 6,53 (dd, J = 6,8 & 11,4 Hz, 1H), 6,43 (m, 1H), 4,06 (m, 1H), 3,89 (s, 3H), 3,63 (dd, J = 3,7 & 11,1 Hz, 1H), 3,49 (dd, J = 6,4 & 11,1 Hz, 1H), 2,3 (dd, J = 9,7 & 16,1 Hz, 1H), 1,77 (dd, J = 1,9 & 16,0 Hz, 1H), 1,37 (m, 1H), 1,25 (m, 1H), 1,21 (m, 2H), 0,86 (m, 2H); *m/z* = 571 $[M-1]^-$.

**Ejemplo 99:**

Preparación de N-(R)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil) ciclopropan-1-sulfonamida



El isómero R puro se obtuvo mediante separación por HPLC quiral de la mezcla racémica. $^1$H-RMN ($CDCl_3$; 300 MHz): δ 7,38 (dd, J = 1,7 y 10,3 Hz,1H), 7,26 (m, 1H), 7,14 (s, 1H), 6,87 (s, 1H), 6,53 (dd, J = 6,8 & 11,4 Hz, 1H), 6,43 (m, 1H), 4,06 (m, 1H), 3,89 (s, 3H), 3,63 (dd, J = 3,7 & 11,1 Hz, 1H), 3,49 (dd, J = 6,4 & 11,1 Hz, 1H), 2,3 (dd, J =

762

9,7 & 16,1 Hz, 1H), 1,77 (dd, J = 1,9 & 16,0 Hz, 1H), 1,37 (m, 1H), 1,25 (m, 1H), 1,21 (m, 2H), 0,86 (m, 2H); *m/z* = 571 $[M-1]^-$.

**Ejemplo 100:**

Preparación del polimorfo cristalino, forma A, de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida

*Preparación i)*

Se cargó N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida (216,10 g) en un Erlenmeyer de 4 l equipado con una barra de agitación magnética grande y una placa de agitación magnética termostatizada. Se agregó acetato de etilo (aproximadamente 600 ml, obtenido de Fisher). Se comenzó con calentamiento y agitación para formar una suspensión marrón. La mezcla se llevó a reflujo suave y se agregó acetato de etilo adicional (aproximadamente 200 ml) para lograr la disolución completa obteniéndose una solución de color marrón oscuro. Se agregó lentamente heptano (obtenido de Acros) por porciones a la solución a reflujo a una velocidad tal que todos los precipitados formados con cada adición eran disueltos rápidamente y se mantuvo el reflujo. Con la adición de 2 l de heptanos a la solución los sólidos formados se

763

disolvieron muy lentamente a reflujo. Se detuvo el calentamiento y se dejó que la mezcla de cristalización se equilibrara a temperatura ambiente con agitación durante 16 h. Se desarrolló una capa espesa de material cristalino alrededor de la superficie del vidrio sobre el período de envejecimiento. La suspensión resultante se equilibró en un baño de hielo/agua con agitación. La suspensión se filtró sobre un embudo Buchner de 25 cm revestido con medio filtrante Whatman N° 1. Los cristales recolectados se lavaron con heptanos (1 l) y se dejó que secaran al aire bajo vacío. Los cristales se secaron además a 40°C/ <1 torr sobre un período de 20 hs para obtener el producto como un sólido cristalino de color rosa (160,99 g, 77,2%).

*Preparación ii)*

Se cargaron los compuestos N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida (13,2 g) y acetato de etilo (30 ml) en un Erlenmeyer equipado con una barra de agitación magnética grande y una placa de agitación magnética termostatizada. Se comenzó con calentamiento y agitación a reflujo suave para lograr una disolución completa obteniéndose una solución de color marrón oscuro. Se agregaron lentamente heptanos por porciones a la solución a reflujo a una velocidad tal que todos los precipitados formados con cada adición eran disueltos rápidamente y se

764

mantuvo el reflujo hasta que la adición de heptanos a la solución causó que los sólidos formados se disolvieran muy lentamente a reflujo (~90 ml de heptanos). Se detuvo el calentamiento y se dejó que la mezcla de cristalización se equilibrara a temperatura ambiente con agitación durante 16 h. Se desarrolló una capa espesa de material cristalino alrededor de la superficie del vidrio sobre el período de envejecimiento. La suspensión resultante se equilibró en un baño de hielo/agua con agitación. La suspensión se filtró sobre un embudo Buchner revestido con medio filtrante Whatman N° 1. Los cristales recolectados se lavaron con heptanos y se dejó que se secaran al aire bajo vacío. Los cristales se secaron además a 40°C/ <1 torr sobre un período de 20 hs para obtener el producto como un sólido cristalino de color rosa.

*Preparación iii)*

Se cargaron los compuestos N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida (44,8g) y acetato de etilo (750 ml) en un Erlenmeyer equipado con una barra de agitación magnética grande y una placa de agitación magnética termostatizada. Se comenzó con calentamiento y agitación a reflujo suave para lograr una disolución completa obteniéndose una solución de color marrón oscuro. Se agregaron lentamente hexanos por porciones a la solución

765

a reflujo a una velocidad tal que todos los precipitados formados con cada adición eran disueltos rápidamente y se mantuvo el reflujo hasta que la adición de hexanos a la solución causó que los sólidos formados se disolvieran muy lentamente a reflujo (~2 l de hexanos). Se detuvo el calentamiento y se dejó que la mezcla de cristalización se equilibrara a temperatura ambiente con agitación durante 16 h. Se desarrolló una capa espesa de material cristalino alrededor de la superficie del vidrio sobre el período de envejecimiento. La suspensión resultante se equilibró en un baño de hielo/agua con agitación. La suspensión se filtró sobre un embudo Buchner revestido con medio filtrante Whatman N° 1. Los cristales recolectados se lavaron y se dejó que se secaran al aire bajo vacío. Los cristales se secaron además a 40°C/ <1 torr sobre un período de 20 hs para obtener el producto como un sólido cristalino de color rosa.

**Ejemplo 101:**

Preparación del polimorfo cristalino de N-(R)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil) ciclopropan-1-sulfonamida

Se carga N-(R)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida (216,10 g) en un Erlenmeyer de 4 l equipado con una barra de agitación

766

magnética grande y una placa de agitación magnética termostatizada. Se agrega acetato de etilo (600 ml aproximadamente). Se comienza con calentamiento y agitación para formar una suspensión marrón. La mezcla se lleva a reflujo suave y se agrega acetato de etilo adicional (aproximadamente 200 ml) para lograr la disolución completa obteniéndose una solución de color marrón oscuro. Se carga heptano a la solución lentamente y por porciones a la solución a reflujo a una velocidad tal que todos los precipitados que se forman con cada adición se disuelven rápidamente y se mantiene el reflujo. Con la adición de 2 l de heptanos a la solución los sólidos formados se disuelven muy lentamente a reflujo. Se detiene el calentamiento y se deja que la mezcla de cristalización se equilibre a temperatura ambiente con agitación durante 16 h. Se desarrolla una capa espesa de material cristalino alrededor de la superficie del vidrio durante el período de envejecimiento. La suspensión resultante se equilibra en un baño de hielo/agua con agitación. La suspensión se filtra sobre un embudo Buchner de 25 cm revestido con medio filtrante Whatman N° 1. Los cristales recolectados se lavan con heptanos (1 l) y se deja que se sequen al aire bajo vacío. Los cristales se secan además a 40 °C/ <1 torr sobre un período de 20 hs.

**Ejemplo 102:**

767

Generación de los datos de IC50

Materiales y preparación de reactivos: Se subclonó el GST-MEK1 humano y el alelo constitutivamente activo GST-MEK1$^{CA}$ (que contiene las mutaciones Ser218Asp y Ser222Asp) en el vector de expresión de levadura pGEM4Z (Promega, Madison, WI) a partir del ADNc de MEK1 de tipo salvaje humano. GST-MEK1$^{CA}$ se expresó en *Escherichia coli* y se purificó parcialmente usando la resina de afinidad Glutatión-Sefarose 4B (Amersham Pharmacia Biotech, Piscataway, NJ). El alelo ERK2 se subclonó a partir del ADNc de MAPK2/Erk2 (de tipo salvaje) en el vector pUSEamp (Upstate Biotechnology, Inc., Waltham, MA) en el vector pET21a (Novagen, Madison, WI) dando como resultado un alelo ERK2 marcado con histidina N-terminal de ratón. ERK2 se expresó y se purificó hasta homogeneidad [Zhang, 1993 N° 33]. La proteína básica de mielina (MBP) se obtuvo de Gibco BRL (Rockville, MD). La adenosina 5'-trifosfato (ATP) ([$\gamma$-$^{33}$P]) EasyTides (NEN Perkin Elmer, Wellesley, MA) era la fuente de la marca radioactiva para todas las reacciones con quinasas. El Raf-1 activado (truncado) y la MAPQuinasa 2/ERK2 activada se obtuvieron de Upstate, Inc. (Lake Placid, NY). Los geles premoldeados Criterion 4-20% se obtuvieron de Bio-Rad (Hercules, CA).

Determinación de la actividad enzimática: Los compuestos se diluyeron a partir de soluciones madre en

766

dimetilsulfóxido (DMSO) en 1xHMNDE (HEPES 20 mM, pH 7,2, $MgCl_2$ 1 mM, NaCl 100 mM, DTT 1,25 mM, EDTA 0,2 mM). Un típico ensayo de 25 microlitros contenía 0,002 nanomoles de $MEK1^{CA}$, 0,02 nanomoles de ERK2, 0,25 de nanomoles MBP, 0,25 de nanomoles de no marcado ATP y 0,1 µCi de [$\gamma^{33}P$] ATP. El ensayo de selección comprendía esencialmente cuatro adiciones. Se dispensaron cinco µl de compuesto diluido en placas de ensayo de 96 cavidades. Luego se agregaron 10 µl de cóctel de enzimas 2,5x ($MEK1^{CA}$ y ERK2 solamente) a cada cavidad seguido por una preincubación durante 30 minutos a temperatura ambiente. A continuación se agregaron 10 µl de cóctel de sustrato 2,5x (ATP marcado y no marcado más MBP), seguido por incubación durante 60 minutos a temperatura ambiente. Finalmente, se agregaron 100 µl de ácido tricloroacético 10% (TCA) y se incubaron durante 30 minutos a temperatura ambiente para detener la reacción y precipitar los productos proteicos marcados radioactivamente. Los productos de reacción se cosecharon sobre placas filtrantes de fibra de vidrio de 96 cavidades prehumedecidas con agua y pirofosfato 1%. La placa filtrante se lavó luego 5 veces con agua. El agua se desplazó con etanol absoluto y se dejó que la placa se secara al aire durante 30 minutos a temperatura ambiente. Se aplicó manualmente un sello de recubrimiento y se dispensaron 40 µl de cóctel de centelleo en cada cavidad. Se aplicó un sello superior y la placa se

769

contó en el TopCount por dos segundos por cavidad. En determinados experimentos se usó una versión truncada de MEK que requiere de activación por la Raf quinasa.

**Ejemplo 103:**

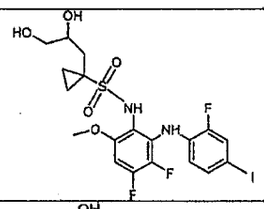
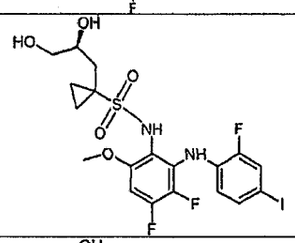
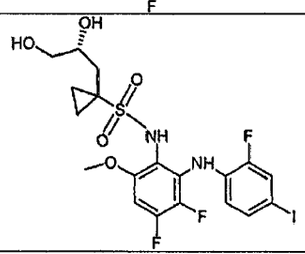
Generación de los datos de EC50

Los efectos de los compuestos en la célula se determinaron por transferencia Western para ERK fosforilada. Se plaquearon células de cáncer de mama MDA-MB-231 en una placa de 48 cavidades a 20.000 células por cavidad y se cultivaron en un incubador con $CO_2$ humidificado a 37°. Al día siguiente, el medio de crecimiento (DMEM + suero fetal bovino 10%) se removió y se reemplazó con medio de deprivación (DMEM + suero fetal bovino 0,1%). Las células se incubaron en el medio de deprivación durante dieciséis horas y luego se trataron con un rango de concentraciones de compuesto por treinta minutos. Después de la incubación con el compuesto, las células fueron estimuladas con EGF 100 ng/ml durante cinco minutos. A continuación, las células se lisaron y analizaron mediante transferencia Western usando un anticuerpo monoclonal generado contra ERK fosforilada. La señal se amplificó usando un anticuerpo secundario conjugado con un colorante del IR-cercano y se detectó con un escáner Licor Odyssey. Se cuantificó la intensidad de la señal y este dato se usó para generar curvas de dosis-respuesta y efectuar los cálculos de EC50.

**Ejemplo 104:**

Datos de la actividad de los compuestos

Los compuestos descritos en los ejemplos 1, 2 y 3 fueron evaluados en los ensayos que se describieron precedentemente. Los resultados se resumen en la siguiente tabla (A, $EC_{50}$ = < 2,0 nM; B, $EC_{50}$ = 2,0-15 nM):

| **N° de compuesto** | **Estructura** | **Actividad** |
|---|---|---|
| Ej. 97 (Racémico) |  | A |
| Ej. 98 (isómero S) |  | A |
| Ej. 99 (isómero R) |  | B |

**Ejemplo 105:**

Datos de XRPD

Las pruebas de XPRD se condujeron con un difractómetro Inel XRG-3000, equipado con un detector curvo sensible a la posición con un rango 2θ de 120°. Los datos en tiempo real se recolectaron usando radiación Cu Kα a una resolución de 0,03 °2θ. El voltaje y amperaje del tubo se definieron en 40 kV y 30 mA, respectivamente. Los patrones se obtuvieron

771

entre 2,5 y 40 °2θ para facilitar las comparaciones directas de patrones. Se prepararon muestras de (S)-N-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida (sintetizada como se describe en la presente) para el análisis empaquetándolas en capilares de vidrio de paredes delgadas. Cada capilar se movió sobre la cabeza del goniómetro que es impulsada por un motor para permitir que el capilar gire durante la adquisición de datos. Las muestras fueron analizadas durante 5 minutos. La calibración del instrumento se efectuaba diariamente usando un estándar de referencia de silicona. La FIG. **5** es un gráfico de un patrón de difracción de rayos X de polvo (PXRD) de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida, Forma A. La FIG. **7** es un gráfico de los patrones de difracción de rayos X de polvo (PXRD) de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida, Forma A (parte superior) y amorfo (parte inferior).

**Ejemplo 106:**

Calorimetría por barrido diferencial (DSC)

Los análisis se llevaron a cabo con un calorímetro de barrido diferencial Q1000 de TA Instruments. El instrumento se calibró usando indio como material de referencia. La

772

muestra se colocó en una bandeja de aluminio estándar para DSC con una configuración de tapa no ajustada, y se registró el peso exacto. Para determinar la temperatura de transición vítrea ($T_g$) de material amorfo, la celda de muestra se cicló varias veces entre -40°C y 140°C. La temperatura final se llevó con rampas a 150°C. La $T_g$ se informa a partir del punto de inflección del último ciclo de transición. La FIG. **6** es un gráfico de un termograma DSC modulado de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida (Forma A). El trazado del gráfico indica el flujo de calor normalizado en vatios/gramo (W/g) versus la temperatura de la muestra medida en °C.

**Ejemplo 107:**

Sorción/desorción dinámica de vapor (DVS)

Los datos de sorción/desorción de humedad se recolectaron con un analizador de sorción de vapor VTI SGA-100. Los datos de sorción y desorción se recolectaron sobre un rango de 5% a 95% de humedad relativa (HR) a intervalos de 10% de HR bajo purga de nitrógeno. No se secaron las muestras antes del análisis. Los criterios de equilibrio usados para el análisis eran menos del 0,0100% de cambio en peso en 5 minutos, con un tiempo máximo de equilibrio de 3 horas si no se cumplía con el criterio de peso. Los datos no fueron corregidos por el contenido inicial de humedad de las

773

muestras. Se usaron cloruro de sodio y polivinilpirrolidina como estándares de calibración. En la FIG. **8** se muestra una isoterma DVS de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida (Forma A). El material exhibe un cambio de peso despreciable durante el experimento.

**Ejemplo 108:**

Termogravimetría (TG)

Los análisis se llevaron a cabo con un analizador termogravimétrico TA Instrument 2950. Los estándares de calibración eran níquel y Alumel™. Cada muestra se colocó en una bandeja para muestras de aluminio y se introdujo en el horno de TG. Las muestras se equilibraron a 25°C, y luego se calentaron bajo un flujo de nitrógeno a una velocidad de calentamiento de 10 °C/min, hasta una temperatura final de 350°C. En la FIG. **9** se muestra un termograma TG de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida (Forma A) donde se demuestra una pérdida de peso despreciable hasta los 140°C, lo cual indica que el polimorfo, forma A, no está solvatado.

**Ejemplo 109:**

Prueba de cáncer *in vitro*

Se cultivaron líneas de células tumorales humanas en

774

medio RPMI 1640 que contiene suero fetal bovino 5% y L-glutamina 2 mM. Las células se inoculan en placas de microtitulación de 96 cavidades en 100 µl a densidades de plaqueado que varían en un rango entre 5.000 y 40.000 células/cavidad dependiendo del tiempo de duplicación de las líneas celulares individuales. Después de inocular las células, las placas de microtitulación se incuban a 37° C, 5% de $CO_2$, 95% de aire y 100% de humedad relativa durante 24 hs antes de la adición de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida.

Después de 24 hs, se fijaron dos placas de cada línea celular *in situ* con TCA, para representar una medida de la población celular para cada línea celular en el momento de la adición de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida (Tz). La N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida se solubilizó en dimetilsulfóxido a una concentración 400 veces mayor que la concentración de prueba máxima final deseada y se guardó congelado antes del uso. En el momento de la adición, se descongela una alícuota de concentrado congelado y se diluye hasta dos veces la concentración de prueba máxima final deseada con medio completo que contiene

775

gentamicina 50 µg/ml. Se realizaron cuatro diluciones en serie, de 10 veces o ½ log, adicionales para proveer un total de cinco concentraciones más el control. Se agregan alícuotas de 100 µl de estas diferentes diluciones a las cavidades de microtitulación apropiadas que ya contienen 100 µl de medio, dando como resultado las concentraciones finales requeridas.

Después de la adición de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida, las placas se incubaron por 48 hs adicionales a 37°C, 5% de $CO_2$, 95% de aire y 100% de humedad relativa. Para las células adherentes, el ensayo se terminó con la adición de TCA frío. Las células se fijan *in situ* mediante la adición suave de 50 µl de TCA frío 50% (p/v) (concentración final, TCA 10%) y se incuban durante 60 minutos a 4°C. Se descarta el sobrenadante y las placas se lavan cinco veces con agua corriente y se secan al aire. Se agrega una solución de sulforodamina B (SRB) (100 µl) a 0,4% (p/v) en ácido acético 1% a cada cavidad, y las placas se incuban durante 10 minutos a temperatura ambiente. Después de la tinción, se remueve el colorante no unido mediante cinco lavados con ácido acético 1% y las placas se secan al aire. A continuación se solubiliza el colorante unido con base trizma 10 mM, y se lee la absorbancia con un lector de

776

placas automático a una longitud de onda de 515 nm. Para las células en suspensión, la metodología es la misma excepto que el ensayo se termina fijando las células asentadas en el fondo de las cavidades por adición suave de 50 µl de TCA 80% (concentración final, TCA 16%). El porcentaje de crecimiento se calculó para cada uno de los niveles de concentración de droga usando las siete mediciones de absorbancia [tiempo cero, (Tz), crecimiento control, (C), y crecimiento de prueba en la presencia de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida a los cinco niveles de concentración (Ti)]. El porcentaje de inhibición del crecimiento se calcula de la siguiente manera:

$$\text{Porcentaje de inhibición del crecimiento} = \frac{(Ti-Tz)}{(C-Tz)} \times 100 \quad \text{(concentraciones donde } Ti \geq Tz\text{)}$$

$$\text{Porcentaje de inhibición del crecimiento} = \frac{(Ti-Tz)}{Tz} \times 100 \quad \text{(concentraciones donde } Ti < Tz\text{)}$$

Se calcularon tres parámetros de dosis-respuesta. La inhibición del crecimiento del 50 % (GI50) se calculó a partir de [(Ti-Tz)/(C-Tz)] x 100 = 50, que es la concentración que da como resultado una reducción del 50% en el incremento neto de la proteína (medido por tinción SRB) en células control durante la incubación con la droga. La concentración de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-

777

dihidroxipropil)ciclopropan-1-sulfonamida que da como resultado una inhibición total del crecimiento (TGI) se calculó a partir de Ti = Tz. El valor de LC50 (concentración de droga que da como resultado una reducción del 50% de proteína medida al final del tratamiento con la droga en comparación con la que se midió al principio) indicativo de una pérdida neta de células después del tratamiento se calcula a partir de [(Ti-Tz)/Tz] x 100 = -50. Los valores se calcularon para cada uno de estos tres parámetros si se alcanzaba el nivel de actividad; sin embargo, si no se alcanzaba el efecto o si era excedido, el valor para dicho parámetro se expresa como mayor o menor que la concentración máxima o mínima evaluada.

Se examinaron paneles correspondientes a leucemia, cáncer de pulmón de células no pequeñas, cáncer de colon, cáncer del CNS, melanoma, cáncer de ovario, cáncer renal, cáncer de próstata y cáncer de mama, para las líneas celulares indicadas y los resultados se muestran a continuación.

| **Panel** | **Línea celular** | **GI50 (μM)** | **LC50 (μM)** | **TGI (μM)** |
|---|---|---|---|---|
| Leucemia | CCRF-CEM | 17,378 | 100,000 | 60,256 |
| Leucemia | HL-60(TB) | 0,010 | 100,000 | 100,000 |
| Leucemia | K-562 | 6,607 | 100,000 | 100,000 |
| Leucemia | MOLT-4 | 10,965 | 100,000 | 69,183 |
| Leucemia | RPMI-8226 | 26,915 | 100,000 | 100,000 |
| Leucemia | SR | 38,019 | 100,000 | 100,000 |
| Cáncer de pulmón de células no pequeñas | A549/ATCC | 0,589 | 100,000 | 64,565 |

| Panel | Línea celular | GI50 (μM) | LC50 (μM) | TGI (μM) |
|---|---|---|---|---|
| Cáncer de pulmón de células no pequeñas | EKVX | 0,214 | 61,660 | 13,804 |
| Cáncer de pulmón de células no pequeñas | HOP-62 | 0,069 | 42,658 | 12,589 |
| Cáncer de pulmón de células no pequeñas | HOP-92 | 0,047 | 58,884 | 0,324 |
| Cáncer de pulmón de células no pequeñas | NCI-H226 | 3,311 | 74,131 | 24,547 |
| Cáncer de pulmón de células no pequeñas | NCI-H23 | 0,056 | 74,131 | 2,884 |
| Cáncer de pulmón de células no pequeñas | NCI-H322M | 0,162 | 46,774 | 15,488 |
| Cáncer de pulmón de células no pequeñas | NCI-H460 | 3,631 | 52,481 | 19,498 |
| Cáncer de pulmón de células no pequeñas | NCI-H522 | 5,248 | 100,000 | 29,512 |
| Cáncer de colon | HCC-2998 | 0,010 | 0,457 | 0,035 |
| Cáncer de colon | HCT-116 | 0,195 | 67,608 | 12,589 |
| Cáncer de colon | HCT-15 | 0,603 | 60,256 | 16,982 |
| Cáncer de colon | HT29 | 0,026 | 29,512 | 3,090 |
| Cáncer de colon | KM12 | 0,229 | 48,978 | 13,490 |
| Cáncer de colon | SW-620 | 0,039 | 66,069 | 12,589 |
| Cáncer del CNS | SF-268 | 2,570 | 100,000 | 25,704 |
| Cáncer del CNS | SF-295 | 9,333 | 53,703 | 23,442 |
| Cáncer del CNS | SF-539 | 1,514 | 60,256 | 20,417 |
| Cáncer del CNS | SNB-19 | 0,251 | 75,858 | 24,547 |
| Cáncer del CNS | SNB-75 | 0,302 | 34,674 | 4,467 |
| Cáncer del CNS | U251 | 0,891 | 44,668 | 17,378 |
| Melanoma | LOX IMVI | 0,195 | 38,905 | 10,715 |
| Melanoma | MALME-3M | 0,010 | 19,953 | 0,014 |
| Melanoma | M14 | 0,015 | 29,512 | 0,166 |
| Melanoma | SK-MEL-28 | 0,028 | 22,387 | 0,214 |
| Melanoma | SK-MEL-5 | 0,062 | 38,905 | 13,804 |
| Melanoma | UACC-257 | 0,020 | 66,069 | 10,233 |
| Melanoma | UACC-62 | 0,014 | 20,893 | 0,170 |
| Cáncer de ovario | IGROV1 | 0,018 | 19,055 | 0,295 |
| Cáncer de ovario | OVCAR-3 | 2,512 | 48,978 | 17,783 |
| Cáncer de ovario | OVCAR-4 | 0,562 | 72,444 | 16,218 |
| Cáncer de ovario | OVCAR-5 | 0,017 | 40,738 | 12,023 |
| Cáncer de ovario | SK-OV-3 | 12,882 | 100,000 | 41,687 |
| Cáncer renal | 786-0 | 5,129 | 63,096 | 23,442 |
| Cáncer renal | A498 | 0,191 | 44,668 | 4,169 |
| Cáncer renal | ACHN | 0,275 | 83,176 | 21,878 |

| Panel | Línea celular | GI50 (μM) | LC50 (μM) | TGI (μM) |
|---|---|---|---|---|
| Cáncer renal | CAKI-1 | 0,389 | 100,000 | 26,915 |
| Cáncer renal | SN12C | 0,851 | 47,863 | 18,621 |
| Cáncer renal | TK-10 | 0,224 | 100,000 | 23,442 |
| Cáncer renal | UO-31 | 0,158 | 40,738 | 11,482 |
| Cáncer de próstata | PC-3 | 8,128 | 100,000 | 37,154 |
| Cáncer de próstata | DU-145 | 2,138 | 95,499 | 22,387 |
| Cáncer de mama | MCF7 | 10,965 | 85,114 | 30,903 |
| Cáncer de mama | NCI/ADR-RES | 3,467 | 100,000 | 25,704 |
| Cáncer de mama | MDA-MB-231 | 0,069 | 35,481 | 10,471 |
| Cáncer de mama | HS 578T | 0,617 | 85,114 | 13,490 |
| Cáncer de mama | MDA-MB-435 | 0,035 | 41,687 | 12,303 |
| Cáncer de mama | BT-549 | 5,754 | 47,863 | 20,893 |
| Cáncer de mama | T-47D | 4,898 | 100,000 | 38,019 |
| Cáncer de mama | MDA-MB-468 | 0,019 | 54,954 | 10,233 |

**Ejemplo 110:**

Actividad anti-proliferativa *in vitro*

En el presente ejemplo, se examinaron los siguientes efectos de la N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida: (1) actividad ($GI_{50}$) contra el crecimiento de varias líneas de células tumorales que contienen diferentes mutaciones; (2) actividad ($GI_{50}$) contra el crecimiento de varias líneas celulares mutantes B-Raf; (3) efectos sobre el crecimiento celular independiente del anclaje; (4) efectos sobre el ciclo celular; y (5) efectos tóxicos sobre células primarias de hígado y riñón.

*Ensayo de inhibición del cultivo/crecimiento celular*

Se obtuvieron células de melanoma humano A375 y células

de cáncer de colon humano Colo205 de ATCC (Manassas, VA). Las células A375 se mantuvieron en DMEM suplementado con suero fetal bovino 10%, glutamina (2 mM), penicilina (100 U/ml) y estreptomicina (100 µg/ml). Las células se mantuvieron a 37°C, 5% de $CO_2$ y 100% de humedad. Las células Colo205 se mantuvieron en RPMI suplementado con suero fetal bovino 10%, glutamina (2 mM), penicilina (100 U/ml) y estreptomicina (100 µg/ml). Para los experimentos de inhibición del crecimiento, las células se plaquearon en microplacas blancas de 384 cavidades a razón de 1000 células/20 µl/cavidad. Después de 24 hs, se agregaron 5 µl de una solución madre de droga 5X. Todas las drogas se prepararon inicialmente como soluciones madre 200X en DMSO, de modo tal que la concentración final de DMSO era del 0,5%. Las células se incubaron durante 48 hs a 37°C y los niveles de ATP se determinaron usando CellTiterGlo (Promega, Madison, WI). La liberación de adenilato quinasa (AK) se determinó usando Toxilight (Cambrex, Walquersville, MD). El ajuste de curva no lineal se efectuó usando GraphPad Prism 4 (GraphPad Software, San Diego, CA). El compuesto 4-amino-8-((2R,3R,4S,5R)-3,4-dihidroxi-5-(hidroximetil)tetrahidrofuran-2-il)pirido[2,3-d]pirimidin-5(8H)-ona (VRX-14686) es un agente citotóxico usado como compuesto de referencia.

Inhibición del crecimiento (%) = (control de vehículo

781

solamente (RLU) - N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida RLU)/(control de vehículo solamente RLU - 1 µM N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida RLU); en base al arresto de crecimiento inducido por N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida, donde se miden los niveles de ATP.

Viabilidad celular (%) = (N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida RLU-10 µM VRX-14686 RLU)/(Control de vehículo solamente RLU-10 µM Tamoxifeno RLU); en base a la muerte celular inducida por VRX-14686, donde se miden los niveles de ATP.

Muerte celular (%) = (N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida RLU- Control de vehículo solamente RLU)/(10 µM Tamoxifeno RLU - Control de vehículo solamente RLU); en base a la muerte celular inducida por Tamoxifeno, donde se mide la liberación de AK.

RLU = Unidades relativas de luminiscencia

*Evaluación del arresto del ciclo celular*

Se plaquearon células A375 en microplacas de 96

787

cavidades a razón de 10.000 células/200 µl/cavidad. Después de 24 hs las células eran confluentes en un 50% aproximadamente y se agregaron 50 µl de una solución madre de droga 5X. Después de otras 24 hs, las células se tripsinizaron, se fijaron en 200 µl de Prefer (Anatech, Battle Creek, MI) y se guardaron a 4° C durante la noche. A continuación, las células se lavaron en PBS, se permeabilizaron y se tiñeron en Triton X-100 0,1%, ARNasa libre de ADNasa 200 µg/ml y ioduro de propidio 25 µg/ml (Molecular Probes, Sunnyvale, CA), y luego se analizaron con el Guava PCA-96 (Guava Technologies, Foster City, CA). Los datos se analizaron usando ModFit LT (versión 3.0, Verity, Topsham, ME).

*(1) Evaluación de la inhibición del crecimiento celular independiente del anclaje*

Se llenaron cavidades de una placa de "unión extra-baja" (Corning, Acton MA) con 60 µl de una solución de agarosa 0,15% en RPMI completo. A continuación, se agregaron 60 µl de RPMI completo que contiene 9000 células Colo205 en agarosa 0,15% por cavidad. Después de 24 hs, se agregaron 60 µl de una solución de droga 3X en RPMI completo sin agarosa. Después de 7 días, se agregaron 36 µl de reactivo MTS 6X (CellTiter 96 Acuoso, Promega, Madison, WI) por cavidad. Después de 2 hs a 37° C, se determinó la absorbancia a 490 nm con el lector de placas M5 (Molecular

783

Devices, Sunnyvale, CA). El ajuste de curva no lineal se efectuó usando GraphPad Prism 4.

*(2) Inhibición del crecimiento ($GI_{50}$) contra el crecimiento de células cancerosas dependiente de MEK*

Se expusieron células mutantes B-Raf en división en fase log A375 (melanoma humano), A431 (melanoma), Colo205 (carcinoma de colon), HT29 (adenocarcinoma colorrectal), MDA-MB231 (adenocarcinoma de mama) y BxPC3 (adenocarcinoma pancreático) al compuesto N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida durante 48 hs y se analizó su contenido de ATP. El 100% de arresto del crecimiento se determinó usando N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida 1 μM.

En la siguiente tabla se muestran las medias de los valores $GI_{50}$ de al menos tres experimentos, para cada línea celular y se muestra que la N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida causó inhibición del crecimiento en tres líneas celulares mutantes B-Raf (A375, Colo205 y HT29), así como en una línea celular con la vía ras/raf/MEK/MAPK de tipo salvaje (A431) con una media de la potencia de 79 nM (± 9 nM).

| **Línea celular** | **Media** | **D.E.** | **C.V.** |
|---|---|---|---|
| **A375** | 71 nM | 12,1 nM | 17% |

784

| | | | |
|---|---|---|---|
| **A431** | 86 nM | 25,4 nM | 30% |
| **Colo205** | 89 nM | 40,1 nM | 45% |
| **HT29** | 70 nM | 12,2 nM | 18% |
| **MDA** | >1 uM | | |
| **BxPC3** | >1 uM | | |

En un estudio separado, se expusieron células mutantes B-Raf en división en fase log A375 (melanoma humano), SK Mel28 (melanoma humano) y Colo205 (carcinoma de colon humano) al compuesto N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida durante 48 hs y se analizó su contenido de ATP. En la siguiente tabla se muestra el valor de $GI_{50}$ para cada línea celular que indica que la N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida causó la inhibición del crecimiento con una potencia que se aproxima a su valor de $EC_{50}$ para la inhibición de MEK.

| **Línea celular** | **$GI_{50}$ (nM)** |
|---|---|
| A375 | 56 |
| SK Mel 28 | 105 |
| Colo205 | 27 |

En las Figuras 10A y 10B se muestra el arresto del crecimiento de células en división en fase log A375 expuestas a concentraciones crecientes de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida.. Se analizó el contenido de ATP en las células. El 100% de arresto del crecimiento se determinó usando N-(S)-(3,4-difluoro-2-(2-

785

fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida 1 µM.

Se analizó la lisis citotóxica en los sobrenadantes celulares midiendo la liberación de adenilato quinasa (AK). Se expusieron células A375 en división en fase log a N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida y PD-325901 durante 48 hs. (el 100% de muerte celular se determinó usando tamoxifeno 20 µM.) Los resultados se muestran en la Figura 11. Este dato indica que la N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida causa un arresto no tóxico del crecimiento en varias líneas de células cancerosas humanas susceptibles, demostrado por i) mediciones del arresto del crecimiento (cuantificación de ATP); y ii) ausencia de lisis citotóxica de las células (liberación de AK). La ausencia de liberación de AK se confirmó para todas las líneas celulares evaluadas.

*Inhibición del crecimiento independiente del anclaje*

Se evaluó cuantitativamente el crecimiento independiente del anclaje de células Colo205, A375 y MDA-MB231 expuestas a N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida durante 7 días, en un formato de microplacas de 96 cavidades. La viabilidad se

786

determinó mediante el ensayo MTS. Los valores de $GI_{50}$ se muestran a continuación:

| **Línea celular** | **Media** | **D.E.** | **C.V.** |
|---|---|---|---|
| Colo205 | 40 nM | 8,1 nM | 20% |
| A375 | 84 nM | 17,2 nM | 21% |
| MDA-MB231 | 81 nM | 55,6 nM | 69% |

Las Figuras 12A-12C muestran la inhibición del crecimiento por N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida de (A) células de carcinoma colorrectal humano Colo205 ($GI_{50}$ = 11 nM); (B) células A375 ($GI_{50}$ = 22 nM) y (C) la inhibición de células MDA-MB231 que no muestran arresto del crecimiento inducido por N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida en ensayos dependientes del anclaje bidimensional.

Se expusieron células en división en fase log A375 al compuesto N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida (1 uM) durante 48 hs y se analizó en los sobrenadantes celulares la inhibición del crecimiento (contenido de ATP) y lisis citotóxica (liberación de AK). El 100% de viabilidad (ensayo de ATP) se determinó en las cavidades de control de vehículo solamente. En la siguiente tabla se muestran los resultados que indican que la N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-

7987

1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida no causa un arresto tóxico del crecimiento en células mutantes B-Raf de melanoma humano A375.

| | **% de control** |
|---|---|
| ATP, viabilidad celular | 27% |
| AK, muerte celular | 4% |

*Inhibición del crecimiento independiente del anclaje*

El crecimiento independiente del anclaje se evaluó cuantitativamente en un formato de microplacas de 96 cavidades. La Figura 13A muestra la inhibición del crecimiento de células de carcinoma colorrectal humano Colo205, con valores de $GI_{50}$ a 6 nM y 11 nM, respectivamente. La Figura 13B muestra la inhibición del crecimiento de células A375 con valores de $GI_{50}$ a 5 nM y 22 nM.

Análisis del ciclo celular del arresto del crecimiento inducido por N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida

Se ha demostrado que la inhibición de MEK induce arresto del ciclo celular en la fase G1/S en células A375.

Se expusieron células en división en fase log A375 a N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida durante 24 hs y se determinaron los porcentajes de células con cantidades de ADN intracelular teñido de

788

manera dependiente de la fase usando citometría de flujo.

En la siguiente tabla se muestra el porcentaje de distribución de células en las respectivas fases de crecimiento en células tratadas con N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida y con control (vehículo solamente).

| | | % por fase | | |
|---|---|---|---|---|
| | | **G1** | **S** | **G2** |
| **Control** | | 61,8 | 27,1 | 11,1 |
| N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida | 111 nM | 84,7 | 11,8 | 3,5 |
| | 37 nM | 74,3 | 18,7 | 7,0 |

La Figura 14A y la Figura 14B muestran el efecto de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida sobre el avance del ciclo celular, demostrando que la exposición de células A375 a la N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida causa un arresto en la fase G1 del ciclo celular, indicado por la depleción de células en ambas fases G2 y S.

Evaluación de la toxicidad en hepatocitos primarios y células renales

Se obtuvieron hepatocitos de rata crioconservados de CellzDirect (Austin, TX) y se plaquearon sobre placas de 96

cavidades recubiertas con colágeno de acuerdo con las instrucciones del proveedor. La droga se agregó 4 hs después del plaqueado (concentración final de DMSO 0,5%).

Los hepatocitos humanos plaqueados se obtuvieron de CellzDirect y se procesaron de acuerdo con las instrucciones del proveedor.

Las células epiteliales de túbulos proximales renales humanas crioconservadas (RPTEC) se obtuvieron de Cambrex y se procesaron de acuerdo con las instrucciones del proveedor. Las células se expandieron durante 4 días y luego se plaquearon en placas de 96 cavidades a razón de 50.000 células/cavidad para la exposición a la droga.

Después de 48 hs, se determinaron los niveles de AK en el sobrenadante usando Toxilight, y se determinaron los niveles de ATP celular usando CellTiterGlo. Los valores de muerte celular total se determinaron usando VRX-14686 15 µM.

Los resultados se muestran a continuación. Se observó muy poca lisis celular. Se observó una toxicidad mínima (81% de sobrevida) con N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida 30 µM en hepatocitos primarios humanos recién plaqueados. Las células RPTEC mostraron una depleción de ATP dependiente de la dosis y una lisis celular evidente a 30 µM.

| **Compuesto A** | **ATP (% de sobrevida celular)** | **Liberación de AK (% de sobrevida celular)** |
|---|---|---|

796

| | Hepatocitos | | RPTEC | Hepatocitos | | RPTEC |
|---|---|---|---|---|---|---|
| | Rata | Humano | Humano | Rata | Humano | Humano |
| **30,0** | 57% | 81% | 34% | 91% | 109% | 41% |
| **10,0** | 72% | 107% | 85% | 93% | 112% | 99% |
| **3,3** | 87% | 104% | 91% | 97% | 102% | 95% |
| **1,1** | 114% | 108% | 94% | 96% | 92% | 96% |

Los datos anteriores ilustran que (1) el compuesto N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida inhibe el crecimiento y división celular en células cancerosas humanas con valores de $GI_{50}$ que varían en un rango de 70-89 nM en ensayos de proliferación dependiente del anclaje sin causar toxicidad determinado con el ensayo de lisis celular; (2) el compuesto N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida inhibe el crecimiento y la división celular en células cancerosas humanas seleccionadas con valores de $GI_{50}$ de 51 nM y 22 nM en ensayos de proliferación dependiente e independiente del anclaje, respectivamente; (3) el compuesto N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida causa el arresto en G1 e inhibe el crecimiento independiente del anclaje en células A375, proporcionando evidencia de actividad anticancerosa en un modelo *in vitro* fisiológicamente relevante; y (4) el compuesto N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-

791

(2,3-dihidroxipropil)ciclopropan-1-sulfonamida muestra poca citotoxicidad contra hepatocitos humanos normales, células epiteliales de túbulo proximal renales humanas y hepatocitos de rata.

**Ejemplo 111:**

Farmacocinética de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida en pacientes con cáncer después de múltiples dosis

| Dosis (mg) | N | $T_{máx}$ (hs) | Cmáx (µg/ml) | $C_{24hs}$ (µg/ml) | $AUC_\tau$ (µg·hs/ml) | $t^{1/2}$- (hs) | $R_{ac}$ $C_{máx}$ | $R_{ac}$ $AUC_\tau$ |
|---|---|---|---|---|---|---|---|---|
| 2 | 3 | 1,33 (21,7) | 0,0504 (49,2) | 0,00938 (82,8) | 0,517 (61,2) | 11,4 (38,8) | 1,76 (35,6) | 1,90 (23,9) |
| 4 | 3 | 1,50 (33,3) | 0,105 (41,0) | 0,0313 (41,1) | 1,39 (42,7) | 14,9 (0,992) | 1,49 (21,6) | 1,91 (36,1) |
| 6 | 3 | 1,50 (33,3) | 0,205 (16,6) | 0,0489 (12,2) | 2,22 (5,79) | 15,6 (23,8) | 1,58 (38,5) | 2,07 (23,5) |

$R_{ac}$: índice de acumulación

* Estimación inexacta debido a un tiempo de muestreo limitado

Después de una dosificación múltiple de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida a razón de 2, 4 ó 6 mg/sujeto, la N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida era absorbida rápidamente con un $T_{máx}$ medio que varían en un rango entre 1,33 y 1,50 hs. Los valores de las medias de los valores de $C_{máx}$, $C_\tau$ y AUC aumentaron de una manera proporcional con la

797

dosis. Los Índices de acumulación varían en un rango entre 1,49 y 1,76 para la $C_{máx}$ y entre 1,90 y 2,07 para AUC, respectivamente, indicativos de una acumulación moderada. Aunque no es posible medir la vida media con precisión debido al tiempo de muestreo limitado después de múltiples dosis, se esperaba que la vida media fuera mayor que 22 hs después de múltiples dosis en base a los índices de acumulación. Estos valores de vida media son significativamente mayores que los observados en el modelo de eficacia de ratón donde se observó un rango típico de 2 - 3 hs. Además, se observaron relaciones de pico-a-mínimo alentadores a todas las dosis.

**Ejemplo 112:**

Farmacocinética de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida en voluntarios saludables después de múltiples dosis

| Dosis (mg) | N | $T_{máx}$ (hs) | Cmáx (µg/ml) | $C_{24hs}$ (µg/ml) | $AUC_\tau$ (µg·hs/ml) | $t_{1/2}$* (hs) | $R_{ac}$ $C_{máx}$ | $R_{ac}$ $AUC_\tau$ |
|---|---|---|---|---|---|---|---|---|
| 10 | 6 | 2,00 (61,2) | 0,182 (35,5) | 0,0318 (53,0) | 1,02 (1,80) (43,7) (39,7) | 14,6 (15,2) | 1,14 (19,0) | 1,29 (13,4) |
| 20 | 6 | 2,25 (39,1) | 0,313 (17,6) | 0,0350 (36,5) | 2,60 (22,0) | 13,4 (21,9) | 1,23 (24,1) | 1,24 (6,51) |

$R_{ac}$: índice de acumulación

* Estimación inexacta debido a un tiempo de muestreo limitado

Después de una dosificación múltiple de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-

793

(2,3-dihidroxipropil)ciclopropan-1-sulfonamida a razón de 10 ó 20 mg/sujeto, la N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida era absorbida rápidamente con un $T_{máx}$ medio que varían en un rango entre 2,00 y 2,25 hs. Los valores promedio de $C_{máx}$, $C_\tau$ y AUC aumentaron con la dosis. Los Índices de acumulación varían en un rango entre 1,14 y 1,23 para la $C_{máx}$ y entre 1,24 y 1,29 para AUC, respectivamente, indicativos de una acumulación insignificante. Las vidas medias eran similar para dos regímenes de dosis, variando en un rango entre 13 y 15 hs. Estos valores de vida media son menores que los observados en los pacientes con cáncer.

**Ejemplo 113:**

Actividad anti-proliferativa *in vitro*

Se examinó el efecto de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida sobre la inhibición de la proliferación celular en una línea celular derivada de un carcinoma gástrico humano ("cáncer de estómago") en un ensayo de proliferación celular.

*Ensayo de inhibición del cultivo/crecimiento celular*

Las células de carcinoma gástrico humano Hs746t se obtuvieron de ATCC (Manassas, VA). Las células Hs746t se mantuvieron en DMEM suplementado con suero fetal bovino 10%,

794

penicilina (100 U/ml) y estreptomicina (100 µg/ml). Las células se mantuvieron a 37°C, 5% de $CO_2$ y 100% de humedad. En los experimentos de proliferación celular, las células se plaquearon en placas blancas de 96 cavidades con fondos claros a razón de 3000 células/100 µl/cavidad. Después de 24 hs, se removió el medio de las células y se reemplazó por medio que contiene distintas dosis de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida. Después de incubar durante 48 horas a 37°C, se determinaron los niveles de ATP usando CellTiterGlo (Promega, Madison, WI) y leyendo los valores de luminiscencia usando un equipo LJL Biosystems Analyst HT (Sunnyvale, CA). El nivel de ATP para cada dosis se determinó por triplicado usando cavidades independientes.

Cantidad relativa de células = (RLU promedio (tratado con N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida))/(RLU promedio de control de vehículo solamente).

La Figura 19 muestra un gráfico de la cantidad de células (con relación al vehículo) versus la concentración de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida y demuestra que la N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-

795

dihidroxipropil)ciclopropan-1-sulfonamida inhibe la proliferación de células de carcinoma gástrico humano Hs746t después de 48 horas de tratamiento

**Ejemplo 114:**

Actividad anti-proliferativa *in vitro*

Se examinó el efecto de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida sobre la inhibición de la proliferación celular en una línea celular derivada de un adenocarcinoma gástrico humano ("cáncer de estómago") en un ensayo de proliferación celular.

*Ensayo de inhibición del cultivo/crecimiento celular*

Las células de adenocarcinoma gástrico humano AGS se obtuvieron de ATCC (Manassas, VA). Las células AGS se mantuvieron en DMEM/F12 suplementado con suero fetal bovino 10%, penicilina (100 U/ml) y estreptomicina (100 µg/ml). Las células se mantuvieron a 37°C, 5% de $CO_2$ y 100% de humedad. En los experimentos de proliferación celular, las células se plaquearon en placas blancas de 96 cavidades con fondos claros a razón de 3000 células/100 µl/cavidad. Después de 24 hs, se removió el medio de las células y se reemplazó por medio que contiene distintas dosis de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida. Después de incubar durante 3 días a 37°C, se determinaron los

796

niveles de ATP usando CellTiterGlo (Promega, Madison, WI) y leyendo los valores de luminiscencia usando un equipo LJL Biosystems Analyst HT (Sunnyvale, CA). El nivel de ATP para cada dosis se determinó por triplicado usando cavidades independientes. En otro experimento, se plaquearon 1000 células/100ul/cavidad y las células fueron tratados durante 6 días y evaluados igual que antes.

Cantidad relativa de células = (RLU promedio (tratado con N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida))/(RLU promedio de control de vehículo solamente).

En la Figura 15A y la Figura 15B se muestra un trazado gráfico de la concentración de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida versus la cantidad de células (con relación al vehículo) después de (A) 3 días y (B) 6 días de exposición a N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida, donde se demuestra que la N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida inhibe la proliferación de la línea celular AGS de adenocarcinoma gástrico humano.

797

**Ejemplo 115:**

Respuesta de crecimiento de tumores ortotópicos Hep3B humanos en ratones desnudos tratados con diferentes cantidades de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida

La eficacia de dosis-respuesta de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida ("Compuesto A"), para inhibir el desarrollo de carcinoma hepático ortotópico Hep3B2.1-7 humano se evaluó en ratones nu/un BALB/c, en comparación con una dosis óptima de 5-fluorouracilo (75 mg/kg).

**Animales:** Se usaron ratones nu/nu BALB/c hembra (Universidad de Adelaida, Waite Campus, SA, Australia), de 10-14 semanas de vida, con un peso corporal en el rango de 19,1-29,94 g (media de 22,95 g) en el estudio. Los ratones se dividieron en 6 grupos de estudio (4 grupos de tratamiento y 2 grupos control) de la siguiente manera:

Cantidad de ratones por grupo: 10 en los Grupos 1 a 5 inclusive

15 en el Grupo control de 'índice positivo' (Grupo 6)

Los ratones se mantuvieron en un ambiente controlado (rangos buscados: temperatura 21 ± 3°C, humedad 30-70%, 10-

718

15 cambios de aire por hora) bajo condiciones de aislamiento (cuarentena) con un ciclo de 12 horas de luz/12 horas de oscuridad. La temperatura y la humedad relativa eran monitoreadas de forma continua. Los animales recibieron una dieta para roedores comercial (Rat and Mouse Cubes, Speciality Feeds Pty Ltd, Glen Forrest, Australia Occidental) y agua corriente *ad libitum*. Los suministros de alimento y agua eran esterilizados por autoclave.

***Inoculación de tumores***: Se cultivaron células de carcinoma hepático humano Hep3B (Pasaje 2 de la solución de trabajo VP-Stock 353) en medio de cultivo celular RPMI1640, suplementado con FBS 10% y penicilina-estreptomicina (concentración final de 50 UI/ml). Las células se cosecharon por tripsinización, se lavaron dos veces en HBSS y se contaron. Las células se resuspendieron luego en HBSS:Matrigel (1:1, v/v) y se ajustaron a un volumen final que contiene 1 x $10^8$ células/ml. Antes de la inoculación, el sitio de incisión se frotó generosamente con alcohol y se practicó una incisión a través de la pared abdominal para exponer el hígado. La aguja se introdujo a través de la superficie del hígado donde se descargaron 10 µl de células (1 x $10^6$ células). La aguja se mantuvo en esta posición por aproximadamente 30 segundos para permitir que el Matrigel® se polimerice con el fin de evitar el escape de células tumorales hacia la cavidad abdominal.

799

El tratamiento comenzó 14 días después de la inoculación. El Día 7 del estudio (21 días después de la inoculación), se descartaron todos los ratones del grupo control de 'índice positivo' y los hígados eran evaluados visualmente por la presencia de tumores.

***Materiales:*** Los respectivos proveedores suministraron los siguientes materiales.

La solución salina estéril (NaCl (ac) 0,9%) se obtuvo de Baxter Healthcare Australia, Old Toongabbie, NSW, Australia. El CremophorEL se obtuvo de Sigma-Aldrich Pty Ltd, Castle Hill, NSW, Australia. El 5-fluorouracilo, formulación clínica, claro, líquido incoloro, se obtuvo de Mayne Pharma Pty Ltd. El medio de cultivo celular RPMI1640, FBS y HBSS se obtuvieron de Invitrogen Australia Pty Ltd, Mt Waverley, VIC, Australia. La penicilina-estreptomicina y azul de Trypan se obtuvieron de Sigma-Aldrich, Castle Hill, NSW, Australia. Las células de carcinoma hepático humano Hep3B2.1-7 eran originarias de *American Type Culture Collection* (ATCC), Rockville, MD, EE.UU. El Matrigel® se obtuvo de BD Biosciences, North Ryde, NSW, Australia.

El uso de Matrigel® en la suspensión de inoculación mejora el índice positivo del tumor y disminuye la variabilidad del tamaño tumoral, y el crecimiento del carcinoma hepático humano Hep3B2.1-7 es más estable cuando se inocula en la presencia de esta matriz extracelular.

800

***Preparación y administración del compuesto***: El control CremophorEL:Salina (1:9, v/v; control de vehículo), N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida ("Compuesto A") o 5-fluorouracilo (compuesto control) se administraron de acuerdo con el programa que se describe a continuación:

| Grupo | Compuesto | Dosis (mg/kg) | Tratamiento programado | Tratamiento administrado |
|---|---|---|---|---|
| 1 | Control de vehículo | 10 ml/kg | Una vez por día durante 21 días (Días 0 a 20) | Una vez por día durante 19 días (Días 0 a 18) |
| 2 | Compuesto A | 0,2 ml @ 10 ml/kg = 2 mg/kg | Una vez por día durante 21 días (Días 0 a 20) | Una vez por día durante 19 días (Días 0 a 18) |
| 3 | Compuesto A | 1,0 ml @ 10 ml/kg = 10 mg/kg | Una vez por día durante 21 días (Días 0 a 20) | Una vez por día durante 19 días (Días 0 a 18) |
| 4 | Compuesto A | 5,0 ml @ 10 ml/kg = 50 mg/kg | Una vez por día durante 21 días (Días 0 a 20) | Una vez por día durante 19 días (Días 0 a 18) |
| 5 | 5'-fluorouracilo | 7,5 ml @ 10 ml/kg = 75 mg/kg | Una vez por semana durante 21 Días (Días 0, 7 y 14) | Una vez por semana durante tres semanas (Días 0, 7 y 14) |
| 6 | Control de 'índice positivo' | Sin tratamiento | - | - |

El control de vehículo, CremophorEL:Salina (1:9, v/v), se administró p.o. en un volumen de dosificación de 10 ml/kg, una vez por día durante 21 días consecutivos (Días 0 a 20).

El compuesto N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-

801

dihidroxipropil)ciclopropan-1-sulfonamida, se formuló en CremophorEL:Salina (1:9, v/v). Se preparó semanalmente una solución madre y se guardó a 4°C. las soluciones para las dosificaciones se prepararon cada día de administración. La N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida se administró p.o. en un volumen de dosificación de 10 ml/kg, una vez por día durante 21 días (Días 0 a 20). El compuesto se administró a dosis de 2, 10 y 50 mg/kg.

La formulación clínica de 5-fluorouracilo se diluyó en salina estéril y se administró por vía i.v. por la vena de la cola a una concentración de 75 mg/kg, en un volumen de dosificación de 10 ml/kg, una vez por semana durante tres semanas (los Días 0, 7 y 14).

No se administró tratamiento alguno a los ratones del Grupo 6 (Control de 'índice positivo'). El Día 7 del estudio (21 días después de la inoculación), se descartaron los ratones y se expuso el hígado para determinar el 'índice positivo' y el tamaño de los tumores en la pared del hígado.

Se midió el peso corporal de cada animal inmediatamente antes de la dosificación. Se calculó el volumen administrado a cada ratón y se ajustó en base al peso corporal.

***Mediciones de los tumores***: Se midió el peso húmedo de los hígados y tumores cuando cada uno era extirpado *post-mortem* el día final del estudio. Al final del estudio, se

302

extirparon los hígados de todos los ratones de cada grupo de estudio y se pesaron. Si había tumores, se contó la cantidad de tumores visibles. Estos tumores eran removidos del hígado y luego se pesaron.

***Programa de medición de datos y de recolección de muestras***

| ***Medición de datos*** | **Cronograma** |
|---|---|
| Peso corporal | Día 0, luego tres veces por semana (lunes, miércoles y Viernes), y el día final del estudio para los Grupos 1 a 5 inclusive. |
| Peso de hígados y de tumores | Peso húmedo de hígados y tumores extirpados de todos los ratones en los Grupos 1 a 5 inclusive, *post-mortem* el día final del estudio y de un ratón en el Grupo 5 que murió el día final del tratamiento. |
| ***Recolección de muestras*** | |
| Hígados y tumores | De todos los ratones del Grupo 6 (control de 'índice positivo') el Día 7 del estudio. |
| Hígados y tumores | De todos los ratones en los Grupos 1 a 5 inclusive, *post-mortem* el día final del estudio y de un ratón en el Grupo 5 que murió el día final del tratamiento. |
| Hígado | De todos los ratones en los Grupos 1 a 5 inclusive, *post-mortem* el día final del estudio y de un ratón en el Grupo 5 que murió el día final del tratamiento. |

***Obtención y cálculo de datos:*** El transpondedor de cada animal (Bar Code Data Systems Pty Ltd, Botany Bay, NSW) se escaneó usando un lector de códigos de barra (LabMax I, DataMars, Suiza) inmediatamente antes de la obtención de

863

datos. Todas las mediciones se obtuvieron con el mismo calibre manual (Absolute Digimatic Model CD-6" CS, Mitutoyo Corporation, Japón). Los datos se sincronizaron con la base de datos relacional segura de *vivo*Pharm usando Pendragon Forms 4.0 (Pendragon® Software Corporation, Libertyville, IL, EE.UU.) como software de transferencia. Se usó AIDAM v2.4 para los informes de datos y los cálculos de datos.

***Estadísticas y cálculos***: Todos los cálculos estadísticos se efectuaron usando SigmaStat 3.0. (SPSS Australasia Pty Ltd, North Sydney, NSW, Australia).

Se usó la prueba t para dos muestras para determinar la significancia en el cambio de peso corporal dentro de un grupo de tratamiento entre el Día 0 y el día final del estudio. Cuando los datos no cumplían con la prueba de Normalidad o la prueba de varianzas iguales, se realizó una prueba de suma de rangos de Mann-Whitney.

El análisis de la varianza de una vía o unidireccional (ANOVA) (todos procedimientos de comparación múltiple por pares y de comparación múltiple versus el grupo control) se efectuó para los datos de peso del hígado y peso del tumor al final del estudio. Cuando esta prueba no pasaba la prueba de varianzas iguales, se empleó el análisis de la varianza de una vía (ANOVA) de Kruskal-Wallis para rangos. Se efectuaron los mismos análisis estadísticos con los datos correspondientes a ratones portadores de tumores en el

804

estudio.

Un valor de p menor que 0,05 era considerado significativo.

*Datos de peso de hígados y peso de tumores para los ratones portadores de tumores y peso promedio de hígados y tumores por ratón por grupo para los ratones portadores de tumores*

| **Grupo** | **Tratamiento** | **Peso promedio de hígados (g)** | **EEM** | **Peso promedio de tumores (g)** | **EEM** | **N° de ratones con tumores (de los 10)** |
|---|---|---|---|---|---|---|
| 1 | Control de vehículo | 4,560 | 0,673 | 3,382 | 0,979 | 4 |
| 2 | Compuesto A @ 2 mg/kg | 2,775 | 0,475 | 1,776 | 0,576 | 6 |
| 3 | Compuesto A @ 10 mg/kg | 2,551 | 0,446 | 1,407 | 0,465 | 7 |
| 4 | Compuesto A @ 50 mg/kg | 1,677 | 0,161 | 0,624 | 0,257 | 4 |
| 5 | 5FU™ @ 75 mg/kg | 1,217 | 0,051 | 0,143 | 0,078 | 4 |

No se recolectaron muestras del ratón en el Grupo 5 (5-fluorouracilo a 75 mg/kg) que fue descartado durante el período de estudio. Debido a la presencia de tumores grandes en algunos de los ratones, indicada por un aspecto hinchado del abdomen, el estudio se terminó 18 días después del tratamiento inicial.

Hay una tendencia evidente dependiente de la dosis en la disminución del peso de hígados y tumores en los grupos tratados con N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-

805

dihidroxipropil)ciclopropan-1-sulfonamida. Cuando solamente se consideran los ratones portadores de tumores, se encontró que el peso promedio de los hígados en los grupos tratados con N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida a las dosis más altas (Grupo 4 a 50 mg/kg) y 5-fluorouracilo (Grupo 5 a 75 mg/kg) era significativamente diferente del grupo de control de vehículo (Grupo 1; $p < 0,05$). Además, se encontró que el peso promedio de los tumores en los grupos tratados con N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida (Grupos 3 y 4 a 10 mg/kg y 50 mg/kg, respectivamente) y 5-fluorouracilo (Grupo 5 a 75 mg/kg) era significativamente diferente al grupo de control de vehículo.

Estos resultados se muestran gráficamente en la Figura 16 (media del peso de hígados - ratones portadores de tumores solamente) y en la Figura 17 (pesos de tumores de hígado - ratones portadores de tumores solamente)

**Ejemplo 116:**

Respuesta de crecimiento de tumores de colon ortotópicos HT-29 humanos en ratones desnudos tratados con diferentes cantidades de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida

La eficacia de dosis-respuesta de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida ("Compuesto A"), para inhibir el desarrollo de adenocarcinoma colorrectal ortotópico HT-29 humano se evaluó en ratones nu/un BALB/c, en comparación con una dosis óptima de 5-fluorouracilo (75 mg/kg).

**Animales**: Se usaron ratones nu/nu BALB/c hembra (Universidad de Adelaida, Waite Campus, SA, Australia), de 7-12 semanas de vida, con un peso corporal en el rango de 16,58-25,39 g (media de 21,52 g) en el estudio. Los ratones se dividieron en 6 grupos de estudio (4 grupos de tratamiento y 2 grupos control) de la siguiente manera:

Cantidad de ratones por grupo: 10 en los Grupos 1 a 5 inclusive

9 en el Grupo control de 'índice positivo' (Grupo 6)

Los ratones se mantuvieron en un ambiente controlado (rangos buscados: temperatura 21 ± 3°C, humedad 30-70%, 10-15 cambios de aire por hora) bajo condiciones de aislamiento (cuarentena) con un ciclo de 12 horas de luz/12 horas de oscuridad. La temperatura y la humedad relativa eran monitoreadas de forma continua. Los animales recibieron una dieta para roedores comercial (Rat and Mouse Cubes, Speciality Feeds Pty Ltd, Glen Forrest, Australia

807

Occidental) y agua corriente *ad libitum*. Los suministros de alimento y agua eran esterilizados por autoclave.

***Inoculación de tumores:*** Se cultivaron células de adenocarcinoma colorrectal humano HT-29 (Pasaje 4 de la solución de trabajo VP-Stock 325) en medio de cultivo celular RPMI1640, suplementado con FBS 10% y penicilina-estreptomicina (concentración final de 50 UI/ml). Las células se cosecharon por tripsinización, se lavaron dos veces en HBSS y se contaron. Las células se resuspendieron luego en HBSS y se ajustaron a un volumen final que contiene $2 \times 10^8$ células/ml. Antes de la inoculación, el sitio de incisión se frotó generosamente con alcohol y se practicó una incisión a través de la pared abdominal para exponer la pared del ciego. La aguja se introdujo a través de la superficie de la pared del ciego donde se descargaron 5 µl de células ($1 \times 10^6$ células).

**Materiales**: Los respectivos proveedores suministraron los siguientes materiales.

La solución salina estéril (NaCl (ac) 0,9%) se obtuvo de Baxter Healthcare Australia, Old Toongabbie, NSW, Australia. El CremophorEL se obtuvo de Sigma-Aldrich Pty Ltd, Castle Hill, NSW, Australia. El 5-fluorouracilo, formulación clínica, claro, líquido incoloro, se obtuvo de Mayne Pharma Pty Ltd. El medio de cultivo celular RPMI1640, FBS y HBSS se obtuvieron de Invitrogen Australia Pty Ltd, Mt

Waverley, VIC, Australia. La penicilina-estreptomicina y azul de Trypan se obtuvieron de Sigma-Aldrich, Castle Hill, NSW, Australia. Las células de adenocarcinoma colorrectal humano HT-29 eran originarias de *American Type Culture Collection* (ATCC), Rockville, MD, EE.UU.

***Preparación y administración del compuesto:*** El control CremophorEL:Salina (1:9, v/v; control de vehículo), N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida o 5-fluorouracilo (compuesto control) se administraron de acuerdo con el programa que se describe a continuación:

| **Grupo** | **Compuesto** | **Dosis (mg/kg)** | **Tratamiento programado** | **Tratamientos administrados** |
|---|---|---|---|---|
| 1 | Control de vehículo | 10 ml/kg | Una vez por día durante 21 días (Días 0 a 20) | Una vez por día durante 21 días (Días 0 a 20) |
| 2 | Compuesto A | 0,2 ml @ 10 ml/kg = 2 mg/kg | Una vez por día durante 21 días (Días 0 a 20) | Una vez por día durante 10 días (Días 0 a 9) |
| 3 | Compuesto A | 1,0 ml @ 10 ml/kg = 10 mg/kg | Una vez por día durante 21 días (Días 0 a 20) | Una vez por día durante 21 días (Días 0 a 20) |
| 4 | Compuesto A | 5,0 ml @ 10 ml/kg = 50 mg/kg | Una vez por día durante 21 días (Días 0 a 20) | Una vez por día durante 8 días (Días 0 a 7) |
| 5 | 5'-fluorouracilo | 7,5 ml @ 10 ml/kg = 75 mg/kg | Una vez por semana durante tres semanas (Días 0, 7 y 14) | Una vez por semana durante 3 semanas (Días 0, 7 y 14) |

| Grupo | Compuesto | Dosis (mg/kg) | Tratamiento programado | Tratamientos administrados |
|---|---|---|---|---|
| 6 | Control de 'índice positivo' | Sin tratamiento | - | - |

El control de vehículo, CremophoreEL:Salina (1:9, v/v), se administró p.o. en un volumen de dosificación de 10 ml/kg, una vez por día durante 21 días consecutivos (Días 0 a 20).

El compuesto N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida, se formuló en CremophorEL:Salina (1:9, v/v). Se preparó semanalmente una solución madre y se guardó a 4°C. las soluciones para las dosificaciones se prepararon cada día de administración. La N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida se administró p.o. a dosis de 2, 10 y 50 mg/kg, en un volumen de dosificación de 10 ml/kg, una vez por día durante 21 días (Días 0 a 20).

La formulación clínica de 5-fluorouracilo se diluyó en salina estéril y se administró por vía i.v. por la vena de la cola a una concentración de 75 mg/kg, en un volumen de dosificación de 10 ml/kg, una vez por semana durante tres semanas (los Días 0, 7 y 14).

No se administró tratamiento alguno a los ratones del Grupo 6 (Control de 'índice positivo'). El Día 7 del estudio

810

(21 días después de la inoculación), se descartaron los ratones y se expuso el colon para determinar el índice positivo y el tamaño de los tumores en la pared del ciego.

Se midió el peso corporal de cada animal inmediatamente antes de la dosificación. Se calculó el volumen administrado a cada ratón y se ajustó en base al peso corporal.

***Mediciones de los tumores***: Se midió el peso húmedo de los ciegos y tumores cuando cada uno era extirpado *post-mortem* el día final del estudio. Al final del estudio, se extirparon los ciegos de todos los ratones en cada grupo de estudio y se pesaron con los tumores intactos. A continuación, se extirparon los tumores del ciego y se pesaron.

Los hígados también se extirparon de todos los ratones en cada grupo al final del estudio y se fijaron en formalina 10% de pH regulado. Se embebieron cinco muestras de hígado del grupo de control de vehículo en parafina, se obtuvieron cortes finos y se tiñeron con hematoxilina y eosina (H&E) para la evaluación histológica de los cambios morfológicos.

**Programa de medición de datos y de recolección de muestras**

| **Medición de datos** | **Cronograma** |
|---|---|
| Peso corporal | Día 0, luego tres veces por semana (lunes, miércoles y Viernes), y el día final del estudio para los Grupos 1 a 5 inclusive. |

811

| **Medición de datos** | **Cronograma** |
|---|---|
| Peso de ciegos y de tumores | Extirpación de ciegos y tumores de cada ratón al final en los Grupos 1 a 5 inclusive |
| ***Recolección de muestras*** | |
| Ciego y tumores | De todos los ratones del Grupo 6 (control de 'índice positivo') *post-mortem* el Día 7 del estudio. |
| Ciego y tumores | De todos los ratones de los Grupos 1 a 5 inclusive *post-mortem*, el día final del estudio, y de los ratones que murieron durante el período de estudio. |
| Hígado | De todos los ratones de los Grupos 1 a 5 inclusive *post-mortem*, el día final del estudio, y de los ratones que murieron durante el período de estudio. |

**Obtención y cálculo de datos**: El transpondedor de cada animal (Bar Code Data Systems Pty Ltd, Botany Bay, NSW) se escaneó usando un lector de códigos de barra (LabMax I, DataMars, Suiza) inmediatamente antes de la obtención de datos. Todas las mediciones se obtuvieron con el mismo calibre manual (Absolute Digimatic Model CD-6" CS, Mitutoyo Corporation, Japón). Los datos se sincronizaron con la base de datos relacional segura de *vivo*Pharm usando Pendragon Forms 4.0 (Pendragon® Software Corporation, Libertyville, IL, EE.UU.) como software de transferencia. Se usó AIDAM v2.4 para los informes de datos y los cálculos de datos.

***Estadísticas y cálculos***: Todos los cálculos estadísticos se efectuaron usando SigmaStat 3.0. (SPSS Australasia Pty Ltd, North Sydney, NSW, Australia).

82

Se usó la prueba t para dos muestras para determinar la significancia en el cambio de peso corporal dentro de un grupo de tratamiento entre el Día 0 y el día final del estudio. En los grupos tratados con N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida a 2 y 50 mg/kg, el tratamiento se discontinuó temprano debido a una pérdida de peso corporal excesivo. En estos grupos, una se usó una prueba t de dos muestras para determinar la significancia del cambio de peso corporal en un grupo de tratamiento entre el Día 0 y el día de tratamiento final del estudio, y entre el último día de tratamiento y el día final del estudio. Cuando los datos no pasaban la prueba de Normalidad o la prueba de varianzas iguales, se realizó una prueba de suma de rangos de Mann-Whitney.

El análisis de la varianza de una vía o unidireccional (ANOVA) (todos procedimientos de comparación múltiple por pares y de comparación múltiple versus el grupo control) se efectuó para los datos de peso del ciego y peso del tumor al final del estudio. Cuando los datos no pasaban la prueba de Normalidad los valores eran convertidos en el logaritmo natural antes de realizar los procedimientos.

Un valor de p menor que 0,05 era considerado significativo.

**Observaciones:** La pérdida de peso corporal promedio se

GB

midió en todos los grupos de estudio, incluyendo el grupo de control de vehículo. Se observó diarrea y signos de deshidratación (pérdida de elasticidad de la piel) en todos los grupos de estudio, incluyendo el control de vehículo. Una pérdida de peso corporal severa en una etapa temprana durante el período de estudio condujo al cese del tratamiento en los grupos que recibían N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida a las dosis más bajas (2 mg/kg) y a las dosis más altas (50 mg/kg) el Día 9 y el Día 7 del estudio, respectivamente. Dado que la pérdida de peso corporal era menos severa en el grupo que recibía N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida a razón de 10 mg/kg, todos los tratamientos para este grupo fueron administrados según lo programado. Las pérdidas promedio de peso corporal al final del estudio para este grupo y en el grupo de tratamiento con 5-fluorouracilo eran significativas.

Aunque el índice positivo de los tumores HT-29 en el grupo de 'índice positivo' 21 días después de la inoculación era del 100%, el tamaño de estos tumores era mucho menor que lo anticipado. Esto puede haber contribuido a que no había una diferencia significativa en los pesos promedio de ciegos y tumores entre los grupos tratados con N-(S)-(3,4-difluoro-

84

2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida y el grupo de control de vehículo. Tampoco hubo efecto del 5-fluorouracilo sobre el peso del ciego y los tumores HT-29.

***Mediciones del peso corporal (± EEM) (Días de tratamiento finales y fecha de terminación del estudio)***

| Grupo | Comp. | Dosis (mg/kg), ruta, cronograma | | | Respuesta del huésped | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Delta de peso corporal (g) (± EEM) día final del tratamiento | % Delta de peso corporal el día final del tratamiento | Delta de peso corporal (g) (± EEM) día final del estudio | % Delta de peso corporal el día final del estudio | N° sobrevida (N° vivos/total) |
| 1 | Control de vehículo | - | p.o. | Una vez por día durante 21 días (Días 0 a 20) | - | - | -0,8 ± 0,4 | -3,6 | 8/10 |
| 2 | Compuesto A | 2 | p.o. | Una vez por día durante diez Días (Días 0 a 9) | -2,4 ± 1,4 (Día 9) | -11,1 | 0,1 ± 0,9 | 0,4 | 4/10 |
| 3 | Compuesto A | 10 | p.o. | Una vez por día durante 21 días (Días 0 a 20) | - | - | -1,5 ± 0,3 | -6,9 | 7/10 |
| 4 | Compuesto A | 50 | p.o. | Una vez por día durante ocho días (Días 0 a 7) | -3,8 ± 0,5 (Día 7) | -17,8 | -1,3 ± 0,9 | -5,9 | 7/10 |
| 5 | 5'-fluorouracilo | 75 | i.v. | Una vez por semana durante tres semanas (Días 0, 7 y 14) | - | - | -3,3 ± 0,4 | -15,2 | 8/10 |

No se recolectaron datos de peso corporal para el Grupo

85

6 (control de 'índice positivo'). El grupo se descartó el Día 7 del estudio (Día 21 después de la inoculación) para evaluar visualmente si los tumores estaban creciendo adecuadamente para el propósito del estudio.

El tratamiento se discontinuó en el Grupo 2 (N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida at 2 mg/kg) el Día 9 del estudio y en el Grupo 4 (N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida a 50 mg/kg) el Día 7 del estudio, porque los ratones estaban perdiendo demasiado peso corporal. Los grupos remanentes recibieron todos los tratamientos programados durante el período de estudio.

El peso tumoral promedio de cada grupo se muestra en la Figura 18. el peso promedio de los tumores para cada grupo incluye solamente los que sobrevivieron hasta el día final del estudio. Los valores de los ratones que murieron durante el período de estudio no están incluido en los valores de promedio calculados.

***Datos del peso de los ciegos y del peso de tumores***

| Grupo | Tratamiento | ID animal | Peso del ciego (g) | Peso tumoral (g) | Peso promedio de ciegos (g) | EEM | Peso promedio de tumores (g) | EEM |
|---|---|---|---|---|---|---|---|---|
| 1 | Control de vehículo (CremophorEL:Salina) | 173811 | 0,290 | 0,070 | 0,413 | 0,081 | 0,149 | 0,080 |
| | | 170774 | 0,331 | 0,160 | | | | |
| | | 170729 | 0,267 | 0,017 | | | | |
| | | 173673 | 0,307 | 0,005 | | | | |
| | | 171429 | 0,311 | 0,326 | | | | |
| | | 175732 | 0,946 | 0,627 | | | | |

816

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 171539 | 0,286 | 0,038 | | | | |
| | | 173576 | 0,287 | 0,002 | | | | |
| | | 170836 | 0,397 | 0,000 | | | | |
| | | 172014 | 0,506 | 0,176 | | | | |
| 2 | Compuesto A @ 2 mg/kg | 175867 | 0,347 | 0,001 | 0,296 | 0,033 | 0,033 | 0,030 |
| | | 170936 | 0,170 | 0,001 | | | | |
| | | 172003 | 0,150 | 0,000 | | | | |
| | | 176472 | 0,205 | 0,005 | | | | |
| | | 171338 | 0,377 | 0,001 | | | | |
| | | 170825 | 0,233 | 0,122 | | | | |
| | | 174466 | 0,251 | 0,005 | | | | |
| | | 171587 | 0,322 | 0,003 | | | | |
| 3 | Compuesto A @ 10 mg/kg | 173623 | 0,287 | 0,000 | 0,244 | 0,025 | 0,078 | 0,059 |
| | | 170793 | 0,198 | 0,000 | | | | |
| | | 172304 | 0,258 | 0,257 | | | | |
| | | 175676 | 0,111 | 0,008 | | | | |
| | | 171003 | 0,263 | 0,422 | | | | |
| | | 171466 | 0,237 | 0,001 | | | | |
| | | 176386 | 0,234 | 0,014 | | | | |
| | | 170858 | 0,289 | 0,004 | | | | |
| | | 175862 | 0,320 | 0,100 | | | | |
| | | 171364 | 0,251 | 0,000 | | | | |
| 4 | Compuesto A @ 50 mg/kg | 175697 | 0,230 | 0,002 | 0,290 | 0,038 | 0,122 | 0,092 |
| | | 171349 | 0,254 | 0,002 | | | | |
| | | 174272 | 0,238 | 0,000 | | | | |
| | | 176335 | 0,201 | 0,004 | | | | |
| | | 171041 | 0,337 | 0,166 | | | | |
| | | 174536 | 0,169 | 0,655 | | | | |
| | | 175656 | 0,328 | 0,001 | | | | |
| | | 173626 | 0,217 | 0,001 | | | | |
| | | 171437 | 0,312 | 0,001 | | | | |
| | | 174501 | 0,463 | 0,026 | | | | |
| 5 | 5FU™ @ 75 mg/kg | 171322 | 0,355 | 0,245 | 0,391 | 0,050 | 0,069 | 0,041 |
| | | 175559 | 0,199 | 0,001 | | | | |
| | | 176302 | 0,360 | 0,000 | | | | |
| | | 176241 | 0,284 | 0,000 | | | | |
| | | 175857 | 0,421 | 0,010 | | | | |
| | | 176242 | 0,706 | 0,329 | | | | |
| | | 174165 | 0,415 | 0,130 | | | | |
| | | 176417 | 0,327 | 0,079 | | | | |
| | | 170592 | 0,237 | 0,000 | | | | |
| | | 171501 | 0,377 | 0,003 | | | | |

Los cuadros sombreados indican las muestras recolectadas de ratones que murieron durante el período de estudio. Los valores promedio calculados para el peso de los ciegos y el peso de los tumores excluían estos valores. Hay una tendencia indicativa de una reducción en los datos de pesos de tumores HT-29 y ciegos después del tratamiento con 10 mg/kg de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-

817

dihidroxipropil)ciclopropan-1-sulfonamida.

**Ejemplo 117**: Retardo del crecimiento tumoral en ratones desnudos portadores de xenoinjertos de melanoma humano A375

Se usaron seis grupos (n = 9) de ratones con tumores. Los grupos control incluyeron uno que recibió el vehículo de Cremophor EL/salina 10% mediante gavaje oral (po), una vez por día durante 14 días (qd x14) y un segundo grupo que recibió paclitaxel como agente de referencia a 30 mg/kg mediante inyección en la vena de la cola (iv), día por medio para cinco dosis (qod x5). Los cuatro grupos experimentales recibieron N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida ("Compuesto A") por vía oral a 25 mg/kg o 50 mg/kg, qd x14, o a 12,5 ó 25 mg/kg, bid x14. El resultado del tratamiento se evaluó por TGD, definido como la diferencia en la mediana de tiempo hasta el volumen tumoral de final en un grupo de tratamiento en comparación con el grupo control. La toxicidad se evaluó mediante mediciones del peso corporal y observaciones clínicas.

**Animales**: Los ratones desnudos (*nu/nu*, Harlan) atímicos hembra tenían 10 a 11 semanas de vida y su peso corporal (BW) variaba en un rango de 19,3 a 25,5 gramos el Día 1 del estudio. Los animales recibieron agua *ad libitum* (ósmosis reversa, 1 ppm de Cl) y alimento Lab Diet® NIH 31 modificado

818

e irradiado que consiste de 18,0% de proteínas crudas, 5,0% de grasas crudas y 5,0% de fibras crudas. Los ratones fueron albergados sobre lechos para animales de laboratorio ALPHA-Dri® bed-o'cobs® irradiados en microjaulas estáticas con un ciclo de 12 horas de luz a 21-22 °C (70-72 °F) y 40-60% de humedad. Se observaron las recomendaciones de la *Guide for Care and Use of Laboratory Animals [Guía para el cuidado y uso de animales de laboratorio]* con respecto a restricciones, cría, procedimientos quirúrgicos, regulación de alimentos y líquido, y cuidado veterinario.

***Implante de tumores***: Se iniciaron xenoinjertos a partir de tumores de melanoma humano A375 mediante transplante en serie en ratones desnudos atímicos. Se implantó por vía subcutánea un fragmento (~ 1 $mm^3$) de tumor A375 en el flanco derecho de cada ratón de prueba, y el crecimiento de los tumores se monitoreó cuando el tamaño promedio alcanzaba 100 - 150 $mm^3$. Trece días después, designado como Día 1 del estudio, los animales se dividieron en seis grupos cada uno de los cuales consistía de nueve ratones (reducido de diez) con volúmenes tumorales individuales que varían en un rango de 63 a 221 $mm^3$ y volúmenes tumorales promedio para el grupo de 125,3 a 125,9 $mm^3$. El volumen tumoral se calculó usando la siguiente fórmula: Volumen tumoral ($mm^3$) = $\frac{w^2 \times l}{2}$, donde $w$ = ancho y $l$ = longitud en mm de un tumor A375.

**Materiales**: Se disolvió N-(S)-(3,4-difluoro-2-(2-

819

fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida hasta una concentración de 5 mg/ml en 10% de Cremophor EL en salina con sonicación, agitación y calentamiento a 35°C para asistir en la disolución. La solución 5 mg/ml sirvió como solución de dosificación para el tratamiento con 50 mg/kg, y las soluciones de dosificación para los tratamientos con 25 mg/kg y 12,5 mg/kg se prepararon por dilución en serie. Las soluciones de dosificación se guardaron por un máximo de una semana a temperatura ambiente y protegidas de la luz.

Las soluciones de dosificación de paclitaxel (NPI) se prepararon a partir de una solución madre 30 mg/ml para el uso diario por dilución a 3 mg/ml en 5% de etanol, 5% de Cremophor EL en 5% de dextrosa en agua (D5W). La dosificación de paclitaxel era de 30 mg/kg.

**Tratamiento**: En la siguiente tabla se muestra el régimen de tratamiento.

| | | **Régimen de tratamiento** | | | |
|---|---|---|---|---|---|
| **Grupo** | **n** | **Agente** | **(mg/kg)** | **Ruta** | **Cronograma** |
| 1 | 9 | Vehículo | - | po | qd x 14 |
| 2 | 9 | Paclitaxel | 30 | iv | qod x 14 |
| 3 | 9 | Compuesto A | 50 | po | qd x 14 |
| 4 | 9 | Compuesto A | 25 | po | bid x 14 primer día<br>1 dosis |
| 5 | 9 | Compuesto A | 25 | po | qd x 14 |
| 6 | 9 | Compuesto A | 12,5 | po | bid x 14 primer día<br>1 dosis |

Los ratones en el Grupo 1 recibieron vehículo que

870

consistía de 10% de Cremophor EL en salina por gavaje oral (po) por día para catorce dosis (qd x14), y sirvieron como control para el progreso tumoral. Los animales del Grupo 2 recibieron paclitaxel por vía intravenosa (iv) como agente de referencia a razón de 30 mg/kg, una vez cada día por medio para cinco dosis (qod x5). Los ratones de los Grupos 3 - 6 recibieron N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida por vía oral con el siguiente cronograma respectivo: 50 mg/kg, qd x14; 25 mg/kg, dos veces por día durante 14 días con una sola dosis el primer y último días (bid x14); 25 mg/kg, qd x14; y 12,5 mg/kg, bid x14. Todas las dosis fueron administradas en volúmenes de 0,2 ml por cada 20 g de peso corporal, y se llevaron a escala para el peso corporal del animal.

***Punto final***: En todos los grupos los tumores se midieron dos veces por semana usando un calibre. Cada animal era sacrificado cuando su tumor alcanzaba el tamaño final de 2000 $mm^3$ o el día final del estudio (Día 60), cualquiera que sucediera primero. El tiempo hasta el punto final (TTE) para cada ratón se calculó a partir de la siguiente ecuación: $\text{TTE (días)} = \frac{\log_{10}(\text{volumen final, mm}^3) - b}{m}$, donde b es la intersección y m es la pendiente de la línea obtenida por regresión lineal de un conjunto de datos de crecimiento tumoral transformado con log.

821

El conjunto de datos estaba compuesto por la primera observación que excedía el volumen final del estudio y las tres observaciones consecutivas que precedían inmediatamente al punto del volumen final. A los animales que no alcanzan el punto final se les asigna un valor de TTE igual al último día del estudio. Los animales clasificados como muertes NTR (no relacionado con el tratamiento) debido a un accidente (NTRa) o debido a causas desconocidas (NTRu) son excluidos de los cálculos de TTE (y todos los análisis adicionales). A los animales clasificados como muertes TR (relacionado con el tratamiento) o NTRm (no relacionado con el tratamiento, debido a metástasis) se les asigna un valor de TTE igual al día de muerte.

El resultado del tratamiento se determinó a partir del retardo del crecimiento tumoral (TGD), definido como el incremento en la mediana del tiempo hasta el punto final (TTE) en un grupo de tratamiento en comparación con el grupo control: TGD = T - C, expresado en días, o como un porcentaje de la mediana de TTE del grupo control: %TGD = $\frac{T-C}{C}$ x 100, donde: T = mediana de TTE para un grupo de tratamiento, C = mediana de TTE para el grupo control (Grupo 1).

El tratamiento puede causar una regresión parcial (PR) o una regresión completa (CR) del tumor en un animal. En una respuesta PR, el volumen tumoral es del 50% o menos de su

822

volumen de Día 1 para tres mediciones consecutivas durante el transcurso del estudio, e igual o mayor que 13,5 $mm^3$ para una o más de estas tres mediciones. En una respuesta CR, el volumen tumoral es menor que 13,5 $mm^3$ para tres mediciones consecutivas durante el transcurso del estudio. Un animal con una respuesta CR al terminar el estudio se clasifica además como un sobreviviente sin tumores (TFS). Se monitorearon y registraron las regresiones tumorales.

***Efectos secundarios***: Los animales eran pesados todos los días durante los primeros cinco días del estudio y luego dos veces por semana. Los ratones eran observados frecuentemente por signos evidentes de cualquier efecto secundario adverso, relacionado con el tratamiento y cuando se observaban signos clínicos eran registrados. La tolerabilidad aceptable se define como un grupo con una pérdida de peso corporal promedio de menos que un 20% durante la prueba y no más que una muerte relacionada con el tratamiento en un grupo de animales. Cualquier régimen de dosificación que no cumpliera con estos criterios se consideraba por encima de la dosis máxima tolerada (MTD). Una muerte se clasifica como TR si es atribuible a efectos secundarios del tratamiento evidenciado por signos clínicos y/o necropsia, o se puede clasificar como TR si se debe a causas desconocidas durante el período de dosificación o dentro de los 10 días de la última dosis. Una muerte se

823

clasifica como NTR si no hay evidencia que dicha muerte estaba relacionada con efectos secundarios del tratamiento.

***Análisis estadísticos y gráficos***: Se usó la prueba Logrank para analizar la significancia de las diferencias entre los valores de TTE de grupos tratados y de control. Se condujeron análisis estadísticos de dos colas con un nivel de significancia $P = 0,05$.

Las curvas de medianas del crecimiento tumoral muestran las medianas de volúmenes tumorales del grupo en función del tiempo. Cuando un animal salía del estudio debido al tamaño tumoral o a una muerte TR, se incluía el volumen tumoral final registrado para el animal con los datos usados para calcular la mediana del volumen tumoral del grupo en subsiguientes tiempos. Las curvas eran truncadas después que el 50% de los animales en un grupo había salido del estudio debido al progreso del tumor. Se construyeron gráficos de Kaplan-Meier para mostrar el porcentaje de animales remanentes en el estudio en función del tiempo, y se usó el mismo conjunto de datos que en la prueba Logrank. Se usó Prism (GraphPad) para Windows 3.03 para todas las presentaciones gráficas y análisis estadísticos.

***Resumen de respuesta al tratamiento***

| **Grupo** | **Mediana de TTE** | **T-C** | **%TGD** | **Significancia estadística** | **MTV (n) Día 60** | **Regresiones** | | | **Media de BW Valor más bajo** |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | PR | CR | TFS | |

824

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 22,8 | - | - | - | - | 0 | 0 | 0 | - |
| 2 | 28,8 | 6,0 | 26 | ** | - | 0 | 0 | 0 | -5,3% Día 15 |
| 3 | 27,5 | 4,7 | 21 | ** | - | 1 | 0 | 0 | - |
| 4 | 59,9 | 37,1 | 163 | *** | 0 (4) | 4 | 5 | 4 | -0,6% Día 15 |
| 5 | 25,6 | 2,8 | 12 | Ns | - | 0 | 0 | 0 | - |
| 6 | 27,5 | 4,7 | 21 | * | - | 1 | 0 | 0 | - |

***Crecimiento de tumores A375 en ratones control (Grupo 1)***: Los animales en el Grupo 1 recibieron el vehículo de 10% de Cremophor EL/salina, po, qd x14. Los tumores en los ratones control crecieron progresivamente hasta el volumen final de 2000 $mm^3$ con una mediana de TTE de 22,8 días, estableciéndose una T-C máxima posible en el estudio de 37,1 días, o 163% de TGD.

***Efecto del tratamiento con paclitaxel (Grupo 2)***: Los animales del Grupo 2 recibieron paclitaxel como agente de referencia, 30 mg/kg, iv, qod x5. Los nueve animales alcanzaron el volumen tumoral final. El crecimiento tumoral era paralelo y ligeramente desplazado hacia la derecha en comparación con el grupo control. El valor de la mediana de TTE era de 28,8 días, correspondiente a un 26% de TGD, un resultado significativo según el análisis Logrank (Tabla 2, $P$ = 0,0088 G1 versus G2). No se asociaron regresiones tumorales con el tratamiento con paclitaxel.

***Efecto del tratamiento con N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-***

825

***dihidroxipropil)ciclopropan-1-sulfonamida (Grupos 3 - 6):*** Los Grupos 3 - 6 recibieron una dosificación oral con N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida como una monoterapia. Los animales del Grupo 3 recibieron 50 mg/kg en un programa de qd x14. Los nueve tumores en el grupo alcanzaron el volumen final. La mediana del volumen tumoral del grupo mostró pocos cambios netos durante los primeros ~ 10 días, luego incrementaron por el resto de la duración del estudio. Un solo animal experimentó PR tumoral. El valor de la mediana de TTE era de 27,5 días, o 21% de TGD, un resultado significativo (P = 0,0054 G1 versus G).

Los animales en el Grupo 4 recibieron 25 mg/kg de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida según un programa de bid x14. Cuatro de los nueve animales en el grupo permanecieron el Día 60, todos TFS. Un adicional de 2/9 de los animales tenían tumores que alcanzaron el volumen final el día antes de terminar el estudio. El grupo tenía 4/9 PR, 5/9 CR y 4/9 TFS. La mediana del volumen tumoral cayó al comienzo de los primeros pocos días del estudio y continuaron por aproximadamente 30 días. El recrecimiento de tumores en 5/9 de los animales representaba un resurgimiento de la mediana del crecimiento tumoral comenzando aproximadamente el Día 32 y continuando

826

hasta el final del estudio. El valor de la mediana de TTE del grupo era de 59,9 días, que representa el máximo posible de 163% de TGD (P < 0,0001, Tabla A1).

Los animales en el Grupo 5 también recibieron 25 mg/kg N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida, pero según un programa menos intenso de qd x14. Los nueve animales en el Grupo 5 alcanzaron el volumen tumoral final, sin regresiones tumorales. El crecimiento tumoral mostró un comportamiento muy semejante al del grupo control. La mediana de TTE era de 25,6 días, o 12% de TGD, un resultado no significativo (P = 0,0662 G1 versus G).

Los animales en el Grupo 6 recibieron 12,5 mg/kg de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida según un programa de bid x14. Todos los tumores en el grupo alcanzaron el volumen final. Al igual que con el Grupo 4, la mediana del volumen tumoral en el Grupo 6 cayó en una etapa temprana del estudio, pero esta reducción solamente era sostenida por nueve días aproximadamente y estaba asociada con una sola respuesta PR. El volumen tumoral incrementó desde el Día 10 hasta el final del estudio. La mediana de TTE para el grupo era de 27,5 días, correspondiente a un valor significativo de 21% de TGD (*P* = 0,0424 G1 versus G6).

874

En resumen, la N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida mostró una actividad antitumoral relacionada con la dosis contra xenoinjertos de melanoma humano A375, con una dosificación oral administrada una vez por día y dos veces por día. La dosificación de dos veces por día era superior a una vez por día en la magnitud de TGD producido y en las cantidades de respuestas objetivas. Por consiguiente, la actividad antitumoral de N-(S)-(3,4-difluoro-2-(2-fluoro-4-iodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida es dependiente de la dosis y del programa de administración.

**Ejemplo 118:**

Actividad contra xenoinjertos subcutáneos de carcinoma de colon humano COLO 205

**Animales:** Los ratones desnudos (*nu/nu*, Harlan) atímicos hembra tenían 12 a 13 semanas de vida y su peso corporal (BW) variaba en un rango de 18,3 a 27,3 gramos el Día 1 del estudio. Los animales recibieron agua *ad libitum* (ósmosis reversa, 1 ppm de Cl) y alimento Lab Diet® NIH 31 modificado e irradiado que consiste de 18,0% de proteínas crudas, 5,0% de grasas crudas y 5,0% de fibras crudas. Los ratones fueron albergados sobre lechos para animales de laboratorio ALPHA-Dri® bed-o'cobs® irradiados en microjaulas estáticas

878

con un ciclo de 12 horas de luz a 21-22 °C (70-72 °F) y 40-60% de humedad. Se observaron las recomendaciones de la *Guide for Care and Use of Laboratory Animals [Guía para el cuidado y uso de animales de laboratorio]* con respecto a restricciones, cría, procedimientos quirúrgicos, regulación de alimentos y líquido, y cuidado veterinario.

***Implante de tumores***: Los xenoinjertos eran iniciados a partir de células de carcinoma de colon humano COLO 205. Las células tumorales se cultivaron en suero fetal bovino inactivado por calor 10%, penicilina G sódica 100 unidades/ml, sulfato de estreptomicina 100 µg/ml, anfotericina B 0,25 µg/ml y gentamicina 25 µg/ml, glutamina 2 mM, piruvato de sodio 1 mM, HEPES 10 mM y bicarbonato de sodio 0,075%. Los cultivos de células se mantuvieron en frascos de cultivo tisular en un incubador humidificado a 37°C, en una atmósfera de 5% de $CO_2$ y 95% de aire. El día del implante de las células tumorales, se cosecharon células Colo 205 en crecimiento logarítmico y se resuspendieron en matriz de Matrigel 50% (BD Biosciences) en PBS a una concentración de 5 x $10^6$ células/ml. Cada ratón de prueba recibió 1 x $10^6$ células Colo 205 implantadas subcutáneamente en el flanco derecho, y se monitoreó el crecimiento de tumores a medida que el tamaño promedio se acercaba a 80 - 120 $mm^3$. Catorce días después, designado Día 1 del estudio, los animales se dividieron en ocho grupos (n = 9) con

879

volúmenes tumorales individuales que varían en un rango de 63 a 196 $mm^3$ y las medias de los volúmenes tumorales del grupo era de 118-119 $mm^3$. El volumen tumoral se calculó usando la siguiente fórmula: Volumen tumoral ($mm^3$) = $\frac{w^2 \times l}{2}$, donde w = ancho y l = longitud en mm de un tumor COLO 205. El peso tumoral se puede estimar con la premisa que 1 mg es equivalente a 1 $mm^3$ de volumen tumoral.

**Materiales:** Las soluciones de dosificación del Compuesto A se prepararon frescas todos los días por disolución de la cantidad requerida de compuesto en 100% de Cremophor EL, y luego dilución 10x con salina normal. Las concentraciones de la solución de dosificación final era de 2,5, 5, 10 ó 20 mg/ml, con el fin de suministrar dosis respectivas de 25, 50, 100 ó 200 mg/kg en un volumen de dosificación de 10 ml/kg. El Paclitaxel (Natural Pharmaceuticals, Inc.) se preparó fresco cada día de dosificación en un vehículo que consistía de 5% de etanol y 5% de Cremophor EL en 90% de D5W (5% de vehículo EC).

**Tratamiento:** En la siguiente tabla se muestra el régimen de tratamiento.

| | | **Régimen de tratamiento** | | | |
|---|---|---|---|---|---|
| **Grupo** | **n** | **Agente** | **(mg/kg)** | **Ruta** | **Cronograma** |
| 1 | 9 | Vehículo | - | po | qd x 14 |
| 2 | 9 | Paclitaxel | 30 | iv | qod x 14 |
| 3 | 9 | Compuesto A | 50 | po | qd x 14 |
| 4 | 9 | Compuesto A | 25 | po | bid x 14 primer día<br>1 dosis |

830

| | | | | | |
|---|---|---|---|---|---|
| 5 | 9 | Compuesto A | 25 | po | qd x 14 |
| 6 | 9 | Compuesto A | 12,5 | po | bid x 14 primer día 1 dosis |

El Grupo 1 recibió el vehículo de la formulación (10% de Cremophor EL en salina), y sirvió como grupo control del crecimiento tumoral. El Grupo 2 recibió la droga de referencia paclitaxel administrada según su cronograma óptimo en ratones desnudos (30 mg/kg i.v. qod x5). Los Grupos 3 - 6 recibieron 25, 50, 100 y 200 mg/kg de dosis, respectivamente, de Compuesto A administrado p.o. qd x14, con discontinuación de la dosificación en el Grupo 6 (200 mg/kg) después de seis días debido a la toxicidad. Todas las dosis se llevaron a escala para el peso del animal (0,2 ml por cada 20 gramos de peso corporal).

***Punto final***: Los tumores se midieron dos veces por semana usando un calibre. Cada animal era sacrificado cuando su tumor alcanzaba el tamaño final predeterminado de 2000 $mm^3$ o el día final del estudio (Día 74), cualquiera que sucediera primero. Sin embargo, los tumores control no exhibieron características de crecimiento logarítmico después de alcanzar un tamaño de aproximadamente 800 $mm^3$. Por ello se usó el tamaño tumoral final de 800 $mm^3$ para el análisis del retardo del crecimiento tumoral (TGD). El tiempo hasta el punto final (TTE) para cada ratón se calculó a partir de la siguiente ecuación: $\mathrm{TTE\,(días)} = \frac{\log_{10}(\text{volumen final}, mm^3) - b}{m}$,

831

donde b es la intersección y m es la pendiente de la línea obtenida por regresión lineal de un conjunto de datos de crecimiento tumoral transformado con log. El conjunto de datos estaba compuesto por la primera observación que excedía el volumen final del estudio y las tres observaciones consecutivas que precedían inmediatamente al punto del volumen final. A los animales que no alcanzan el punto final se les asigna un valor de TTE igual al último día del estudio. Los animales clasificados como muertes NTR (no relacionado con el tratamiento) debido a un accidente (NTRa) o debido a causas desconocidas (NTRu) son excluidos de los cálculos de TTE (y todos los análisis adicionales). A los animales clasificados como muertes TR (relacionado con el tratamiento) o NTRm (muerte no relacionada con el tratamiento, debida a metástasis) se les asigna un valor de TTE igual al día de muerte.

El resultado del tratamiento se evaluó a partir del retardo del crecimiento tumoral (TGD), que se define como el incremento en la mediana del tiempo hasta el punto final (TTE) en un grupo de tratamiento en comparación con el grupo control: TGD = T - C, expresado en días, o como un porcentaje de la mediana de TTE del grupo control: %TGD = $\frac{T-C}{C}$ x 100, donde: T = mediana de TTE para un grupo de tratamiento, C = mediana de TTE para el grupo control.

El grupo control se especificó como ratones del Grupo

832

1.

El tratamiento puede causar una regresión parcial (PR) o una regresión completa (CR) del tumor en un animal. En una respuesta PR, el volumen tumoral es del 50% o menos de su volumen de Día 1 para tres mediciones consecutivas durante el transcurso del estudio, e igual o mayor que 13,5 $mm^3$ para una o más de estas tres mediciones. En una respuesta CR, el volumen tumoral es menor que 13,5 $mm^3$ para tres mediciones consecutivas durante el transcurso del estudio. Se monitorearon y registraron las respuestas de regresiones.

***Efectos secundarios***: Los animales eran pesados todos los días durante los primeros cinco días del estudio y luego dos veces por semana. Los ratones eran observados frecuentemente por signos evidentes de cualquier efecto secundario adverso, relacionado con el tratamiento y cuando se observaban signos clínicos de toxicidad eran registrados. Una toxicidad aceptable se define como una media de pérdida de peso corporal del grupo de menos que un 20% durante el estudio y de no más que una muerte relacionada con el tratamiento (TR) entre diez animales tratados, y se considera que cualquier régimen de dosificación que diera como resultado una mayor toxicidad se encuentra por encima de la dosis máxima tolerada (MTD). Una muerte se clasifica como TR si es atribuible a efectos secundarios del tratamiento evidenciado por signos clínicos y/o necropsia, o

833

se puede evaluar como TR si se debe a causas desconocidas durante el período de dosificación o dentro de los 10 días de la última dosis. Una muerte se clasifica como NTR si no hay evidencia que dicha muerte estaba relacionada con efectos secundarios del tratamiento. Los animales fueron monitoreados por efectos secundarios por medio de una observación frecuente y mediciones de BW. Los cambios de BW no fueron notorios, y todos los tratamientos eran aceptablemente tolerados, excepto el Grupo 6. Seis dosis p.o. de una vez por día de 200 mg/kg de Compuesto A dio como resultado una muerte TR evaluada el Día 7 y dos muertes TR adicionales el Día 8. Todos los ratones en el Grupo 6 exhibieron síntomas clínicos de la toxicidad incluyendo posturas encorvada, hipoactividad y deposiciones sueltas.

***Análisis estadísticos y gráficos***: Se usó la prueba Logrank para analizar la significancia de las diferencias entre los valores de TTE de grupos tratados y de control. Se condujeron análisis estadísticos de dos colas con un nivel de significancia $P = 0,05$.

Las curvas de medianas del crecimiento tumoral muestran las medianas de volúmenes tumorales del grupo graficadas a escala log en función del tiempo. Cuando un animal salía del estudio debido al tamaño tumoral o a una muerte TR, se incluía el volumen tumoral final registrado para el animal con los datos usados para calcular la mediana del volumen

834

tumoral del grupo en subsiguientes tiempos. Las curvas eran truncadas después que el 50% de los animales en un grupo había salido del estudio debido al progreso del tumor o después de la segunda muerte TR en un grupo. Se construyeron gráficos de Kaplan-Meier para mostrar el porcentaje de animales remanentes en el estudio en función del tiempo, y se usó el mismo conjunto de datos que en la prueba Logrank. Se usó Prism (GraphPad) para Windows 3.03 para todas las presentaciones gráficas y análisis estadísticos.

***Resumen de respuesta al tratamiento***

| **Grupo** | **Mediana** | **T-C** | **%TGD** | **SS** | **MTV (n) Día 74** | **No de** | | | | | **Media de BW** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | **PR** | **CR** | **TFS** | **TR** | **NTR** | |
| 1 | 41,0 | - | - | - | 322 (2) | 0 | 0 | 0 | 0 | 0 | - |
| 2 | 60,0 | 19,0 | 46% | ns | 0 (3) | 1 | 0 | 0 | 2 | 2 | - |
| 3 | 47,9 | 6,9 | 17% | ns | 0 (3) | 1 | 0 | 0 | 2 | 2 | - |
| 4 | 59,1 | 18,1 | 44% | ns | 195 (1) | 4 | 0 | 0 | 0 | 0 | - |
| 5 | 74,0 | 33,0 | 80% | ns | 320 (5) | 4 | 0 | 0 | 1 | 0 | - |
| 6 | 57,8 | 16,8 | 41% | ne | 0 (3) | 1 | 3 | 0 | 2 | 2 | 0,1% Día 22 |

***Crecimiento de tumores COLO 205 en ratones control (Grupo 1):***

Los tumores del Grupo 1 exhibieron un crecimiento lento, heterogéneo. Los tumores de 7/9 ratones control del Grupo 1 tratado con vehículo alcanzó el volumen tumoral final de 800 $mm^3$ y dos ratones permanecieron hasta el final del estudio. La mediana de TTE del Grupo 1 era de 41,0

635

días, y por ello el valor máximo de TGD en este estudio de 74 días era de 33,0 días (80%).

***Efecto del tratamiento con paclitaxel (Grupo 2):***

Ocho ratones del Grupo 2 (n = 9) que recibieron tratamiento con paclitaxel permanecieron en el estudio el Día 74 con un valor de MTV de 143 $mm^3$. Esto corresponde al valor máximo posible de TGD (33,0 días u 80%) y una actividad estadísticamente significativa (*P* = 0,002). Se documentaron cinco respuestas PR. La curva de la mediana de crecimiento tumoral muestra una disminución en el MTV hasta el Día 19, seguido por pocos cambios hasta el Día 47 cuando vuelve a observarse crecimiento tumoral.

*Efecto del tratamiento con el Compuesto A (Grupos 3-6)*

Los Grupos 3, 4, 5 produjeron medianas de TTE de 47,9, 59,1 y 74,0 días, respectivamente. Los Grupos 3 y 4 mostraron resultados logrank no significativos, y la prueba Logrank para el Grupo 5 alcanzó una significancia límite (*P* = 0,058). Estos tratamientos produjeron regresiones dependientes de la dosis, no obstante, el tipo de respuesta de regresión (PR versus CR) y la cantidad de sobrevivientes a los 74 días por grupo no se correlaciona con la dosis. Las curvas de la mediana del crecimiento tumoral indican actividades similares para los tres niveles de dosis en la etapa temprana del estudio (hasta el Día 29), seguido por retardos dependientes de la dosis en el recrecimiento de

836

tumores. El Grupo 6 produjo tres muertes TR, y la dosificación se detuvo después del Día 6. Por ello se consideró que un tratamiento con 200 mg/kg se encontraba por encima de MTD y no evaluable para TGD.

El Compuesto A demostró una actividad dependiente de la dosis contra xenoinjertos del carcinoma de colon COLO 205. Cuando se administraba a 25 mg/kg, el Compuesto A exhibió un valor de TGD del 3%. A 50 mg/kg, el Compuesto A produjo un valor de TGD del 46%. El tratamiento con 100 mg/kg era aceptablemente tolerado y, al igual que el tratamiento con paclitaxel, dio como resultado el máximo valor de TGD posible en el experimento con una cantidad similar de respuestas de regresión. El tratamiento con 200 mg/kg produjo 3/9 muertes TR y se encontraba por encima del valor de MTD. Se observó una disminución inicial más pronunciada en la carga tumoral para el Compuesto A en comparación con paclitaxel; sin embargo, la duración del efecto era más corto. El recrecimiento de tumores en los grupos 25 y 50 mg/kg avanzó inicialmente más rápidamente en comparación con los controles, y hacia el final del estudio, los MTV se acercaron a los valores de los controles. El tratamiento con 100 mg/kg no exhibió este rápido recrecimiento, pero mostró un crecimiento tumoral más rápido en comparación con el de paclitaxel.

**Ejemplo 119:**

837

*Ensayo clínico humano*

Se realizará un ensayo clínico humano de seguridad/eficacia de fase I, randomizado, doble ciego, de etiqueta abierta, de control histórico, de asignación a grupos individuales, con el compuesto A versus placebo en pacientes con cáncer pancreático avanzado o metastásico que no han sido tratados previamente con una quimioterapia.

El propósito primario del estudio es evaluar la seguridad y tolerabilidad del compuesto A. Un resultado secundario será evaluar el índice de respuesta, el beneficio clínico y la disminución del tumor después del tratamiento con el compuesto A. Además, el estudio será diseñado para evaluar el tiempo hasta el avance de la enfermedad y la sobrevida global de los pacientes con cáncer pancreático. Además, se evaluarán los cambios farmacodinámicos en los parámetros vasculares del tumor (incluyendo, por ejemplo, el flujo de sangre, el volumen de sangre, la curva de características del operador receptor-ROC de tiempo hasta el pico) por DCE-MRI.

Más aún, se usarán marcadores biológicos, tales como polimorfismos genéticos y proteómicas séricas de MEK1 y MEK2 para correlacionar los resultados. Esto también permitirá determinar el índice de resección de tumores después del tratamiento, así como evaluar el valor de MTD para el compuesto A.

838

Durante el estudio, el compuesto A será administrado a dosis variables de aproximadamente 1 mg, aproximadamente 1,5 mg, aproximadamente 2 mg, aproximadamente 2,5 mg, aproximadamente 3 mg, aproximadamente 3,5 mg, aproximadamente 4,0 mg, aproximadamente 4,5 mg, aproximadamente 5 mg, aproximadamente 5,5 mg, aproximadamente 6 mg, aproximadamente 6,5 mg, aproximadamente 7 mg, aproximadamente 7,5 mg, aproximadamente 8 mg, aproximadamente 8,5 mg, aproximadamente 9 mg, aproximadamente 9,5 mg, aproximadamente 10 mg, aproximadamente 10,5 mg, aproximadamente 11 mg, aproximadamente 11,5 mg, aproximadamente 12 mg, aproximadamente 12,5 mg, aproximadamente 13 mg, aproximadamente 13,5 mg, aproximadamente 14 mg, aproximadamente 14,5 o de aproximadamente 15 mg.

Los criterios de inclusión para el estudio se basarán en los siguientes factores:

- Cáncer pancreático no resecable o no resecable límite localmente avanzado confirmado histológica/patológicamente, y sin evidencia de enfermedad metastásica.

- Diagnosis de cáncer pancreático no resecable localmente avanzado basado en la evaluación por tomografía axial computada de doble fase y/o ultrasonido endoscópico

839

(EUS) (el EUS se describe en el Apéndice F).

- Enfermedad que se puede medir de acuerdo con RECIST y que se puede obtener por tomografía axial computada de doble fase dentro de los 14 días antes de registrarla para el protocolo de terapia.

- Tamaño tumoral mayor o igual a 2 cm según una tomografía axial computada de doble fase.

- Función adecuada del órgano documentada dentro de los 14 días del registro evidenciado por: recuento absoluto de neutrófilos > 1500/mm3; recuento de plaquetas de 100.000/mm3; hemoglobina $^{3}$ 9 gm/dl sin requerimiento de transfusión en las 4 semanas anteriores; bilirrubina total ≤ 1,5 veces el límite superior de lo normal (ULN); transaminasas (AST y/o ALT) ≤ 2,5 x ULN; PT (o INR) ≤ 1,5 x ULN y aPTT dentro de límites normales (se permitirá que participen los pacientes que reciben tratamiento de anticoagulación con un agente tal como warfarina o heparina; para los pacientes que reciben warfarina, se efectuará un monitoreo cuidadoso con por lo menos evaluaciones semanales hasta que el valor de INR sea estable en base a una medición a la predosis, definido por la norma de cuidado local; depuración de creatinina de > 60 ml/ min calculada usando la fórmula de Cockcroft-Gault.

Los criterios de exclusión incluirán: antes del tratamiento con el compuesto A dentro de los 6 meses antes

240

del registro; evidencia clínica de invasión tumoral en la mucosa duodenal (documentada por endoscopía o ultrasonido endoscópico); procedimientos quirúrgico menores (por ejemplo, aspiración con aguja fina o biopsia con aguja) dentro de los 14 días del registro de estudio; procedimientos de cirugía mayor, lesión traumática significativa, o heridas serias que no cicatrizan, úlcera o fractura de huesos dentro de los 21 días del registro en el estudio; cualquiera de los siguientes dentro de los 6 meses antes de la administración de la droga en estudio: angina severa/inestable (síntomas de angina en reposo), inicio de angina (comenzó dentro de los últimos 3 meses) o infarto de miocardio, insuficiencia cardíaca congestiva, arritmias ventriculares cardíacas que requieren de una terapia anti-arrítmica; historia de eventos trombóticos o embólicos tales como accidente cerebrovascular o ataque isquémico transitorio dentro de los últimos 6 meses; historia de aneurisma o malformación arteriovenosa; infección conocida por el virus de inmunodeficiencia humana (HIV) o hepatitis B o C crónica; infección activa clínicamente seria mayor que CTCAE de grado 2; ingesta de cualquier agente de investigación dentro de las 4 semanas del registro en el estudio; hipertensión descontrolada definida como presión sanguínea sistólica mayor que 150 mm Hg o presión diastólica mayor que 90 mm Hg, a pesa de una gestión médica óptima;

841

evento de hemorragia/sangrado pulmonar mayor que CTCAE de Grado 2 dentro de las 4 semanas del registro en el estudio; cualquier otro evento de hemorragia/sangrado mayor que CTCAE de Grado 3 dentro de las 4 semanas del registro en el estudio; evidencia o historia de diátesis hemorrágica o coagulopatía; crónica, por tratamiento diario con aspirina u otras medicaciones anti-inflamatorias no esteroides; uso de hierba de San Juan, rifampin (rifampicina), ketoconazol, itraconazol, ritonavir o jugo de pomelo; alergia conocida o sospechada al compuesto A; cualquier condición que dificulte la capacidad del paciente para tragar una píldora entera; cualquier problema de malabsorción; otra condición médica o psiquiátrica severa, aguda o crónica, o anomalía de laboratorio que pueda incrementar el riesgo asociado con la participación en el estudio o con la administración de la droga del estudio o que pueda interferir con la interpretación de los resultados del estudio, y que a juicio del investigador volvería inapropiada la entrada del paciente en este estudio; historia de enfermedad vascular por colágeno; cualquier contraindicación para realizar un diagnóstico por imágenes por resonancia magnética.

**Ejemplo 120:**

*Ensayo clínico humano*

Se conducirá un ensayo clínico humano de seguridad/eficacia de fase I randomizado, doble ciego, de

842

etiqueta abierta, de control histórico, de asignación a grupos individuales, con el compuesto A en pacientes con cáncer de estómago avanzado o metastásica que no han sido tratados previamente con quimioterapia de la misma manera que se prescribió en el ejemplo 117, excepto que los pacientes enrolados tendrán un diagnóstico de linfoma, tumores de estroma gástrico o tumores carcinoides de estómago.

**Ejemplo 121:**

*Edema de pata inducida por carragenina (CPE) en ratas*

Se administró compuesto A (6, 20 y 60 mg/kg) o indometacina (3 mg/kg) por vía oral 2 hs antes de la inyección de una suspensión de carragenina 1% en la almohadilla plantar posterior derecha de ratas Sprague-Dawley macho (N = 6 por grupo de tratamiento). El edema de la pata posterior se midió 3 hs después evaluando el volumen de la pata por pletismografía. La reducción del edema de la pata posterior en un 30% o más indica una actividad anti-inflamatoria aguda significativa. Se usó indometacina (Indo) como droga de control positivo. En la Figura 22 se muestran los incrementos en el volumen de la pata en cada uno de los grupos de tratamiento que demuestran que la administración oral del Compuesto A dieron como resultado una significativa actividad anti-inflamatoria en el modelo de edema de pata con carragenina en rata en todos los grupos

843

de dosis.

**Ejemplo 122:**

*Ensayo de inflamación de artritis por adyuvante en rata*

En el modelo de artritis inducido por adyuvante, se inyecta adyuvante de Freund completo (CFA) en la pata posterior derecha de ratas para inducir patologías similares a artritis reumatoide en humanos. El Compuesto A se administró por vía oral durante 5 días consecutivos a razón de 2, 6 y 20 mg/kg. También se administró dexametasona a razón de 5 mg/kg por vía oral durante 5 días. Se administró enbrel a razón de 10 mg/kg mediante inyección subcutánea los días 1 y 4. Se inyectó CFA en la pata posterior derecha una hora después de la primera dosis el día 1. Se determinó el porcentaje de inhibición de hinchazón la pata posterior derecha con relación a los controles tratados con vehículo los días 1 y 5 para la fase aguda, en tanto el porcentaje de inhibición de hinchazón de la pata posterior izquierda con relación a los controles tratados con vehículo los días 14 y 18 se determinó para la fase retardada. La poliartritis se calificó como presencia de hinchazón en patas anteriores, cola, nariz u oreja.

En la Figura 23A y en la Figura 23B se muestra el porcentaje de inhibición de hinchazón con relación al control para los diferentes grupos de tratamiento. El Compuesto A a razón de 20 mg/kg mostró una reducción

844

significativa de hinchazón en ambas fases aguda y retardada. Según la calificación de poliartritis, los 6 animales en el grupo tratado con vehículo presentaba hinchazón en las patas anteriores y la cola. En el caso del grupo de Compuesto A a 20 mg/kg, 2 de 6 animales no mostraron hinchazón de patas anteriores y 4 de 6 no mostraron hinchazón en la cola. Para el grupo con enbrel, ninguno de los animales estaba protegido contra la hinchazón de patas anteriores y 3 de 6 animales no mostraron hinchazón en la cola.

**Ejemplo 123:**

Inhibición de artritis inducida por anticuerpos contra colágeno (CAIA) en ratones

Se aplicaron inyecciones por vía intravenosa (vena de la cola) a ratones Balb/c macho (N = 8 por grupo de tratamiento) con 2 mg de cóctel de anticuerpos contra colágeno (Chondrex) el día 0. Se administró RDEA119 (1, 3 y 10 mg/kg QD) o dexametasona (1 mg/kg QD) por vía oral los días 0-4, en tanto Enbrel se administró mediante inyección por vía subcutánea los días 1 y 3. Se aplicó una inyección intraperitoneal de LPS (50 µg) el día 3 a todos los ratones excepto los animales naïve. Se efectuó una determinación de las calificaciones artríticas para todas las extremidades y se muestran en la Figura 24 (calificación máxima de 16). Se observó una actividad anti-inflamatoria significativa con todos los artículos de prueba y drogas de referencia. Se usó

845

enbrel y dexametasona como controles positivos.

**Ejemplo 124:**

Ensayo de proliferación celular in vivo

El método para determinar las cuentas de proliferación celular en células cancerosas tratadas con un inhibidor de MEK proteína quinasa, es conocido en el arte y se describe en Kenny, L.M. et al., *Positron Emission Tomography (PET) Imaging of Cell Proliferation in Oncology, Clinical Oncology*, 16:176-185 (2004), que se incorpora por completo en la presente a modo de referencia. Se examina un inhibidor de MEK proteína quinasa (por ejemplo el Compuesto A) *in vivo* para determinar su efecto sobre la proliferación de células cancerosas. Se enrolaron voluntariamente 50 pacientes en el estudio, todos los cuales sufren de cáncer pancreático en una etapa similar de desarrollo del cáncer. A 25 pacientes se les administra una combinación del compuesto A. Los últimos 25 pacientes reciben placebo. A cada paciente se le administra una dosis diaria durante 14 días de un trazador radiomarcado, por ejemplo fluoro-2-deoxi-DF-glucosa (FDG) marcado.

Después de 14 días de tratamiento, un médico entrenado detecta la proliferación de células tumorales usando un aparato de diagnóstico por imágenes no invasivo por tomografía de emisión de positrones (PET). Más aún, el médico entrenado determinará las cuentas de proliferación

846

celular de para tejidos con células tumorales y normales en pacientes tratados con Compuesto A y placebo. Los resultados indicarán una disminución en las cuentas de proliferación celular entre el inhibidor de MEK proteína quinasa (por ejemplo Compuesto A) y placebo. Este ensayo para determinar las cuentas de proliferación celular usando trazadores marcados y diagnóstico por imágenes con PET se denomina en la presente "método de proliferación celular *in vivo*". Hay otros métodos de proliferación celular *in vivo* que son conocidos en el arte.

Se pueden emplear análisis similares para determinar la disminución del tamaño tumoral.

**Ejemplo 125:**

Ensayo de apoptosis in vivo

Se examina un inhibidor de MEK, por ejemplo, el Compuesto A, *in vivo* con el fin de determinar su efecto sobre la apoptosis de células cancerosas. Se enrolaron voluntariamente 40 pacientes en el estudio, todos los cuales sufren de cáncer pancreático en una etapa similar de desarrollo del cáncer. A 20 pacientes se les administra el compuesto A y a 20 pacientes se les administra placebo. A cada paciente se le administra una dosis durante 14 días.

Después de 14 días, cada paciente va a ingerir un reactivo de una proteína de unión a lipopolisacáridos (LBP) detectable acoplado a una marca. De acuerdo con

WO/2006/054068, que se incorpora por completo en la presente a modo de referencia, cada paciente es ubicado luego en el campo de un escáner, donde dicho escáner detecta el reactivo consumido unido a células muertas. La cantidad de células muertas se puede correlacionar con el nivel apoptosis de cada paciente. Los niveles de apoptosis en pacientes que recibieron las combinaciones y en los que recibieron agentes individuales se pueden comparar entre sí, así como con respecto al grupo de cohorte que recibió placebo. Este ensayo para detectar los niveles de apoptosis usando una proteína de unión a lipopolisacáridos y un escáner se denomina "método de apoptosis *in vivo*" en la presente.

**Ejemplo 126:**

Estudios de disolución

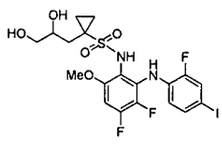
Se prepararon cápsulas que contienen Compuesto A como se describió en los ejemplos anteriores. Se obtuvieron los siguientes datos de disolución usando el método de disolución USP<711>.

| | **Forma de 1 mg** | **Forma de 10 mg** |
|---|---|---|
| **Tiempo (min)** | **% de liberación (%RSD)** | **% de liberación (%RSD)** |
| 15 | 78 (8,3) | 80 (7,3) |
| 30 | 82 (7,1) | 87 (9,2) |
| 45 | 82 (6,7) | 92 (9,6) |
| 60 | 88 (6,3) | 92 (7,2) |
| 70 | 86 (5,7) | 95 (5,4) |

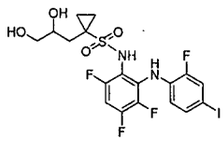
848

**REIVINDICACIONES:**

1. Una composición que comprende un compuesto seleccionado entre:




y




.

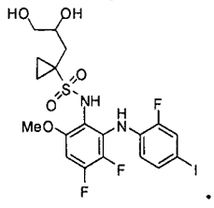
2. La composición de la reivindicación 1, en la cual el carbono 2-OH en el compuesto es de configuración R.
3. La composición de la reivindicación 1, en la cual el carbono 2-OH en el compuesto es de configuración S.
4. La composición de la reivindicación 1, la cual se encuentra sustancialmente libre del isómero S del compuesto.
5. La composición de la reivindicación 1, la cual se encuentra sustancialmente libre del isómero R del compuesto.
6. La composición de la reivindicación 1, en la cual el compuesto contiene menos de 10% del isómero S del compuesto.
7. La composición de la reivindicación 1, en la cual el compuesto contiene menos de 10% del isómero R del compuesto.
8. La composición de la reivindicación 1, en la cual el compuesto contiene menos de 5% del isómero S del compuesto.
9. La composición de la reivindicación 1, en la cual el

849

compuesto contiene menos de 5% del isómero R del compuesto.

10. La composición de la reivindicación 1, en la cual el compuesto contiene menos de 1% del isómero S del compuesto.

11. La composición de la reivindicación 1, en la cual el compuesto contiene menos de 1% del isómero R del compuesto.

12. La composición de cualquiera de las reivindicaciones precedentes, que comprende aproximadamente 1-100 mg de un compuesto que tiene la siguiente estructura: 

.

13. La composición de la reivindicación 12, donde la composición permite la liberación modificada del compuesto.

14. La composición de la reivindicación 12, donde la composición permite la liberación sostenida del compuesto.

15. La composición de la reivindicación 12, donde la composición permite la liberación retardada del compuesto.

16. La composición de la reivindicación 12, en la cual el compuesto se encuentra presente en una cantidad de aproximadamente 1-50 mgs.

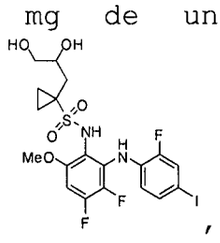
856

17. La composición de la reivindicación 12, en la cual el compuesto se encuentra presente en una cantidad de aproximadamente 1-10 mgs.

18. La composición de la reivindicación 12, en la cual el compuesto se encuentra presente en una cantidad de aproximadamente 10-20 mgs.

19. La composición de la reivindicación 12, en la cual el compuesto se encuentra presente en una cantidad de aproximadamente 20-40 mgs.

20. La composición de la reivindicación 12, en la cual el compuesto se encuentra presente en una cantidad de aproximadamente 40-50 mgs.

21. La composición de cualquiera de las reivindicaciones 1-15, que comprende: aproximadamente 1-50 mg de un compuesto que tiene la siguiente estructura 

, donde la composición tiene en cuenta la liberación modificada de la droga.

22. La composición de cualquiera de las reivindicaciones 1-21, que además comprende celulosa microcristalina.

23. La composición de cualquiera de las reivindicaciones 1-22, que además comprende croscarmelosa de sodio.

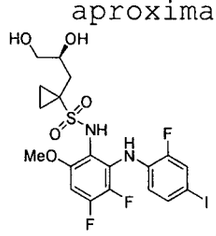
24. La composición de cualquiera de las reivindicaciones 1-23, que además comprende lauril sulfato de sodio.

851

25. La composición de cualquiera de las reivindicaciones 1-24, que además comprende estearato de magnesio.

26. La composición de cualquiera de las reivindicaciones 1-15, que comprende

aproximadamente 1mg de un compuesto de estructura:



;

aproximadamente 222,2mg de celulosa microcristalina;

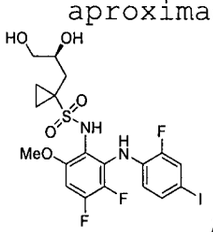
aproximadamente 12,0mg de croscarmelosa de sodio;

aproximadamente 2,4mg de lauril sulfato de sodio; y

aproximadamente 2,4mg de estearato de magnesio.

27. La composición de cualquiera de las reivindicaciones 1-15, que comprende :

aproximadamente 10mg de un compuesto de estructura



;

aproximadamente 213,2mg de celulosa microcristalina;

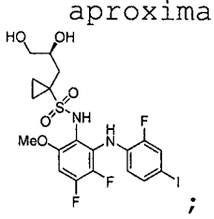
aproximadamente 12,0mg de croscarmelosa de sodio;

aproximadamente 2,4mg de lauril sulfato de sodio; y

aproximadamente 2,4mg de estearato de magnesio.

28. La composición de cualquiera de las reivindicaciones 1-15, que comprende:

852

aproximadamente 20mg de un compuesto de estructura  ;

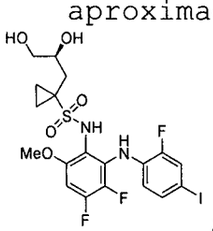
aproximadamente 203,2mg de celulosa microcristalina;

aproximadamente 12,0mg de croscarmelosa de sodio;

aproximadamente 2,4mg de lauril sulfato de sodio; y

aproximadamente 2,4mg de estearato de magnesio.

29. La composición de cualquiera de las reivindicaciones 1-15, que comprende:

aproximadamente 40mg de un compuesto de estructura  ;

aproximadamente 183,2mg de celulosa microcristalina;

aproximadamente 12,0mg de croscarmelosa de sodio;

aproximadamente 2,4mg de lauril sulfato de sodio; y

aproximadamente 2,4mg de estearato de magnesio.

30. La composición de cualquiera de las reivindicaciones 1-15, que comprende: aproximadamente 0,4% en peso de un compuesto de estructura  ; y aproximadamente 99,6% en peso de un vehículo farmacéuticamente aceptable.

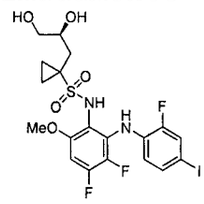
31. La composición de la reivindicación 30, en la cual el

813

vehículo farmacéuticamente aceptable comprende celulosa microcristalina.

32. La composición de la reivindicación 31, en la cual la celulosa microcristalina es de aproximadamente 92,6% en peso de la composición.

33. La composición de la reivindicación 32, que además comprende: aproximadamente 5% en peso de croscarmelosa de sodio; aproximadamente 1% en peso de lauril sulfato de sodio; y aproximadamente 1% en peso de estearato de magnesio.

34. La composición de cualquiera de las reivindicaciones 1-15, que comprende: aproximadamente 4,2% en peso de un compuesto de estructura 

; y aproximadamente 95,8 % en peso de un vehículo farmacéuticamente aceptable.

35. La composición de la reivindicación 34, en la cual el vehículo farmacéuticamente aceptable comprende celulosa microcristalina.

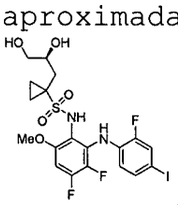
36. La composición de la reivindicación 35, en la cual la celulosa microcristalina es de aproximadamente 88,8% en peso de la composición.

37. La composición de la reivindicación 36, que además comprende: aproximadamente 5% en peso de croscarmelosa de

854

sodio; aproximadamente 1% en peso de lauril sulfato de sodio; y aproximadamente 1% en peso de estearato de magnesio.

38. La composición de cualquiera de las reivindicaciones 1-15, que comprende: entre aproximadamente 2% y aproximadamente 10% en peso de un compuesto de estructura



; y entre aproximadamente 98% y aproximadamente 90% en peso de un vehículo farmacéuticamente aceptable.

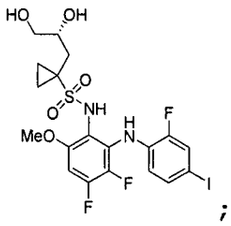
39. La composición de la reivindicación 38, en la cual el vehículo farmacéuticamente aceptable comprende celulosa microcristalina.

40. La composición de la reivindicación 39, en la cual la celulosa microcristalina es entre aproximadamente 85% y aproximadamente 95% en peso de la composición.

41. La composición de la reivindicación 40, que además comprende: entre aproximadamente 1% y aproximadamente 6% en peso de croscarmelosa de sodio; entre aproximadamente 0,1% y aproximadamente 2% en peso de lauril sulfato de sodio; y entre aproximadamente 0,25% y aproximadamente 1,5% en peso de estearato de magnesio.

42. La composición de cualquiera de las reivindicaciones 1-15, que comprende:

aproximadamente 1mg de un compuesto de estructura:



;

aproximadamente 222,2mg de celulosa microcristalina;

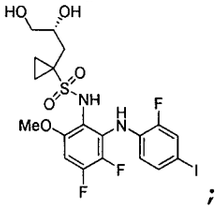
aproximadamente 12,0mg de croscarmelosa de sodio;

aproximadamente 2,4mg de lauril sulfato de sodio; y

aproximadamente 2,4mg de estearato de magnesio.

43. La composición de cualquiera de las reivindicaciones 1-15, que comprende:

aproximadamente 10mg de un compuesto de estructura:



;

aproximadamente 213,2mg de celulosa microcristalina

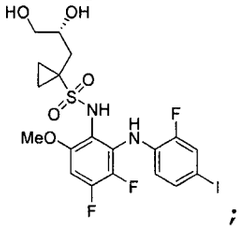
aproximadamente 12,0mg de croscarmelosa de sodio;

aproximadamente 2,4mg de lauril sulfato de sodio; y

aproximadamente 2,4mg de estearato de magnesio.

44. La composición de cualquiera de las reivindicaciones 1-15, que comprende:

aproximadamente 20mg de un compuesto de estructura:



;

aproximadamente 203,2mg de celulosa microcristalina;

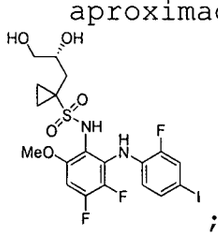
aproximadamente 12,0mg de croscarmelosa de sodio;

aproximadamente 2,4mg de lauril sulfato de sodio; y

aproximadamente 2,4mg de estearato de magnesio.

45. La composición de cualquiera de las reivindicaciones 1-15, que comprende:

aproximadamente 40mg de un compuesto de estructura:



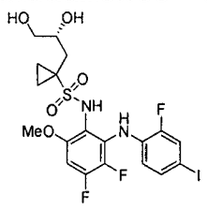
;

aproximadamente 183,2mg de celulosa microcristalina;

aproximadamente 12,0mg de croscarmelosa de sodio;

aproximadamente 2,4mg de lauril sulfato de sodio; y

aproximadamente 2,4mg de estearato de magnesio.

46. La composición de cualquiera de las reivindicaciones 1-15, que comprende: aproximadamente 0,4% en peso de un compuesto de estructura:  ; y aproximadamente 99,6% en peso de un vehículo farmacéuticamente aceptable.

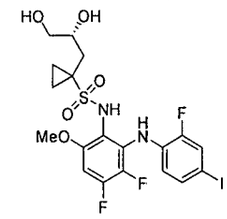
47. La composición de la reivindicación 46, en la cual el vehículo farmacéuticamente aceptable comprende celulosa microcristalina.

48. La composición de la reivindicación 47, en la cual la

857

celulosa microcristalina es de aproximadamente 92,6% en peso de la composición.

49. La composición de la reivindicación 48, que además comprende: aproximadamente 5% en peso de croscarmelosa de sodio; aproximadamente 1% en peso de lauril sulfato de sodio; y aproximadamente 1% en peso de estearato de magnesio.

50. La composición de cualquiera de las reivindicaciones 1-15, que comprende: aproximadamente 4,2% en peso de un compuesto de estructura:  y aproximadamente 95,8 % en peso de un vehículo farmacéuticamente aceptable.

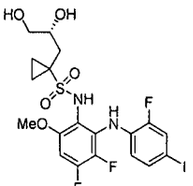
51. La composición de la reivindicación 50, en la cual el vehículo farmacéuticamente aceptable comprende celulosa microcristalina.

52. La composición de la reivindicación 51, en la cual la celulosa microcristalina es de aproximadamente 88,8% en peso de la composición.

53. La composición de la reivindicación 52, que además comprende: aproximadamente 5% en peso de croscarmelosa de sodio; aproximadamente 1% en peso de lauril sulfato de sodio; y aproximadamente 1% en peso de estearato de

858

magnesio.

54. La composición de cualquiera de las reivindicaciones 1-15, que comprende: entre aproximadamente 2% y aproximadamente 10% en peso de un compuesto de estructura:  ; y entre aproximadamente 98% y aproximadamente 90% en peso de un vehículo farmacéuticamente aceptable.

55. La composición de la reivindicación 54, en la cual el vehículo farmacéuticamente aceptable comprende celulosa microcristalina.

56. La composición de la reivindicación 55, en la cual la celulosa microcristalina es entre aproximadamente 85% y aproximadamente 95% en peso de la composición.

57. La composición de la reivindicación 56, que además comprende: entre aproximadamente 1% y aproximadamente 6% en peso de croscarmelosa de sodio; entre aproximadamente 0,1% y aproximadamente 2% en peso de lauril sulfato de sodio; y entre aproximadamente 0,25% y aproximadamente 1,5% en peso de estearato de magnesio.

58. La composición de cualquiera de las reivindicaciones precedentes, que además comprende al menos un vehículo farmacéuticamente aceptable.

59. Un polimorfo cristalino de forma A de N-(-)-(3,4-

difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida, que exhibe un patrón de difracción de rayos X en polvo que comprende al menos 50% de los picos identificados en el patrón de difracción de rayos X en polvo que se muestra en FIG. **5**.

60. El polimorfo cristalino de forma A de la reivindicación 59, en el cual el patrón de difracción de rayos X en polvo comprende al menos 70% de los picos identificados en el patrón de difracción de rayos X en polvo que se muestra en FIG. **5**.

61. El polimorfo cristalino de forma A de la reivindicación 59, en el cual el patrón de difracción de rayos X en polvo comprende al menos 90% de los picos identificados en el patrón de difracción de rayos X en polvo que se muestra en FIG. **5**.

62. El polimorfo cristalino de forma A de la reivindicación 59, en el cual el patrón de difracción de rayos X en polvo sustancialmente igual as el patrón de difracción de rayos X en polvo que se muestra en FIG. **5**.

63. El polimorfo cristalino de cualquiera de las reivindicaciones 59-62, que tiene una temperatura del comienzo de la fusión según se determinó mediante calorimetría diferencial de barrido en aproximadamente 143°C.

64. El polimorfo cristalino de cualquiera de las reivindicaciones 59-62, que se encuentra sustancialmente libre de agua.

65. El polimorfo cristalino de cualquiera de las reivindicaciones 59-62, que se encuentra sustancialmente libre de solvente.

66. Una composición farmacéutica que comprende una cantidad efectiva del polimorfo cristalino de cualquiera de las reivindicaciones 59-62 y al menos un excipiente o vehículo.

67. Un polimorfo cristalino de forma A de N-(-)-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida, que exhibe un patrón de calorimetría diferencial de barrido sustancialmente igual al patrón de calorimetría diferencial de barrido que se muestra en FIG. **6**.

68. El polimorfo cristalino de la reivindicación 67, que tiene una temperatura del comienzo de la fusión según se determinó mediante calorimetría diferencial de barrido en aproximadamente 143°C.

69. El polimorfo cristalino de la reivindicación 67 o 68, que se encuentra sustancialmente libre de agua.

70. El polimorfo cristalino de cualquiera de las reivindicaciones 67-69, que se encuentra sustancialmente libre de solvente.

861

71. Una composición farmacéutica que comprende una cantidad efectiva del polimorfo cristalino de cualquiera de las reivindicaciones 67-70 y al menos un excipiente o vehículo.

72. Una forma polimórfica de N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida, que se obtiene mediante un método que comprende el paso de cristalizar N-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)-6-metoxifenil)-1-(2,3-dihidroxipropil)ciclopropan-1-sulfonamida amorfa.

73. La forma polimórfica de la reivindicación 72, en la cual el paso de cristalización comprende cristalizar a partir de una mezcla de acetato de etilo y heptano.

74. La forma polimórfica de la reivindicación 73, en la cual la mezcla de acetato de etilo y heptano es en una relación de entre aproximadamente 1-4 partes de acetato de etilo y aproximadamente 2-10 partes de heptano.

75. La forma polimórfica de la reivindicación 73, en la cual la mezcla de acetato de etilo y heptano es en una relación de entre aproximadamente 2 partes de acetato de etilo y aproximadamente 5 partes de heptano.

76. Un método para inhibir las enzimas MEK, que comprende poner en contacto dicha enzima MEK con un compuesto o composición de acuerdo a cualquiera de las

867

reivindicaciones 1-75, donde el compuesto se encuentra presente en una cantidad suficiente para inhibir dicha enzima en al menos 25%.

77. El método de la reivindicación 76, en el cual dicha enzima MEK es MEK quinasa.

78. El método de la reivindicación 76, en el cual dicho contacto ocurre dentro de una célula.

79. Un método de tratamiento de un trastorno mediado por MEK en un individuo que sufre de dicho desorden, que comprende administrar a dicho individuo una cantidad efectiva de un compuesto o composición de acuerdo a cualquiera de las reivindicaciones 1-75.

80. El método de la reivindicación 79, que se aplica en combinación con una terapia adicional.

81. El método de la reivindicación 80, en el cual dicha terapia adicional es terapia de radiación, terapia sin inhibidor de MEK-quinasa, quimioterapia, cirugía, Glucocorticoide, metotrexato, modificadores de la respuesta biológica, o cualquier combinación de los mismos.

82. El método de la reivindicación 79, en el cual dicho trastorno mediado por MEK se selecciona entre el grupo que consiste en enfermedades inflamatorias, infecciones, trastornos autoinmunes, accidente cerebrovascular, esquemia, trastorno cardíaco, trastornos neurológicos,

863

trastornos fibrogenéticos, trastornos proliferativos, trastornos hiperproliferativos, tumores, leucemias, neoplasmas, cánceres, carcicomas, trastornos metabólicos y enfermedades malignas.

83. El método de la reivindicación 79, en el cual dicho trastorno mediado por MEK es una enfermedad hiperproliferativa.

84. El método de la reivindicación 79, en el cual dicho trastorno mediado por MEK es cáncer, tumores, leucemias, neoplasmas, o carcinomas.

85. El método de la reivindicación 79, en el cual dicho trastorno mediado por MEK es una enfermedad inflamatoria.

86. El método de la reivindicación 85, en el cual dicha enfermedad inflamatoria es artritis reumatoide o esclerosis múltiple.

87. Un método para el tratamiento o profiaxis de una enfermedad proliferativa en un individuo, que comprende administrar a dicho individuo una cantidad efectiva de un compuesto o composición de acuerdo a cualquiera de las reivindicaciones 1-75.

88. El método de la reivindicación 87, en el cual dicha enfermedad proliferativa es cáncer, psoriasis, restenosis, enfermedad, o ateroesclerosis.

89. El método de la reivindicación 87, en el cual dicha enfermedad proliferativa es cáncer.

864

90. El método de la reivindicación 89, en el cual dicho cáncer es cáncer de cerebro, cáncer de mama, cáncer de pulmón, cáncer de ovario, cáncer de páncreas, cáncer de próstata, cáncer de riñón, cáncer colorrectal, leucemia, leucemia mieloide, glioblastoma, linfoma folicular, leucemia aguda pre-B, leucemia linfocítica crónica de células B, cáncer de estómago, mesotelioma o cáncer de pulmón de célula pequeña.

91. El método de cualquiera de las reivindicaciones 87-90, que comprende además administrar al menos un agente terapéutico.

92. El método de cualquiera de las reivindicaciones 87-90, que comprende además administrar al menos una terapia de cáncer adicional.

93. El método de la reivindicación 92, en el cual dicha terapia adicional es terapia de radiación, terapia sin inhibidor de MEK-quinasa, quimioterapia, cirugía, Glucocorticoide, metotrexato, modificadores de la respuesta biológica, o cualquier combinación de los mismos.

94. Un método para el tratamiento o profilaxis de una enfermedad inflamatoria en un individuo, que comprende administrar a dicho individuo una cantidad efectiva de una composición que comprende un compuesto de cualquiera de las reivindicaciones 1-75.

865

95. El método de la reivindicación 94, en el cual dicha enfermedad inflamatoria es artritis reumatoide o esclerosis múltiple.

96. Un método para degradar, inhibir el crecimiento de o matar células cancerígenas, que comprende poner en contacto las células con una cantidad del compuesto o composición de cualquiera de las reivindicaciones 1-75 efectiva para degradar, inhibir el crecimiento de o matar células cancerígenas.

97. El método de la reivindicación 96, en el cual dichas células cancerígenas comprenden células cancerígenas de cerebro, pecho, ovario, páncreas, próstata, riñón, hígado, estómago o colorectal.

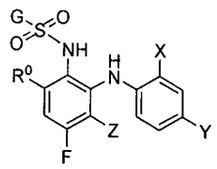
98. Un método para inhibir el incremento de tamaño de un tumor, reducir el tamaño de un tumor, reducir la proliferación de un tumor o prevenir la proliferación de un tumor en un individuo, que comprende administrar a dicho individuo una cantidad efectiva del compuesto o composición de cualquiera de las reivindicaciones 1-75 para inhibir el incremento de tamaño del tumor, reducir el tamaño de un tumor, reducir la proliferación del tumor o prevenir la proliferación del tumor.

99. El método de la reivindicación 98, que es para inhibir el incremento de tamaño de un tumor o reducir el tamaño de un tumor donde dicho tumor ocurre en el cerebro,

pecho, pulmón, ovarios, páncreas, próstata, riñón, hígado, estómago, colon o recto.

100. El método de la reivindicación 98, que es para inhibir el incremento de tamaño de un tumor o reducir el tamaño de un tumor donde dicho individuo es un mamífero.

101. Un método para tratar o prevenir espondilitis anquilosante, gota, tendinitis, bursitis o ciática, que comprende administrar a un sujeto en necesidad del mismo una cantidad efectiva de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo:



; donde:

Z es H o F;

X es F, Cl, $CH_3$, $CH_2OH$, $CH_2F$, $CHF_2$, o $CF_3$;

Y es I, Br, Cl, $CF_3$, $C_1$-$C_3$ alquilo, $C_2$-$C_3$ alquenilo, $C_2$-$C_3$ alquinilo, ciclopropilo, OMe, OEt, SMe, fenilo o Het, donde Het es un grupo heterocíclico mono o bicíclico de 5 a 10 miembros, el cual es saturado, olefínico o aromático, que contiene 1-5 heteroátomos en el anillo seleccionados en forma independiente entre N, O, y S; donde

todos dichos grupos fenilo o Het están opcionalmente sustituidos con F, Cl, Br, I, acetilo, metilo, CN, $NO_2$, $CO_2H$, $C_1$-$C_3$ alquilo, $C_1$-$C_3$ alcoxi, $C_1$-$C_3$

867

alquil-C(=O)-, $C_1$-$C_3$ alquil-C(=S)-, $C_1$-$C_3$ alcoxi-C(=S)-, $C_1$-$C_3$ alquil-C(=O)O-, $C_1$-$C_3$ alquil-O-(C=O)-, $C_1$-$C_3$ alquil-C(=O)NH-, $C_1$-$C_3$ alquil-C(=NH)NH-, $C_1$-$C_3$ alquil-NH-(C=O)-, di-$C_1$-$C_3$ alquil-N-(C=O)-, $C_1$-$C_3$ alquil-C(=O)N($C_1$-$C_3$ alquil)-, $C_1$-$C_3$ alquil-$S(=O)_2NH$- o trifluorometilo;

todos dichos grupos metilo, etilo, $C_1$-$C_3$ alquilo, y ciclopropilo están opcionalmente sustituidos con OH;

todos dichos grupos metilo están opcionalmente sustituidos con uno, dos o tres átomos de F;

$R^0$ es H, F, Cl, Br, I, $CH_3NH$-, $(CH_3)_2N$-, $C_1$-$C_6$ alquilo, $C_1$-$C_4$ alcoxi, $C_3$-$C_6$ cicloalquilo, $C_2$-$C_6$ alquenilo, $C_2$-$C_6$ alquinilo, fenilo, fenilo monosustituido, O($C_1$-$C_4$ alquilo), O-C(=O)($C_1$-$C_4$ alquilo) o C(=O)O($C_1$-$C_4$ alquil); donde

dichos grupos alquilo, alcoxi, cicloalquilo, alquenilo, alquinilo y fenilo están opcionalmente sustituidos con 1-3 sustituyentes seleccionados en forma independiente entre F, Cl, Br, I, OH, CN, cianometilo, nitro, fenilo y trifluorometilo;

dichos grupos $C_1$-$C_6$ alquilo y $C_1$-$C_4$ alcoxi también están opcionalmente sustituidos con $OCH_3$ o $OCH_2CH_3$;

G es $G_1$, $G_2$, $R_{1a}$, $R_{1b}$, $R_{1c}$, $R_{1d}$, $R_{1e}$, $Ar_1$, $Ar_2$ o $Ar_3$; donde

$G_1$ es $C_1$-$C_6$ alquilo opcionalmente sustituido con un grupo amino, $C_1$-$C_3$ alquilamino, o dialquilamino, dicho

grupo dialquilamino comprende dos grupos $C_1$-$C_4$ alquilo los cuales pueden ser idénticos o no idénticos; o

$G_1$ es un grupo $C_3$-$C_8$ diaminoalquilo;

$G_2$ es un anillo de 5 o 6 miembros, el cual es saturado, no saturado o aromático, que contiene 1-3 heteroátomos en el anillo seleccionados en forma independiente entre N, O, y S, opcionalmente sustituidos con 1-3 sustituyentes seleccionados en forma independiente entre F, Cl, OH, O($C_1$-$C_3$ alquilo), $OCH_3$, $OCH_2CH_3$, $CH_3C(=O)NH$, $CH_3C(=O)O$, CN, $CF_3$, y un grupo heterocíclico aromático de 5 miembros que contiene 1-4 heteroátomos en el anillo seleccionados en forma independiente entre N, O , y S;

$R_{1a}$ es metilo, opcionalmente sustituido con 1-3 átomos de flúor o 1-3 átomos de cloro, o con OH, ciclopropoxi, o $C_1$- $C_3$ alcoxi, donde dicho grupo ciclopropoxi o las unidades $C_1$-$C_3$ alquilo de dichos grupos $C_1$-$C_3$ alcoxi están opcionalmente sustituidos con un grupo hidroxi o metoxi, y donde todos los grupos $C_3$-alquilo dentro de dicho $C_1$- $C_4$ alcoxi están opcionalmente sustituidos adicionalmente con un segundo grupo OH;

$R_{1b}$ es $CH(CH_3)$-$C_{1-3}$ alquilo o $C_3$-$C_6$ cicloalquilo, dichos grupos alquilo y cicloalquilo opcionalmente sustituido con 1-3 sustituyentes seleccionados en forma

869

independiente entre F, Cl, Br, I, OH, $OCH_3$, y CN;

$R_{1c}$ es $(CH_2)_nO_mR'$; donde

m es 0 o 1; y donde

cuando m es 0, n es 1 o 2;

cuando m es 1, n es 2 o 3;

R' es $C_1$-$C_6$ alquilo, opcionalmente sustituido con 1-3 sustituyentes seleccionados en forma independiente entre F, Cl, OH, $OCH_3$, $OCH_2CH_3$, y $C_3$-$C_6$ cicloalquilo;

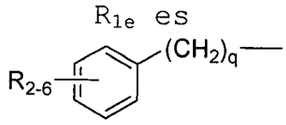
$R_{1d}$ es C(A)(A')(B)-; donde

B es H o $C_{1-4}$ alquilo, opcionalmente sustituido con uno o dos grupos OH;

A y A' son en forma independiente H o $C_{1-4}$ alquilo, opcionalmente sustituido con uno o dos grupos OH; o

A y A', junto con el átomo de carbono al cual se encuentran unidos, forman un anillo saturado de 3 a 6 miembros;

$R_{1e}$ es




**$R_{1e}$**

donde

q es 1 o 2;

$R_2$ y $R_3$ son en forma independiente entre sí, H,

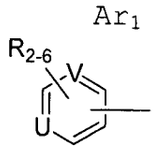
F, Cl, Br, $CH_3$, $CH_2F$, $CHF_2$, $CF_3$ $OCH_3$, $OCH_2F$, $OCHF_2$, $OCF_3$, etilo, *n*-propilo, isopropilo, ciclopropilo, isobutilo, *sec*-butilo, *tert*-butilo o metilsulfonilo;

$R_4$ es H, F, Cl, Br, $CH_3$, $CH_2F$, $CHF_2$, $CF_3$ $OCH_3$, $OCH_2F$, $OCHF_2$, $OCF_3$, etilo, *n*-propilo, isopropilo, ciclopropilo, isobutilo, *sec*-butilo, *tert*-butilo, metilsulfonilo, nitro, acetamido, amidinilo, ciano, carbamoilo, metilcarbamoilo, dimetilcarbamoilo, 1,3,4-oxadiazol-2-ilo, 5-metil-1,3,4- oxadiazol, 1,3,4-tiadiazol, 5-metil-1,3,4-tiadiazol 1H-tetrazolilo, N-morfolilo carbonilo amino, N-morfolilsulfonilo y N-pirrolidinilcarbonilamino;

$R_5$ es H, F, Cl o metilo;

$R_6$ es H, F, Cl o metilo;

$Ar_1$ es




**$Ar_1$**

donde

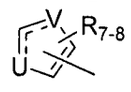
U y V son, en forma independiente, N, $CR_2$ o $CR_3$;

$R_2$, $R_3$ y $R_4$ son, en forma independiente, H, F, Cl, Br, $CH_3$, $CH_2F$, $CHF_2$, $CF_3$ $OCH_3$, $OCH_2F$, $OCHF_2$, $OCF_3$, etilo, *n*-propilo, isopropilo, ciclopropilo, isobutilo, *sec*-butilo, *tert*-butilo, acetamido, amidinilo, ciano, carbamoilo, metilcarbamoilo,

dimetilcarbamoilo, 1,3,4-oxadiazol-2-ilo, 5-metil-1,3,4-oxadiazolilo, 1,3,4-tiadiazolilo, 5-metil-1,3,4-tiadiazolilo, 1H-tetrazolilo, N-morfolilcarbonilamino, N-morfolilsulfonilo, N-pirrolidinilcarbonilamino, y metilsulfonilo;

$R_5$ y $R_6$ son, en forma independiente, H, F, Cl o metilo;

$Ar_2$ es




**$Ar_2$**

donde

la línea de guiones representa ubicaciones formales alternativas para la unión doble del segundo anillo;

U es -S-, -O- o -N =, y donde

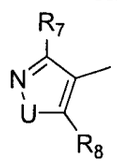
cuando U es -O- o -S-, V es -CH=, -CCl= o -N =;

cuando U es -N =, V es -CH=, -CCl=, o -N=;

$R_7$ es H o metilo;

$R_8$ es H, acetamido, metilo, F o Cl;

$Ar_3$ es



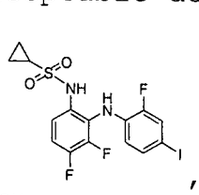
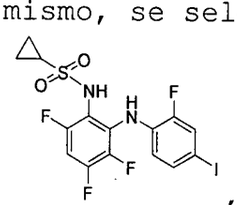
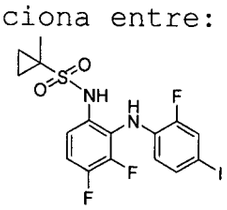
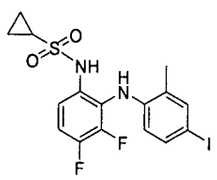
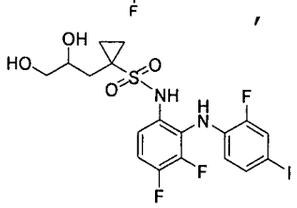
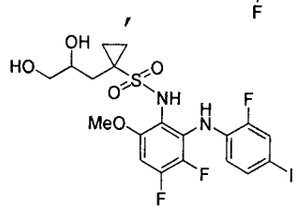
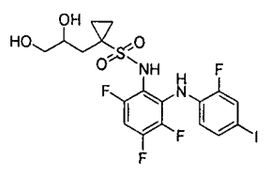
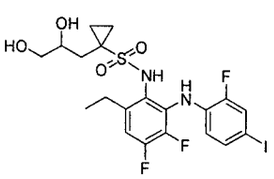
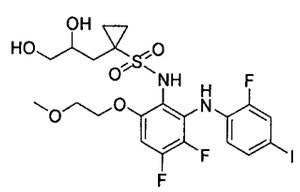
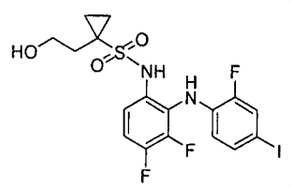
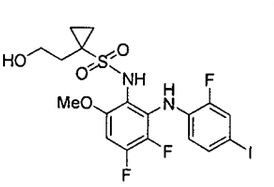
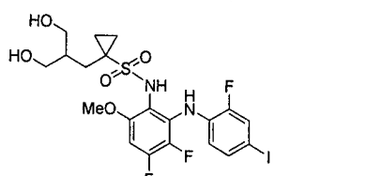

**$Ar_3$**

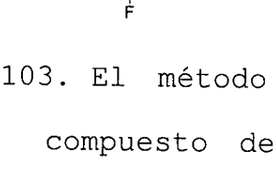
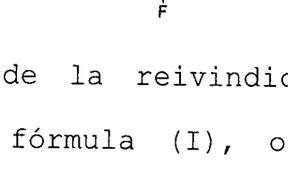
donde

U es -NH-, $-NCH_3-$ o -O-;

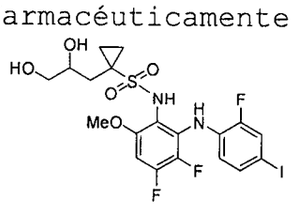
$R_7$ y $R_8$ son, en forma independiente, H, F, Cl, o metilo.

102. El método de la reivindicación 101, en el cual el compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, se selecciona entre:

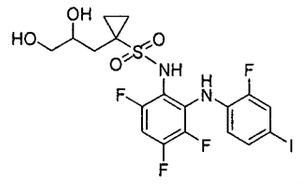













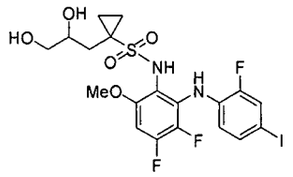
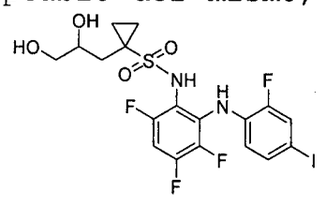


y

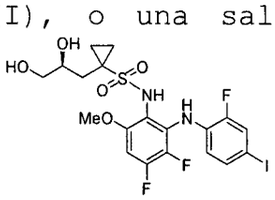
103. El método de la reivindicación 101, en el cual el compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, se selecciona entre

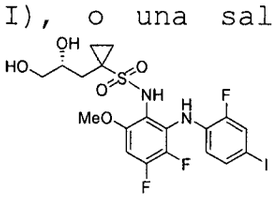


873

y  ; donde el carbono 2-OH es de configuración R.

104. El método de la reivindicación 101, en el cual el compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, se selecciona entre  y  ; donde el carbono 2-OH es de configuración S.

105. El método de la reivindicación 167, en el cual el compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, es  .

106. El método de la reivindicación 167, en el cual el compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, es  .

107. Un método para tratar cáncer de estómago, que requiere la administración de una cantidad terapéuticamente eficaz

874

de un compuesto o composición de acuerdo a cualquiera de las reivindicaciones 1-75.

108. Un método para tratar leucemia, melanoma, o hepatoma, que requiere la administración de una cantidad terapéuticamente eficaz de un compuesto o composición de acuerdo a cualquiera de las reivindicaciones 1-75.

109. Un método para tratar cáncer de pulmón de célula no pequeña, que requiere la administración de una cantidad terapéuticamente eficaz de un compuesto o composición de acuerdo a cualquiera de las reivindicaciones 1-75.

110. Un método para tratar cáncer de colon, que requiere la administración de una cantidad terapéuticamente eficaz de un compuesto o composición de acuerdo a cualquiera de las reivindicaciones 1-75.

111. Un método para tratar cáncer del sistema nervioso central, que requiere la administración de una cantidad terapéuticamente eficaz de un compuesto o composición de acuerdo a cualquiera de las reivindicaciones 1-75.

112. Un método para tratar cáncer de ovario, que requiere la administración de una cantidad terapéuticamente eficaz de un compuesto o composición de acuerdo a cualquiera de las reivindicaciones 1-75.

113. Un método para tratar cáncer de riñón, que requiere la administración de una cantidad terapéuticamente eficaz de un compuesto o composición de acuerdo a cualquiera de las

875

reivindicaciones 1-75.

114. Un método para tratar cáncer de próstata, que requiere la administración de una cantidad terapéuticamente eficaz de un compuesto o composición de acuerdo a cualquiera de las reivindicaciones 1-75.

115. Un método para tratar cáncer de mama, que requiere la administración de una cantidad terapéuticamente eficaz de un compuesto o composición de acuerdo a cualquiera de las reivindicaciones 1-75.

116. El método de cualquiera de las reivindicaciones 107-115, que comprende además administrar al menos un agente terapéutico.

117. El método de cualquiera de las reivindicaciones 107-115, que comprende además administrar al menos una terapia de cáncer adicional.

118. El método de la reivindicación 117, en el cual dicha terapia de cáncer adicional es terapia de radiación, quimioterapia, cirugía, o cualquier combinación de los mismos.

119. El método de cualquiera de las reivindicaciones 76-118, en el cual el compuesto o composición se administra oralmente.

120. El método de cualquiera de las reivindicaciones 76-118, en el cual el compuesto o composición se administra una vez al día o dos veces al día.

876

121. El método de cualquiera de las reivindicaciones 76-118, en el cual el compuesto o composición se administra una vez al día por al menos una semana.

122. Un método para tratar o prevenir la psoriasis, que requiere la administración de una cantidad terapéuticamente eficaz de un compuesto o composición de acuerdo a cualquiera de las reivindicaciones 1-75 en forma de dosificación tópica.

123. El método de cualquiera de las reivindicaciones 76-121, en el cual $T_{max}$ del compuesto se alcanza entre 1 hora y 3 horas luego de la administración de la composición a un sujeto en ayunas.

124. El compuesto, composición o método de cualquiera de las reivindicaciones precedentes, en el cual luego de la administración a un sujeto, el compuesto alcanza una $C_{max}$ entre aproximadamente 0,01 µg/ml y aproximadamente 1,0 µg/ml en el día 1.

125. El compuesto, composición o método de la reivindicación 124, en el cual luego de la administración a un sujeto, el compuesto alcanza una $C_{max}$ entre aproximadamente 0,01 µg/ml y aproximadamente 0,8 µg/ml en el día 1.

126. El compuesto, composición o método de la reivindicación 124, en el cual luego de la administración a un sujeto, el compuesto alcanza una $C_{max}$ entre aproximadamente 0,03 µg/ml y aproximadamente 0,5 µg/ml en el día 1.

127. El compuesto, composición o método de cualquiera de las reivindicaciones precedentes, en el cual luego de la administración a un grupo de 10 sujetos, el compuesto alcanza una $C_{max}$ media entre aproximadamente 0,01 µg/ml y aproximadamente 1,0 µg/ml en el día 1.

128. El compuesto, composición o método de la reivindicación 127, en el cual luego de la administración a un grupo de 10 sujetos, el compuesto alcanza una $C_{max}$ media entre aproximadamente 0,01 µg/ml y aproximadamente 0,8 µg/ml en el día 1.

129. El compuesto, composición o método de la reivindicación 127, en el cual luego de la administración a un grupo de 10 sujetos, el compuesto alcanza una $C_{max}$ media entre aproximadamente 0,03 µg/ml y aproximadamente 0,5 µg/ml en el día 1.

130. El compuesto, composición o método de cualquiera de las reivindicaciones 124-126, en el cual el compuesto tiene un AUC entre aproximadamente 0,1 µg hr/ml y aproximadamente 5,0 µg hr/ml entre 0-12 horas.

131. El compuesto, composición o método de la reivindicación 130, en el cual el compuesto tiene un AUC entre aproximadamente 0,1 µg hr/ml y aproximadamente 4,0 µg hr/ml.

132. El compuesto, composición o método de la reivindicación 130, en el cual el compuesto tiene un AUC entre

878

aproximadamente 0,5 µg hr/ml y aproximadamente 3,0 µg hr/ml.

133. El compuesto, composición o método de cualquiera de las reivindicaciones 127-129, en el cual el compuesto tiene un AUC medio entre aproximadamente 0,1 µg hr/ml y aproximadamente 5,0 µg hr/ml.

134. El compuesto, composición o método de la reivindicación 134, en el cual el compuesto tiene un AUC medio entre aproximadamente 0,1 µg hr/ml y aproximadamente 4,0 µg hr/ml.

135. El compuesto, composición o método de la reivindicación 134, en el cual el compuesto tiene un AUC medio entre aproximadamente 0,5 µg hr/ml y aproximadamente 3,0 µg hr/ml.

136. El compuesto, composición o método de cualquiera de las reivindicaciones 124-126 y 130-132, en el cual el compuesto tiene un $T_{max}$ entre 0,5 y 5,0 horas.

137. El compuesto, composición o método de la reivindicación 133, en el cual el compuesto tiene un $T_{max}$ entre 1,0 y 3,0 horas.

138. El compuesto, composición o método de la reivindicación 133, en el cual el compuesto tiene un $T_{max}$ entre 1,0 y 2,5 horas.

139. El compuesto, composición o método de cualquiera de las reivindicaciones 127-129 y 133-135, en el cual el

879

compuesto tiene un $T_{max}$ medio entre 0,5 y 5,0 horas.

140. El compuesto, composición o método de la reivindicación 139, en el cual el compuesto tiene un $T_{max}$ medio entre 1,0 y 3,0 horas.

141. El compuesto, composición o método de la reivindicación 139, en el cual el compuesto tiene un $T_{max}$ medio entre 1,0 y 2,5 horas.

142. El compuesto, composición o método de cualquiera de las reivindicaciones 124-126, 130-132 y 136-138, en el cual el compuesto tiene una concentración en el plasma mayor a aproximadamente 0,01 mg/ml luego de 5 horas luego de una única dosis.

143. El compuesto, composición o método de cualquiera de las reivindicaciones 124-126, 130-132 y 136-138, en el cual el compuesto tiene una concentración en el plasma mayor a aproximadamente 0,01 mg/ml luego de 10 horas luego de una única dosis.

144. El compuesto, composición o método de cualquiera de las reivindicaciones 124-126, 130-132 y 136-138, en el cual el compuesto tiene una concentración en el plasma mayor a aproximadamente 0,01 mg/ml luego de 15 horas luego de una única dosis.

145. El método de cualquiera de las reivindicaciones 76-141, en el cual luego de la administración diaria de la droga por 5 días, el tumor disminuye en volumen en al menos

aproximadamente 25%.

146. El método de cualquiera de las reivindicaciones 76-141, en el cual luego de la administración diaria de la droga por 5 días, el tumor disminuye en volumen en al menos aproximadamente 50%.

147. El método de cualquiera de las reivindicaciones 76-141, en el cual luego de la administración diaria de la droga por 5 días, el tumor disminuye en volumen en al menos aproximadamente 20-70%.

148. El método de cualquiera de las reivindicaciones 76-141, en el cual luego de la administración diaria de la droga por 15 días, el tumor disminuye en volumen en al menos aproximadamente 25%.

149. El método de cualquiera de las reivindicaciones 76-141, en el cual luego de la administración diaria de la droga por 15 días, el tumor disminuye en volumen en al menos aproximadamente 50%.

150. El método de cualquiera de las reivindicaciones 76-141, en el cual luego de la administración diaria de la droga por 15 días, el tumor disminuye en volumen en al menos aproximadamente 20-70%.

151. El método de cualquiera de las reivindicaciones 76-141, en el cual luego de la administración diaria de la droga por 30 días, el tumor disminuye en volumen en al menos aproximadamente 25%.

881

152. El método de cualquiera de las reivindicaciones 76-141, en el cual luego de la administración diaria de la droga por 30 días, el tumor disminuye en volumen en al menos aproximadamente 50%.

153. El método de cualquiera de las reivindicaciones 76-141, en el cual luego de la administración diaria de la droga por 30 días, el tumor disminuye en volumen en al menos aproximadamente 20-70%.

154. El método de cualquiera de las reivindicaciones 76-141, en el cual luego de la administración de la droga, el crecimiento del tumor de inhibe en al menos aproximadamente 20%.

155. El método de cualquiera de las reivindicaciones 76-141, en el cual luego de la administración de la droga, el crecimiento del tumor de inhibe en al menos aproximadamente 40%.

156. El método de cualquiera de las reivindicaciones 76-141, en el cual luego de la administración de la droga, el crecimiento del tumor de inhibe en al menos aproximadamente 60%.

157. El método de cualquiera de las reivindicaciones 76-141, en el cual luego de la administración de la droga, el crecimiento del tumor de inhibe en al menos aproximadamente 80%.

158. El método de cualquiera de las reivindicaciones 76-141,

en el cual luego de la administración de la droga, el crecimiento del tumor de inhibe en entre aproximadamente 20% y aproximadamente 100%.

159. El método de cualquiera de las reivindicaciones 76-141, en el cual luego de la administración de la droga, el crecimiento del tumor se inhibe sustancialmente.

160. El método de cualquiera de las reivindicaciones 145-159, en el cual la droga se administra dos veces al día.

161. El método de cualquiera de las reivindicaciones 145-159, en el cual la droga se administra una vez al día.

162. El método de cualquiera de las reivindicaciones 76-157, en el cual el inhibidor de MEK no interfiere con la coadministración de un segundo agente supresor de tumores.

163. El compuesto, composición o método de cualquiera de las reivindicaciones precedentes, en el cual la composición se presenta en forma de una tableta, a cápsula, una cápsula de gelatina, un comprimido oblongo, un pélet o una esfera.

164. El compuesto, composición o método de la reivindicación 163, en el cual la composición se presenta en forma de dosificación de cápsula o tableta con un peso total entre aproximadamente 50 mg y aproximadamente 1000 mg.

165. El compuesto, composición o método de la reivindicación 163, en el cual la composición se presenta en forma de

883

cápsula o tableta tiene un peso total seleccionado entre el grupo que consiste en 50 mg, 75mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, y 500 mg.

166. El compuesto, composición o método de la reivindicación 163, en el cual la composición se presenta en forma de cápsula o tableta y tiene un peso total de aproximadamente 240 mg.

167. La composición o método de cualquiera de las reivindicaciones 1-58, 66, 71 o 76-166, en la cual la composición comprende además al menos un relleno seleccionado entre celulosa microcristalina, celulosa microcristalina silicificada, lactosa, un azúcar compresible, xilitol, sorbitol, mannitol, almidón pregelatinizado, maltodextrina, fosfato de calcio, carbonato de calcio, almidón y un silicato de calcio.

168. La composición o método de cualquiera de las reivindicaciones 1-58, 66, 71 o 76-166, en la cual la composición comprende además al menos un desintegrante seleccionado entre croscarmelosa de sodio, glicolato sódico de almidón, crospovidona, metilcelulosa, ácido algínico, alginato de sodio, almidón derivados, betonita y veegum.

169. La composición o método de cualquiera de las reivindicaciones 1-58, 66, 71 o 76-166, en la cual la composición comprende además al menos un lubricante

884

seleccionado entre estearato de magnesio, estearatos metálicos, talco, estearil fumarato de sodio y ácido esteárico.

170. La composición o método de cualquiera de las reivindicaciones 1-58, 66, 71 o 76-166, en la cual la composición comprende además al menos un agente humectante o tensioactivo seleccionado entre lauril sulfato de sodio, glicerol, oleatos de sorbitan, sorbitan estearatos, laurato de sorbitan polioxietilenado, palmitato, estearato, oleato o hexaolato, alcohol estearílico polioxietileno y monolaurato de sorbitan.

171. La composición o método de cualquiera de las reivindicaciones 1-58, 66, 71 o 76-170 que se presenta en una formulación en forma de una cápsula o tableta y la cápsula o tableta libera al menos 60 por ciento de la droga al cabo de 30 minutos usando el Aparato II de *U.S. Pharmacopeia* (USP) a 50 rpm con lauril sulfato de sodio al 1% en agua como medio de disolución.

172. El compuesto, composición o método de la reivindicación 171, en el cual la composición se presenta como una formulación en forma de cápsula o tableta y la cápsula o tableta libera aproximadamente 60-100 por ciento de la droga al cabo de 30 minutos usando el Aparato II de *U.S. Pharmacopeia* (USP) a 50 rpm con lauril sulfato de sodio al 1% en agua como medio de disolución.

885

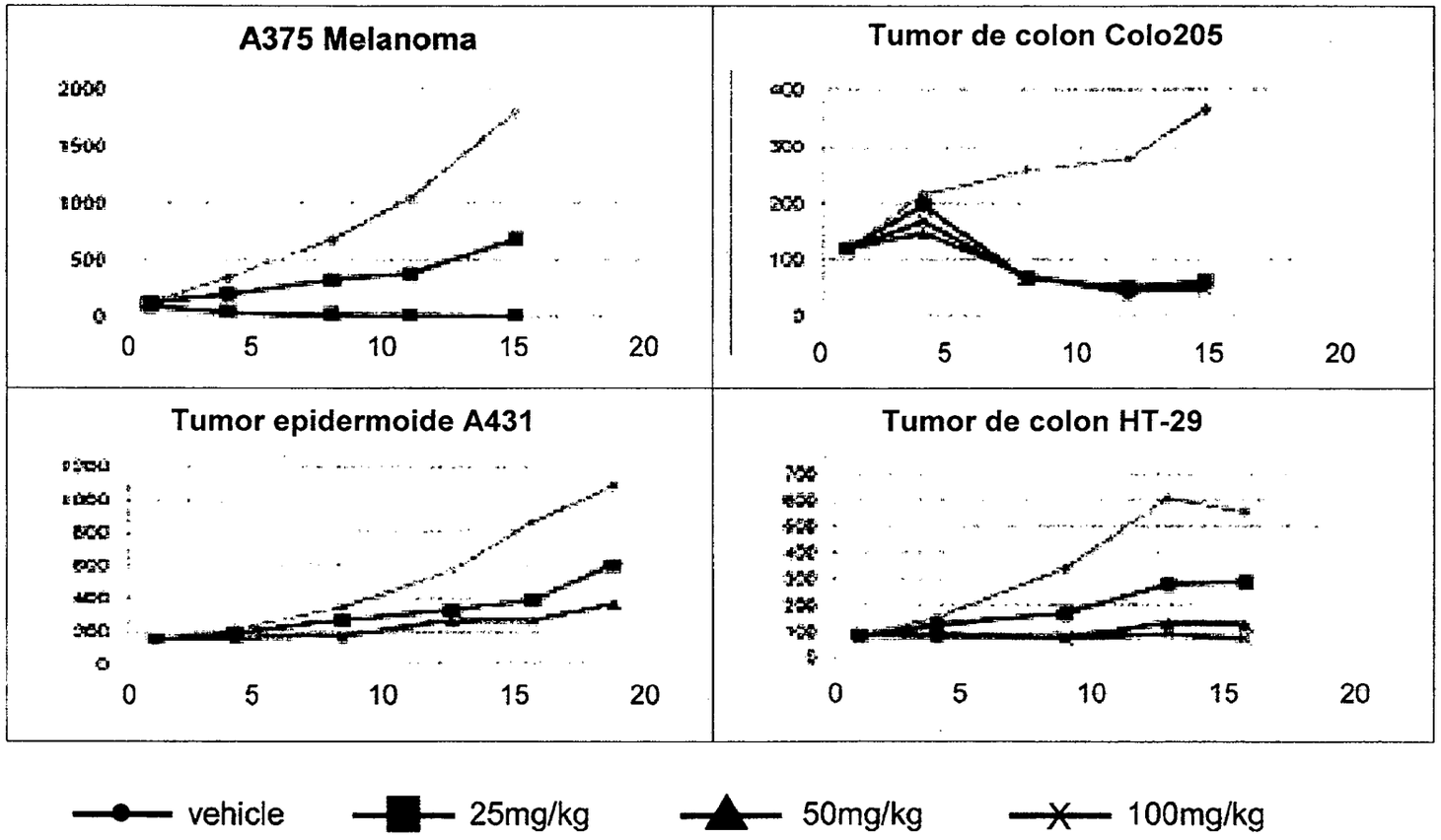
173. El compuesto, composición o método de la reivindicación 171, en el cual la composición se presenta como una formulación en forma de cápsula o tableta y la cápsula o tableta libera aproximadamente 60-90 por ciento de la droga al cabo de 30 minutos usando el Aparato II de *U.S. Pharmacopeia* (USP) a 50 rpm con lauril sulfato de sodio al 1% en agua como medio de disolución.

174. El compuesto, composición o método de la reivindicación 171, en el cual la composición se presenta como una formulación en forma de cápsula o tableta y la cápsula o tableta libera aproximadamente 60-80 por ciento de la droga al cabo de 30 minutos usando el Aparato II de *U.S. Pharmacopeia* (USP) a 50 rpm con lauril sulfato de sodio al 1% en agua como medio de disolución.

175. Un lote de cápsulas o tabletas, en el cual cada una de las cuales comprende entre aproximadamente 1 y aproximadamente 50 mg de un compuesto de cualquiera de las reivindicaciones 1-75, con un valor de aceptación USP para la uniformidad del contenido inferior a aproximadamente 15.

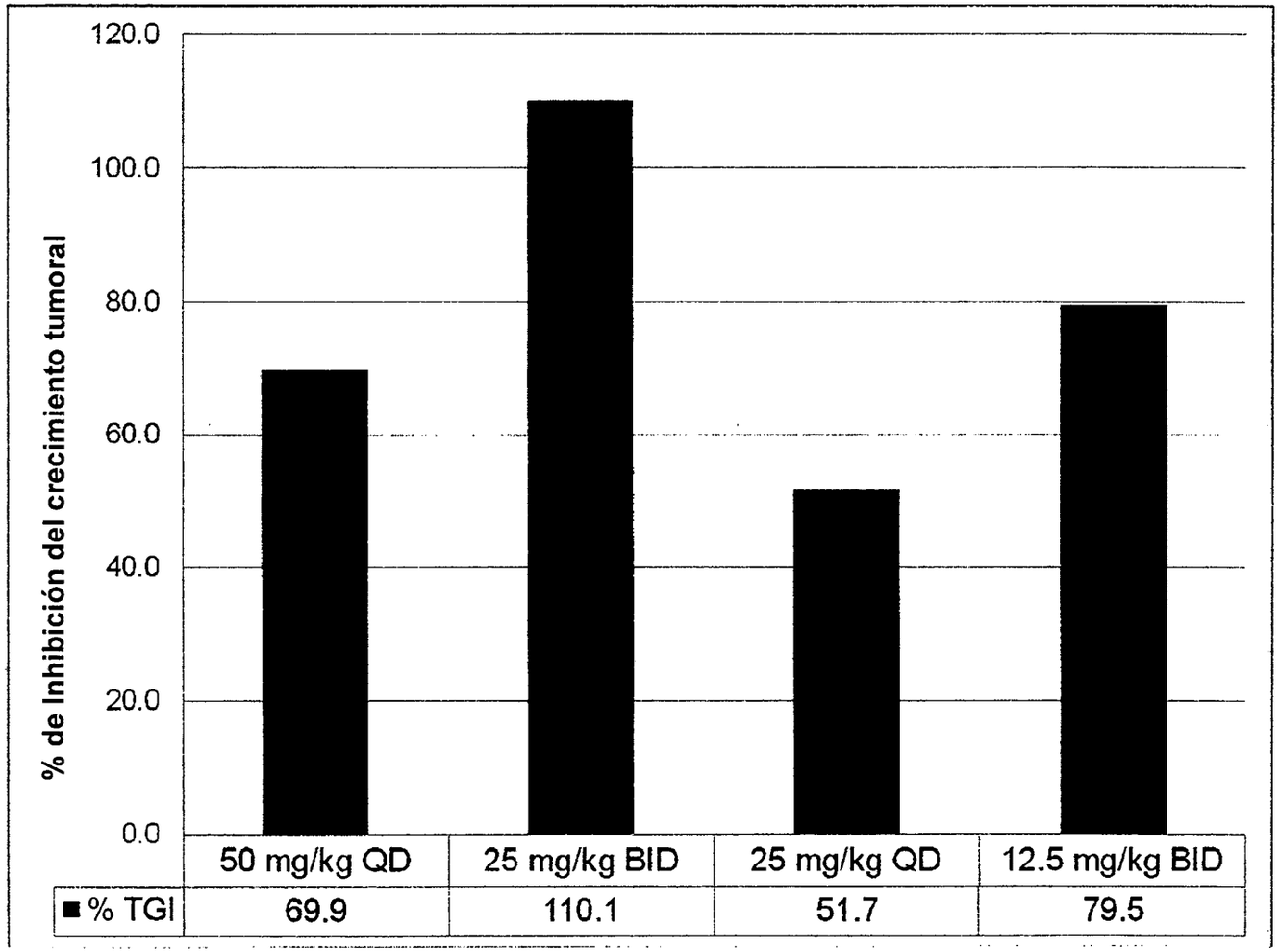
176. Un método para tratar cáncer de hígado, que requiere la administración de una cantidad terapéuticamente eficaz de un compuesto o composición de acuerdo a cualquiera de las reivindicaciones 1-75.

FIGURA 1



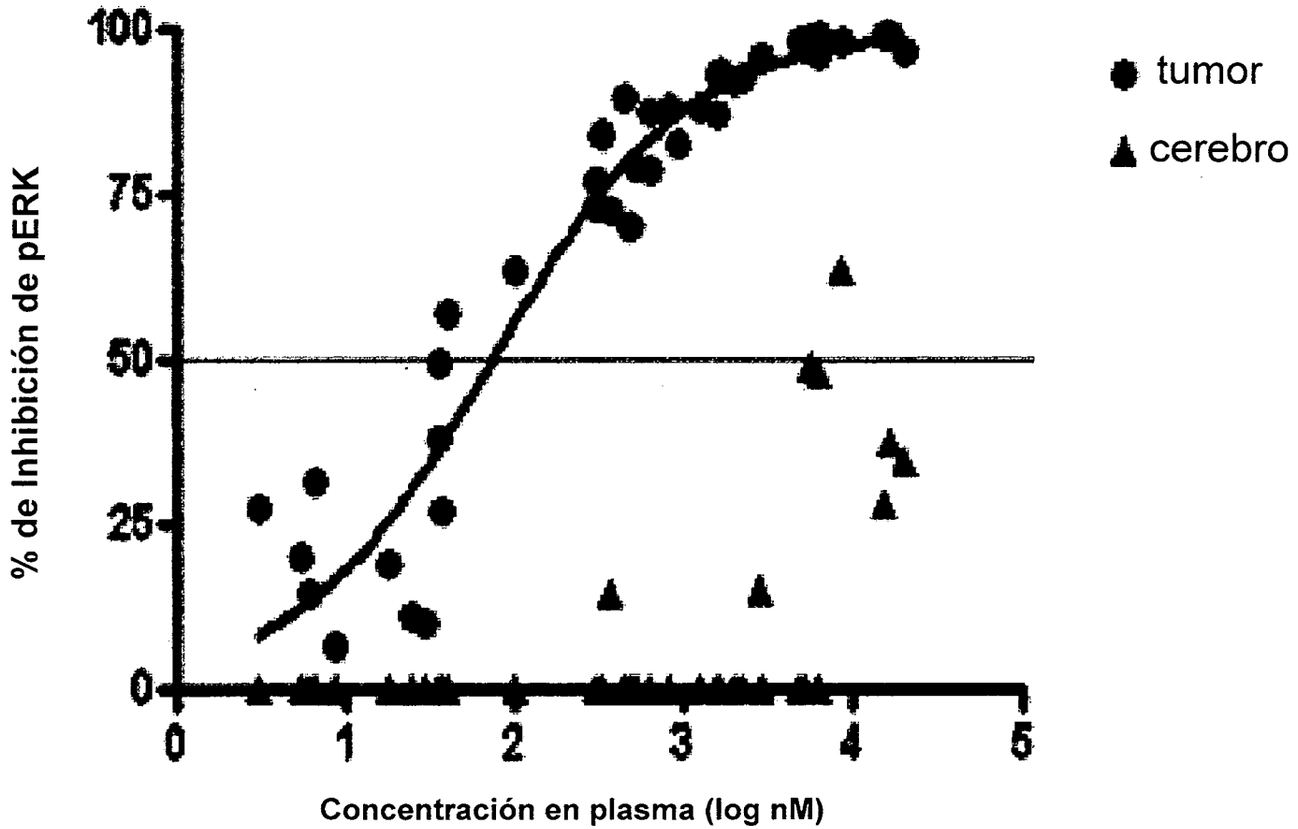

Hoja de reemplazo (regla 26)

FIGURA 2



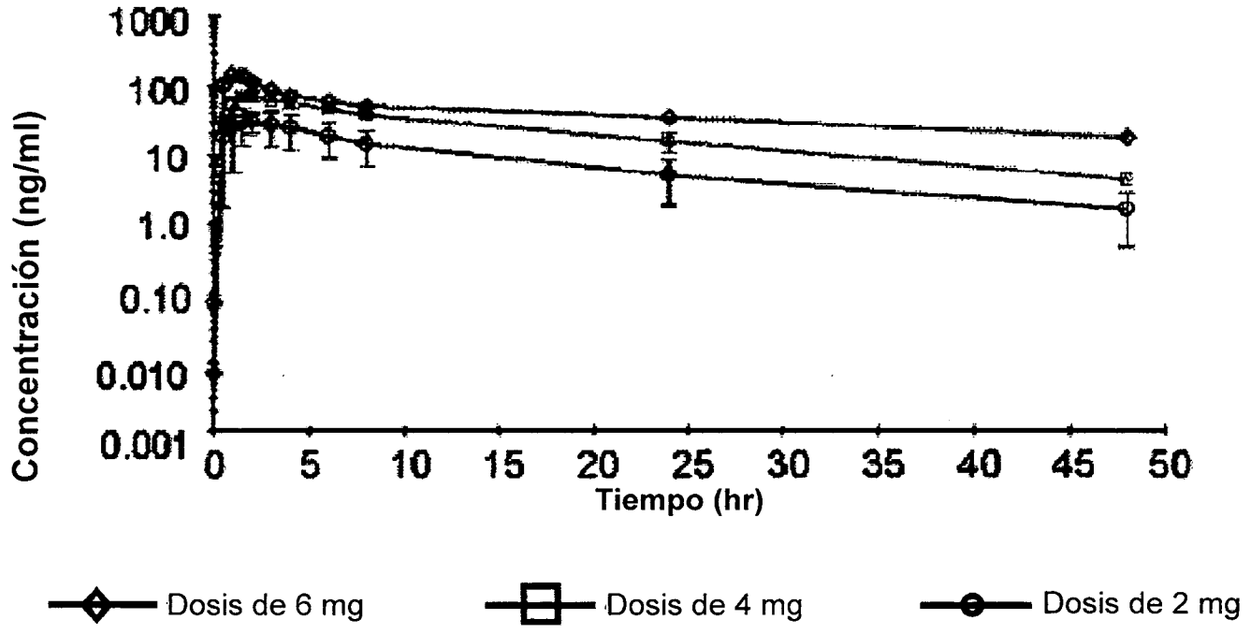

Hoja de reemplazo (regla 26)

FIGURA 3



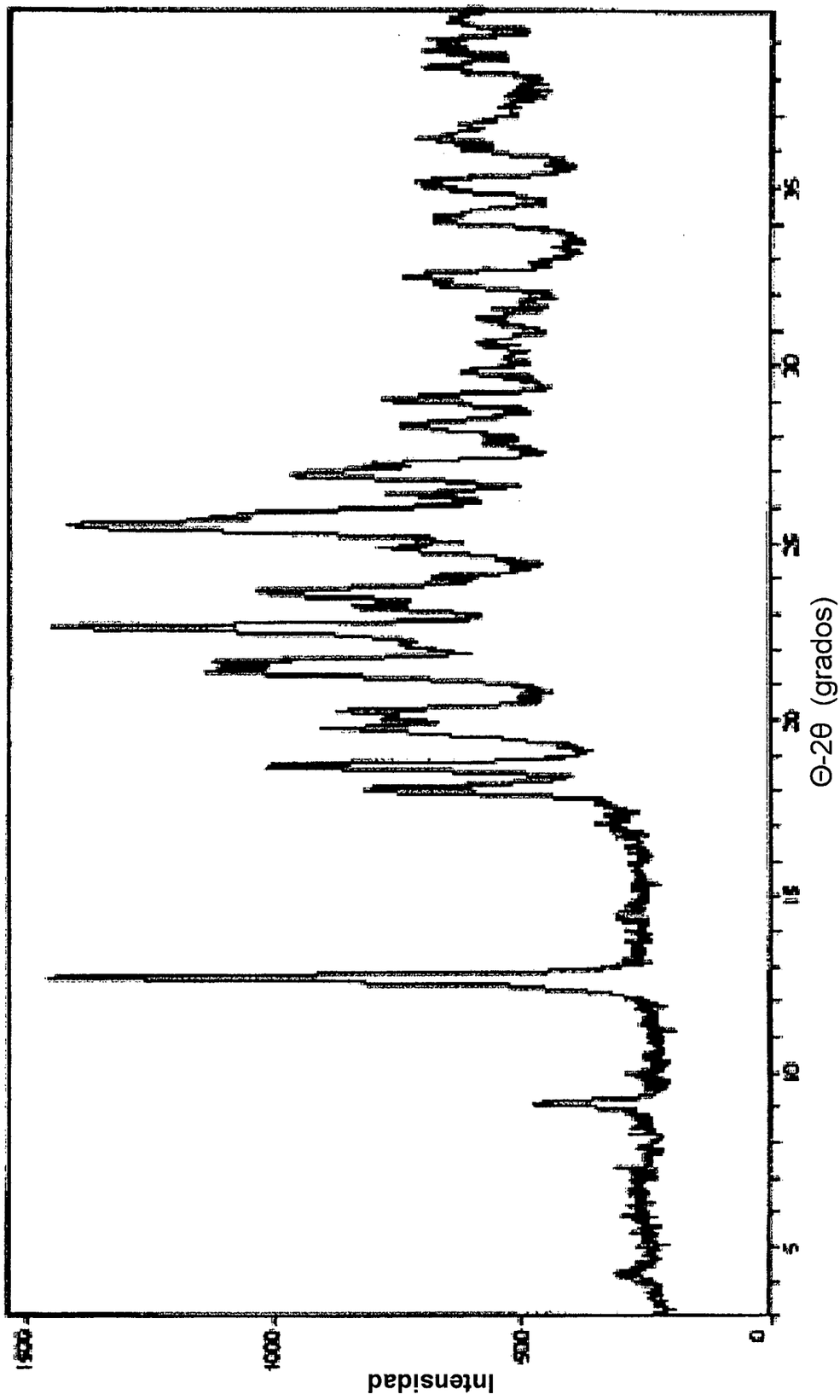

Hoja de reemplazo (regla 26)

FIGURA 4




Hoja de reemplazo (regla 26)

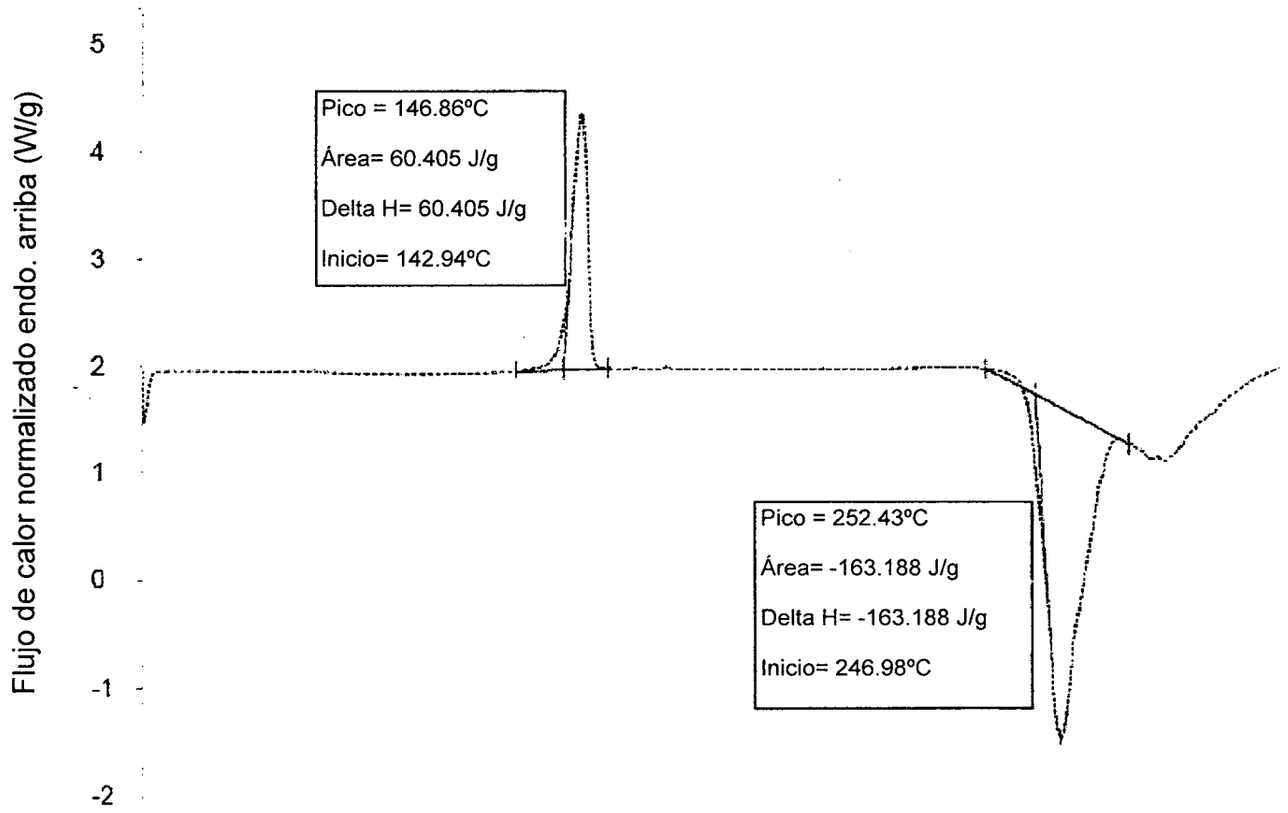
FIGURA 5





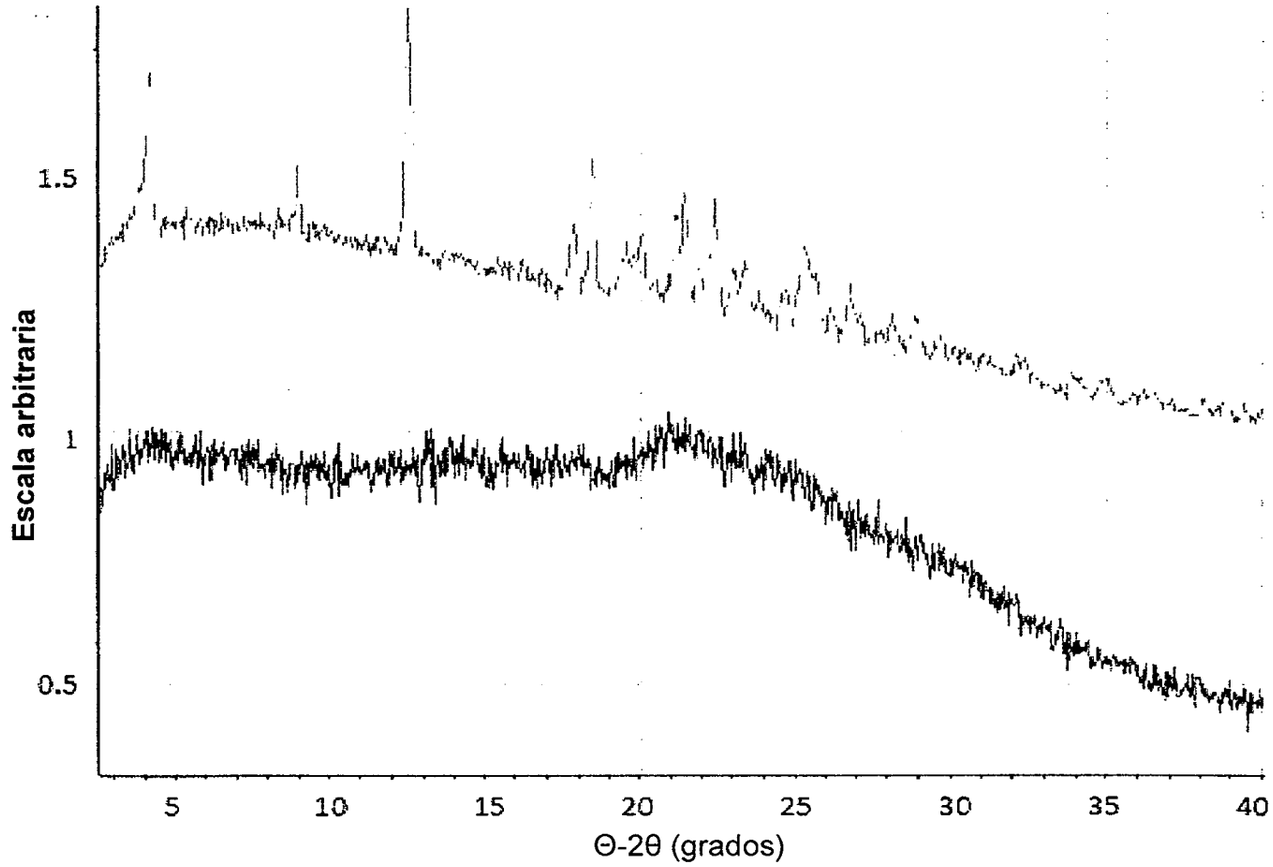

890

FIGURA 6



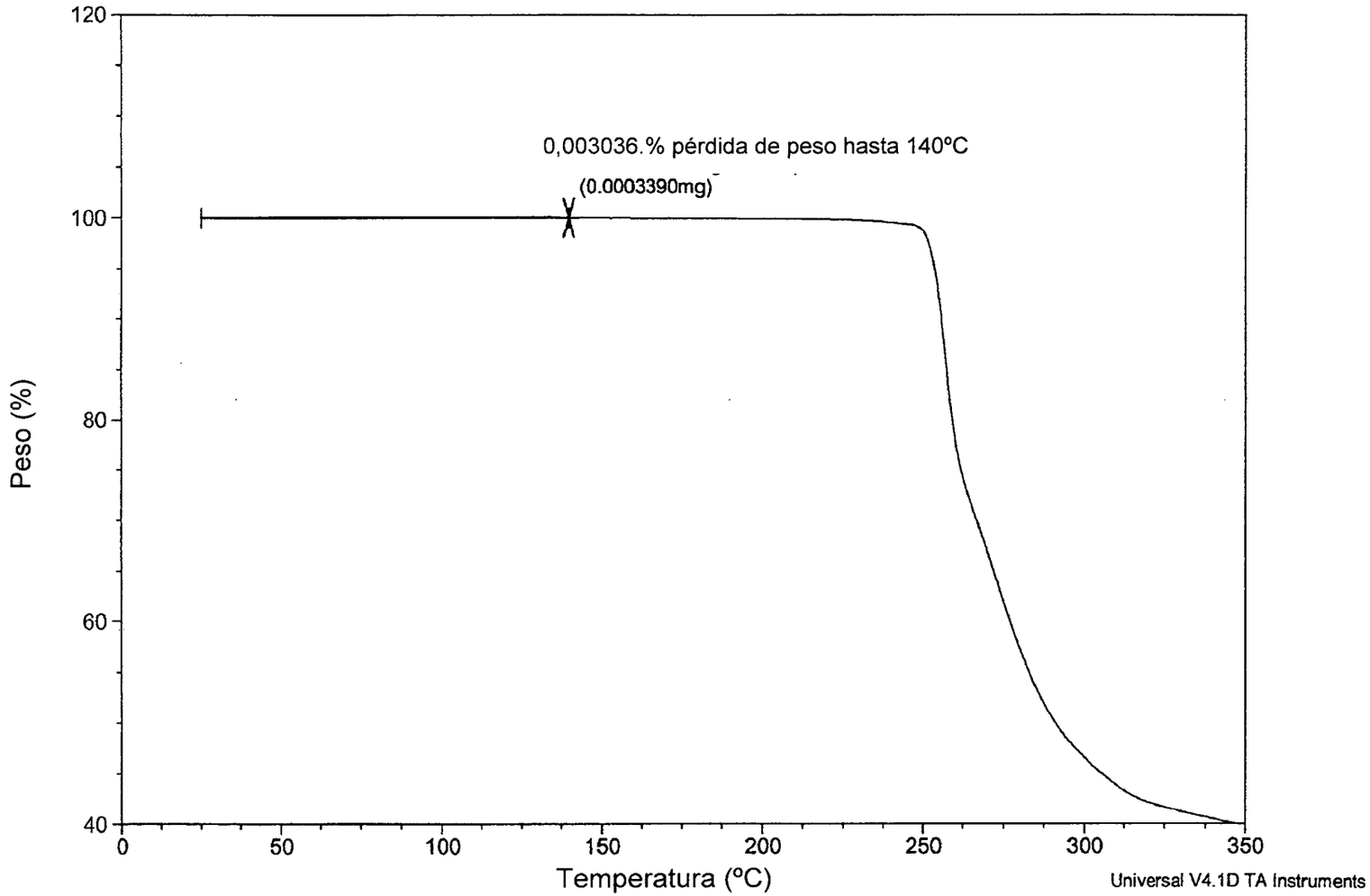

Hoja de reemplazo (regla 26)

FIGURA 7




Hoja de reemplazo (regla 26)

FIGURA 8




Hoja de reemplazo (regla 26)

FIGURA 9

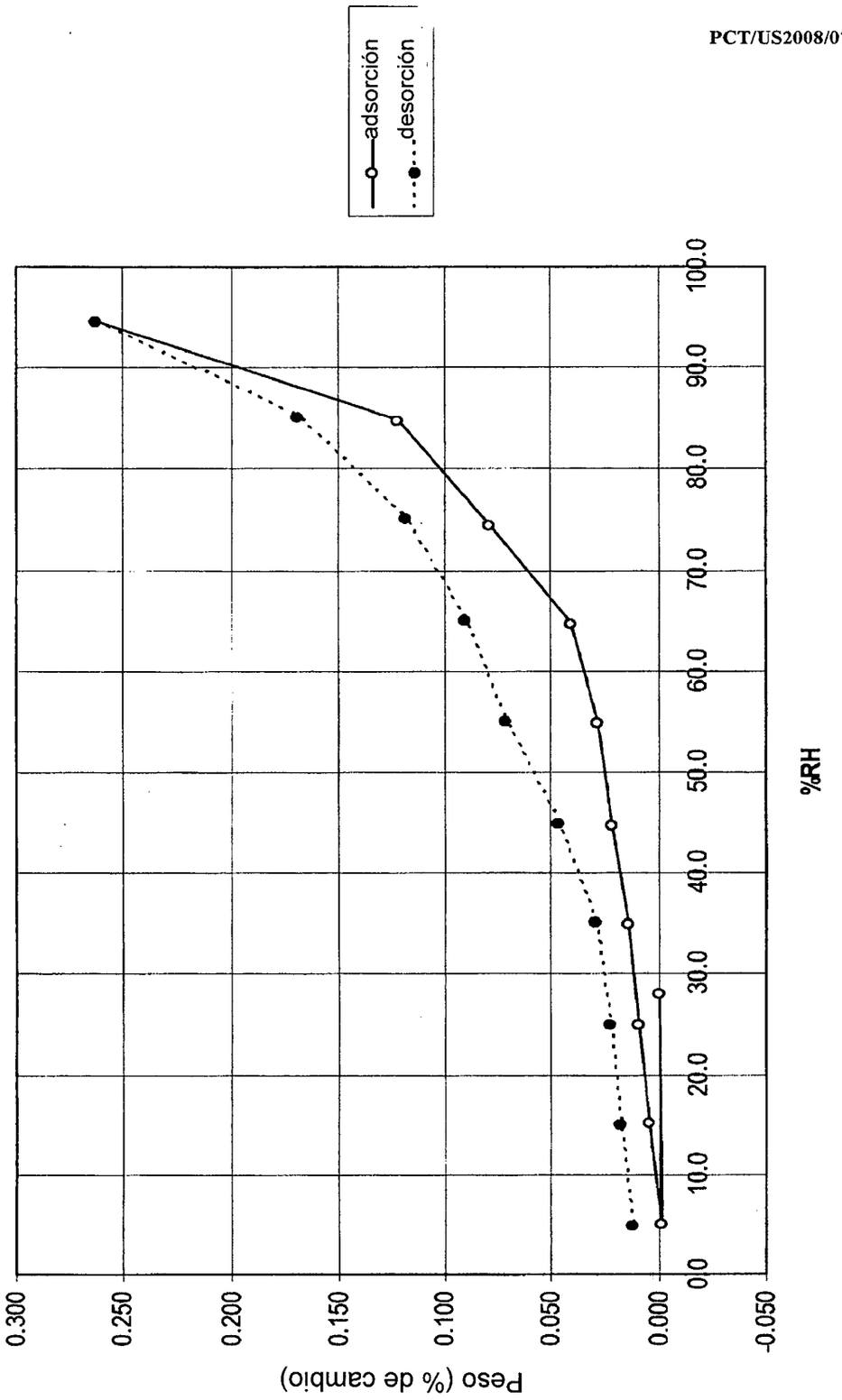

adsorción
desorción
Peso (% de cambio)
0.300
0.250
0.200
0.150
0.100
0.050
0.000
-0.050
%RH
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0

FIGURA 10

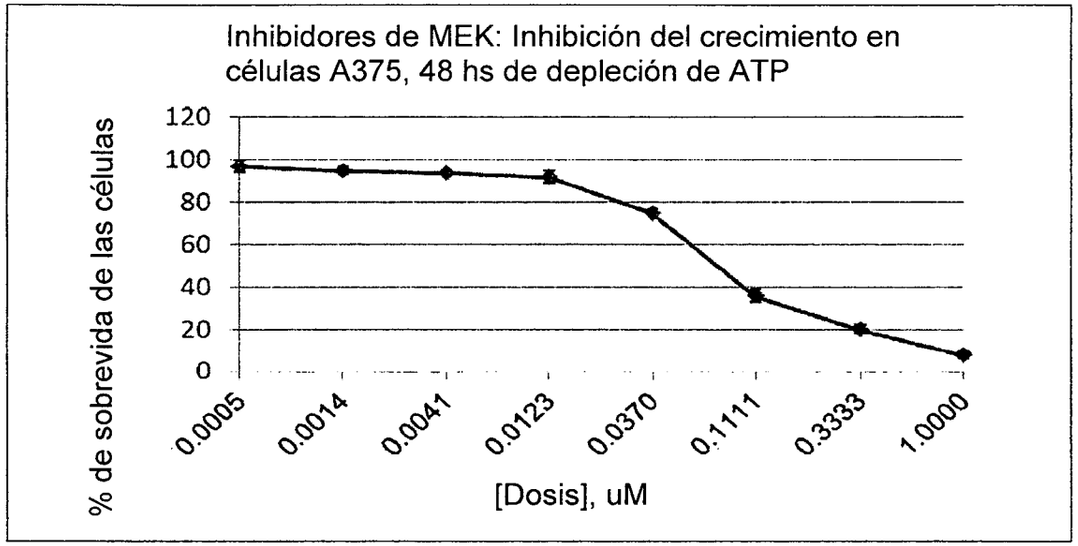



Fig 10(A)

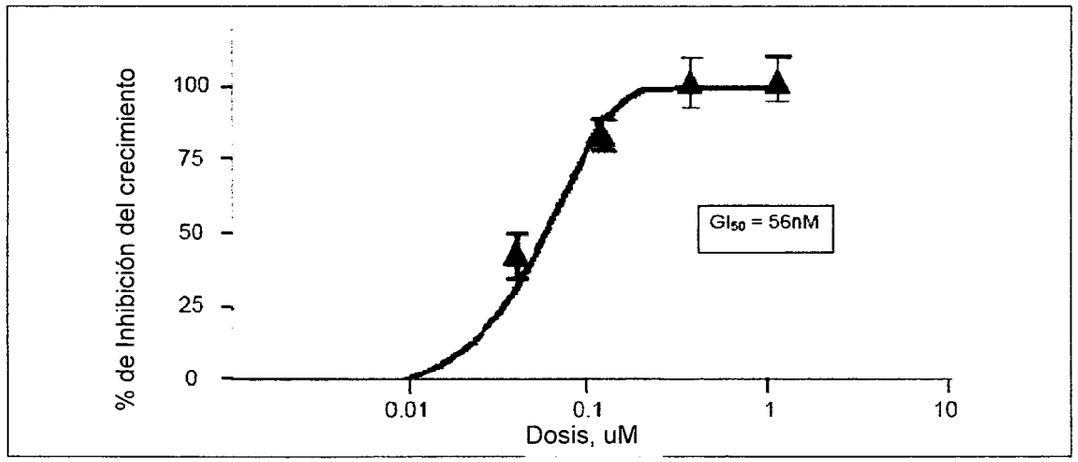
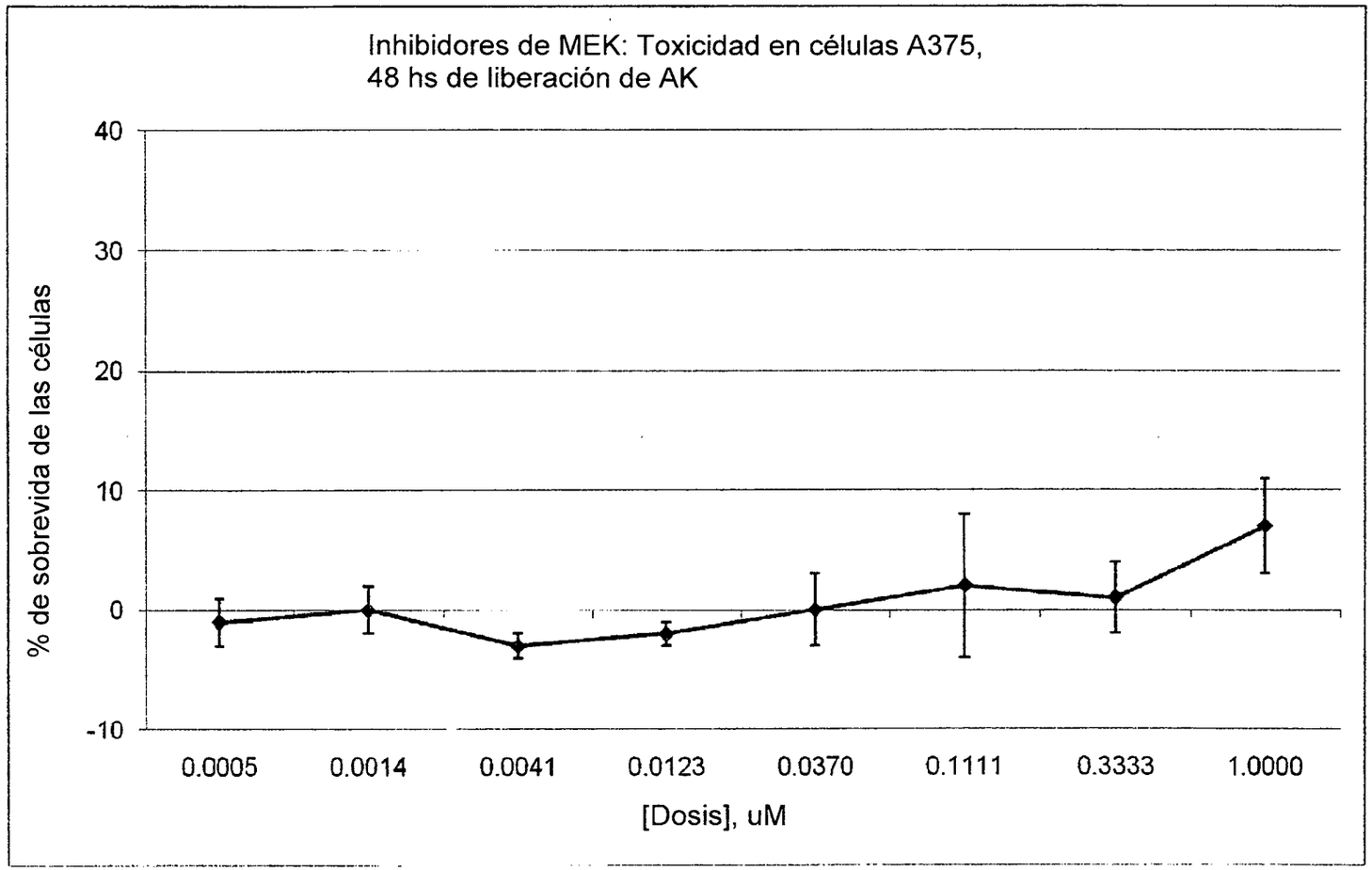



Fig 10(B)

Hoja de reemplazo (regla 26)

FIGURA 11




Hoja de reemplazo (regla 26)

# FIGURA 12

Ensayo MTS, 7 días: 3 días de inhibición del crecimiento

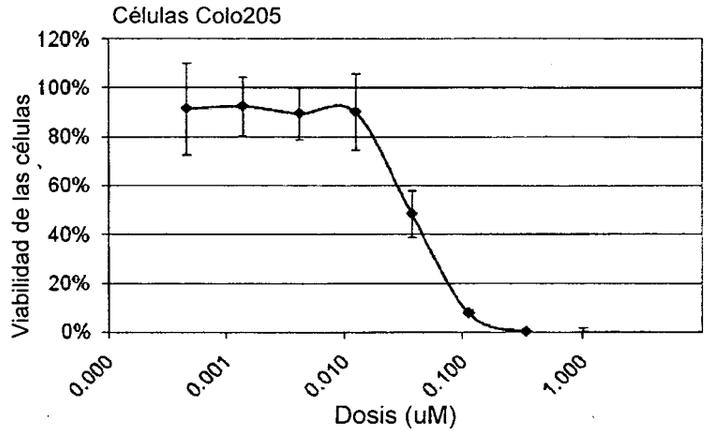



**Fig 12 (A)**

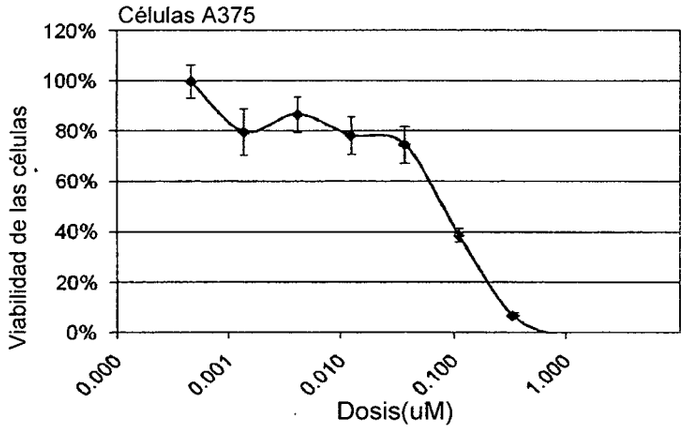



**Fig 12 (B)**

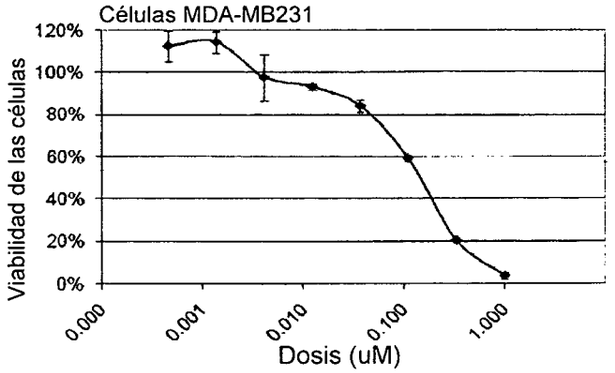



**Fig 12 (C)**

**Hoja de reemplazo (regla 26)**

FIGURA 13

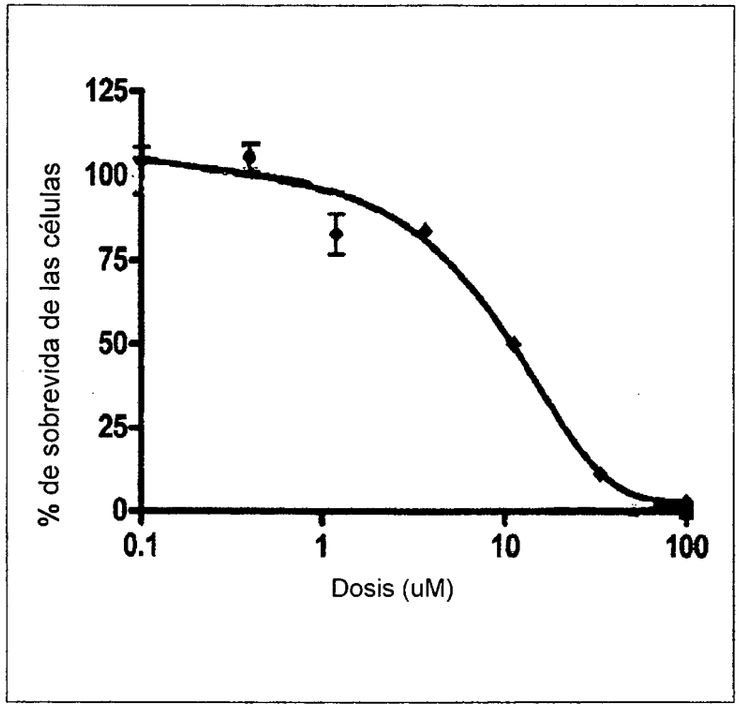



Fig 13(A)

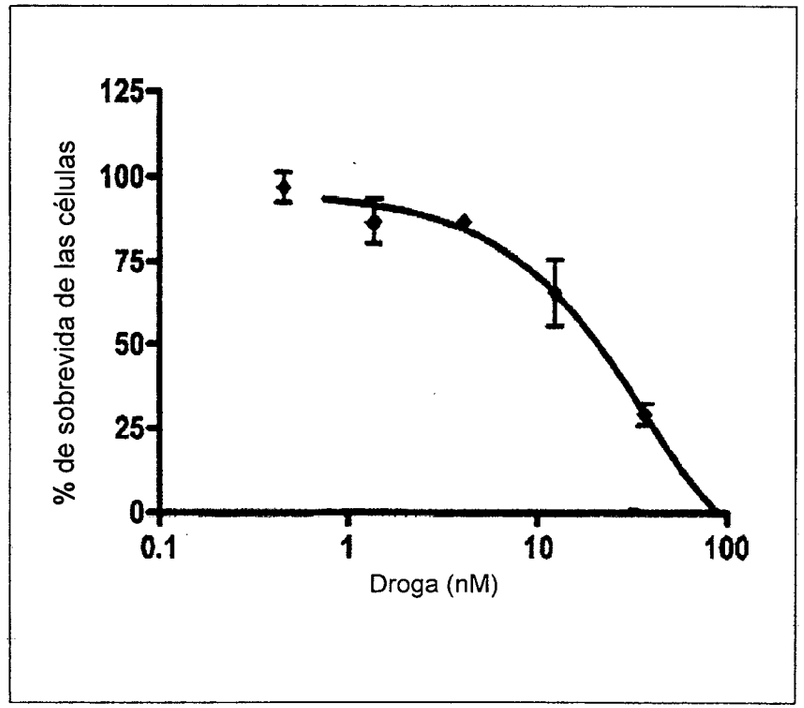



Fig 13(B)

Hoja de reemplazo (regla 26)

FIGURA 14

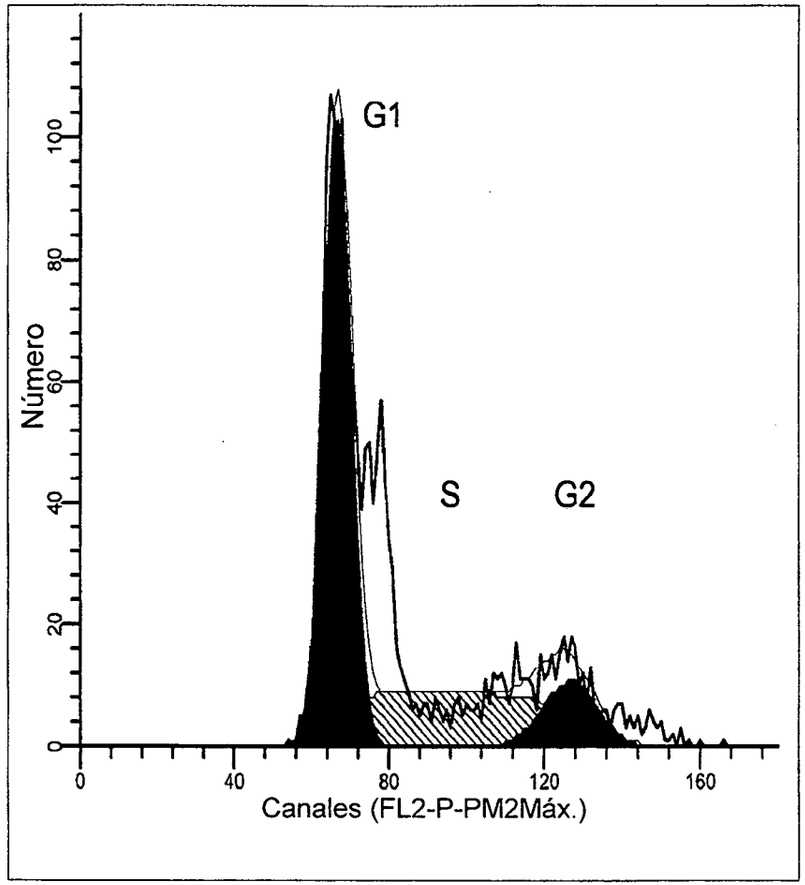



Fig 14(A)

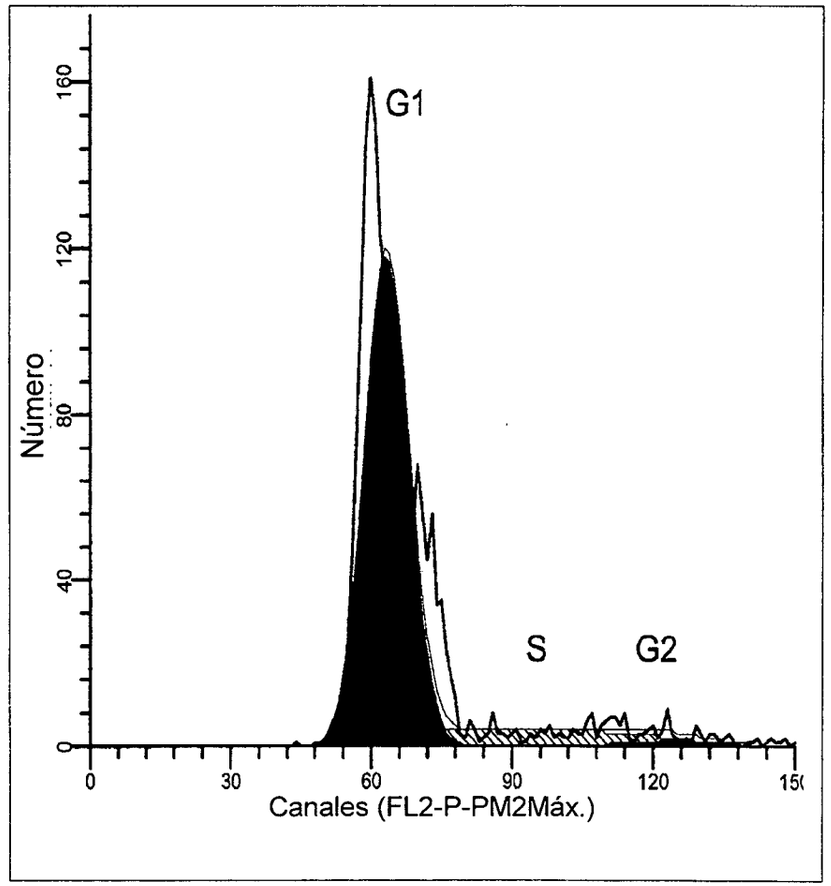



Fig 14(B)

Hoja de reemplazo (regla 26)

FIGURA 15

Inhibición de la proliferación de células AGS

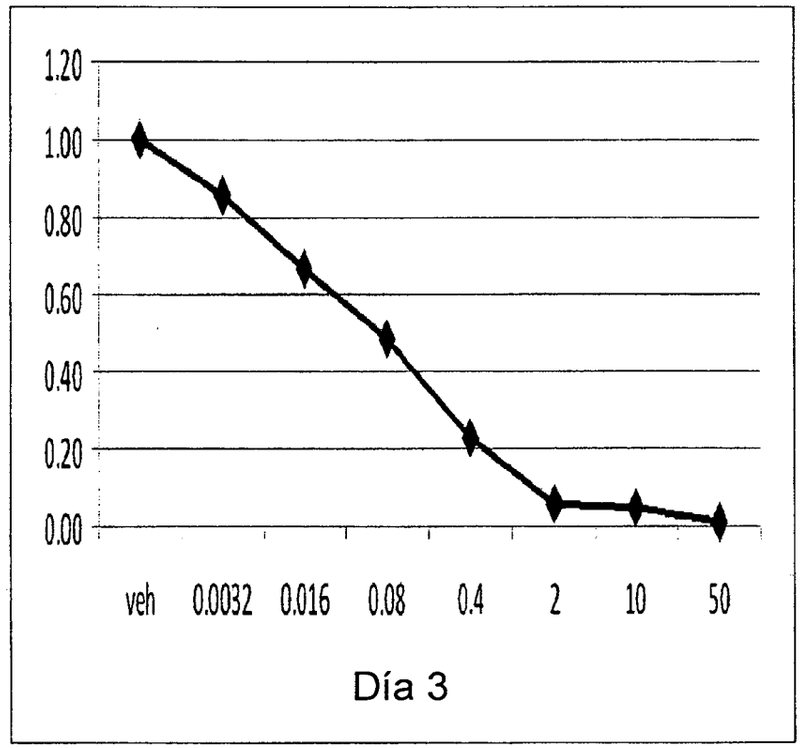



Fig 15(A)

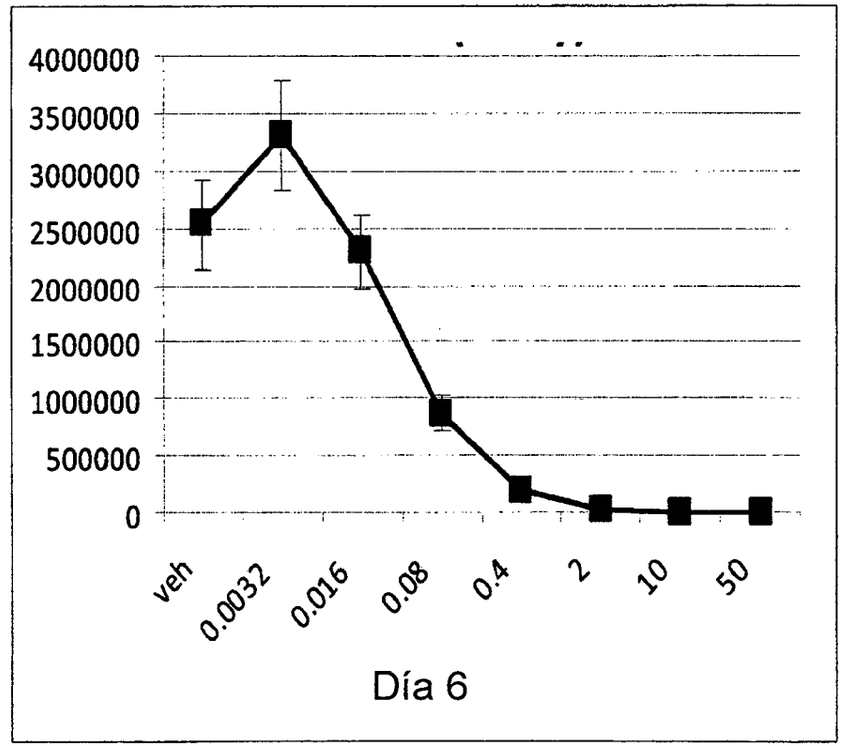
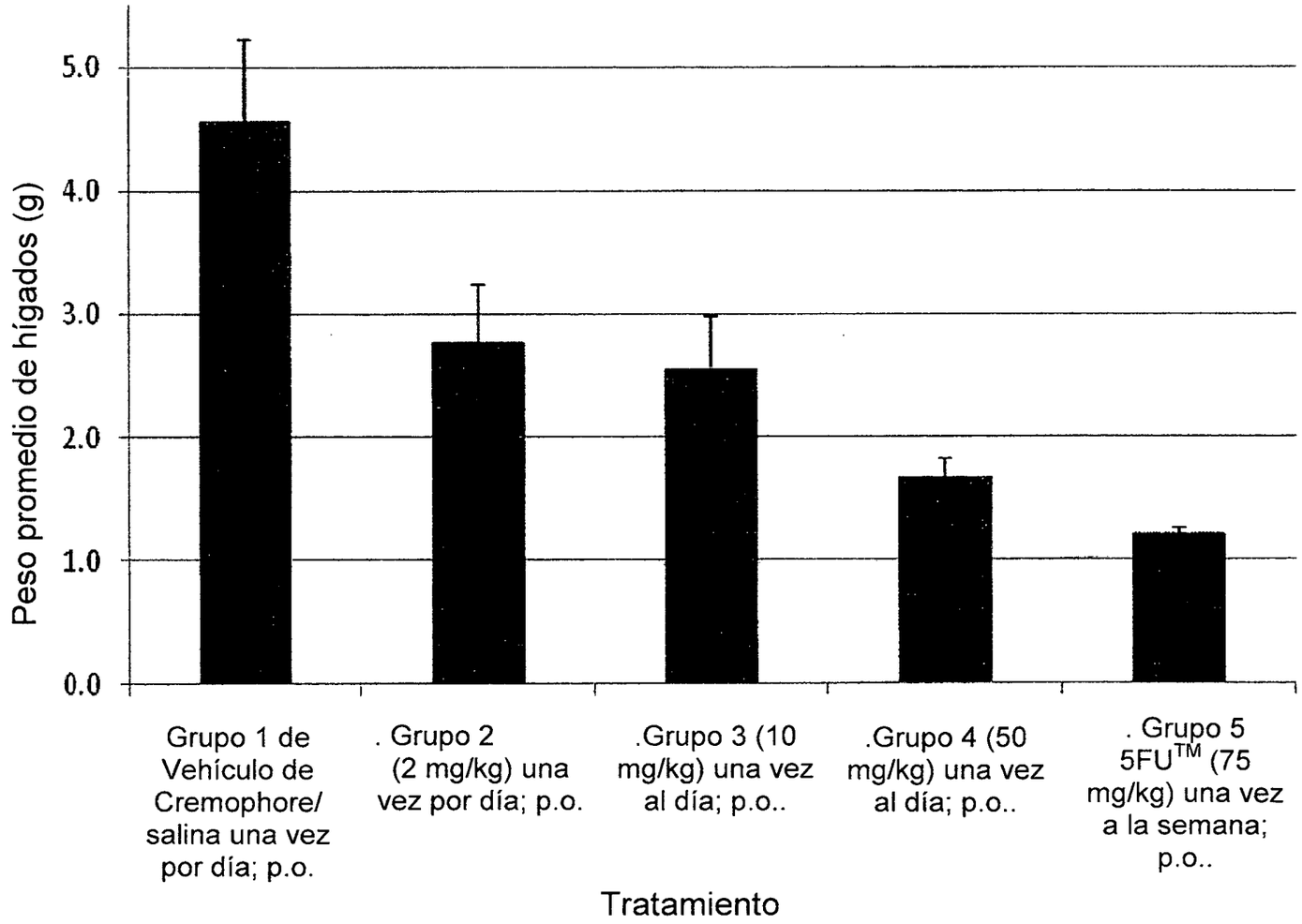



Fig 15(B)

Hoja de reemplazo (regla 26)

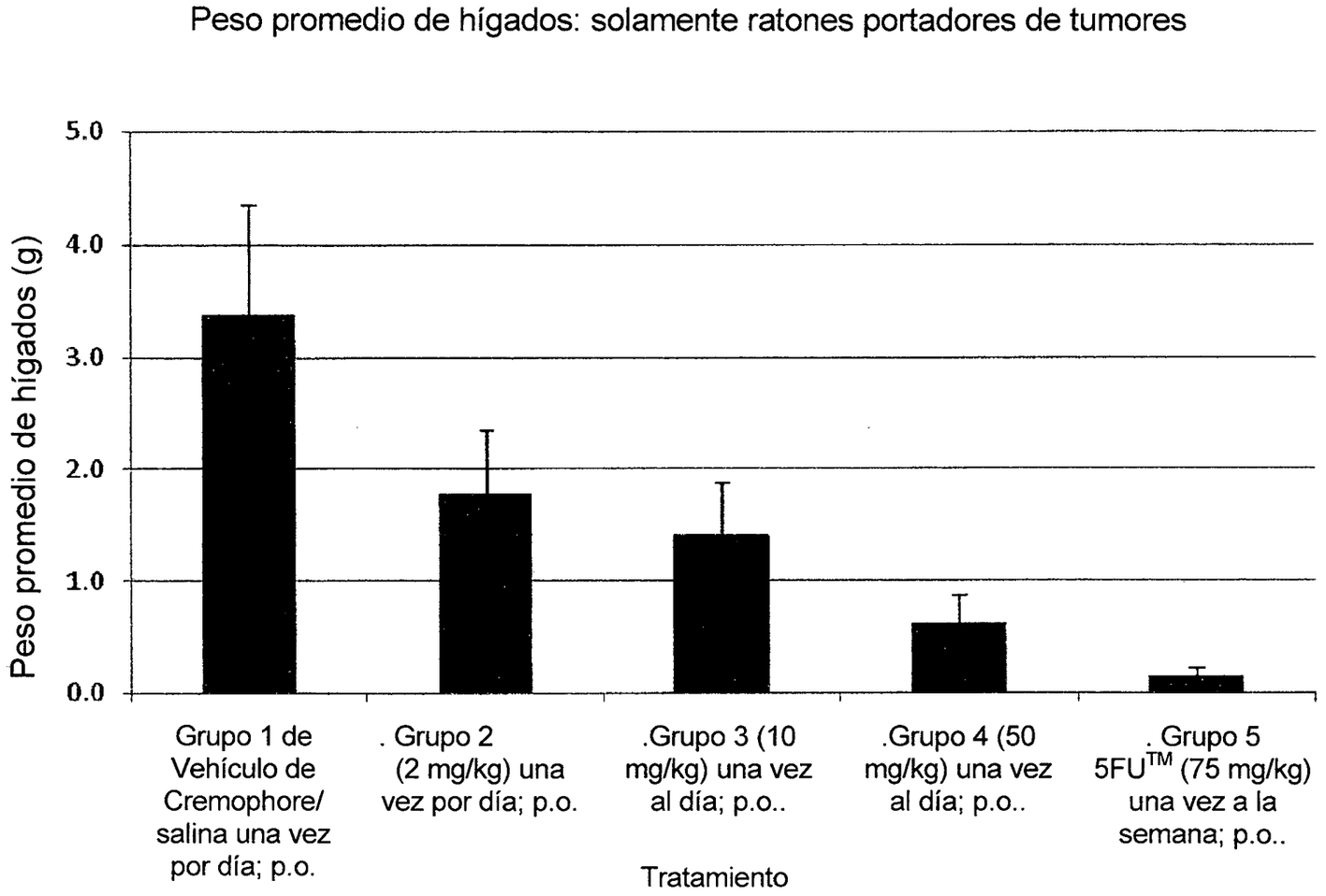
FIGURA 16

Peso promedio de hígados: solamente ratones portadores de tumores




Hoja de reemplazo (regla 26)

FIGURA 17




Hoja de reemplazo (regla 26)

202

FIGURA 18

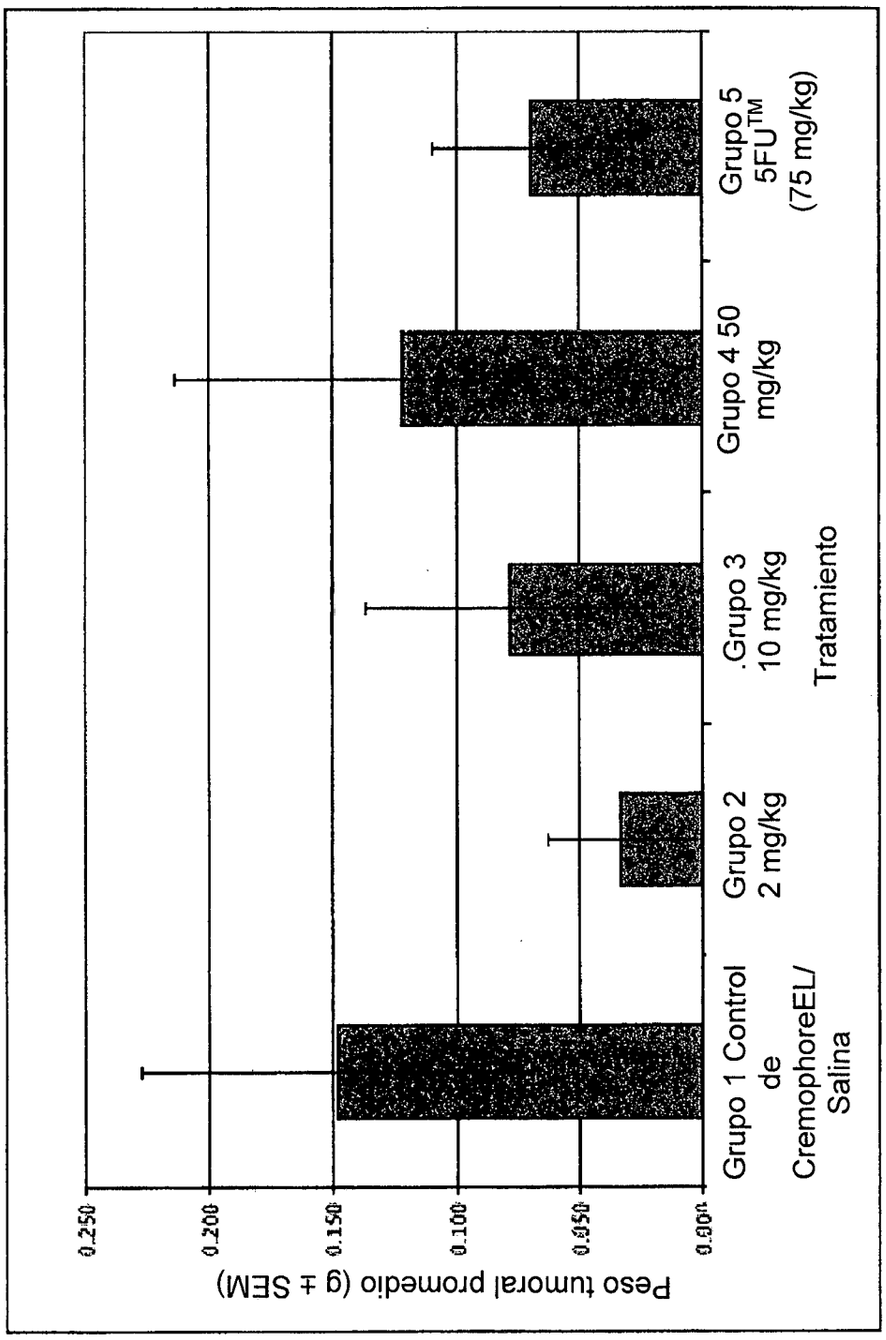
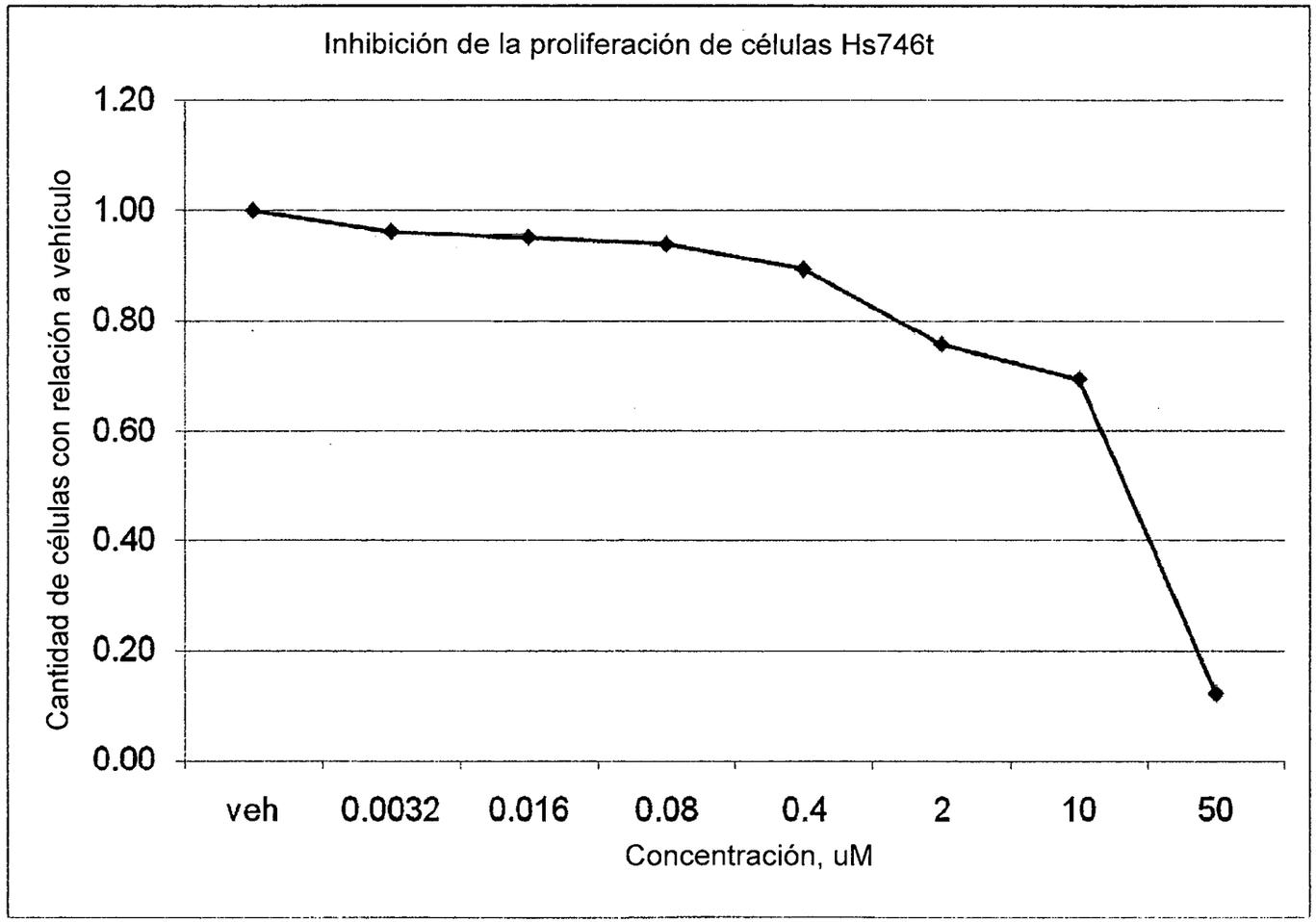

Peso tumoral promedio (g ± SEM)
0.250
0.200
0.150
0.100
0.050
0.000
Grupo 1 Control de CremophoreEL/ Salina
Grupo 2 2 mg/kg
.Grupo 3 10 mg/kg
Grupo 4 50 mg/kg
Grupo 5 5FU™ (75 mg/kg)
Tratamiento

FIGURA 19




Hoja de reemplazo (regla 26)

# FIGURA 20

Todas las figuras: eje horizontal = conc (uM); eje vertical = % de muerte celular

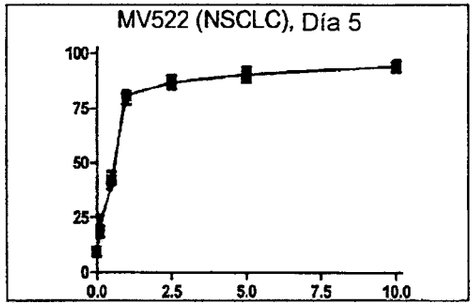



Fig 20(A)

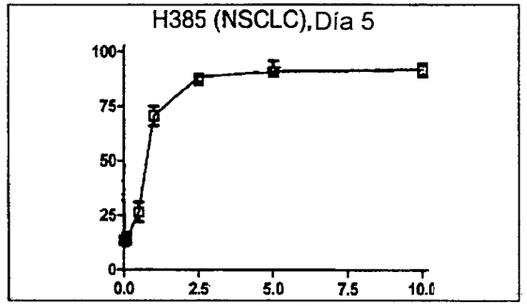



Fig 20(B)

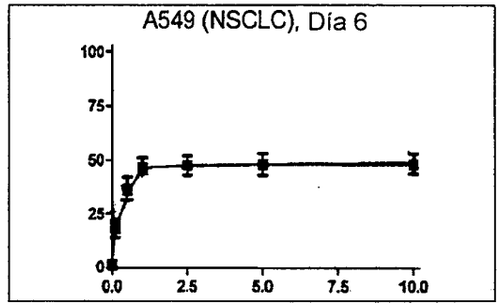



Fig 20(C)

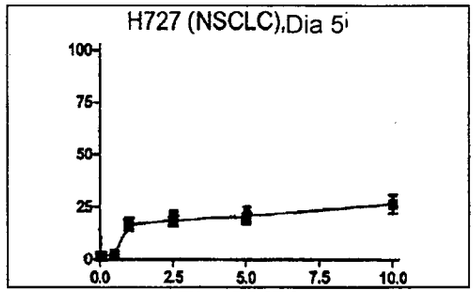



Fig 20(D)

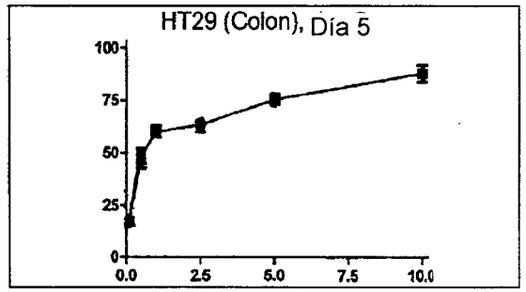



Fig 20(E)

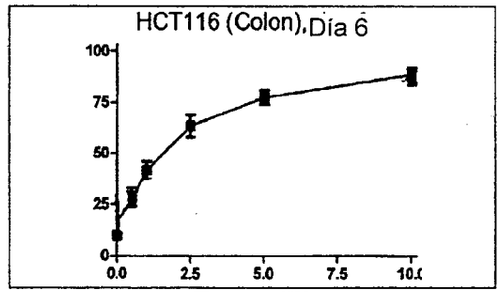



Fig 20(F)

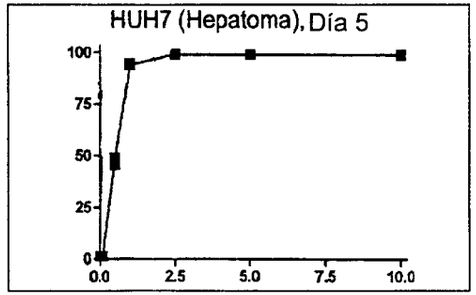



Fig 20(G)

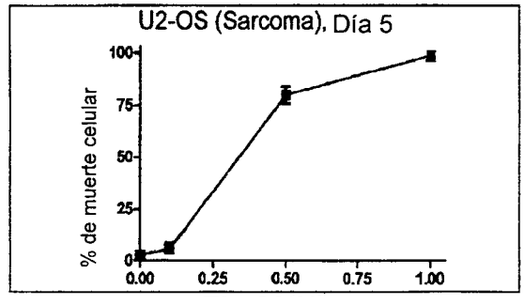



Fig 20(H)

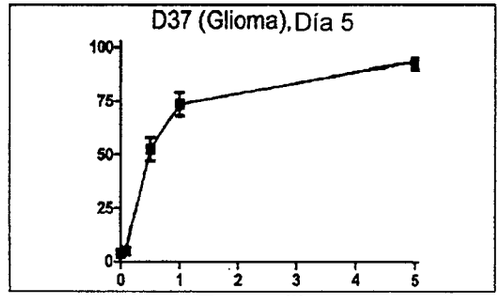



Fig 20(I)

Hoja de reemplazo (regla 26)

906

# INFORME DE BÚSQUEDA INTERNACIONAL

Referencia Internacional
*PCT/US 08/71392*

**A. CLASIFICACIÓN DEL OBJETO DE LA SOLICITUD**

*IPC(8) A01N41/06 A61K31/18 (2008.04)*
*USPC 514/601.605*

Según la clasificación internacional de patentes (IPC) o las clasificaciones nacional e IPC

**B. ÁMBITOS INVESTIGADOS**

Documentación mínima investigada (Sistema de clasificación y símbolos de clasificación)
*USPC: 514/601.605*

Publicaciones investigadas pero no pertenecientes al material mínimo investigado, en tanto pertenezcan al ámbito investigado
*USPC: 514/117.647; (ver expresiones de búsqueda abajo)*

Banco electrónico de datos consultado durante la búsqueda internacional (nombre del banco de datos y expresiones de búsqueda eventualmente empleadas)
*USTPO WEST – (PGPUB, EPAB, JPAB, USPT), Google Patent, Google Scholar, palabras clave utilizadas: aryl sulphonamide, 2-arylamino, crystaline or polymorphic, isomer or racemic or optical, lauryl sulfate, calorimetry, aryl sulfonamide, water or solvent*

**C. ANTECEDENTES CONSIDERADOS RELEVANTES**

| Categoría* | Denominación de la publicación, así como, de ser requerido, indicación de los pasajes relevantes | Con referencia a reivindicación Nº |
|---|---|---|
| *Y* | *US 6,545,030 B1 (Barret et al.)*<br>*08 de abril de 2003 (04.08.2003)*<br>*col 43; col. 48, renglones 2-13* | *1-20, 59-69, 72-75 y 101-106* |
| *Y* | *US 7,115,632 B1 (Bedell et al.)*<br>*03 de octubre de 2006 (03.10.2006))*<br>*col 29* | *1-20, 59-69, 72-75 y 101-106* |
| *Y* | *US 2004/0176418 A1 (Thiruvengadam et al.)*<br>*09 de septiembre de 2004 (09.09.2004)*<br>*fig. 3; párrafos [0013] - [0017], [0036], [0061], [0115], [0364]* | *59-69 y 72-75* |
| *Y* | *US 6,780,870 B2 (Carter et al.)*<br>*24 de agosto de 2004 (24.08.2004)*<br>*col 5, rnglones 4-46* | *101-105* |

☐ Otras publicaciones están listadas en la continuación del campo C

☐ Ver familia de patentes en el anexo

* Categorías particulares indicadas en publicaciones

"A" publicación que define el estado general de la técnica pero no considerada como particularmente importante

"B" documento anterior pero publicado recién o después de la de la fecha de presentación internacional

"L" publicación adecuada para hacer aparecer como dudosa una reivindicación de prioridad, o mediante la cual debe ser considerada la fecha de divulgación de otra publicación mencionada en el informe de búsqueda o que es indicada por otra razón particular (como realizada)

"O" publicación que se refiere a una revelación oral, a una utilización, a una exposición o a otras disposiciones

"P" publicación realizada antes de la fecha de presentación internacional pero luego de la fecha de prioridad reivindicada

"T" publicaciones posteriores a las difundidas en la fecha de presentación internacional o de la fecha de prioridad y que no colisionan con la solicitud, sino que solo están indicadas para mayor entendimiento del principio fundamental de la invención o de la teoría sobre la cual se basa

"X" publicación de particular importancia: la invención reivindicada no puede ser considerada, solo como consecuencia de esta publicación, como novedosa o apoyarse en una actividad inventiva

"Y" publicación de particular importancia: la invención reivindicada no puede ser considerada como apoyada en una actividad inventiva cuando puede ser relacionada con una o varias otras publicaciones de esta categoría y tal relación es notoria para un especialista

"&" publicación que es miembro de la misma familia

| Fecha de finalización de la búsqueda internacional | Fecha de envío del Informe de Búsqueda Internacional |
|---|---|
| *19 de octubre de 2008 (19.10.2008)* | *16 OCT 2008 (sellado)* |
| Nombre y Dirección Postal del ISA/US<br>Mail Stop PCT, Attn. ISA/US<br>Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Fax: 571-273-3201 | Funcionario Apoderado<br>*Lee W. Young*<br>Mesa de ayuda de PCT: 571-272-4300<br>PCT OSP: 571-272-7774 |

967

# INFORME DE BÚSQUEDA INTERNACIONAL

Referencia Internacional

*PCT/US 2008/71392*

**Campo II: Observaciones acerca de porque determinadas reivindicaciones no eran investigables (continuación del ítem 2 de la hoja 1)**

Este Informe de Búsqueda Internacional no fue realizado con respecto a algunas reivindicaciones, según el artículo 17(2)(a), por las siguientes razones:

1. ☐ Reivindicaciones Nº:
porque se refieren a objetos que no requieren ser investigados por este Organismo, a saber:

2. ☐ Reivindicaciones Nº:
porque se refieren a partes de la Solicitud Internacional que no cumplen con los requisitos prescriptos en una extensión que no permite llevar a cabo una búsqueda internacional, específicamente:

3. ☒ Reivindicaciones Nº: 21-58, 70-71, 76-100 y 107-176
porque son reivindicaciones dependientes y no están desarrolladas en acordanza con la segunda y la tercera frase de la regla 6.4(a).

**Campo III: Observaciones por falta de uniformidad de la invención (continuación del ítem 3 de la hoja 1)**

Este Organismo de Búsqueda Internacional encontró invenciones múltiples en esta solicitud internacional, a saber:

1. ☐ Como todas las tasas adicionales requeridas fueron abonadas en término por el solicitante, este Informe de Búsqueda Internacional cubre todas las reivindicaciones investigables.

2. ☐ Como todas las reivindicaciones investigables pueden ser investigadas sin un esfuerzo que justifique una tasa adicional, este Organismo no solicita ningún pago o tasa adicional.

3. ☐ Como solo algunas de las tasas adicionales fueron abonadas en término por el solicitante, este Informe de Búsqueda Internacional cubre solo aquellas reivindicaciones para los cuales fueron abonadas las tasas, específicamente, las reivindicaciones Nº:

4. ☐ Ninguna de las tasas adicionales requeridas fue abonada en término por el solicitante. En consecuencia, este Informe de Búsqueda Internacional está restringido a la invención mencionada inicialmente en las reivindicaciones; estando la misma cubierta por las reivindicaciones Nº:

**Observaciones sobre protestas**

☐ Las tasas de búsqueda adicionales fueron acompañadas por la protesta del solicitante y, cuando correspondía, el pago de la tasa de protesta

☐ Las tasas de búsqueda adicionales fueron acompañadas por la protesta del solicitante pero la tasa de protesta solicitada no fue pagada en el plazo especificado en la intimación

☐ El pago de las tasas de búsquedas adicionales no fue acompañado por ninguna protesta.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/71392

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 41/06; A61K 31/18 (2008.04)
USPC - 514/601, 605
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)
USPC: 514/601, 605

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/117, 647 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic Databases Searched: USPTO WEST (PGPUB, EPAB, JPAB, USPT), Google Patent, Google Scholar. Search Terms Used: aryl sulfonamide, 2-arylamino, crystalline or polymorphic, isomer$ or recemic or oprtical, lauryl sulfate, calorimetry, aryl sulfonamide, water or solvent

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | US 6,545,030 B1 (Barrett et al.) 08 April 2003 (08.04.2003) col 43; col 48, ln 2-13 | 1-20, 59-69, 72-75 and 101-106 |
| Y | US 7,115,632 B1 (Bedell et al.) 03 October 2006 (03.10.2006) col 29 | 1-20, 59-69, 72-75 and 101-106 |
| Y | US 2004/0176418 A1 (Thiruvengadam et al.) 09 September 2004 (09.09.2004) Fig 3; para [0013]-[0017], [0036], [0061], [0115], [0364] | 59-69 and 72-75 |
| Y | US 6,780,870 B2 (Carter et al.) 24 August 2004 (24.08.2004) col 5, ln 4-46 | 101-106 |

☐ Further documents are listed in the continuation of Box C. ☐

* 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 application or patent 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 |
|---|---|
| 19 October 2008 (10.10.2008) | 16 OCT 2008 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | Authorized officer:<br>Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/71392

**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.: Claims 21-58, 70-71, 76-100 and 107-176
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying 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.

☐ No protest accompanied the payment of additional search fees.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-009526- -00000-0000
Fecha: 2010-01-29 17:28:10 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 909

9P

**PATENTE DE INVENCIÓN** ☐ **MODELO DE UTILIDAD** ☐ **Art 33 Decisión 486/00**

- ☐ 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 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 establec

Completa ☐ Incompleta ☐