

QF

  
**Industria y Comercio**  
SUPERINTENDENCIA

Delegatura de propiedad Industrial  
División de Nuevas Creaciones

**P.C.T.**  
SOLICITUD

**PATENTE DE INVENCION**

21 EXPEDIENTE No.

03-107114

54 TÍTULO BENZOILSULTANAMIDAS Y SULFONIL BENZAMIDAS  
QUE SE USAN COMO AGENTES

51 CLASIFICACIÓN INTERNACIONAL AGIK 31/18

71 SOLICITANTE ELI LILLY AND COMPANY

DOMICILIO INDIANAPOLIS, INDIANA 46285  
ESTADOS UNIDOS DE AMERICA

74 APODERADO CARLOS TR OLARTE

22 BOGOTÁ, D. C., DICIEMBRE 5, 2003

**SUPERINTENDENCIA Y ATENCION**  
 Radicacion : 0510/114 00000000 Folio(s) 133  
 Fecha (HH): 2016-12-05 09:16:57  
**Es** From: 011 PDI-PALENI J/S PALE NI 411 PDI-PALENI  
 Dependencia: 2020 DIVISION DE MANEJO DE RECURSOS

## ENTRADA EN FASE NACIONAL

|                                                                                                                                                                                         |                                                                                                                                                                                                                                                     |                                                                                                                                                                                                  |                                               |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| <b>1</b> SOLICITUD DE :                                                                                                                                                                 |                                                                                                                                                                                                                                                     |                                                                                                                                                                                                  |                                               |
| <input type="checkbox"/> Patente de Invención<br><input type="checkbox"/> Capítulo I.                                                                                                   | <input type="checkbox"/> Patente de Modelo de Utilidad<br><input checked="" type="checkbox"/> Capítulo II.                                                                                                                                          |                                                                                                                                                                                                  |                                               |
| <b>2</b><br><b>SOLICITANTE</b><br>(71)                                                                                                                                                  | Nombre: ELI LILLY AND COMPANY.<br>Dirección: Indianapolis, Indiana 46285. Estados Unidos de America.<br>Nacionalidad o Domicilio:<br>Lugar de Constitución: Indianapolis, Estados Unidos de América.<br>Teléfono: _____ Fax: _____<br>E-Mail: _____ | <b>IDENTIFICACION</b><br>C.C. <input type="checkbox"/> NIT <input type="checkbox"/><br>C.E. <input type="checkbox"/> Otro <input type="checkbox"/><br>Número _____ Cual _____                    |                                               |
| <b>3</b><br><b>REPRESENTANTE</b><br><b>O APODERADO</b>                                                                                                                                  | Nombre: CARLOS R. OLARTE<br>Dirección: World Trade Center Torre C, Calle 100 No. 8A-55 Piso 10.<br>Teléfono: 6386200 Fax: 6386201<br>E-Mail: filings@olarteraisbeck.com                                                                             | <b>IDENTIFICACION</b><br>C.C. <input checked="" type="checkbox"/> NIT <input type="checkbox"/><br>C.E. <input type="checkbox"/> Otro <input type="checkbox"/><br>Número 79.782.747 Bta TP 74.295 |                                               |
| <b>4</b><br><b>INVENTOR (ES)</b><br>(72)                                                                                                                                                | Nombre: VER PAGINA ADJUNTA.<br>Dirección: VER PAGINA ADJUNTA.<br>Nacionalidad o Domicilio: VER PAGINA ADJUNTA.                                                                                                                                      |                                                                                                                                                                                                  |                                               |
| <b>5</b> PCT (86)<br>Solicitud Internacional No. <u>PCT/US02/15142</u> Fecha <u>Junio 29, 2001</u><br>Publicación Internacional No. <u>WO 02/098848</u> Fecha <u>Diciembre 12, 2002</u> |                                                                                                                                                                                                                                                     |                                                                                                                                                                                                  |                                               |
| <b>6</b> Título (54) <u>BENZOILSULFANAMIDAS Y SULFONILBENZAMIDINAS QUE SE USAN COMO AGENTES</u><br><u>ANTITUMORALES.</u>                                                                |                                                                                                                                                                                                                                                     |                                                                                                                                                                                                  |                                               |
| <b>7</b> Clasificación Internacional (51) <u>A61K31/18</u>                                                                                                                              |                                                                                                                                                                                                                                                     |                                                                                                                                                                                                  |                                               |
| <b>8</b> Prioridad<br>SI <input checked="" type="checkbox"/> NO <input type="checkbox"/>                                                                                                | (33) País de Origen<br><u>US</u>                                                                                                                                                                                                                    | (32) Fecha<br><u>Junio 6, 2001</u>                                                                                                                                                               | (31) Número de Solicitud<br><u>60/296,350</u> |
| <b>9</b> Comprobante de pago No. <u>82782</u> Fecha <u>12-11-03</u>                                                                                                                     |                                                                                                                                                                                                                                                     |                                                                                                                                                                                                  |                                               |

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

10

ANEXOS

2

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica
- ☒ Poderes, si fuere el caso
- ☒ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar 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.
- ☒ Otros: BUSQUEDA INTERNACIONAL

11 FIGURA CARATERISTICA

12 Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

FIRMA:

C.C. 74.782.747 de Btá T.P. 74.295

3  
Thomas Hughes CORBETT  
1259 Grayton  
Grosse Pointe, Michigan 48230  
Estados Unidos de América.  
Nacionalidad: Estadounidense.

Cora Sue GROSSMAN  
5838 Baron Court  
Indianapolis, Indiana 46250  
Estados Unidos de América.  
Estados Unidos de America.

Karen Lynn LOBB  
5625 East Lowell Avenue  
Indianapolis, Indiana 46219  
Estados Unidos de América.  
Nacionalidad: Estadounidense.

Chuan SHIH  
12532 Pebblepointe Pass  
Carmel, Indiana 46033  
Estados Unidos de América.  
Nacionalidad: Estadounidense.

Philip Arthur Hipskind  
4255 South Cabin Court  
New Palestine, Indiana 46163  
Estados Unidos de América.  
Nacionalidad: Estadounidense.

Ho-Shen LIN  
8128 Trevellian Way  
Indianapolis, Indiana 46217  
Estados Unidos de América.  
Nacionalidad: Estadounidense.

26 4

RECIBO OFICIAL DE CAJA : 03 - 82,762  
FECHA : NOVIEMBRE 12 DE 2003

| DEPOSITANTE      | TIPO PAGO    | BANCO         | CUENTA      | No. PAGO | FECHA PGO  | Vr. PAGO      |
|------------------|--------------|---------------|-------------|----------|------------|---------------|
| JORGE LUIS GOMEZ | CONSIGNACION | BANCO POPULAR | 050-00110-6 | 11025952 | 12/11/2003 | 80,420,000.00 |

| CANT. | RENTISTICO  | CONCEPTO    | TOTAL CONCEPTO                    |
|-------|-------------|-------------|-----------------------------------|
| 1     | 50005-01-01 | SOLICITUDES |                                   |
|       |             | 1           | TRAMITES DE SOL. DE PATENTE DE IN |
|       |             |             | 400,000.00                        |
|       |             | TOTAL :     | \$ 400,000.00                     |

**SON: CUATROCIENTOS MIL PESOS**

**RESPONSIBLE :**

RECIBO DE CABA APLICADO AL EXPEDIENTE No.

25

Traducción oficial del Inglés por Marlén Neira Castro, resolución 2117 del Ministerio de Justicia de Colombia

**APOSTILLA EN PODER DE REPRESENTACIÓN DE**

**ELI LILLY AND COMPANY** ✓

Bilingüe inglés- español otorgado en Indianapolis, Indiana, Estados Unidos el 17 de julio de 2003 y firmado por Peter G. Stringer, Director Ejecutivo y Patentes Internacionales de Ely Lilly & Company.

Todd Rokita                                      Secretario de Estado

Secretario de Estado de Indiana              Estado de Indiana /

**APOSTILLA**

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

1. País: Estados Unidos de América- Este documento Público
2. ha sido firmado por Catherine Michel
3. Quien ejerce funciones de Secretario de la Corte del Circuito en y para el condado Johnson
4. Lleva el sello del Secretario de la Corte del Circuito en y para el estado de Indiana

**CERTIFICADO**

5. En Indianapolis, Indiana
6. El 22 de julio de 2003
7. Por el Secretario de Estado de Indiana
8. No. A2003- 11279
9. Gran Sello del Estado de Indiana
10. Firma legible de Todd Rokita- Secretario de Estado de Indiana

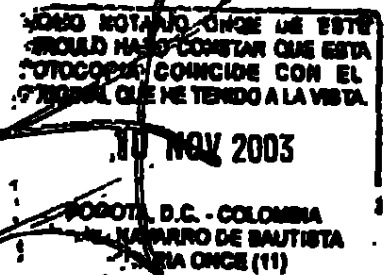
\* Vigente desde el 1 mayo de 2003, todas las apostillas del Secretario de Estado de Indiana tienen el sello impreso electrónicamente.

The Statehouse, Indianapolis, Indiana 46204, (317) 232-6531, fax (317) 233-3283

**CERTIFICACION NOTARIAL**

Bilingüe inglés- español, el 17 de julio de 2003 el suscrito notario Catherine Michel certifica que Peter G. Stringer, domiciliado en 7620 Castleton Farms, West Drive, Indianapolis, Indiana - 46256 Estados Unidos ejercía funciones de Director Ejecutivo y Patentes Internacionales de Ely Lilly & Company, con sede en Indianapolis, Indiana, Estados Unidos.

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



El otorgante fundamenta sus certificaciones en este documento: Delegación de Autoridad concerniente a Ciertas Materias de Patentes, suscrito el 20 de enero de 2003: conforme al poder otorgado al Asesor General de la Compañía por el Comité ejecutivo de la Junta Directiva de Eli Lilly and Company.

Firma del notario público Catherine Michel certifica

Sus funciones vencen el 21 de octubre de 2008 - residente en el condado Johnson

Sello de notario público de Indiana

--

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 28 de julio-2003.

Marlen Neira C

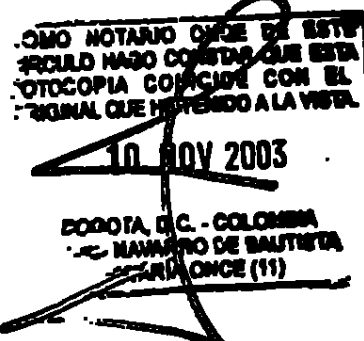
*Marlen Neira C*

MARLEN NEIRA CASTRO

Traductor e Intérprete Oficial

Inglés - Español - Inglés

Resolución No. 2117 del 7 Oct 1987



# OLARTE RAISBECK

OLARTE RAISBECK & FREEM, LTDA.  
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER - TORRE C  
CALLE 100 NO. 8A-85 PISO 10  
BOGOTA, COLOMBIA  
TELEPHONE: +57-1 638-8200  
Fax: +57-1 638-8201

www.olarteraisbeck.com

## Power of Attorney

The undersigned,

domiciled in

**ELI LILLY AND COMPANY**

Lilly Corporate Center, Indianapolis, Indiana 46285 US

by means of these presents hereby grants to **Carlos R. Olarte, J. Ian Ralsbeck and Ana Maria Frieler** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's Patents, Utility Models and Industrial Designs in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, appeals, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

## Poder

El suscrito,

domiciliado en

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

Signature/Firma

Date/Fecha: 17 July 2003

City/Country/Ciudad, País: Indianapolis, Indiana, United States of America

COMO NOTAR QUE DE ESTE  
SERIAL HAY CONSTANCIA QUE ESTA  
NOTA A COMIENZO CON EL  
SERIAL QUE HE TENIDO A LA VISTA

18 NOV 2003

BOGOTA, D.C. - COLOMBIA  
P. JUAN MANUEL DE BAUTISTA  
P. MARIA ONCE (11)



Todd Rokita  
Secretary of State

SECRETARY OF STATE  
STATE OF INDIANA

**APOSTILLE**

(Convention de la Haye du 5 Octobre 1961)

1. Country: United States of America
2. This public document has been signed by *Catherine Michel*
3. acting in the capacity of circuit court clerk in & for *Johnson County*
4. and bears the seal/stamp of circuit court clerk in & for the State of Indiana

Certified

5. at Indianapolis, Indiana
6. this *Twenty-second* day of *July*, 2003
7. by Secretary of State of Indiana
8. No. A2003- 11279
9. Seal/Stamp:

10. Signature:

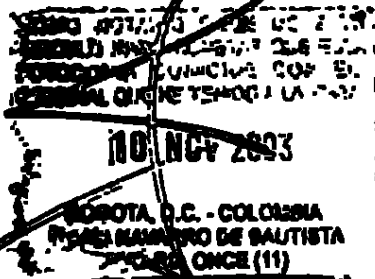


*Todd Rokita*  
Todd Rokita

Indiana Secretary of State

\*Effective May 1, 2003 all apostilles from the Indiana Secretary of State will have an electronically printed seal.

The Statehouse, Indianapolis, Indiana 46204, (317) 232-6531, Fax (317) 233-3283



# OLARTER AISBECK

OLARTE RABBECK & FREEM, LTDA.  
LEGAL & PROFESSIONAL SERVICES

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75 9

## Notarial Certification

On this date,  
17 July 2003

The undersigned Notary Public certifies:

1. That

of legal age and domiciled in

7620 Castleton Farms, West Drive,  
signed the foregoing document.

2. That the grantor has executed the foregoing  
document as Executive Director, International  
Patents  
of ELI LILLY AND COMPANY

3. That ELI LILLY AND COMPANY  
having its principal place of business located in  
Indianapolis, Indiana, United States of  
America

is duly incorporated, is currently in existence, and  
that the purposes for which the Power of Attorney is  
granted are within the scope of its corporate  
purposes.

4. That the grantor has the authority to execute the  
Power of Attorney and that his/her representation is  
legal.

5. The foundation for my certifications contained in  
points 2, 3 and 4 was the exhibition of the following  
authentic document(s):

Delegation of Authority Concerning Certain  
Patent Matters, executed January 20, 2003;  
pursuant to the authority granted to the  
General Counsel of the Company by the  
executive Committee of the Board of  
Directors of Eli Lilly and Company

NOTARY PUBLIC (Signature):



En esta fecha,

el Notario Público suscrito certifica:

1. Que

Peter G. Stringer  
mayor de edad y domiciliado  
Indianapolis, Indiana 46256 US  
suscribió el documento que antecede.

2. Que el otorgante ha suscrito el referido  
documento en su carácter de  
de

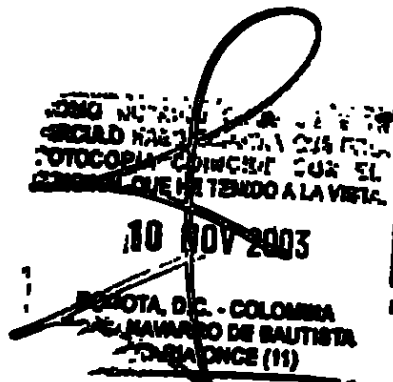
4. Que  
con sede principal ubicada en

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

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

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

A handwritten signature in cursive script, appearing to read "Catherine Michel".  
Catherine Michel  
My Commission Expires October 21, 2008  
Resident of Johnson County





Europäisches  
Patentamt

European  
Patent office

Office européen  
des brevets

Ersender / Sender / Expéditeur

Patent Division  
ELI LILLY AND COMPANY  
P. O. Box 6288  
Indianapolis, Indiana 46206-6288

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Fax (+31-70) 340-3018  
DE D-10938 Berlin  
☎ (+49-30) 25901-0  
Fax (+49-30) 25901-640

**BEGLEITSCHREIBEN FÜR NACHGEREICHTE UNTERLAGEN / LETTER ACCOMPANYING SUBSEQUENTLY  
FILED ITEMS / LETTRE D'ACCOMPAGNEMENT RELATIVE A DES PIECES PRODUITES POSTERIEUREMENT  
AU DEPOSIT**

Die untenbezeichnete(n) Unterlage(n) wird (werden) nachgereicht zu folgender Patentanmeldung/folgendem Patent:  
The item(s) indicated below is (are) subsequently filed for the following application/patent:  
La (Les) pièce(s) désignée(s) ci-après est (sont) produite(s) postérieurement au dépôt, pour la demande (le brevet) suivant(e) :

PCT/US02/15142

Aktenzeichen / File number / Numéro de dossier  
(Nur ein Aktenzeichen pro Formblatt)  
(Only one file number per form)  
(Un numéro de dossier par formulaire seulement)

X-14778

Zeichen des Anmelders oder Vertreters  
Applicant's or representative's reference  
Référence du demandeur ou du mandataire

| Bezeichnung der Unterlagen/ Description of items /<br>Description des pièces |                                                                                                     | Bemerkungen des EPA/Comments of<br>EPO / Remarques de l'OEB |
|------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|-------------------------------------------------------------|
| 1                                                                            | Demand 4 pages                                                                                      |                                                             |
| 2                                                                            | Fee Calculation Sheet: 1 page                                                                       |                                                             |
| 3                                                                            | Letter Requesting Non-Rationalized Exam 1 page                                                      |                                                             |
| 4                                                                            | pages                                                                                               |                                                             |
| 5                                                                            | Please confirm by fax to 317-378-3881 and charge the appropriate fee to<br>Deposit Account 28300288 |                                                             |

Datum / Date Unterschrift(en) des (der) Anmelders(s) oder Vertreters(s) / Signature(s) of applicant(s) or  
representative(s) / Signature(s) du (des) demandeur(s) ou du (des) mandataire(s)

19 Dec 2002

Lawrence T. WELCH, Agent for Applicant Eli Lilly and Company

Name des (der) Unterschrifteten bitte in Druckschrift wiederholen. Bei juristischen Personen bitte die Stellung des (der) Unterschrifteten innerhalb der  
Gesellschaft in Druckschrift angeben / Please print name under signature. In case of legal persons, the position of the signatory within the company  
should also be printed / Le ou les noms des signataires doivent être indiqués en caractères d'imprimerie. S'il s'agit d'une personne morale, la position  
occupée au sein de celle-ci par le ou les signataire(s) doit être indiquée en caractères d'imprimerie.

**EINGANGSBESTÄTIGUNG / ACKNOWLEDGEMENT OF RECEIPT / ACCUSE DE RECEPTION**

Der Eingang der oben angegebenen Unterlagen wird bestätigt, falls im Feld "Bemerkungen des EPA" nicht anderweitig vermerkt.  
Datum und Ort des Eingangs sind aus der Perforation dieser Eingangsbestätigung ersichtlich (M + Datum = Einreichungsort  
München; H + Datum = Einreichungsort Den Haag; Datum + B = Einreichungsort Berlin).

Unless otherwise indicated in the space "Comments of EPO", receipt of the items indicated is acknowledged. Date and place of  
receipt are shown by the perforation appearing on this receipt (M + date = Munich as place of receipt; H + date = The Hague as  
place of receipt; date + B = Berlin as place of receipt).

La réception des pièces susmentionnées est confirmée, sauf mention contraire à l'emplacement "Remarques de l'OEB". La date et  
le lieu de réception sont indiqués par la perforation du présent accusé de réception (M + date = pièces reçues à Munich ;  
H + date = pièces reçues à La Haye ; date + B = pièces reçues à Berlin).

Post- und Annahmestelle / Post Room and Filing Office / Service du courrier et bureau de réception

9 11

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below.

IPEA/ \_\_\_\_\_

# PCT

## CHAPTER II

### DEMAND

under Article 31 of the Patent Cooperation Treaty:  
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

|                                                                                                                                                                                                                                                                                                            |                                                                             |                                                                             |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| For International Preliminary Examining Authority use only                                                                                                                                                                                                                                                 |                                                                             |                                                                             |
| Identification of IPEA                                                                                                                                                                                                                                                                                     | Date of receipt of DEMAND                                                   |                                                                             |
| <b>Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION</b>                                                                                                                                                                                                                                           |                                                                             |                                                                             |
| Applicant's or agent's file reference<br><b>X-14776</b>                                                                                                                                                                                                                                                    |                                                                             |                                                                             |
| International application No.<br><b>PCT/US02/15142</b>                                                                                                                                                                                                                                                     | International filing date (day/month/year)<br><b>24 May 2002 (24.05.02)</b> | (Earliest) Priority date (day/month/year)<br><b>06 June 2001 (06.06.01)</b> |
| Title of invention<br><b>ANTITUMOR COMPOUNDS AND METHODS</b>                                                                                                                                                                                                                                               |                                                                             |                                                                             |
| <b>Box No. II APPLICANT(S)</b>                                                                                                                                                                                                                                                                             |                                                                             |                                                                             |
| Name and address: (Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country.)<br><b>ELI LILLY AND COMPANY</b><br><b>Lilly Corporate Center</b><br><b>Indianapolis, Indiana 46285</b><br><b>United States of America</b> |                                                                             | Telephone No.<br><b>(317) 277-3537</b>                                      |
|                                                                                                                                                                                                                                                                                                            |                                                                             | Facsimile No.<br><b>(317) 276-3861</b>                                      |
|                                                                                                                                                                                                                                                                                                            |                                                                             | Teleprinter No.                                                             |
| Applicant's registration No. with the Office                                                                                                                                                                                                                                                               |                                                                             |                                                                             |
| State (that is, country) of nationality:<br><b>US</b>                                                                                                                                                                                                                                                      | State (that is, country) of residence:<br><b>US</b>                         |                                                                             |
| Name and address: (Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country.)<br><b>CORBETT, Thomas Hughes</b><br><b>1259 Grayton</b><br><b>Grosse Pointe, Michigan 48230</b><br><b>United States of America</b>        |                                                                             |                                                                             |
| State (that is, country) of nationality:<br><b>US</b>                                                                                                                                                                                                                                                      | State (that is, country) of residence:<br><b>US</b>                         |                                                                             |
| Name and address: (Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country.)<br><b>GROSSMAN, Cora Sue</b><br><b>5838 Baron Court</b><br><b>Indianapolis, Indiana 46250</b><br><b>United States of America</b>          |                                                                             |                                                                             |
| State (that is, country) of nationality:<br><b>US</b>                                                                                                                                                                                                                                                      | State (that is, country) of residence:<br><b>US</b>                         |                                                                             |
| <input checked="" type="checkbox"/> Further applicants are indicated on a continuation sheet.                                                                                                                                                                                                              |                                                                             |                                                                             |

16 12

Sheet No. 2.

International application No.  
PCT/US02/15142

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)  
LOBB, Karen Lynn  
5625 East Lowell Avenue  
Indianapolis, Indiana 46219  
United States of America

State (that is, country) of nationality:  
US

State (that is, country) of residence:  
US

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)  
SHIH, Chuan  
12532 Pebblepointe Pass  
Carmel, Indiana 46033  
United States of America

State (that is, country) of nationality:  
US

State (that is, country) of residence:  
US

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)  
HIPSKIND, Phillip Arthur  
4255 South Cabin Court  
New Palestine, Indiana 46163  
United States of America

State (that is, country) of nationality:  
US

State (that is, country) of residence:  
US

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)  
LIN, Ho-Shen  
8128 Trevellian Way  
Indianapolis, Indiana 46217  
United States of America

State (that is, country) of nationality:  
US

State (that is, country) of residence:  
US

☐ Further applicants are indicated on another continuation sheet.

**Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE**The following person is ☒ agent ☐ common representativeand ☐ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☒ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*Ivan BURNSIDE  
ELI LILLY AND COMPANY  
P. O. Box 6288  
Indianapolis, Indiana 46206-6288  
United States of America

Telephone No.

+44-1276-48-3104

Facsimile No.

(317) 276-3861

Teleprinter No.

276051 ELI LILLY IND

Agent's registration No. with the Office

GA 307

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.**Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION**

Statement concerning amendments:\*

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filedthe description ☒ as originally filed☐ as amended under Article 34the claims ☒ as originally filed☐ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34the drawings ☐ as originally filed☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

\* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English☒ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☐ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.**Box No. V ELECTION OF STATES**The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

## Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- |                                                                          |   |        |
|--------------------------------------------------------------------------|---|--------|
| 1. translation of international application                              | : | sheets |
| 2. amendments under Article 34                                           | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19  | : | sheets |
| 5. letter                                                                | : | sheets |
| 6. other (specify)                                                       | : | sheets |

For International Preliminary  
Examining Authority use only

- | received                 | not received             |
|--------------------------|--------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> |

The demand is also accompanied by the item(s) marked below:

- |                                                                                          |                                                                        |
|------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| 1. <input checked="" type="checkbox"/> fee calculation sheet                             | 5. <input type="checkbox"/> statement explaining lack of signature     |
| 2. <input type="checkbox"/> original separate power of attorney                          | 6. <input type="checkbox"/> sequence listing in computer readable form |
| 3. <input type="checkbox"/> original general power of attorney                           | 7. <input checked="" type="checkbox"/> other (specify): Form 1038      |
| 4. <input type="checkbox"/> copy of general power of attorney; reference number, if any: |                                                                        |

## Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

ELI LILLY AND COMPANY

BY: 

Lawrence T. WELCH  
Attorney

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

15

CHAPTER II

PCT.

FEE CALCULATION SHEET

Annex to the Demand

|                                                                                                                                                                                                                                                   |                                                                                                 |          |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|----------|
| International application No. <b>PCT/US02/15142</b>                                                                                                                                                                                               | For International Preliminary Examining Authority use only                                      |          |
| Applicant's or agent's file reference <b>X-14776</b>                                                                                                                                                                                              | Date stamp of the IPEA                                                                          |          |
| Applicant<br><b>ELI LILLY AND COMPANY</b>                                                                                                                                                                                                         |                                                                                                 |          |
| <b>CALCULATION OF PRESCRIBED FEES</b>                                                                                                                                                                                                             |                                                                                                 |          |
| 1. Preliminary examination fee .....                                                                                                                                                                                                              | <b>1,530. EUR</b>                                                                               | <b>P</b> |
| 2. Handling fee ( <i>Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee</i> ) .....      | <b>159. EUR</b>                                                                                 | <b>H</b> |
| 3. Total of prescribed fees<br>Add the amounts entered at P and H<br>and enter total in the TOTAL box .....                                                                                                                                       | <b>1,689. EUR</b>                                                                               |          |
|                                                                                                                                                                                                                                                   | <b>TOTAL</b>                                                                                    |          |
| <b>MODE OF PAYMENT</b>                                                                                                                                                                                                                            |                                                                                                 |          |
| <input checked="" type="checkbox"/> authorization to charge deposit account with the IPEA (see below)                                                                                                                                             | <input type="checkbox"/> cash                                                                   |          |
| <input type="checkbox"/> cheque                                                                                                                                                                                                                   | <input type="checkbox"/> revenue stamps                                                         |          |
| <input type="checkbox"/> postal money order                                                                                                                                                                                                       | <input type="checkbox"/> coupons                                                                |          |
| <input type="checkbox"/> bank draft                                                                                                                                                                                                               | <input type="checkbox"/> other (specify):                                                       |          |
| <b>AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT</b><br>( <i>This mode of payment may not be available at all IPEAs</i> )                                                                                                                   |                                                                                                 |          |
| <input checked="" type="checkbox"/> Authorization to charge the total fees indicated above.                                                                                                                                                       | IPEA/ <b>EP</b>                                                                                 |          |
| <input checked="" type="checkbox"/> ( <i>This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit</i> ) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above. | Deposit Account No.: <b>28300299</b>                                                            |          |
|                                                                                                                                                                                                                                                   | Date: <b>19 Dec 2002</b>                                                                        |          |
|                                                                                                                                                                                                                                                   | Name: <b>Lawrence T. WELCH</b>                                                                  |          |
|                                                                                                                                                                                                                                                   | Signature:  |          |

VIA FACSIMILE

**IN THE EUROPEAN PATENT OFFICE ACTING AS PRELIMINARY EXAMINATION  
AUTHORITY UNDER THE PCT**

Applicant Docket: X-14776

International Application No.: PCT/US02/15142

Applicant(s): ELI LILLY AND COMPANY, CORBETT, Thomas, et.al.

International Filing Date: 24 May 2002 (24.05.2002)

Earliest Priority Date: 06 June 2001 (06.06.2001)

Invention: ANTITUMOR COMPOUNDS AND METHODS

**REQUEST FOR NON-RATIONALIZED EXAMINATION**

European Patent Office  
D-80298  
Munich, Germany

Attn: IPEA/EP

Dear Sir/Madam:

In connection with the Demand for Preliminary Examination for the above-identified PCT application, which is being filed concurrently herewith, applicant requests that this application receive a detailed, non-rationalized, examination under the new EPO preliminary examination guidelines. Applicant further requests the opportunity for an interview in the event that, after reviewing this application, the Examiner intends to issue an IPER which is not entirely positive.

Respectfully submitted,



Lawrence T. Welch  
Attorney  
Registration No.: 29,487

ELI LILLY AND COMPANY  
Lilly Corporate Center  
Indianapolis, Indiana 46285  
/9 December 2002

**ASSIGNMENT**

WHEREAS we, CHUAN SHIH of the City of Carmel, County of Hamilton, State of Indiana; CORA SUE GROSSMAN, of the City of Indianapolis, County of Marion, State of Indiana; KAREN LYNN LOBB of the City of Indianapolis, County of Marion, State of Indiana; HO-SHEN LIN, of the City of Indianapolis, County of Marion, State of Indiana and PHILIP ARTHUR HIPSKIND, of the City of New Palestine, County of Hancock, State of Indiana have made an invention which is the subject of an international application under the Patent Cooperation Treaty ("PCT") patent application entitled ANTITUMOR COMPOUNDS AND METHODS, containing 36 pages, and which is to be filed in the United States Patent and Trademark Office acting as PCT Receiving Office ("Application"); and we hereby authorize and direct our common representative to insert below the filing date and application number when they become known: PCT/US 02/15142, filed MAY 2002; and

WHEREAS ELI LILLY AND COMPANY, an Indiana corporation having its principal place of business at Lilly Corporate Center, Indianapolis, Indiana 46285, wishes to acquire the entire interest in all inventions disclosed in such Application;

NOW, THEREFORE, in consideration of good and valuable consideration, the receipt of which is hereby acknowledged, we hereby sell, assign, transfer and set over unto Eli Lilly and Company, its successors and assigns (collectively "Lilly") our entire right, title and interest in, to and under the Application, including all priority rights for other countries arising therefrom, all inventions therein disclosed, and any and all present or future patent applications to such inventions that may be filed in the United States or any foreign country, inclusive of, but not limited to, continuations, continuations-in-part, divisions, substitutions, reexaminations, reissues, international applications under the Patent Cooperation Treaty ("PCT"), United States provisional patent applications, certificates of addition, utility models, petty patents, as well as all other intellectual property related to the Application, inclusive of, but not limited to, supplementary protection certificates, copyrights, trademarks, and data package exclusivity rights; and any and all Letters Patent of the United States and of all foreign countries and all related patent term extensions which may be granted for Letters Patent with respect to the Application; all of the above to be held and enjoyed by Lilly for its own use and enjoyment to the full and of the term or terms for which such Letters Patent and related intellectual property rights may be granted, as fully and entirely as the same would have been held and enjoyed by us had this Assignment and sale to Lilly not been made.

For ourselves and for our heirs, successors and legal representatives, we covenant that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this Assignment.

For ourselves and for our heirs, successors and legal representatives, we further covenant and agree with Lilly that upon request we and they will, without further consideration than that now paid, but at the expense of Lilly: (i) execute original, provisional, substitute, continuation, divisional, continuation-in-part, reexamined, or reissued applications, amended specifications, or rightful declarations or oaths for such application; (ii) communicate to Lilly any facts known to us or them relating to such inventions or the history thereof; (iii) execute preliminary statements and testify in any

interference proceedings, litigation discovery proceedings and depositions, oppositions, cancellation proceedings, priority contests, public use proceedings, administrative agency proceedings, litigation and other court actions and the like; (iv) execute and deliver any application papers, affidavits, declarations, assignments, or other instruments; and (v) do all other acts which, in the opinion of counsel for Lilly, may be necessary or desirable to secure the grant of Letters Patent and related intellectual property to Lilly or its nominees, in the United States and in all other countries where Lilly may desire to have such inventions, or any of them, patented, with specifications and claims in such form as shall be approved by counsel for Lilly and to vest and confirm in Lilly or its nominees the full and complete legal and equitable title to all such Letters Patent and related intellectual property.

.. IN WITNESS WHEREOF, we have executed this assignment on the date indicated below.

May 6, 2002  
Date

Chuan Shih  
CHUAN SHIH

May 6, 2002  
Date

Cora Sue Grossman  
CORA SUE GROSSMAN

May 8, 2002  
Date

Karen Lynn Lobb  
KAREN LYNN LOBB

May 8, 2002  
Date

Ho-Shen Lin  
HO-SHEN LIN

May 8, 2002  
Date

Philip Arthur Hipkind  
PHILIP ARTHUR HIPSKIND

STATE OF INDIANA )  
COUNTY OF MARION ) ss:

Before me, a Notary Public for Johnson County, State of Indiana, personally appeared CHUAN SHIH, CORA SUE GROSSMAN, KAREN LYNN LOBB, HO-SHEN LIN and PHILIP ARTHUR HIPSKIND and acknowledged the execution of the foregoing instrument this 8 day of MAY, 2002.

Catherine Michel  
Notary Public

My commission expires:

CATHERINE MICHEL  
MY COMMISSION EXPIRES  
OCTOBER 21, 2008  
RESIDENT OF JOHNSON COUNTY

**ASSIGNMENT**

WHEREAS I, THOMAS HUGHES CORBETT, of the City of Grosse Pointe Park, State of Michigan, have made an invention which is the subject of an international application under the Patent Cooperation Treaty ("PCT") patent application entitled **ANTITUMOR COMPOUNDS AND METHODS**, containing 36 pages, and which is to be filed in the United States Patent and Trademark Office acting as PCT Receiving Office ("Application"); and I hereby authorize and direct our common representative to insert below the filing date and application number when they become known: PCT/US 12/15142 filed 24 MAY 2002; and

WHEREAS ELI LILLY AND COMPANY, an Indiana corporation having its principal place of business at Lilly Corporate Center, Indianapolis, Indiana 46285, wishes to acquire the entire interest in all inventions disclosed in such Application;

NOW, THEREFORE, in consideration of good and valuable consideration, the receipt of which is hereby acknowledged, I hereby sell, assign, transfer and set over unto Eli Lilly and Company, its successors and assigns (collectively "Lilly") my entire right, title and interest in, to and under the Application, including all priority rights for other countries arising therefrom, all inventions therein disclosed, and any and all present or future patent applications to such inventions that may be filed in the United States or any foreign country, inclusive of, but not limited to, continuations, continuations-in-part, divisions, substitutions, reexaminations, reissues, international applications under the Patent Cooperation Treaty ("PCT"), United States provisional patent applications, certificates of addition, utility models, petty patents, as well as all other intellectual property related to the Application, inclusive of, but not limited to, supplementary protection certificates, copyrights, trademarks, and data package exclusivity rights; and any and all Letters Patent of the United States and of all foreign countries and all related patent term extensions which may be granted for Letters Patent of the United States and of all foreign countries and all related patent term extensions which may be granted for Letters Patent with respect to the Application; all of the above to be held and enjoyed by Lilly for its own use and enjoyment to the full end of the term or terms for which such Letters Patent and related intellectual property rights may be granted, as fully and entirely as the same would have been held and enjoyed by me had this Assignment and sale to Lilly not been made.

For myself and for my heirs, successors and legal representatives, I covenant that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this Assignment.

For myself and for my heirs, successors and legal representatives, I further covenant and agree with Lilly that upon request I and they will, without further consideration than that now paid, but at the expense of Lilly: (i) execute original, provisional, substitute, continuation, divisional, continuation-in-part, reexamined, or reissued applications, amended specifications, or rightful declarations or oaths for

20

such application; (ii) communicate to Lilly any facts known to us or them relating to such inventions or the history thereof; (iii) execute preliminary statements and testify in any interference proceedings, litigation discovery proceedings and depositions, oppositions, cancellation proceedings, priority contests, public use proceedings, administrative agency proceedings, litigation and other court actions and the like; (iv) execute and deliver any application papers, affidavits, declarations, assignments, or other instruments; and (v) do all other acts which, in the opinion of counsel for Lilly, may be necessary or desirable to secure the grant of Letters Patent and related intellectual property to Lilly or its nominees, in the United States and in all other countries where Lilly may desire to have such inventions, or any of them, patented, with specifications and claims in such form as shall be approved by counsel for Lilly and to vest and confirm in Lilly or its nominees the full and complete legal and equitable title to all such Letters Patent and related intellectual property.

IN WITNESS WHEREOF I have executed this assignment on the date indicated below.

7<sup>th</sup> day, 5 month 2002  
Date

Thomas Hughes Corbett  
THOMAS HUGHES CORBETT

STATE OF MICHIGAN )  
COUNTY OF Wayne ) ss:

Before me, a Notary Public for Wayne County, State of MI, personally appeared THOMAS HUGHES CORBETT and acknowledged the execution of the foregoing instrument this 7<sup>th</sup> day of May, 2002.

Donald J. Gardner  
Notary Public

My commission expires:  
6-5-04

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
12 December 2002 (12.12.2002)

PCT

(10) International Publication Number  
WO 02/098848 A1

(51) International Patent Classification: C07C 311/51,  
321/28, C07D 213/34, 215/12, 307/38, 333/18, 521/00,  
A61K 31/18, 31/63, A61P 35/00

(21) International Application Number: PCT/US02/15142

(22) International Filing Date: 24 May 2002 (24.05.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data: 60/296,350 6 June 2001 (06.06.2001) US

(71) Applicant (for all designated States except US): ELI  
LILLY AND COMPANY [US/US]; Lilly Corporate  
Center, Indianapolis, IN 46285 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): CORBETT,  
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Arthur [US/US]; 4255 South Cabin Court, New Palestine,  
IN 46163 (US). LIN, Ho-Shen [US/US]; 8128 Trevellian  
Way, Indianapolis, IN 46217 (US).

(74) Agents: TUCKER, Tina, M. et al.; Eli Lilly And Com-  
pany, P. O. Box 6288, Indianapolis, IN 46206-6288 (US).

(81) Designated States (national): AE, AG, AL, AM, AT (uti-  
lity model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA,  
CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (uti-  
lity model), DE, DK (utility model), DK, DM, DZ, EC, EE

(utility model), EE, ES, FI (utility model), FI, GB, GD, GE,  
GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ,  
LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN,  
MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD,  
SE, SG, SI, SK (utility model), SK, SL, TJ, TM, TN, TR,  
TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

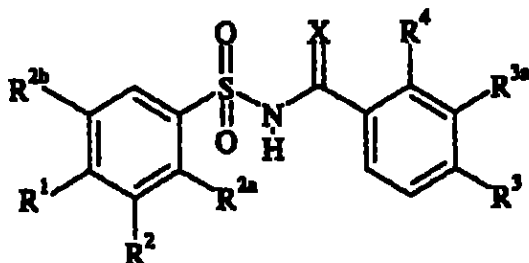
(84) Designated States (regional): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),  
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,  
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent  
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,  
NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted  
a patent (Rule 4.17(i)) for the following designations AE,  
AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA,  
CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES,  
FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,  
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG,  
MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU,  
SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG,  
UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS,  
MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent  
(AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent  
(AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU,  
MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI,  
CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- as to the applicant's entitlement to claim the priority of the  
earlier application (Rule 4.17(ii)) for the following desig-  
nations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY,  
BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC,  
EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN,  
IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV,  
MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,  
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR,  
TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent

[Continued on next page]

(54) Title: BENZOYLSULFONAMIDES AND SULFONYLBENZAMIDINES FOR USE AS ANTITUMOUR AGENTS



(I)

(57) Abstract: The present invention  
provides antitumor compounds of the  
formula(I), and antitumor methods.

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(GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),  
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB,  
GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ,  
CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,  
TG)

— before the expiration of the time limit for amending the  
claims and to be republished in the event of receipt of  
amendments

**Published:**  
— with international search report

For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

## BENZOYL SULFONAMIDES AND SULFONYLBENZAMIDINES FOR USE AS ANTITUMOUR AGENTS

## BACKGROUND OF THE INVENTION

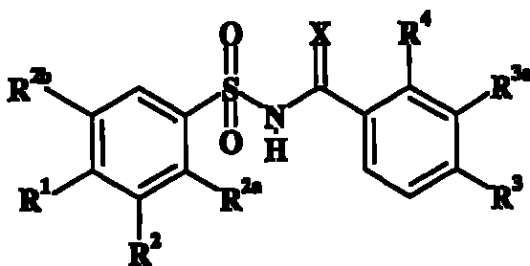
In recent years fundamental advances have been made in the development of chemical agents and regimens of therapy to combat neoplastic diseases. Despite these continuing advances, cancers continue to exact intolerable levels of human pain and suffering. The need for new and better methods of treating malignant neoplasms and leukemias continues to fuel efforts to create new classes of compounds, especially in the area of inoperable or metastatic solid tumors. The recent avalanche of information regarding the basic biological processes involved in neoplasms has led to a deeper understanding of the heterogeneity of tumors. It is because of this extreme heterogeneity among populations of neoplastic cells that new chemotherapeutic agents should have a wide spectrum of activity and an acceptable therapeutic index. In addition, such agents must be chemically stable and compatible with other agents. It is also important that any chemotherapeutic regimen be as convenient and painless as possible to the patient.

Chemotherapy and radiation are frequently used in the treatment of cancer and, although they often produce some response in the malignant disease, they are rarely curative. Most solid tumors increase in mass through the proliferation of malignant cells and stromal cells, including endothelial cells. In order for a tumor to grow larger than 2-3 millimeters in diameter, it must form a vasculature, a process known as angiogenesis. Suppression of tumor-induced angiogenesis by angiostatin and endostatin has been reported to result in antitumor activity (O'Reilly, *et al.*, *Cell*, 88, 277-285 (1997)). Because angiogenesis is a critical component of the mass expansion of most solid tumors, the development of new agents for the inhibition of this process represents a promising approach for antitumor therapy. This approach to antitumor therapy may lack the toxic side effects or drug resistance-inducing properties of conventional chemotherapy (Judah Folkman, Endogenous Inhibitors of Angiogenesis, The Harvey Lectures, Series 92, pages 65-82, Wiley-Liss Inc., (1998)).

The *N*-[benzoyl]-phenylsulfonamides are well known in the agricultural chemical arts as insecticides and herbicides (DE 2744137). The use of *N*-[benzoyl]-phenylsulfonamides as antitumor agents generally, or as inhibitors of angiogenesis specifically, were heretofore not appreciated.

## BRIEF SUMMARY OF THE INVENTION

The present invention provides a compound of Formula I:



I

5 where:

X is O or NH;

R<sup>1</sup> is hydrogen, halo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> alkylthio, CF<sub>3</sub>, OCF<sub>3</sub>, SCF<sub>3</sub>, (C<sub>1</sub>-C<sub>4</sub> alkoxy)carbonyl, nitro, azido, O(SO<sub>2</sub>)CH<sub>3</sub>, N(CH<sub>3</sub>)<sub>2</sub>, hydroxy, phenyl, substituted phenyl, pyridinyl, thienyl, furyl, quinolinyl, or triazolyl;

10 R<sup>2</sup> is hydrogen, halo, cyano, CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkyl, (C<sub>1</sub>-C<sub>4</sub> alkoxy)carbonyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, phenyl, or quinolinyl;

R<sup>2a</sup> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkoxy;

R<sup>2b</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl provided that at least one of R<sup>2a</sup> and R<sup>2b</sup> is hydrogen;

15 R<sup>3</sup> is hydrogen, halo, C<sub>1</sub>-C<sub>6</sub> alkyl, CF<sub>3</sub>, or nitro;

R<sup>3a</sup> is hydrogen, halo, or C<sub>1</sub>-C<sub>6</sub> alkyl provided that when R<sup>3a</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl, R<sup>3</sup> is hydrogen and R<sup>4</sup> is halo; and

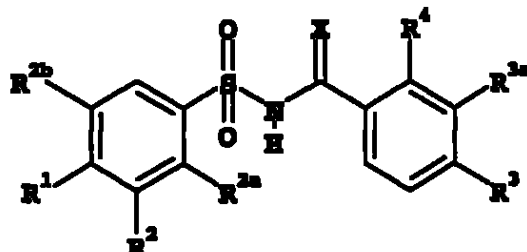
R<sup>4</sup> is halo, C<sub>1</sub>-C<sub>6</sub> alkyl, or CF<sub>3</sub> provided that only one of R<sup>3</sup> and R<sup>4</sup> may be C<sub>1</sub>-C<sub>6</sub> alkyl and provided that when R<sup>4</sup> is halo or C<sub>1</sub>-C<sub>6</sub> alkyl only one of R<sup>3</sup> and R<sup>3a</sup> is

20 hydrogen; or a pharmaceutically acceptable base addition salt thereof, provided that:

a) when R<sup>3</sup> and R<sup>4</sup> are both chloro and R<sup>2</sup> is hydrogen, R<sup>1</sup> is bromo, iodo, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> alkylthio, CF<sub>3</sub>, OCF<sub>3</sub>, nitro, azido, O(SO<sub>2</sub>)CH<sub>3</sub>, N(CH<sub>3</sub>)<sub>2</sub>, hydroxy, phenyl, substituted phenyl, pyridinyl, thienyl, furyl, or triazolyl;

25 b) when R<sup>3</sup> and R<sup>4</sup> are both chloro and R<sup>1</sup> is hydrogen, R<sup>2</sup> is bromo, fluoro, CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, phenyl, or quinolinyl.

The present invention further provides a method of treating susceptible neoplasms in a mammal comprising administering to a mammal in need of such treatment an oncolytically effective amount of a compound of Formula II:



II

where:

X is O or NH;

$R^1$  is hydrogen, halo,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_4$  alkoxy,  $C_1$ - $C_4$  alkylthio,  $CF_3$ ,  $OCF_3$ ,  $SCF_3$ , ( $C_1$ - $C_4$  alkoxy)carbonyl, nitro, azido,  $O(SO_2)CH_3$ ,  $N(CH_3)_2$ , hydroxy, phenyl, substituted phenyl, pyridinyl, thienyl, furyl, quinolinyl, or triazolyl;

$R^2$  is hydrogen, halo, cyano,  $CF_3$ ,  $C_1$ - $C_6$  alkyl, ( $C_1$ - $C_4$  alkoxy)carbonyl,  $C_1$ - $C_4$  alkoxy, phenyl, or quinolinyl;

$R^{2a}$  is hydrogen or  $C_1$ - $C_4$  alkoxy;

$R^{2b}$  is hydrogen or  $C_1$ - $C_6$  alkyl provided that at least one of  $R^{2a}$  and  $R^{2b}$  is hydrogen;

$R^3$  is hydrogen, halo,  $C_1$ - $C_6$  alkyl,  $CF_3$ , or nitro;

$R^{3a}$  is hydrogen, halo, or  $C_1$ - $C_6$  alkyl provided that when  $R^{3a}$  is  $C_1$ - $C_6$  alkyl,  $R^3$  is hydrogen and  $R^4$  is halo; and

$R^4$  is halo,  $C_1$ - $C_6$  alkyl, or  $CF_3$  provided that only one of  $R^3$  and  $R^4$  may be  $C_1$ - $C_6$  alkyl and provided that when  $R^4$  is halo or  $C_1$ - $C_6$  alkyl only one of  $R^3$  and  $R^{3a}$  is hydrogen; or a pharmaceutically acceptable base addition salt thereof.

The present invention also provides a method of suppressing tumor angiogenesis in a mammal comprising administering to a mammal in need of such treatment an angiogenesis suppressing amount of a compound of Formula II or a pharmaceutically acceptable base addition salt thereof.

The present invention also provides a pharmaceutical formulation comprising a compound of Formula II or a pharmaceutically acceptable base addition salt thereof, in combination with a pharmaceutically acceptable carrier, diluent or excipient.

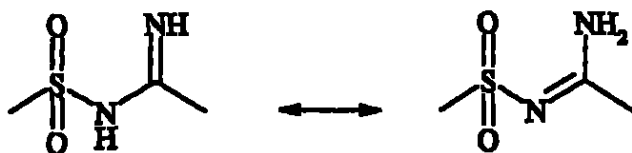
This invention also provides the use of a compound of Formula II for the manufacture of a medicament for the treatment of susceptible neoplasms. Additionally, this invention provides a pharmaceutical formulation adapted for the treatment of susceptible neoplasms containing a compound of Formula II. Furthermore, this invention includes a method for the treatment of susceptible neoplasms that comprises administering an effective amount of a compound of Formula II.

### DETAILED DESCRIPTION OF THE INVENTION

The general chemical terms used in the formulae above have their usual meanings.

For example, the term "C<sub>1</sub>-C<sub>6</sub> alkyl" includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, and hexyl moieties. The term "C<sub>1</sub>-C<sub>4</sub> alkyl" is included within the meaning of C<sub>1</sub>-C<sub>6</sub> alkyl and is taken to mean methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, and *tert*-butyl. The term "C<sub>1</sub>-C<sub>4</sub> alkoxy" is taken to mean a C<sub>1</sub>-C<sub>4</sub> alkyl group linked to the parent molecule through an oxygen atom, and includes the groups methoxy, ethoxy, and isopropoxy. Likewise, the term "C<sub>1</sub>-C<sub>4</sub> alkylthio" is taken to mean a C<sub>1</sub>-C<sub>4</sub> alkyl group linked to the parent molecule through a sulfur atom, and includes methylthio, ethylthio, and isobutylthio. The term "halo" is taken to mean chloro, fluoro, bromo, and iodo. The term "substituted phenyl" means a mono-substituted phenyl wherein the substitutions are selected from the group consisting of C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> alkylthio, C<sub>1</sub>-C<sub>4</sub> acyl, trifluoromethyl, and halo. The term "acyl" refers to an organic acid group in which the OH of the carboxy group is replaced by some other substituent (RCO-).

When X=NH, the molecule can exist in two tautomeric forms,



The present invention contemplates both of these forms.

While all of the compounds of Formula II are useful antitumor agents, certain classes of compounds are preferred. The following paragraphs describe such preferred classes.

a) R<sup>1</sup> is hydrogen and R<sup>2</sup> is bromo;

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- b)  $R^1$  is fluoro and  $R^2$  is chloro;  
c)  $R^1$  is fluoro;  
d)  $R^1$  is chloro;  
e)  $R^1$  is methyl;  
5 f)  $R^1$  is methylthio;  
g)  $R^2$  is hydrogen;  
h)  $R^3$  is chloro, bromo, or  $CF_3$ ;  
i)  $R^3$  is chloro;  
j)  $R^3$  is bromo;  
10 k)  $R^3$  is  $CF_3$ ;  
l)  $R^{3a}$  is hydrogen;  
m)  $R^4$  is chloro, bromo, methyl, or  $CF_3$ ;  
n)  $R^4$  is chloro;  
o)  $R^4$  is bromo;  
15 p)  $R^4$  is methyl;  
q)  $R^4$  is  $CF_3$ ;  
r)  $R^3$  and  $R^4$  are both chloro;  
s)  $R^3$  and  $R^4$  are both  $CF_3$ ;  
t)  $R^3$  is bromo and  $R^4$  is chloro;  
20 u)  $R^{3a}$  is hydrogen and  $R^3$  and  $R^4$  are other than hydrogen;  
v) X is O;  
w) The compound of Formula II wherein the compound is a pharmaceutically acceptable base addition salt;  
x) The compound of Formula II wherein the compound is a sodium salt;  
25 y)  $R^1$ ,  $R^{2a}$ , and  $R^{2b}$  are hydrogen and  $R^2$  is selected from the group consisting of halo,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy, cyano, trifluoromethyl, and quinolinyl;  
z)  $R^2$  and  $R^{2b}$  are hydrogen,  $R^1$  is halo or  $C_1$ - $C_4$  alkyl, and  $R^{2a}$  is  $C_1$ - $C_4$  alkyl or  $C_1$ - $C_4$  alkoxy; or  
aa)  $R^{2a}$  is hydrogen,  $R^1$  is  $C_1$ - $C_4$  alkoxy, and  $R^2$  and  $R^{2b}$  are  $C_1$ - $C_4$  alkyl.  
30 Additionally, the following classes are especially preferred.  
a)  $R^2$ ,  $R^{2a}$ , and  $R^{2b}$  are hydrogen and  $R^1$  is selected from the group consisting of hydrogen, halo,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_4$  alkoxy,  $C_1$ - $C_4$  alkylthio,  $CF_3$ ,  $OCF_3$ ,  $SCF_3$ ,

- (C<sub>1</sub>-C<sub>4</sub> alkoxy)carbonyl, nitro, azido, O(SO<sub>2</sub>)CH<sub>3</sub>, N(CH<sub>3</sub>)<sub>2</sub>, hydroxy, phenyl, substituted phenyl, pyridinyl, thienyl, furyl, quinoliny, and triazolyl; or
- b) R<sup>2a</sup> and R<sup>2b</sup> are hydrogen and R<sup>1</sup> is selection from the group consisting of halo and C<sub>1</sub>-C<sub>4</sub> alkyl, and R<sup>2</sup> is selected from the group consisting of halo, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>1</sub>-C<sub>4</sub> alkoxy carbonyl.

It will be understood that the above preferred and especially preferred classes may be combined to form additional preferred and especially preferred classes.

The compounds of Formula II are antineoplastic agents. Thus, the present invention also provides a method of treating a susceptible neoplasm in a mammal that comprises administering to a mammal in need of said treatment an oncolytically effective amount of a compound of Formula II. The present compounds are believed to be useful in treating carcinomas such as neoplasms of the central nervous system: glioblastoma multiforme, astrocytoma, oligodendroglial tumors, ependymal and choroid plexus tumors, pineal tumors, neuronal tumors, medulloblastoma, schwannoma, meningioma, meningeal sarcoma; neoplasms of the eye: basal cell carcinoma, squamous cell carcinoma, melanoma, rhabdomyosarcoma, retinoblastoma; neoplasms of the endocrine glands: pituitary neoplasms, neoplasms of the thyroid, neoplasms of the adrenal cortex, neoplasms of the neuroendocrine system, neoplasms of the gastroenteropancreatic endocrine system, neoplasms of the gonads; neoplasms of the head and neck: head and neck cancer, oral cavity, pharynx, larynx, odontogenic tumors; neoplasms of the thorax: large cell lung carcinoma, small cell lung carcinoma, non-small cell lung carcinoma, malignant mesothelioma, thymomas, primary germ cell tumors of the thorax; neoplasms of the alimentary canal: neoplasms of the esophagus, neoplasms of the stomach, neoplasms of the liver, neoplasms of the gallbladder, neoplasms of the exocrine pancreas, neoplasms of the small intestine, vermiform appendix and peritoneum, adenocarcinoma of the colon and rectum, neoplasms of the anus; neoplasms of the genitourinary tract: renal cell carcinoma, neoplasms of the renal pelvis and ureter, neoplasms of the bladder, neoplasms of the urethra, neoplasms of the prostate, neoplasms of the penis, neoplasms of the testis; neoplasms of the female reproductive organs: neoplasms of the vulva and vagina, neoplasms of the cervix, adenocarcinoma of the uterine corpus, ovarian cancer, gynecologic sarcomas; neoplasms of the breast; neoplasms of the skin: basal cell carcinoma, squamous cell carcinoma, dermatofibrosarcoma, Merkel cell tumor, malignant

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melanoma; neoplasms of the bone and soft tissue: osteogenic sarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, primitive neuroectodermal tumor, angiosarcoma; neoplasms of the hematopoietic system: myelodysplastic syndromes, acute myeloid leukemia, chronic myeloid leukemia, acute lymphocytic leukemia, HTLV-1 and  
5 T-cell leukemia/lymphoma, chronic lymphocytic leukemia, hairy cell leukemia, Hodgkin's disease, non-Hodgkin's lymphomas, mast cell leukemia; and neoplasms of children: acute lymphoblastic leukemia, acute myelocytic leukemias, neuroblastoma, bone tumors, rhabdomyosarcoma, lymphomas, renal tumors. In particular, the present compounds are believed to be useful in treating solid tumors, especially tumors of the  
10 colon and rectum. It is preferred that the mammal to be treated by the administration of the compounds of Formula II is human.

The compounds of the present invention are acidic in nature and accordingly may react with any of a number of inorganic and organic bases, including amines and quaternary ammonium bases, to form pharmaceutically acceptable base addition salts. It  
15 is preferable to convert the compounds of Formula II to their pharmaceutically acceptable base addition salts for ease of administration when aqueous solutions of the subject compound are required. The Formula II compounds can react with basic materials such as alkali metal- or alkaline earth metal hydroxides, carbonates, and bicarbonates including, without limitation, sodium hydroxide, sodium carbonate, potassium hydroxide, calcium  
20 hydroxide, lithium hydroxide, etc. to form pharmaceutically acceptable salts such as the corresponding sodium, potassium, lithium, or calcium salt. The sodium and potassium salts are especially preferred.

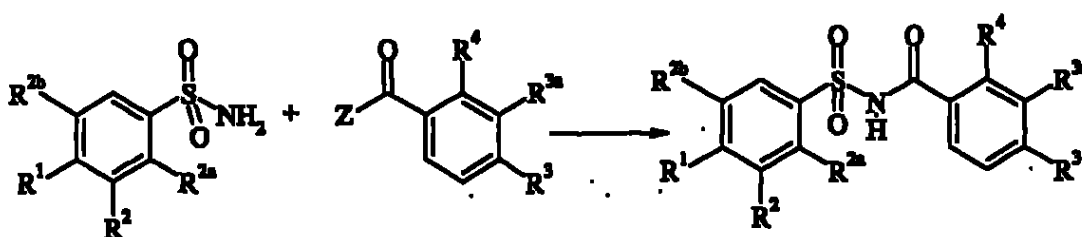
Examples of amines suitable for forming salts are: primary, secondary and tertiary aliphatic and aromatic amines, such as methylamine, ethylamine, propylamine,  
25 i-propylamine, the four isomeric butylamines, dimethylamine, diethylamine, diethanolamine, dipropylamine, diisopropylamine, di-n-butylamine, pyrrolidine, piperidine, morpholine, trimethylamine, triethylamine, tripropylamine, quinuclidine, pyridine, quinoline and isoquinoline, especially ethyl-, propyl-, diethyl- or triethylamine, but particularly isopropylamine and diethanolamine.

30 Examples of quaternary ammonium bases are in general the cations of haloammonium salts, for example the tetramethylammonium cation, the trimethylbenzylammonium cation, the triethylbenzylammonium cation, the

tetraethylammonium cation or the trimethylethylammonium cation, but also the ammonium cation.

The compounds of the present invention may be prepared by methods well known to one of ordinary skill in the art. Generally, the *N*-[benzoyl]-phenylsulfonamides of Formula II are prepared by coupling an appropriately substituted phenylsulfonamide with an appropriately substituted benzoic acid or benzoic acid derivative as illustrated in the following scheme. The variables  $R^1$ ,  $R^2$ ,  $R^{2a}$ ,  $R^{2b}$ ,  $R^3$ ,  $R^{3a}$ , and  $R^4$  are as previously defined and Z is OH, Cl, Br, methanesulfonyloxy, or trifluoromethanesulfonyloxy.

#### 10 Synthetic Scheme I



When Z is OH, the corresponding benzoic acid is coupled to the phenylsulfonamide under standard peptide coupling conditions well known to the skilled artisan. Specifically, the phenylsulfonamide and the benzoic acid are coupled in the presence of a peptide coupling reagent, optionally in the presence of a catalyst. Suitable peptide coupling reagents include *N,N'*-carbonyldiimidazole (CDI), *N,N'*-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), and 1-(3-(1-pyrrolidinyl)propyl)-3-ethylcarbodiimide (PEPC). Polymer supported forms of EDC (*Tetrahedron Letters*, 34(48), 7685 (1993)) and PEPC (U.S. Patent #5,792,763) have been described, and are very useful for the preparation of the compounds of the present invention. Suitable catalysts for the coupling reaction include *N,N*-dimethyl-4-aminopyridine (DMAP). All of the reagents are combined in a suitable solvent, typically dichloromethane, chloroform, tetrahydrofuran, dioxane, or diethyl ether and are stirred for from 1 to 72 hours at a temperature of from ambient to about the reflux temperature of the solvent. The desired product may be isolated by standard extractive and crystallization techniques, and purified by chromatography or

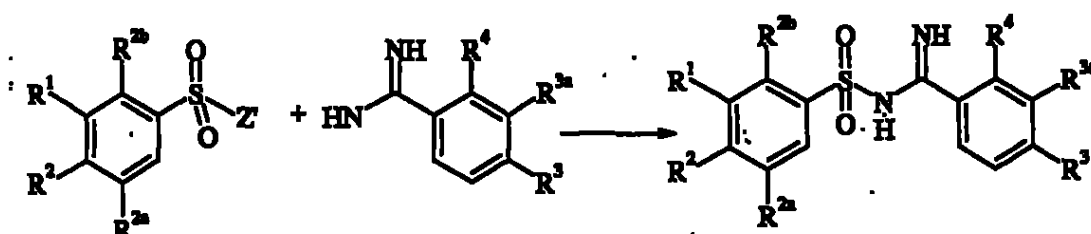
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crystallization as necessary or desired. Where polymer-bound reagents are employed, they may be conveniently removed from the reaction mixture by filtration.

Alternatively, the sulfonamide may be reacted with a benzoic acid derivative, such as compounds where Z is chloro, bromo, methanesulfonyloxy, or trifluoromethanesulfonyloxy, in the presence of an acid scavenger such as pyridine, triethylamine, or a basic resin, optionally in the presence of a catalyst. The reagents are combined, and products isolated, essentially as described *supra*.

One skilled in the art would appreciate that compounds of Formula II where X is NH may be prepared as illustrated in Scheme II where R<sup>1</sup>, R<sup>2</sup>, R<sup>2a</sup>, R<sup>2b</sup>, R<sup>3</sup>, R<sup>3a</sup>, and R<sup>4</sup> are as previously defined.

#### Synthetic Scheme II



An appropriately substituted benzamidine is reacted with sulfonyl derivatives, such as compounds where Z' is chloro, bromo, methanesulfonyloxy, or trifluoromethanesulfonyloxy, in the presence of an acid scavenger such as pyridine, triethylamine, or a basic resin, optionally in the presence of a catalyst. The reagents are combined, and products isolated, essentially as described *supra*.

The requisite benzoic acids, benzoic acid derivatives, benzamidines, sulfonyl derivatives and sulfonamides are either commercially available or may be prepared by methods well known to the skilled artisan.

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## PREPARATION 1

## 2,4-dibromobenzonitrile

- A solution of copper(I) cyanide (2.32 g, 25.9 mmol) in anhydrous dimethylsulfoxide (50 mL) is stirred at 60°C, and to this solution is added *tert*-butylnitrite (7.1 mL, 59.7 mmol) all at once. A solution of 2,4-dibromoaniline (5.0 g, 19.9 mmol) in anhydrous dimethylsulfoxide (30 mL) is added dropwise, via cannula, to the mixture. After the addition is complete the reaction mixture is stirred for 1 hr, cooled to 45°C, and then treated slowly with 5N HCl (50 mL). Five minutes later, the reaction mixture is cooled to ambient temperature and extracted with 1:1 ethyl acetate:hexane (2 x 300 mL).
- The combined organic layers are washed with water (100 mL) and saturated aqueous sodium chloride (100 mL), dried, concentrated under reduced pressure and the residue subjected to silica gel chromatography, eluting with hexane containing from 0-5% ethyl acetate. Fractions containing product are combined and concentrated under reduced pressure to provide the title compound (1.61 g, 31% yield).
- mp = 76-78°C
- FDMS:  $m/e = 261$  ( $M^+$ ).

## PREPARATION 2

## 2,4-dibromobenzoic acid

- A stirred suspension of 2,4-dibromobenzonitrile (1.57 g, 6.0 mmol) in sulfuric acid (6 M, 150 mL) is heated to reflux for 3 days. The reaction mixture is cooled down to ambient temperature and then extracted with ethyl acetate (2 x 75 mL). The combined organic layers are washed with water (100 mL) and saturated aqueous sodium chloride (50 mL), dried, concentrated, then subjected to silica gel chromatography, eluting with chloroform containing 0.5% methanol and 0.1% acetic acid. Fractions containing product are combined and concentrated under reduced pressure to provide the title compound (0.81 g, 48% yield).
- mp = 171-172°C
- ESIMS:  $m/e = 279$  ( $M^+-1$ ).

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## PREPARATION 3

## 2-bromo-4-chlorobenzoic acid

- A solution of sodium nitrite (2.21 g) in water (15 mL) is added dropwise to a stirred ice-cooled mixture of 2-amino-4-chlorobenzoic acid (5.00 g, 29.1 mmol) and 48% hydrobromic acid (150 mL) in water (150 mL). The reaction mixture is stirred for 2 hr at 0°C and is then treated dropwise with a solution of copper(II) bromide (7.81 g) in water (20 mL). Upon the completion of addition, the reaction mixture is allowed to warm to ambient temperature and is stirred overnight. The reaction mixture is then extracted with 3:1 ethyl acetate:hexane (2 x 400 mL). The combined organic layers are washed with saturated aqueous sodium chloride (200 mL), dried, concentrated under reduced pressure, and the residue subjected to silica gel chromatography, eluting with chloroform containing 1% methanol and 0.5% acetic acid. Fractions containing product are combined and concentrated under reduced pressure to provide the title compound (4.04 g, 59% yield).
- mp = 154-155°C
- ESIMS:  $m/e = 233, 235 (M^+-1)$ .

## PREPARATION 4

## 4-sulfamoylbenzoic acid methyl ester

- 4-Carboxyphenylsulfonamide (2.00 g, 9.9 mmol) is suspended in 3:1 chloroform:methanol (200 mL). (Trimethylsilyl)-diazomethane is added as a 2.0 M solution in Hexanes (7.4 mL, 14.8 mmol) at ambient temperature and stirred for 5 min. The solution is concentrated *in vacuo*, and the crude is chromatographed on silica gel, 0.5% MeOH/0.1% AcOH in CH<sub>2</sub>Cl<sub>2</sub>. The product is a white solid, 2.11 g, 98% yield.
- mp 180°C
- ESIMS  $m/e$  214 ( $M^+-1$ ).

## PREPARATION 5

## 3,4-dibromophenylsulfonamide

- 3,4-Dibromo-phenylsulfonyl chloride (20 mmol; Aldrich) is suspended in 40 mL of 30% aqueous NH<sub>4</sub>OH, and the mixture is stirred. Acetone is added slowly, portionwise, to form a homogeneous reaction mixture (5-10 mL). This addition is

- exothermic, with vigorous bubbling. The reaction is stirred at room temperature and monitored by ESI-MS. The mixture is concentrated by rotary evaporation to remove the acetone, and a solid formed. The solid is collected by suction filtration, washed with water, and allowed to air dry. The material is used as obtained, without further
- 5 purification. ESIMS: 312, 314, 316 ( $M^+ - 1$ ); mp 169-171°C; lit mp 175-176°C Huntress, E. H.; Carten, F. H. *J. Am. Chem. Soc.* 1940, 62, 511-514.

The compounds of PREPARATION 6-15 are prepared essentially as described in the procedure of PREPARATION 5.

| PREP.<br># | Product                             | Mass Spectral Data<br>(m/e)                                                                                                                                                                      |
|------------|-------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 6          | 3-chloro-4-fluoro-phenylsulfonamide | ESIMS: 210 ( $M^+ - 1$ )                                                                                                                                                                         |
| 7          | 4-iodo-phenylsulfonamide            | ESIMS: 284 ( $M^+ - 1$ )                                                                                                                                                                         |
| 8          | 3,4-dichlorophenylsulfonamide       | ESIMS $m/e$ 224( $M^+ - 1$ ; $^{35}\text{Cl}$ , $^{35}\text{Cl}$ )<br>and 226 ( $M^+ - 1$ ; $^{35}\text{Cl}$ , $^{37}\text{Cl}$ ) and 228<br>( $M^+ - 1$ ; $^{37}\text{Cl}$ , $^{37}\text{Cl}$ ) |
| 9          | 4-isopropylphenylsulfonamide        | ESIMS $m/e$ 198( $M^+ - 1$ )                                                                                                                                                                     |
| 10         | 4-ethylphenylsulfonamide            | ESIMS $m/e$ 184( $M^+ - 1$ )                                                                                                                                                                     |
| 11         | 3-trifluoromethyl-phenylsulfonamide | ESIMS: 224 ( $M^+ - 1$ )                                                                                                                                                                         |
| 12         | 3-fluoro-phenylsulfonamide          | ESIMS: 174 ( $M^+ - 1$ )                                                                                                                                                                         |
| 13         | toluene-3-sulfonamide               | ESIMS: 170 ( $M^+ - 1$ )                                                                                                                                                                         |
| 14         | 3-bromophenylsulfonamide            | ESIMS: 237 ( $M^+ - 1$ )                                                                                                                                                                         |
| 15         | 4-bromophenylsulfonamide            | ESIMS: 237 ( $M^+ - 1$ )                                                                                                                                                                         |

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## PREPARATION 16

## 2-chloro-4-methylbenzoic acid

- To 4-bromo-3-chlorotoluene (4.97 g, 24.2 mmol) in DMF (25 mL) is added  $\text{Pd}(\text{OAc})_2$  (0.54 g, 2.42 mmol), 1,3-bis(diphenylphosphino)propane (0.998 g, 2.42 mmol), triethylamine (12.5 mL) and methanol (12.5 mL). The reaction vessel is
- 15 evacuated and purged three times with carbon monoxide gas. A balloon filled with carbon monoxide gas is used to maintain the carbon monoxide atmosphere. The reaction mixture is heated at 80°C for 8 hr. After cooling  $\text{H}_2\text{O}$  (50 mL) is added. The mixture is extracted with hexanes (2 x 50 mL). The combined organic layers are dried over  $\text{Na}_2\text{SO}_4$ ,

filtered, concentrated and chromatographed with 0-3% EtOAc in hexanes. 1.24 g (28%) of methyl 2-chloro-4-methylbenzoate is isolated as a colorless oil. EIMS  $m/e$  184 ( $M^+$ ;  $^{35}\text{Cl}$ ) and 186 ( $M^+$ ;  $^{37}\text{Cl}$ ).

To methyl 2-chloro-4-methylbenzoate (1.00 g, 5.42 mmol) in THF (10 mL) MeOH (5 mL) and  $\text{H}_2\text{O}$  (2.5 mL) is added 2N LiOH (8.12 mL, 16.2 mmol). The reaction mixture is heated at 50 °C for 2.5 hr, cooled to room temperature, then quenched with 5N HCl (3.24 mL). The mixture is concentrated to remove the THF and MeOH. A white precipitate is formed and is filtered. After drying, 0.922 g (100%) of 2-chloro-4-methylbenzoic acid is isolated. ESIMS  $m/e$  169 ( $M^-$ ;  $^{35}\text{Cl}$ ) and 171 ( $M^-$ ;  $^{37}\text{Cl}$ ).

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## PREPARATION 17

4-(*tert*-butyldimethylsilyloxy)phenylsulfonamide

4-Hydroxyphenylsulfonamide (3.46 g, 20 mmol) is dissolved in DMF (40 mL) and treated with *tert*-butyl-dimethylsilylchloride (3.31 g, 22.0 mmol) and imidazole (1.50 g, 22.0 mmol) at room temperature. After 20 hr, the reaction mixture is diluted with EtOAc (100 mL) and washed with 1.0 N HCl (2 x 50 mL). The organic phase is dried ( $\text{MgSO}_4$ ), filtered, and concentrated to yield an oil. The crude oil is purified by Biotage column chromatography (40M  $\text{SiO}_2$  column, eluted at 75 mL/min with 1:1 hexanes:EtOAc). A white solid is obtained (4.24 g, 15.4 mmol, 77%). ESI-MS  $m/e$  288.1 ( $M^+ + \text{H}$ ); mp 117-118°C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.78 (d, 2 H), 6.89 (d, 2 H), 4.86 (br s, 2 H), 0.97 (s, 9 H), 0.20 (s, 6 H).

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## PREPARATION 18

*N*-(2,4-dichlorobenzoyl)-4-(*tert*-butyldimethylsilyloxy)-phenylsulfonamide

To a stirring solution of 2,4-dichlorobenzoic acid (1.25 eq) in dry dichloromethane (10 mL/mmol), 4-(*tert*-butyl-dimethylsilyloxy)phenylsulfonamide (1.0 eq) is added in one portion followed by EDC (1.25-1.5 eq) and finally, *N,N*-dimethyl-4-aminopyridine (1.2 equiv). The mixture is vigorously stirred under nitrogen for 16 hr, concentrated under reduced pressure, and the residue partitioned between ethyl acetate and water. The organic layer is washed with 1N hydrochloric acid (4 times, 20 mL/mmol), then the combined aqueous phases extracted with ethyl acetate (twice, 20 mL/mmol). The combined organic layers are finally washed with water and saturated aqueous sodium

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chloride, dried over sodium sulfate and concentrated under reduced pressure. The residue is purified by silica gel chromatography or crystallization if necessary or desired. ESI-MS  $m/e$  458.0 ( $M^+ - H$ ); 460.0 ( $M^+ + H$ ).

- 5 The compounds of PREPARATION 19-21 are prepared essentially as described in the procedure of PREPARATION 18.

| PREP.<br># | Product                                                     | Mass Spectral Data<br>( $m/e$ )     |
|------------|-------------------------------------------------------------|-------------------------------------|
| 19         | 3-Bromo- <i>N</i> -(2,4-dichloro-benzoyl)-phenylsulfonamide | ESI-MS $m/e$<br>409.0( $M^+ - H$ )  |
| 20         | 4-Iodo- <i>N</i> -(2,4-dichloro-benzoyl)-phenylsulfonamide  | ESI-MS $m/e$<br>455.08( $M^+ - H$ ) |
| 21         | 4-Bromo- <i>N</i> -(2,4-dichloro-benzoyl)-phenylsulfonamide | ESI-MS $m/e$<br>409.0( $M^+ - H$ )  |

#### General Coupling Procedure

- To a stirring solution of the benzoic acid (1.25 eq) in dry dichloromethane (10 mL/mmol), the phenylsulfonamide (1.0 eq) is added in one portion followed by EDC (1.25-1.5 eq) and finally, *N,N*-[dimethyl]-4-aminopyridine (1.2 equiv). The mixture is vigorously stirred under nitrogen for 16 hr, concentrated under reduced pressure, and the residue partitioned between ethyl acetate and water. The organic layer is washed with 1N hydrochloric acid (4 times, 20 mL/mmol), then the combined aqueous phases extracted with ethyl acetate (twice, 20 mL/mmol). The combined organic layers are finally washed with water and saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure. The residue may be subjected to silica gel chromatography or crystallization if necessary or desired.

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The compounds of EXAMPLES 1-86 are prepared essentially as described in this general procedure.

| EXAMPLE # | Product                                                            | Mass Spectral Data (m/e)                                                      |
|-----------|--------------------------------------------------------------------|-------------------------------------------------------------------------------|
| 1         | <i>N</i> -[2,4-dichlorobenzoyl]-3-bromophenylsulfonamide           | MS(ES): 408 [M-H] <sup>-</sup>                                                |
| 2         | <i>N</i> -[2,4-dichlorobenzoyl]-3-chlorophenylsulfonamide          | MS(ES): 362 [M-H] <sup>-</sup>                                                |
| 3         | <i>N</i> -[2,4-dichlorobenzoyl]-4-methoxyphenylsulfonamide         | MS(ES): 360 [M-H] <sup>-</sup>                                                |
| 4         | <i>N</i> -[2,4-dibromobenzoyl]-4-methylphenylsulfonamide           | ESIMS: 434 (M <sup>+</sup> +1)                                                |
| 5         | <i>N</i> -[2,4-dibromobenzoyl]-4-tert-butylphenylsulfonamide       | ESIMS: 476 (M <sup>+</sup> +1)                                                |
| 6         | <i>N</i> -[2,4-dibromobenzoyl]-4-chlorophenylsulfonamide           | ESIMS: 454,456(M <sup>+</sup> +1)                                             |
| 7         | <i>N</i> -[2-bromo-4-chlorobenzoyl]-4-methylphenylsulfonamide      | ESIMS: 388,390(M <sup>+</sup> +1)                                             |
| 8         | <i>N</i> -[2-bromo-4-chlorobenzoyl]-4-chlorophenylsulfonamide      | ESIMS: 408,410(M <sup>+</sup> +1)                                             |
| 9         | <i>N</i> -[2,4-dichlorobenzoyl]-3-chloro-4-fluorophenylsulfonamide | ESIMS: 380(M <sup>+</sup> -2), 382(M <sup>+</sup> ), 384(M <sup>+</sup> +2)   |
| 10        | <i>N</i> -[2-chloro-4-nitrobenzoyl]-4-chlorophenylsulfonamide      | ESIMS: 373(M <sup>+</sup> -2), 375(M <sup>+</sup> ), 377(M <sup>+</sup> +2)   |
| 11        | <i>N</i> -[2-chloro-4-bromobenzoyl]-phenylsulfonamide              | ESIMS: 372(M <sup>+</sup> -2), 374(M <sup>+</sup> )                           |
| 12        | <i>N</i> -[2-methyl-4-bromobenzoyl]-phenylsulfonamide              | ESIMS: 352(M <sup>+</sup> -2), 354(M <sup>+</sup> )                           |
| 13        | <i>N</i> -[2-chloro-4-nitrobenzoyl]-phenylsulfonamide              | ESIMS: 339(M <sup>+</sup> -1), 341(M <sup>+</sup> +1)                         |
| 14        | <i>N</i> -[2-chloro-4-bromobenzoyl]-4-bromophenylsulfonamide       | ESIMS: 450(M <sup>+</sup> -3), 452(M <sup>+</sup> -1), 454(M <sup>+</sup> +1) |
| 15        | <i>N</i> -[2-chloro-4-nitrobenzoyl]-4-bromophenylsulfonamide       | ESIMS: 417(M <sup>+</sup> -2), 419(M <sup>+</sup> )                           |

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| 16 | <i>N</i> -[2-chloro-4-bromobenzoyl]-4-fluorophenylsulfonamide      | ESIMS: 390( $M^+-2$ ),<br>392( $M^+$ )                                                                                                                                                                              |
| 17 | <i>N</i> -[2-chloro-4-bromobenzoyl]-3-chlorophenylsulfonamide      | ESIMS: 406( $M^+-3$ ),<br>408( $M^+-1$ ), 410( $M^++1$ )                                                                                                                                                            |
| 18 | <i>N</i> -[2-chloro-4-bromobenzoyl]-4-methoxyphenylsulfonamide     | ESIMS: 402( $M^+-2$ ),<br>404( $M^+$ ), 406( $M^++2$ )                                                                                                                                                              |
| 19 | <i>N</i> -[2-methyl-4-bromobenzoyl]-4-methoxyphenylsulfonamide     | ESIMS: 382( $M^+-2$ ),<br>384( $M^+$ )                                                                                                                                                                              |
| 20 | <i>N</i> -[2-chloro-4-nitrobenzoyl]-4-methoxyphenylsulfonamide     | ESIMS: 369( $M^+-1$ ),<br>371( $M^+$ )                                                                                                                                                                              |
| 21 | <i>N</i> -[2-chloro-4-nitrobenzoyl]-3,4-dichlorophenylsulfonamide  | ESIMS: 407( $M^+-2$ ),<br>409( $M^+$ ), 411( $M^++2$ )                                                                                                                                                              |
| 22 | <i>N</i> -[2-methyl-4-chlorobenzoyl]-3-chlorophenylsulfonamide     | ESIMS: 342( $M^+-1$ ),<br>344( $M^+-1$ ), 346( $M^+-1$ )                                                                                                                                                            |
| 23 | <i>N</i> -[2-methyl-4-chlorobenzoyl]-4-methylphenylsulfonamide     | ES Negative Ion MS<br>[ $M-H$ ] ions observed:<br>$m/z$ 342 ( $^{35}\text{Cl}$ , $^{35}\text{Cl}$ ), $m/z$<br>344 ( $^{35}\text{Cl}$ , $^{37}\text{Cl}$ ) and $m/z$<br>346 ( $^{37}\text{Cl}$ , $^{37}\text{Cl}$ ). |
| 24 | <i>N</i> -[2,4-dichlorobenzoyl]-3,4-dibromophenylsulfonamide       | ES Negative Ion MS<br>[ $M-H$ ] ions observed:<br>$m/z$ 322 ( $^{35}\text{Cl}$ ) and $m/z$<br>324 ( $^{37}\text{Cl}$ ).                                                                                             |
| 25 | <i>N</i> -[2,4-dichlorobenzoyl]-3-trifluoromethylphenylsulfonamide | ESIMS:<br>395.9476/395.9469                                                                                                                                                                                         |
| 26 | <i>N</i> -[2,4-dichlorobenzoyl]-3-fluorophenylsulfonamide          | ESIMS:<br>345.9508/345.9515                                                                                                                                                                                         |
| 27 | <i>N</i> -[2,4-dichlorobenzoyl]-3-methylphenylsulfonamide          | ESIMS:<br>365.9734/365.9747                                                                                                                                                                                         |

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| 28 | <i>N</i> -[2-methyl-4-bromobenzoyl]-4-chlorophenylsulfonamide                    | ESIMS <i>m/e</i> 386.0, 387.9, and 389.9 ( $M^+-1$ ; $^{79}\text{Br}$ , $^{35}\text{Cl}$ ; $^{79}\text{Br}$ , $^{37}\text{Cl}$ ; $^{81}\text{Br}$ , $^{37}\text{Cl}$ )  |
| 29 | <i>N</i> -[2-methyl-4-bromobenzoyl]-4-methylphenylsulfonamide                    | ESIMS <i>m/e</i> 366.0 and 368.0 ( $M^+-1$ ; $^{79}\text{Br}$ , $^{81}\text{Br}$ )                                                                                      |
| 30 | <i>N</i> -[2-bromo-4-chlorobenzoyl]-4-methoxycarbonylphenylsulfonamide           | ESIMS <i>m/e</i> 430.0, 431.9 and 433.9 ( $M^+-1$ ; $^{35}\text{Cl}$ , $^{79}\text{Br}$ , $^{37}\text{Cl}$ , $^{79}\text{Br}$ , $^{37}\text{Cl}$ , $^{81}\text{Br}$ )   |
| 31 | <i>N</i> -[2,4-dibromobenzoyl]-4-methoxycarbonylphenylsulfonamide                | ESIMS <i>m/e</i> 473.8, 475.9, and 477.9 ( $M^+-1$ ; $^{79}\text{Br}$ , $^{79}\text{Br}$ , $^{79}\text{Br}$ , $^{81}\text{Br}$ , $^{81}\text{Br}$ , $^{81}\text{Br}$ )  |
| 32 | <i>N</i> -[2-bromo-4-chlorobenzoyl]-3-methoxycarbonyl-4-methoxyphenylsulfonamide | ESIMS <i>m/e</i> 459.9, 461.9, 463.9 ( $M^+-1$ ; $^{79}\text{Br}$ , $^{35}\text{Cl}$ ; $^{81}\text{Br}$ , $^{35}\text{Cl}$ ; $^{81}\text{Br}$ , $^{37}\text{Cl}$ )      |
| 33 | <i>N</i> -[2-bromo-4-chlorobenzoyl]-4- <i>tert</i> -butylphenylsulfonamide       | ESIMS <i>m/e</i> 428.2, 430.2, and 432.2; ( $M^+-1$ ; $^{79}\text{Br}$ , $^{35}\text{Cl}$ ; $^{81}\text{Br}$ , $^{35}\text{Cl}$ ; $^{81}\text{Br}$ , $^{37}\text{Cl}$ ) |
| 34 | <i>N</i> -[2,4-dibromobenzoyl]-3-methoxycarbonyl-4-methoxyphenylsulfonamide      | ESIMS <i>m/e</i> 503.9, 506.0 and 508.0; ( $M^+-1$ ; $^{79}\text{Br}$ , $^{79}\text{Br}$ , $^{81}\text{Br}$ , $^{79}\text{Br}$ , $^{81}\text{Br}$ , $^{81}\text{Br}$ )  |
| 35 | <i>N</i> -[2-methyl-4-bromobenzoyl]-3-chloro-4-fluorophenylsulfonamide           | ESIMS <i>m/e</i> 404.0, 406.0, 408.0 ( $M^+-1$ ; $^{79}\text{Br}$ , $^{35}\text{Cl}$ ; $^{81}\text{Br}$ , $^{35}\text{Cl}$ ; $^{81}\text{Br}$ , $^{37}\text{Cl}$ )      |

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| 36 | <i>N</i> -[2-methyl-4-bromobenzoyl]-4-iodophenylsulfonamide     | ESIMS <i>m/e</i> 478.0 and 480.0 ( $M^+-1$ ; $^{79}\text{Br}$ , $^{81}\text{Br}$ )                                                                                                                                              |
| 37 | <i>N</i> -[2-methyl-4-bromobenzoyl]-3-methylphenylsulfonamide   | ESIMS <i>m/e</i> 366.1 and 368.1 ( $M^+-1$ ; $^{79}\text{Br}$ , $^{81}\text{Br}$ )                                                                                                                                              |
| 38 | <i>N</i> -[2,4-dibromobenzoyl]-4-iodophenylsulfonamide          | ESIMS <i>m/e</i> 541.9, 543.9 and 545.9 ( $M^+-1$ ; $^{79}\text{Br}$ , $^{79}\text{Br}$ , $^{81}\text{Br}$ , $^{79}\text{Br}$ , $^{81}\text{Br}$ , $^{81}\text{Br}$ )                                                           |
| 39 | <i>N</i> -[2,4-dichlorobenzoyl]-4-iodophenylsulfonamide         | ESIMS <i>m/e</i> 454 ( $M^+-1$ ; $^{35}\text{Cl}$ , $^{35}\text{Cl}$ ) and 456 ( $M^+-1$ ; $^{35}\text{Cl}$ , $^{37}\text{Cl}$ ) and 458 ( $M^+-1$ ; $^{37}\text{Cl}$ , $^{37}\text{Cl}$ )                                      |
| 40 | <i>N</i> -[2-chloro-4-bromobenzoyl]-4-iodophenylsulfonamide     | ES Negative Ion MS [M-H] <sup>-</sup> ions observed: <i>m/z</i> 498 ( $^{79}\text{Br}$ , $^{35}\text{Cl}$ ), <i>m/z</i> 500 ( $^{81}\text{Br}$ , $^{35}\text{Cl}$ ) and <i>m/z</i> 502 ( $^{81}\text{Br}$ , $^{37}\text{Cl}$ ). |
| 41 | <i>N</i> -[2-methyl-4-chlorobenzoyl]-4-methoxyphenylsulfonamide | ES Negative Ion MS [M-H] <sup>-</sup> ions observed: <i>m/z</i> 338 ( $^{35}\text{Cl}$ ) and <i>m/z</i> 340 ( $^{37}\text{Cl}$ ).                                                                                               |
| 42 | <i>N</i> -[2-methyl-4-chlorobenzoyl]-4-fluorophenylsulfonamide  | ES Negative Ion MS [M-H] <sup>-</sup> ions observed: <i>m/z</i> 326 ( $^{35}\text{Cl}$ ) and <i>m/z</i> 328 ( $^{37}\text{Cl}$ ).                                                                                               |
| 43 | <i>N</i> -[2-methyl-4-chlorobenzoyl]-4-bromophenylsulfonamide   | ES Negative Ion MS [M-H] <sup>-</sup> ions observed: <i>m/z</i> 386 ( $^{79}\text{Br}$ , $^{35}\text{Cl}$ ), <i>m/z</i> 388 ( $^{81}\text{Br}$ , $^{35}\text{Cl}$ ) and <i>m/z</i> 390 ( $^{81}\text{Br}$ , $^{37}\text{Cl}$ ). |

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| 44 | <i>N</i> -[2-methyl-4-chlorobenzoyl]-2-methoxy-4-methylphenylsulfonamide | ES Negative Ion MS<br>[M-H] <sup>-</sup> ions observed:<br><i>m/z</i> 352 ( <sup>35</sup> Cl) and <i>m/z</i> 354 ( <sup>37</sup> Cl).                                                                                          |
| 45 | <i>N</i> -[2-methyl-4-chlorobenzoyl]-3-chloro-4-methylphenylsulfonamide  | ES Negative Ion MS<br>[M-H] <sup>-</sup> ions observed:<br><i>m/z</i> 356( <sup>35</sup> Cl, <sup>35</sup> Cl), <i>m/z</i> 358 ( <sup>35</sup> Cl, <sup>37</sup> Cl) and <i>m/z</i> 360 ( <sup>37</sup> Cl, <sup>37</sup> Cl). |
| 46 | <i>N</i> -[2,4-bis-trifluoromethylbenzoyl]-4-fluorophenylsulfonamide     | ES Negative Ion MS<br>[M-H] <sup>-</sup> ion observed:<br><i>m/z</i> 414.                                                                                                                                                      |
| 47 | <i>N</i> -[2,4-bis-trifluoromethylbenzoyl]-4-methoxyphenylsulfonamide    | ES Negative Ion MS<br>[M-H] <sup>-</sup> ion observed:<br><i>m/z</i> 426.                                                                                                                                                      |
| 48 | <i>N</i> -[2,4-bis-trifluoromethylbenzoyl]-4-methylphenylsulfonamide     | ES Negative Ion MS<br>[M-H] <sup>-</sup> ion observed:<br><i>m/z</i> 410.                                                                                                                                                      |
| 49 | <i>N</i> -[2,4-bis-trifluoromethylbenzoyl]-4-bromophenylsulfonamide      | ES Negative Ion MS<br>[M-H] <sup>-</sup> ions observed:<br><i>m/z</i> 474 ( <sup>79</sup> Br) and <i>m/z</i> 476 ( <sup>81</sup> Br).                                                                                          |
| 50 | <i>N</i> -[2,4-bis-trifluoromethylbenzoyl]-3-methylphenylsulfonamide     | ES Negative Ion MS<br>[M-H] <sup>-</sup> ion observed:<br><i>m/z</i> 410.                                                                                                                                                      |
| 51 | <i>N</i> -[2-methyl-4-chlorobenzoyl]-4-trifluoromethoxyphenylsulfonamide | ES Negative Ion MS<br>[M-H] <sup>-</sup> ions observed:<br><i>m/z</i> 392 ( <sup>35</sup> Cl) and <i>m/z</i> 394 ( <sup>37</sup> Cl).                                                                                          |

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|----|-------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 52 | <i>N</i> -[2,4-bis-trifluoromethylbenzoyl]-3,4-dichlorophenylsulfonamide      | ES Negative Ion MS<br>[M-H] <sup>-</sup> ions observed:<br><i>m/z</i> 464 ( <sup>35</sup> Cl, <sup>35</sup> Cl), <i>m/z</i> 466 ( <sup>35</sup> Cl, <sup>37</sup> Cl) and <i>m/z</i> 468 ( <sup>37</sup> Cl, <sup>37</sup> Cl). |
| 53 | <i>N</i> -[2,4-bis-trifluoromethylbenzoyl]-3,4-difluorophenylsulfonamide      | ES Negative Ion MS<br>[M-H] <sup>-</sup> ion observed:<br><i>m/z</i> 432.                                                                                                                                                       |
| 54 | <i>N</i> -[2-methyl-4-chlorobenzoyl]-3-chloro-4-fluorophenylsulfonamide       | ES Negative Ion MS<br>[M-H] <sup>-</sup> ions observed:<br><i>m/z</i> 360 ( <sup>35</sup> Cl, <sup>35</sup> Cl), <i>m/z</i> 362 ( <sup>35</sup> Cl, <sup>37</sup> Cl) and <i>m/z</i> 364 ( <sup>37</sup> Cl, <sup>37</sup> Cl). |
| 55 | <i>N</i> -[2-methyl-4-chlorobenzoyl]-3-methylphenylsulfonamide                | ES Negative Ion MS<br>[M-H] <sup>-</sup> ions observed:<br><i>m/z</i> 322 ( <sup>35</sup> Cl) and <i>m/z</i> 324 ( <sup>37</sup> Cl).                                                                                           |
| 56 | <i>N</i> -[2-methyl-4-chlorobenzoyl]-4-iodophenylsulfonamide                  | ES Negative Ion MS<br>[M-H] <sup>-</sup> ions observed:<br><i>m/z</i> 434 ( <sup>35</sup> Cl) and <i>m/z</i> 436 ( <sup>37</sup> Cl).                                                                                           |
| 57 | <i>N</i> -[2-methyl-4-chlorobenzoyl]-3,4-difluorophenylsulfonamide            | ES Negative Ion MS<br>[M-H] <sup>-</sup> ions observed:<br><i>m/z</i> 344 ( <sup>35</sup> Cl) and <i>m/z</i> 346 ( <sup>37</sup> Cl).                                                                                           |
| 58 | <i>N</i> -[2,4-bis-trifluoromethylbenzoyl]-3-chloro-4-fluorophenylsulfonamide | ES Negative Ion MS<br>[M-H] <sup>-</sup> ions observed:<br><i>m/z</i> 448 ( <sup>35</sup> Cl) and <i>m/z</i> 450 ( <sup>37</sup> Cl).                                                                                           |

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| 59 | <i>N</i> -[2-chloro-4-methylbenzoyl]-3-chloro-4-fluorophenylsulfonamide | ES Positive Ion MS<br>[M+H] <sup>+</sup> ions observed:<br><i>m/z</i> 362 ( <sup>35</sup> Cl) and <i>m/z</i> 364 ( <sup>37</sup> Cl).                                                                                           |
| 60 | <i>N</i> -[2-methyl-4-chlorobenzoyl]-phenylsulfonamide                  | ES Positive Ion MS<br>[M+H] <sup>+</sup> ions observed:<br><i>m/z</i> 310 ( <sup>35</sup> Cl) and <i>m/z</i> 312 ( <sup>37</sup> Cl).                                                                                           |
| 61 | <i>N</i> -[2-methyl-4-bromobenzoyl]-4-ethylthiophenylsulfonamide        | ES Negative Ion MS<br>[M-H] <sup>-</sup> ions observed:<br><i>m/z</i> 412 ( <sup>79</sup> Br) and <i>m/z</i> 414 ( <sup>81</sup> Br).                                                                                           |
| 62 | <i>N</i> -[2,4-dichlorobenzoyl]-4-ethylthiophenylsulfonamide            | ES Negative Ion MS<br>[M-H] <sup>-</sup> ions observed:<br><i>m/z</i> 388 ( <sup>35</sup> Cl, <sup>35</sup> Cl), <i>m/z</i> 390 ( <sup>35</sup> Cl, <sup>37</sup> Cl) and <i>m/z</i> 392 ( <sup>37</sup> Cl, <sup>37</sup> Cl). |
| 63 | <i>N</i> -[2,4-bis-trifluoromethylbenzoyl]-4-isopropylphenylsulfonamide | ES Negative Ion MS<br>[M-H] <sup>-</sup> ion observed:<br><i>m/z</i> 438.                                                                                                                                                       |
| 64 | <i>N</i> -[2-chloro-4-bromobenzoyl]-4-isopropylphenylsulfonamide        | ES Negative Ion MS<br>[M-H] <sup>-</sup> ions observed:<br><i>m/z</i> 414 ( <sup>79</sup> Br, <sup>35</sup> Cl), <i>m/z</i> 416 ( <sup>81</sup> Br, <sup>35</sup> Cl) and <i>m/z</i> 418 ( <sup>81</sup> Br, <sup>37</sup> Cl). |
| 65 | <i>N</i> -[2,4-dibromobenzoyl]-4-ethylphenylsulfonamide                 | ES Negative Ion MS<br>[M-H] <sup>-</sup> ions observed:<br><i>m/z</i> 444 ( <sup>79</sup> Br, <sup>79</sup> Br), <i>m/z</i> 446 ( <sup>79</sup> Br, <sup>81</sup> Br) and <i>m/z</i> 448 ( <sup>81</sup> Br, <sup>81</sup> Br). |

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| 66 | <i>N</i> -[2-methyl-4-bromobenzoyl]-4-ethylphenylsulfonamide  | ES Negative Ion MS<br>[M-H] <sup>-</sup> ions observed:<br><i>m/z</i> 380 ( <sup>79</sup> Br) and <i>m/z</i> 382 ( <sup>81</sup> Br).                                                                                           |
| 67 | <i>N</i> -[2,4-dibromobenzoyl]-4-isopropylphenylsulfonamide   | ES Positive Ion MS<br>[M+H] <sup>+</sup> ions observed:<br><i>m/z</i> 460 ( <sup>79</sup> Br, <sup>79</sup> Br), <i>m/z</i> 462 ( <sup>79</sup> Br, <sup>81</sup> Br) and <i>m/z</i> 464 ( <sup>81</sup> Br, <sup>81</sup> Br). |
| 68 | <i>N</i> -[2,4-dichlorobenzoyl]-4-isopropylphenylsulfonamide  | ES Negative Ion MS<br>[M-H] <sup>-</sup> ions observed:<br><i>m/z</i> 370 ( <sup>35</sup> Cl, <sup>35</sup> Cl), <i>m/z</i> 372 ( <sup>35</sup> Cl, <sup>37</sup> Cl) and <i>m/z</i> 374 ( <sup>37</sup> Cl, <sup>37</sup> Cl). |
| 69 | <i>N</i> -[2,4-dichlorobenzoyl]-4-ethylphenylsulfonamide      | ES Negative Ion MS<br>[M-H] <sup>-</sup> ions observed:<br><i>m/z</i> 356 ( <sup>35</sup> Cl, <sup>35</sup> Cl), <i>m/z</i> 358 ( <sup>35</sup> Cl, <sup>37</sup> Cl) and <i>m/z</i> 360 ( <sup>37</sup> Cl, <sup>37</sup> Cl). |
| 70 | <i>N</i> -[2-methyl-4-chlorobenzoyl]-4-ethylphenylsulfonamide | ES Negative Ion MS<br>[M-H] <sup>-</sup> ions observed:<br><i>m/z</i> 336 ( <sup>35</sup> Cl) and <i>m/z</i> 338 ( <sup>37</sup> Cl).                                                                                           |
| 71 | <i>N</i> -[2-chloro-4-bromobenzoyl]-4-ethylphenylsulfonamide  | ES Negative Ion MS<br>[M-H] <sup>-</sup> ions observed:<br><i>m/z</i> 400 ( <sup>79</sup> Br, <sup>35</sup> Cl), <i>m/z</i> 402 ( <sup>81</sup> Br, <sup>35</sup> Cl) and <i>m/z</i> 404 ( <sup>81</sup> Br, <sup>37</sup> Cl). |

|    |                                                                             |                                                                                                                                                                                                                           |
|----|-----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 72 | <i>N</i> -[2-bromo-4-chlorobenzoyl]-4-ethylphenylsulfonamide                | ES Negative Ion MS [M-H] <sup>-</sup> ions observed: <i>m/z</i> 400 ( <sup>79</sup> Br, <sup>35</sup> Cl), <i>m/z</i> 402 ( <sup>81</sup> Br, <sup>35</sup> Cl) and <i>m/z</i> 404 ( <sup>81</sup> Br, <sup>37</sup> Cl). |
| 73 | <i>N</i> -[2-bromo-4-chlorobenzoyl]-4-isopropylphenylsulfonamide            | ES Negative Ion MS [M-H] <sup>-</sup> ions observed: <i>m/z</i> 414 ( <sup>79</sup> Br, <sup>35</sup> Cl), <i>m/z</i> 416 ( <sup>81</sup> Br, <sup>35</sup> Cl) and <i>m/z</i> 418 ( <sup>81</sup> Br, <sup>37</sup> Cl). |
| 74 | <i>N</i> -[2-chloro-4-iodobenzoyl]-4-azidophenylsulfonamide                 | ESIMS <i>m/e</i> 460.9 (M-1)                                                                                                                                                                                              |
| 75 | <i>N</i> -[2-methyl-4-chlorobenzoyl]-4-methylthiophenylsulfonamide          | ES Positive Ion MS [M+H] <sup>+</sup> ions observed: <i>m/z</i> 356 ( <sup>35</sup> Cl) and <i>m/z</i> 358 ( <sup>37</sup> Cl).                                                                                           |
| 76 | <i>N</i> -[2-methyl-4-chlorobenzoyl]-4-trifluoromethylthiophenylsulfonamide | ES Negative Ion MS [M-H] <sup>-</sup> ions observed: <i>m/z</i> 408 ( <sup>79</sup> Br, <sup>35</sup> Cl), <i>m/z</i> 410 ( <sup>81</sup> Br, <sup>35</sup> Cl) and <i>m/z</i> 412 ( <sup>81</sup> Br, <sup>37</sup> Cl). |
| 77 | <i>N</i> -[2-methyl-4-chlorobenzoyl]-3-trifluoromethylphenylsulfonamide     | ES Positive Ion MS [M+H] <sup>+</sup> ions observed: <i>m/z</i> 378 ( <sup>35</sup> Cl) and <i>m/z</i> 380 ( <sup>37</sup> Cl).                                                                                           |
| 78 | <i>N</i> -[2-methyl-4-bromobenzoyl]-3-trifluoromethylphenylsulfonamide      | ES Positive Ion MS [M+H] <sup>+</sup> ions observed: <i>m/z</i> 422 ( <sup>79</sup> Br) and <i>m/z</i> 424 ( <sup>81</sup> Br).                                                                                           |

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|    |                                                                         |                                                                                      |
|----|-------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| 79 | <i>N</i> -[2-trifluoromethyl-4-methylbenzoyl]-4-methylphenylsulfonamide | ES Positive Ion MS<br>[M+H] <sup>+</sup> ion observed:<br><i>m/z</i> 358.            |
| 80 | <i>N</i> -[2,4-dichlorobenzoyl]-3-methoxyphenylsulfonamide              | <sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ<br>7.68 – 7.15 (m, 7 H);<br>3.80 (s, 3 H). |
| 81 | <i>N</i> -[2,4-dichlorobenzoyl]-4-trifluoromethylphenylsulfonamide      | ESI-MS <i>m/e</i> 395.9<br>(M <sup>+</sup> - H)                                      |
| 82 | <i>N</i> -[2,4-dichlorobenzoyl]-4-hydroxyphenylsulfonamide              | Mp 155-157 °C; ESI-MS<br><i>m/e</i> 344.0 (M <sup>+</sup> - H)                       |
| 83 | <i>N</i> -[4-Bromo-2-methyl-benzoyl]-3,4-dimethylphenylsulfonamide      | MS (ES):<br>[M-H] <sup>-</sup> 379.9943                                              |
| 84 | <i>N</i> -[2,4-Bis-trifluoromethyl-benzoyl]-3-fluorophenylsulfonamide   | MS (ES):<br>[M-H] <sup>-</sup> 414.0049                                              |

## EXAMPLE 85

*N*-[2-chloro-4-bromobenzoyl]-4-chlorophenylsulfonamide

5 An 8 mL reaction vial is charged with 2-chloro-4-bromobenzoic acid (0.39 mmol, 1.5 eq) and 2.0 mL of dichloromethane. A stock solution (4.0 mL) containing 4-chlorophenylsulfonamide (0.26 mmol, 1 eq) and *N,N*-[dimethyl]-4-aminopyridine (48 mg, 0.39 mmol, 1.5 eq) in dichloromethane is added, followed by 0.261 g carbodiimide polystyrene resin (2.0 mmol/g, 0.52 mmol, 2.0 eq, Novabiochem) and the vial is capped

10 and rotated. After 72 hr, 0.77 g sulphonated polystyrene resin (MP-TsOH) is added (1.53 mmol/g, 1.17 mmol, Argonaut). After about 18 hr the reaction mixture is filtered and concentrated under a stream of nitrogen. The residue is subjected to reverse phase HPLC; CombiPrep column, YMC ODS-A 20X50 mm column with 5 micron, C18, 120 Angstrom pore size, gradient: 5% to 95% CH<sub>3</sub>CN/0.01 HCl aqueous solution. Fractions

15 containing product are combined and concentrated under reduced pressure to provide the title compound.

ESIMS: *m/e* = 408(M<sup>+</sup>+1), 406(M<sup>+</sup>-1), 410(M<sup>+</sup>+3).

The compounds of Examples 86-107 are prepared essentially as described in Example 85.

| EXAMPLE # | Product                                                                 | Mass Spectral Data (m/e)                              |
|-----------|-------------------------------------------------------------------------|-------------------------------------------------------|
| 86        | <i>N</i> -[2,4-dichlorobenzoyl]-4-methylphenylsulfonamide               | ESIMS: 342( $M^+-1$ ), 344( $M^++1$ )                 |
| 87        | <i>N</i> -[2,4-dichlorobenzoyl]-4-methylthiophenylsulfonamide           | ESIMS: 374( $M^+-1$ ), 376( $M^++1$ )                 |
| 88        | <i>N</i> -[2,4-dichlorobenzoyl]-4- <i>tert</i> -butylphenylsulfonamide  | ESIMS: 384( $M^+-1$ ), 386( $M^++1$ )                 |
| 89        | <i>N</i> -[2,4-dichlorobenzoyl]-3-chloro-4-methylphenylsulfonamide      | ESIMS: 378( $M^++1$ ), 376( $M^+-1$ ), 380( $M^++3$ ) |
| 90        | <i>N</i> -[2-methyl-4-chlorobenzoyl]-3-bromophenylsulfonamide           | ESIMS: 388( $M^++1$ ), 386( $M^+-1$ ), 390( $M^++3$ ) |
| 91        | <i>N</i> -[2,4-dichlorobenzoyl]-4-fluorophenylsulfonamide               | ESIMS: 346( $M^+-1$ ), 348( $M^++1$ )                 |
| 92        | <i>N</i> -[2,4-dichlorobenzoyl]-3,4-dichlorophenylsulfonamide           | ESIMS: 398( $M^++1$ ), 396( $M^+-1$ ), 400( $M^++3$ ) |
| 93        | <i>N</i> -[2-methyl-4-chlorobenzoyl]-4-chlorophenylsulfonamide          | ESIMS: 342( $M^+-1$ ), 344( $M^++1$ )                 |
| 94        | <i>N</i> -[2,4-dichlorobenzoyl]-4-bromophenylsulfonamide                | ESIMS: 408( $M+1$ ), 406( $M-1$ ), 410( $M+3$ )       |
| 95        | <i>N</i> -[2,4-dichlorobenzoyl]-4-methylsulfonyloxyphenylsulfonamide    | ESIMS: 422 ( $M-2$ ), 424 ( $M$ ), 426 ( $M+2$ )      |
| 96        | <i>N</i> -[2,4-dichlorobenzoyl]-4-trifluoromethoxyphenylsulfonamide     | ESIMS: 412 ( $M-2$ ), 414 ( $M$ ), 416 ( $M+2$ )      |
| 97        | <i>N</i> -[2,4-dichlorobenzoyl]-4-methoxy-3,5-dimethylphenylsulfonamide | ESIMS: 368 ( $M-2$ ), 370 ( $M$ ), 372 ( $M+2$ )      |

|     |                                                                             |                                        |
|-----|-----------------------------------------------------------------------------|----------------------------------------|
| 98  | <i>N</i> -[2,4-dichlorobenzoyl]-4-dimethylaminophenylsulfonamide            | ESIMS: 371 (M-2), 373 (M)              |
| 99  | <i>N</i> -[2,4-bis-trifluoromethylbenzoyl]-4-chlorophenylsulfonamide        | ESIMS: 430 (M-1), 432 (M+1)            |
| 100 | <i>N</i> -[2-methyl-4-bromobenzoyl]-4-bromophenylsulfonamide                | ESIMS: 430 (M-3), 432 (M-1), 434 (M+1) |
| 101 | <i>N</i> -[2-chloro-4-nitrobenzoyl]-4-fluorophenylsulfonamide               | ESIMS: 357 (M-1)                       |
| 102 | <i>N</i> -[2-chloro-3-methylbenzoyl]-4-chlorophenylsulfonamide              | ESIMS: 342 (M-1) 344 (M+1)             |
| 103 | <i>N</i> -[2,4-dichlorobenzoyl]-4-nitrophenylsulfonamide                    | ESIMS: 373 (M-1) 375 (M+1)             |
| 104 | <i>N</i> -[2-methyl-4-chlorobenzoyl]-3,4-dichlorophenylsulfonamide          | ESIMS: 378 (M+1) 376 (M-1) 380 (M+3)   |
| 105 | <i>N</i> -[2-methyl-4-chlorobenzoyl]-4- <i>tert</i> -butylphenylsulfonamide | ESIMS: 364 (M-1) 366 (M+1)             |
| 106 | <i>N</i> -[2-methyl-4-chlorobenzoyl]-3-cyanophenylsulfonamide               | ESIMS: 333 (M-1)                       |
| 107 | <i>N</i> -[2,4-dichlorobenzoyl]-4-[1,2,4]triazol-4-ylphenylsulfonamide      | 395 (M)                                |

## EXAMPLE 108

*N*-[2,4-dichlorobenzoyl]-4-(1-methylsulfanylo-phen-4-yl)phenylsulfonamide

5 Step A: Procedure for activation of the resin

The Rink amide resin (CA Novabiochem, 0.53 mmol/g) was suspended in a 30% solution of pyridine in DMF and stirred at room temperature for 3 hours. The mixture was filtered and the resin was washed twice with DMF and then, alternatively with CH<sub>2</sub>Cl<sub>2</sub> and MeOH. The activated resin having a free amino group was dried and used without

0 further purification.

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The Rink amide resin (0.53 mmol/g) was suspended in a 1:1 mixture  $\text{CH}_2\text{Cl}_2/\text{THF}$  and  $\text{Et}_3\text{N}$  (4 eq), 4-iodophenylsulfonamide (3 eq) and DMAP (catalytic amount). The solution was stirred overnight at room temperature. The mixture was filtered and the resin was washed alternatively with  $\text{CH}_2\text{Cl}_2$  and MeOH. The 4-iodophenylsulfonamide Rink resin was dried under vacuum.

The corresponding 4-iodophenylsulfonamide Rink resin (0.26 mmol, 0.53 mmol/g), Methylsulfanyl-phenyl boronic acid (2 eq), potassium carbonate (6 eq) and the Palladium acetate (0.5 eq) were mixed together and suspended in 7 mL of a mixture dioxane/water 6:1. This mixture was heated in an Argovant® QUEST® 210 at 100°C for 24 hours. Then, the resin was washed twice with 5 mL of a mixture dioxane/water 6:1 and then six times with  $\text{CH}_2\text{Cl}_2$  (7 mL) followed each time by MeOH (7 mL).

3 mL of a 95% aqueous solution of trifluoroacetic acid were added to the resin previously dissolved in 3 mL of  $\text{CH}_2\text{Cl}_2$ . The mixture was stirred for 30 min at room temperature, filtered as described above. The 4'-methylsulfanyl-biphenyl-4-sulfonamide was employed without further purification.

To a stirred solution of 2,4-Dichloro-benzoic acid (1.25 eq) in dry  $\text{CH}_2\text{Cl}_2$  (10 mL/mmol), 4'-Methylsulfanyl-biphenyl-4-sulfonamide (1.0 eq) was added in one portion followed by HDC (1.25 or 1.5 eq) and finally, DMAP (1.2 equiv). The mixture was vigorously stirred under nitrogen for 16 hours, then evaporated *in vacuo* and the residue partitioned between EtOAc and water. The organic layer was washed with 1N HCl (4 times, 20 mL/mmol), then the aqueous phase was extracted with EtOAc (twice, 20 mL/mmol). The combined organic layers were finally washed with water and brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo*. The crude product was purified by silica gel chromatography using the appropriate eluent afford the title compound.

ESI-MS ( $\text{M}^+-\text{H}$ ) 450.9870 / 450.0.

#### EXAMPLE 109

##### *N*-[2,4-dichlorobenzoyl]-4-3'-acetyl-biphenylsulfonamide

A suspension of 4-iodophenylsulfonamide Rink resin (0.26 mmol, 0.53 mmol/g), 3-acetylphenyl boronic acid (2 eq) and 2,4-dichloro-benzoic acid (1.25 eq); were used essentially as described in Example 108 to prepare the title compound.

ESI-MS ( $\text{M}^+-\text{H}$ ) 447.0099 / 446.0.

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## EXAMPLE 110

*N*-[2,4-dichlorobenzoyl]phenylsulfonamide

To a mixture of phenylsulfonamide (0.16 mol; 25.12 g) and potassium carbonate (0.2 mol; 27.6 g) in 500 mL dioxane is added dropwise 2,4-dichlorobenzoyl chloride (0.13 mole; 18.0 mL). The mixture is warmed to reflux under nitrogen for 16 hr. The reaction is then diluted with water (500 mL), neutralized to pH 5 with concentrated hydrochloric acid, and extracted 3 times with ethyl acetate. The combined ethyl acetate layers are washed with saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure to a white solid. The solid residue is subjected to silica gel chromatography, eluting with dichloromethane containing from 0-5% methanol. Fractions containing the product are combined and concentrated under reduced pressure to provide the title compound.

MS(ES):  $m/e = 329.9 (M^+ + 1), 327.9 (M^+ - 1)$ .

## EXAMPLE 111

*N*-[2,4-dichlorobenzoyl]-4-chlorophenylsulfonamide

A mixture of 4-chlorophenylsulfonamide (0.1 mol; 19.0 g) and 2,4-dichlorobenzoyl chloride (0.12 mol; 16.8 mL); the title compound was prepared essentially as described in Example 110.

MS(ES):  $m/e = 363.9 (M^+)$

EA: Calculated for  $C_{13}H_8Cl_3NO_2S$ : Theory: C, 42.82; H, 2.21; N, 3.84. Found: C, 42.56; H, 2.14; N, 3.76.

## EXAMPLE 112

*N*-[2-chloro-4-bromobenzoyl]-4-chlorophenylsulfonamide

To a reaction mixture of 4-chlorophenylsulfonamide (15.6 g, 81.4 mmol), CDI (15.82 g, 97.7 mmol) and ethyl acetate (300 mL) at room temperature is added a slurry of 2-chloro-4-bromobenzoic acid (23.0 g, 97.7 mmol) in ethyl acetate (100.0 mL) over a period of 15.0 min (note: gas evolution is observed which can be controlled by the rate of addition of the slurry; reaction mixture goes into solution by the end of addition of the slurry; reaction can be monitored by HPLC or TLC with 1:1 ethyl acetate/heptane eluent. The reaction is then stirred at room temperature for 30 min and then heated at 60°C for 90

min or until no gas evolution is observed. The reaction is cooled to 40°C, and 1,8-diazabicyclo[5.4.0]undec-7-ene is (14.63 mL) added (all at once). The reaction temperature goes from 40°C to 45°C. The mixture is stirred until it reaches room temperature before quenching with deionized water (400 mL). The top organic layer is separated, washed with 1N HCl (300.0 mL), dried with anhydrous MgSO<sub>4</sub>, filtered and the cake washed with ethyl acetate (20.0 mL). The filtrate is concentrated to 50.0 g of syrupy solution, then heptane (250.0 mL) is added with vigorous stirring. With heating, a white slurry is formed and is refluxed and then allowed to equilibrate to room temperature. The white precipitate is filtered and the cake is washed with heptane (20.0 mL). The precipitate is dried in a house vacuum at 55°C for 18 hr. (mass = 29.12 g, 87.4% wt yield).

A mixture of 19.17 g of the product and 1:2 ethyl acetate/heptane (150.0 mL) is heated at reflux for 30 min, and then cooled to room temperature. The off white precipitate is filtered and then the cake is washed with heptane (50.0 mL). The precipitate is dried in a house vacuum at 50°C for 18 hr. (mass = 14.93 g; 78% recovery).

ESIMS:  $m/e = 408(M^+ + 1)$ ,  $406(M^+ - 1)$ ,  $410(M^+ + 3)$ .

#### EXAMPLE 13

##### *N*-[2-chloro-4-bromobenzoyl]-4-chlorophenylsulfonamide sodium salt

To a solution of *N*-[2-chloro-4-bromobenzoyl]-4-chlorophenylsulfonamide (5.2 g, 12.72 mmol) and *tert*-butyl methyl ether (88.0 mL) at room temperature is added sodium methoxide (0.69 g, 12.72 mmol) all at once. The reaction is then stirred for 5 hr, after which heptane (88.0 mL) is added followed by vigorous stirring for 60 min. A white precipitate is formed, filtered off under a positive nitrogen pressure, and the cake subsequently washed with heptane (2 x 44.0 mL). The cake is dried to semi-dryness, followed by drying in a house vacuum oven at 130°C for 18 hr (mass = 4.4 g, 80% wt. Yield; <sup>1</sup>H nmr (DMSO d<sub>6</sub>) 7.8-7.85 (m, 1H), 7.81-7.82 (m, 1H), 7.58-7.59 (d, 1H, *J* = 1.76 Hz), 7.51-7.52 (m, 1H), 7.48-7.49 (m, 1H), 7.44-7.45 (d, 1H, *J* = 1.76) 7.37-7.4 (d, 1H).

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## EXAMPLE 114

*N*-[3-chloro-4-fluorophenylsulfonyl]-3-fluoro-4-methylbenzamidine

Add 3-fluoro-4-methylbenzamidine hydrochloride (0.025 g, 0.133 mmol) in THF (0.5 mL) to 3-chloro-4-fluorophenyl sulfonylchloride (0.0304 g, 0.133 mmol) followed by  
5 *N*-methylmorpholine (0.2 mL). The reaction mixture was concentrated and chromatographed using reverse phase chromatography (gradient of 5-95% (0.1% TFA in CH<sub>3</sub>CN) in (0.1% TFA in H<sub>2</sub>O). A white solid (16.4 mg, 36%) was isolated. ES Positive Ion MS [M+H]<sup>+</sup> ions observed: *m/z* 345 (<sup>35</sup>Cl) and *m/z* 347 (<sup>37</sup>Cl).

## EXAMPLE 115

*N*-[3-chloro-4-fluorophenylsulfonyl]-4-chlorobenzamidine

4-chlorobenzamidine hydrochloride (0.025 g, 0.133 mmol) and 3-chloro-4-fluorophenyl sulfonylchloride (0.0304 g, 0.133 mmol); were used essentially as described in Example 114 to prepare the title compound. ES Positive Ion MS [M+H]<sup>+</sup> ions  
15 observed: *m/z* 347 (<sup>35</sup>Cl, <sup>35</sup>Cl), *m/z* 349 (<sup>35</sup>Cl, <sup>37</sup>Cl) and *m/z* 351 (<sup>37</sup>Cl, <sup>37</sup>Cl).

## EXAMPLE 116

*N*-[3-chloro-4-fluorophenylsulfonyl]-3-chloro-4-fluorobenzamidine

A mixture of 3-chloro-4-fluorobenzamidine hydrochloride (0.025 g, 0.133 mmol) and 3-chloro-4-fluorophenyl sulfonylchloride (0.0304 g, 0.133 mmol); the title compound is prepared essentially as described in Example 115. ES Positive Ion MS [M+H]<sup>+</sup> ions  
20 observed: *m/z* 365 (<sup>35</sup>Cl, <sup>35</sup>Cl), *m/z* 367 (<sup>35</sup>Cl, <sup>37</sup>Cl) and *m/z* 369 (<sup>37</sup>Cl, <sup>37</sup>Cl).

## EXAMPLE 117

*N*-[2,4-dichlorobenzoyl]-4-hydroxyphenylsulfonamide

4-Methoxy-phenyl-4-sulfonamide (0.0608 g, 0.132 mmol) is dissolved in THF (1.25 mL) and treated with tetrabutylammonium fluoride (1.0 N/THF; 200  $\mu$ L, 2.0 mmol) at room temperature with stirring for 18 hr. The reaction mixture is diluted with EtOAc (10 mL) and washed with saturated aq. NH<sub>4</sub>Cl (1 mL), H<sub>2</sub>O (2 x 1 mL), and brine (1 mL).  
30 The organic phase is dried MgSO<sub>4</sub>, filtered, and concentrated by rotary evaporation. (Lyophilized from H<sub>2</sub>O/MeOH to obtain a glassy solid, 20 mg (0.058 mmol, 58%).

Purified by preparative HPLC.) mp 155-157°C; ESI-MS m/e 344.0 (M+ - H); <sup>1</sup>H NMR (d6-DMSO) 7.90 (d, 2 H); 7.68 (s, 1 H); 7.44 (s, 2 H); 6.90 (d, 2H); 3.43 (br s, 3 H).

## EXAMPLE 118

5 *N*-[2,4-dichlorobenzoyl]-4-(thien-3-yl)-phenylsulfonamide

To a solution of *N*-(2,4-dichlorobenzoyl)-4-iodo-phenylsulfonamide (0.10 mmol) in toluene/ethanol 20/1 (3 mL) is added 3-thiopheneboronic acid (0.18 mmol, 0.18 mL, 1.0M solution in DMF) and tetrakis-(triphenylphosphine) palladium (0) (10 mol%). Then 2M aqueous Na<sub>2</sub>CO<sub>3</sub> is added (0.3 mL) and the stirred mixture is heated to 100°C overnight (17 hr)(Buchi Syncore system). The reaction mixture is concentrated (Genevac apparatus), then water is added (2.5 mL) and ethyl acetate (5 mL). The phases are separated and the aqueous layer is extracted with ethyl acetate (3 x 5 mL). This process is automatically carried out using a Tecan system. The solvents are evaporated and the corresponding crude product is purified by HPLC to give the title compound.

15 ESI-MS m/e 410.96 / 410.0 [M<sup>+</sup>-H]

The compounds of EXAMPLES 119-130 are prepared essentially as described in the procedure for EXAMPLE 118.

| EXAMPLE # | Product                                                                         | Mass Spectral Data (m/e)                      |
|-----------|---------------------------------------------------------------------------------|-----------------------------------------------|
| 119       | <i>N</i> -[2,4-dichlorobenzoyl]-4-(1-trifluoromethylphen-4-yl)phenylsulfonamide | ESI-MS m/e 472.99 / 472.2 [M <sup>+</sup> -H] |
| 120       | <i>N</i> -[2,4-dichlorobenzoyl]-4-(1-fluoro-phen-3-yl)-phenylsulfonamide        | ESI-MS m/e 422.99 / 422.0 [M <sup>+</sup> -H] |
| 121       | <i>N</i> -[2,4-dichloro-benzoyl]-4-furan-2-yl-phenylsulfonamide                 | ESI-MS m/e 394.98 / 394.2 [M <sup>+</sup> -H] |
| 122       | <i>N</i> -[2,4-dichlorobenzoyl]-4-(1-methoxy-phen-2-yl)phenylsulfonamide        | ESI-MS m/e 435.01 / 434.0 [M <sup>+</sup> -H] |

|     |                                                                                  |                                                    |
|-----|----------------------------------------------------------------------------------|----------------------------------------------------|
| 123 | <i>N</i> -[2,4-dichlorobenzoyl]-4-(1-methoxycarbonyl-phen-4-yl)phenylsulfonamide | ESI-MS m/e 447.07 / 446.0<br>[M <sup>+</sup> -H]   |
| 124 | <i>N</i> -[2,4-dichlorobenzoyl]-4-quinolin-8-yl-phenylsulfonamide                | ESI-MS m/e 456.01 / 455.1<br>[M <sup>+</sup> -H]   |
| 125 | <i>N</i> -[2,4-dichloro-benzoyl]-3-quinolin-8-yl-phenylsulfonamide               | ESI-MS m/e 456.01 / 457.2<br>[M <sup>+</sup> +H]   |
| 126 | <i>N</i> -[2,4-dichlorobenzoyl]-4-fur-3-yl-phenylsulfonamide                     | ESI-MS m/e 394.98/<br>394.0<br>[M <sup>+</sup> -H] |
| 127 | <i>N</i> -[2,4-dichlorobenzoyl]-4-pyridin-3-yl-phenylsulfonamide                 | ESI-MS m/e 406.0<br>[M <sup>+</sup> -H]            |
| 128 | <i>N</i> -[2,4-dichloro-benzoyl]-3-biphenylsulfonamide                           | ESI-MS m/e 405.1<br>[M <sup>+</sup> -H]            |
| 129 | <i>N</i> -[2,4-dichloro-benzoyl]-4'-methoxy-4-biphenylsulfonamide                | ESI-MS m/e 435.2<br>[M <sup>+</sup> -H]            |
| 130 | <i>N</i> -[2,4-dichlorobenzoyl]-4-thiophen-2-yl-phenylsulfonamide                | ESI-MS m/e 411.1<br>[M <sup>+</sup> -H]            |

All of the compounds concerned are orally available and are normally administered orally, and so oral administration is preferred. However, oral administration is not the only route or even the only preferred route. For example, transdermal administration may be very desirable for patients who are forgetful or petulant about taking oral medicine, and the intravenous route may be preferred as a matter of convenience or to avoid potential complications related to oral administration. Compounds of Formula II may also be administered by the percutaneous, intramuscular, intranasal or intrarectal route in particular circumstances. The route of administration may be varied in any way, limited by the physical properties of the drugs, the convenience of the patient and the caregiver, and other relevant circumstances (Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Co. (1990)).

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The pharmaceutical compositions are prepared in a manner well known in the pharmaceutical art. The carrier or excipient may be a solid, semi-solid, or liquid material that can serve as a vehicle or medium for the active ingredient. Suitable carriers or excipients are well known in the art. The pharmaceutical composition may be adapted for oral, inhalation, parenteral, or topical use and may be administered to the patient in the form of tablets, capsules, aerosols, inhalants, suppositories, solutions, suspensions, or the like.

The compounds of the present invention may be administered orally, for example, with an inert diluent for capsules or compressed into tablets. For the purpose of oral therapeutic administration, the compounds may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums and the like. These preparations should contain at least 4% of the compound of the present invention, the active ingredient, but may be varied depending upon the particular form and may conveniently be between 4% to about 70% of the weight of the unit. The amount of the compound present in compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations of the present invention may be determined by methods well known to the skilled artisan.

The tablets, pills, capsules, troches, and the like may also contain one or more of the following adjuvants: binders such as povidone, hydroxypropyl cellulose, microcrystalline cellulose, or gelatin; excipients or diluents such as: starch, lactose, microcrystalline cellulose or dicalcium phosphate; disintegrating agents such as: croscarmellose, crospovidone, sodium starch glycolate, corn starch and the like; lubricants such as: magnesium stearate, steric acid, talc or hydrogenated vegetable oil; glidants such as colloidal silicon dioxide; wetting agents such as: sodium lauryl sulfate and polysorbate 80 (CAS No.9005-65-6); and sweetening agents such as: sucrose, aspartame or saccharin may be added or a flavoring agent such as: peppermint, methyl salicylate or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or a fatty oil. Other dosage unit forms may contain other various materials that modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, hydroxypropyl methylcellulose, polymethacrylates, or other coating agents. Syrups may contain, in addition to the present compounds, sucrose as a sweetening agent and certain

preservatives, dyes and colorings and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

5       Injections for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions and emulsions. Aqueous solutions and suspensions may include distilled water for injection or physiological salt solution. Non-aqueous solutions and suspensions may include propylene glycol, polyethylene glycol, vegetable oil such as olive oil, alcohol such as ethanol or polysorbate 80. Injections may comprise additional ingredients other than inert diluents: e.g. preserving agents, wetting agents, emulsifying agents, dispersing agents, stabilizing agents (such as lactose), assisting agents such as agents to assist dissolution (e.g. glutamic acid or aspartic acid). They may be sterilized for example, by filtration through a bacteria-retaining filter, by incorporation of sterilizing agents in the compositions or by irradiation. They may also be manufactured in the form of sterile solid compositions which may be dissolved in sterile water or some other sterile diluent(s) for injection immediately before use.

15       The compounds of Formula II are generally effective over a wide dosage range. For example, dosages per day normally fall within the range of about 10 to about 300 mg/kg of body weight. 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, and therefore the above dosage range is not intended to limit the scope of the invention in any way. It will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound or compounds administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms.

#### Inhibition of HUVEC Proliferation

30       Human umbilical vein endothelial cells (HUVEC; BioWhittaker/Clonetics, Walkersville, MD) were maintained in endothelial cell growth medium (ECGM) containing basal medium (EBM) with bovine brain extract, human epidermal growth factor, hydrocortisone, gentamicin, amphotericin B and 2% fetal bovine serum. For the assay, HUVEC ( $5 \times 10^3$ ) in EBM (200  $\mu$ l) with 0.5% fetal bovine serum were added to wells in a

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96-well cell culture plate and incubated at 37°C for 24 hr in humidified 5% carbon dioxide/air. The test compounds were serially diluted in dimethyl sulfoxide (DMSO) in concentrations from 0.0013 to 40  $\mu$ M and added to the wells in 20  $\mu$ l. Then human vascular endothelial growth factor (VEGF) (20 ng/mL in wells; R&D Systems, Minneapolis, MN) prepared from a stock solution of 100  $\mu$ g/mL in phosphate buffered normal saline containing 0.1 % bovine serum albumin, was added to the wells. The HUVEC were incubated at 37°C for 72 hr in humidified 5% carbon dioxide/air. WST-1 cell proliferation reagent (20  $\mu$ l; Boehringer Mannheim, Indianapolis, IN) was added to the wells and the plates returned to the incubator for 1 hr. The absorbance of each well at 440 nm was measured. The growth fraction was determined from the absorbance of treated wells with and without VEGF divided by the absorbance obtained from control wells set to zero and 1.0. The exemplified compounds were tested in this assay and all exhibited an  $IC_{50} \leq 1.0 \mu$ M.

#### 15 Rat Corneal Micropocket Assay

Fisher 344 female rats (145-155 grams; Taconic, Inc., Germantown, NY) were anesthetized with acepromazine (2.5 mg/kg, ip) 20 minutes prior to initiation of 2-3% isoflurane/oxygen inhalation. The body temperature was maintained with a circulating hot water pad. The surgery was performed using an ophthalmic operating microscope (OMS.75 Operating Microscope, TopCon Corporation, Japan). A scalpel blade (#15) was used to make a vertical half-thickness linear corneal incision just lateral to the center of the eye. The tip of the scalpel blade was used to gently undermine the superior corneal layer of the cornea nearest to the limbus. A pocket was formed in the cornea using blunt dissection with corneal scissors (Roboz, Rockville, MD). Nitrocellulose filters (0.45  $\mu$ m, Millipore, Bedford, MA) were cut into small disks using a 20 gauge needle punch. The disks were soaked in 2  $\mu$ l of human VEGF solution (0.82  $\mu$ g/ $\mu$ l; R&D Systems) or human basic fibroblast growth factor (0.20  $\mu$ g/ $\mu$ l; R&D Systems) for 10 minutes on ice. Using forceps, the disks impregnated with the angiogenic factor (VEGF or bFGF) were inserted into the corneal pocket so that the disk is firmly covered with corneal epithelium. The animals were treated with the compound of Example 110 (160 mg/kg) administered orally by gavage in phosphate buffered saline once per day on days 1 through 10 post implantation of the disks. The eyes were photographed on days 7 and 14 post

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implantation of the disks. For photography, the animals were treated with atropine sulfate (AmTech Group, Inc., Phoenix Scientific, Inc., St. Joseph, MO) topically for mydriasis and anesthetized with 2-3% isoflurane/oxygen. The eyes were photographed using the ophthalmic microscope and the images were saved using Image Pro-Plus software. The images were analyzed by converting the area of interest to high contrast black and white reversed image and counting the bright pixels as a determination of the vascular area. The data are images from at least 6 eyes. The compound of Example 110 was a very effective inhibitor of VEGF-induced neoangiogenesis, but was not an effective inhibitor of bFGF-induced neoangiogenesis.

#### HCT116 Colon Carcinoma Cell Growth Inhibition

Human HCT116 colon carcinoma cells were grown monolayer culture in RPMI 1640 medium supplemented with 10% fetal bovine serum and 1% penicillin-streptomycin (GibcoBRL, Grand Island, NY). HCT116 cells in exponential growth phase were exposed to various concentrations of the test compounds at 37°C for 72 hr in 5% carbon dioxide/air. After exposure to the agent, the cells were washed with 0.9% phosphate buffered saline. Growth inhibition was determined using WST-1 cell proliferation reagent as described above. The results are expressed as the growth fraction of treated cells compared with control cultures. Representative compounds of the present invention were tested for efficacy against the human colon HCT116 tumor cells. The data from these experiments are summarized in TABLE I.

TABLE I

| <u>EXAMPLE</u> | <u>IC<sub>50</sub> (μM)</u> | <u>EXAMPLE</u> | <u>IC<sub>50</sub> (μM)</u> |
|----------------|-----------------------------|----------------|-----------------------------|
| 1              | 4.2                         | 62             | 19.3                        |
| 3              | 2.5                         | 63             | 24.7                        |
| 5              | 3.8                         | 64             | 18.2                        |
| 6              | 4.0                         | 70             | 16.9                        |
| 9              | 1.7                         | 73             | 8.3                         |
| 10             | 12.1                        | 79             | 5.2                         |
| 11             | 5.5                         | 80             | 12.3                        |

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|    |      |     |      |
|----|------|-----|------|
| 14 | 40.0 | 81  | 11.3 |
| 15 | 10.4 | 82  | 12.4 |
| 16 | 3.8  | 86  | 1.6  |
| 17 | 15.8 | 87  | 5.5  |
| 18 | 9.3  | 88  | 4.8  |
| 20 | 2.4  | 89  | 4.8  |
| 21 | 30.4 | 90  | 4.5  |
| 23 | 15.9 | 92  | 17.4 |
| 24 | 37.1 | 93  | 18.1 |
| 25 | 9.6  | 94  | 3.6  |
| 26 | 6.1  | 95  | 4.3  |
| 30 | 10.1 | 96  | 34.7 |
| 32 | 7.8  | 97  | 7.0  |
| 33 | 7.8  | 98  | 13.0 |
| 34 | 16.5 | 99  | 33.5 |
| 35 | 17.0 | 100 | 9.2  |
| 36 | 28.4 | 101 | 12.4 |
| 37 | 15.5 | 102 | 6.3  |
| 38 | 13.9 | 103 | 11.9 |
| 41 | 14.5 | 104 | 22.2 |
| 42 | 3.3  | 105 | 14.8 |
| 44 | 18.7 | 106 | 4.6  |
| 45 | 20.7 | 108 | 16.0 |
| 46 | 4.8  | 109 | 25.1 |
| 47 | 8.7  | 110 | 3.5  |
| 49 | 14.7 | 111 | 15.0 |
| 50 | 10.5 | 112 | 2.8  |
| 51 | 26.7 | 115 | 33.6 |
| 53 | 11.2 | 116 | 5.9  |

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60

|    |      |     |      |
|----|------|-----|------|
| 55 | 9.5  | 117 | 12.4 |
| 56 | 16.8 | 121 | 24.5 |
| 57 | 5.0  | 122 | 25.8 |
| 59 | 15.0 | 123 | 37.7 |
| 60 | 6.6  | 124 | 5.6  |
| 61 | 14.2 | 126 | 18.5 |

#### Conventional Murine Tumor and Human Tumor Xenograft Assays

Inhibition of tumors transplanted into mice is an accepted procedure for studying the efficacy of antitumor agents (Corbett, *et al.*, In vivo Methods for Screening and

5 Preclinical Testing: Use of rodent solid tumors for drug discovery., In: Anticancer Drug Development Guide: Preclinical Screening, Clinical Trials, and Approval, B. Teicher (ed), Humana Press Inc., Totowa, NJ, Chapter 5, pages 75-99 (1997); (Corbett, *et al.*, Int. J. Pharmacog., 33, Supplement, 102-122 (1995)). Murine tumors or human xenographs were implanted essentially as described by Corbett in In vivo Methods for Screening and

10 Preclinical Testing: Use of rodent solid tumors for drug discovery. Briefly, the murine tumor or human xenograph was implanted subcutaneously using either 12-gauge trocar implants or counted number of cells. The location for the trocar insertion is midway between the axillary and inguinal region along the side of the mouse. The trocar is slipped approximately 3/4 of an inch subcutaneously up toward the axilla before  
15 discharging the tumor fragment, and pinching the skin as the trocar is removed. Alternatively, human tumor cells prepared from a brie of donor tumors ( $5 \times 10^6$  cells) were implanted subcutaneously in a hind-leg of a male or female nude mouse (Charles River). Either a test compound in vehicle or vehicle alone was administered by  
20 intravenous bolus injection (iv), intraperitoneal injection (ip), or oral gavage (po). Each treatment group, as well as a group of untreated control animals, consisted of five animals per group in each experiment. Subcutaneous tumor response was monitored by tumor volume measurement performed twice each week over the course of the experiment (60-120 days). Body weights were taken as a general measure of toxicity. The subcutaneous tumor data were analyzed by determining the median tumor weight for each treatment  
25 group over the course of the experiment and calculating the tumor growth delay as the

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difference in days for the treatment versus the control tumors to reach a volume of either 500 or 1000 mm<sup>3</sup>.

The compound of Example 110 was tested against a variety of murine and human tumors substantially as described supra. The data from these tests are summarized in  
5 TABLES II-XIII. The parameters measured in each experiment are summarized in the following paragraphs.

Tumor Weight(mg) =  $(a \times b^2)/2$  where a = tumor length (mm) and b = tumor width (mm).

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Tumor Growth Delay = T - C where T is the median time (days) required for the treatment group tumors to reach a predetermined size, and C is the median time (days) for the control group tumors to reach the same size. Tumor-free survivors are excluded from this calculation, and are tabulated separately (Tumor Free).

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Log Kill = Tumor Growth Delay  
(3.32)(Td)

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where Tumor Growth Delay is as previously defined and Td is tumor volume doubling time (days), estimated from the best fit straight line from a log-linear growth plot of the control group of tumors in exponential growth (100-800 mg range)

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%T/C mass - The treatment and control groups are measured when the control group tumors reach approximately 700 to 1200 mg in size (median group). The median tumor weight of each group is determined (including zeros). The T/C value in percent is an indication of antitumor effectiveness. A T/C  $\leq 42\%$  is considered significant antitumor activity. A T/C < 10% is considered to indicate highly significant antitumor activity.

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Body Weight Loss Nadir - A body weight loss nadir (mean of group) of greater than 20% or drug deaths greater than 20% are considered to indicate an excessively toxic dosage in single course trials.

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Activity Rating – the Activity Rating is derived from the Log Kill according to the following table:

| ANTITUMOR ACTIVITY | LOG KILL | ACTIVITY RATING |
|--------------------|----------|-----------------|
| HIGHLY ACTIVE      | >2.8     | ++++            |
|                    | 2.0-2.8  | +++             |
|                    | 1.3-1.9  | ++              |
|                    | 0.7-1.2  | +               |
| INACTIVE           | <0.7     | -               |

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TABLE II  
EARLY STAGE MURINE COLON ADENOCARCINOMA-38  
(BDF1 male mice, CRL-Raleigh)

| TOTAL DOSE (mg/kg) | % BODY WT LOSS AT NADIR | DRUG DEATHS | % T/C MASS | GROWTH DELAY (DAYS) | LOG KILL | TUMOR FREE AT DAY 144 | ACTIVITY RATING |
|--------------------|-------------------------|-------------|------------|---------------------|----------|-----------------------|-----------------|
| 0                  | +6.3%                   | 0/5         | -          | -                   | -        | 0/5                   | -               |
| 1200 <sup>a</sup>  | -5.2%                   | 0/6         | 0%         | All cures           | >4.5     | 6/6                   | +++             |
| 920 <sup>b</sup>   | +7.7%                   | 0/5         | 0%         | All cures           | >4.5     | 5/5                   | +++             |
| 272 <sup>c</sup>   | +3.1%                   | 0/5         | 0%         | All cures           | >4.5     | 5/5                   | +++             |

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<sup>a</sup>Drug was administered IV at 80 mg/kg on day 3, 160 mg/kg on day 4, 240 mg/kg on day 5, and 120 mg/kg/injection BID on days 7-9

<sup>b</sup>Drug was administered IV at 40 mg/kg on day 3, 80 mg/kg on day 4, and 160 mg/kg/injection QD on days 5-9

<sup>c</sup>Drug was administered IV at 20 mg/kg on day 3, 40 mg/kg on day 4, and 106 mg/kg/injection QD on days 5-6

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TABLE III  
EARLY STAGE MURINE MAMMARY ADENOCARCINOMA-16/C  
(C3H female mice, CRL-Kingston)

| TOTAL DOSE (mg/kg) | % BODY WT LOSS AT NADIR | DRUG DEATHS | % T/C MASS | GROWTH DELAY (DAYS) | LOG KILL | TUMOR FREE AT DAY 14 | ACTIVITY RATING |
|--------------------|-------------------------|-------------|------------|---------------------|----------|----------------------|-----------------|
| 0                  | +0.0%                   | 0/5         | -          | -                   | -        | 0/5                  | -               |
| DILUENT INFUSION   | +10.8                   | 0/4         | 60%        | 0.7                 | 0.22     | 0/4                  | -               |
| 560 <sup>a</sup>   | DEATH                   | 5/5         | -          | DEATH               | -        | 0/5                  | DEATH           |
| 560 <sup>b</sup>   | +10.9%                  | 0/4         | 37%        | 2.0                 | 0.6      | 0/4                  | ±               |
| 680 <sup>c</sup>   | +7.6%                   | 0/5         | 39%        | 2.5                 | 0.75     | 0/5                  | +               |

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<sup>a</sup>Drug was administered at 560 mg/kg by IV infusion over 3 hours on day 3  
<sup>b</sup>Drug was administered at 280 mg/kg/by IV infusion on days 3 and 7  
<sup>c</sup>Drug was administered IV at 80 mg/kg/injection on days 3-6, 120 mg/kg/injection on days 7-

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TABLE IV  
EARLY STAGE HUMAN COLON ADENOCARCINOMA-HCT116  
(Balb/C SCID female mice, NCI)

| TOTAL DOSE (mg/kg) | % BODY WT LOSS AT NADIR | DRUG DEATHS | % T/C MASS | GROWTH DELAY (DAYS) | LOG KILL | TUMOR FREE AT DAY 115 | ACTIVITY RATING |
|--------------------|-------------------------|-------------|------------|---------------------|----------|-----------------------|-----------------|
| 0                  | -4.2%                   | -           | -          | -                   | -        | 0/5                   | -               |
| 560 <sup>a</sup>   | -4.0%                   | 0/5         | 0%         | 56                  | 6.7      | 2/5                   | ++++            |
| 280 <sup>b</sup>   | 0%                      | 0/5         | 0%         | 28                  | 3.4      | 2/5                   | ++++            |

<sup>a</sup>Drug was administered 140 mg/kg/injection IV on days 3, 4, 5, and 9

<sup>b</sup>Drug was administered 70 mg/kg/injection IV on days 3, 4, 5, and 9

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TABLE V  
EARLY STAGE TAXOL SENSITIVE HUMAN COLON ADENOCARCINOMA #15/0  
(Balb/C SCID female mice, NCI)

| TOTAL<br>DOSE (mg/kg) | % BODY WT<br>LOSS AT<br>NADIR | DRUG<br>DEATHS | % T/C MASS | GROWTH<br>DELAY<br>(DAYS) | LOG KILL | TUMOR<br>FREE AT<br>DAY 151 | ACTIVITY<br>RATING |
|-----------------------|-------------------------------|----------------|------------|---------------------------|----------|-----------------------------|--------------------|
| 0                     | +4.3%                         | 0/5            | -          | -                         | -        | 0/5                         | -                  |
| 420*                  | 0%                            | 0/5            | 0%         | 33.5                      | 5.0      | 1/5                         | +++                |

\*Drug was administered 140 mg/kg/injection IV on days 3, 5, and 7

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TABLE VI  
EARLY STAGE MURINE SQUAMOUS LUNG LC-12  
(Balb/C female mice, NCI-Kingston)

| TOTAL<br>DOSE (mg/kg) | % BODY WT<br>LOSS AT<br>NADIR | DRUG<br>DEATHS | % T/C MASS | GROWTH<br>DELAY<br>(DAYS) | LOG KILL | TUMOR<br>FREE AT<br>DAY 174 | ACTIVITY<br>RATING |
|-----------------------|-------------------------------|----------------|------------|---------------------------|----------|-----------------------------|--------------------|
| 0                     | +6.5%                         | 0/5            | -          | -                         | -        | 0/5                         | -                  |
| 640 <sup>a</sup>      | 0%                            | 0/4            | 14%        | 12.5                      | 1.7      | 0/4                         | ++                 |
| 1391 <sup>b</sup>     | +1.6%                         | 0/5            | 20%        | 15.5                      | 2.1      | 0/5                         | +++                |

<sup>a</sup>Drug was administered at 160 mg/kg/injection IV on days 4, 6, 8, and 10

<sup>b</sup>Drug was administered at 107 mg/kg/injection IV on days 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28

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TABLE VII  
EARLY STAGE HUMAN PROSTATE LNCaP  
(Balb/C SCID female mice, NCI)

| TOTAL<br>DOSE (mg/kg) | % BODY WT<br>LOSS AT<br>NADIR | DRUG<br>DEATHS | % T/C MASS | GROWTH<br>DELAY<br>(DAYS) | LOG KILL         | TUMOR<br>FREE AT<br>DAY 185 | ACTIVITY<br>RATING |
|-----------------------|-------------------------------|----------------|------------|---------------------------|------------------|-----------------------------|--------------------|
| 0                     | +3.9%                         | -              | -          | -                         | -                | 0/5                         | -                  |
| 840 <sup>a</sup>      | +5.6%                         | 0/5            | 0          | 60 <sup>b</sup>           | 7.2 <sup>b</sup> | 4/5                         | ++++               |

<sup>a</sup>Drug was administered at 140 mg/kg/injection IV on days 3, 5, 7, 9, 10, and 11

<sup>b</sup>One mouse

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TABLE VIII  
UPSTAGED HUMAN BREAST WSU-Br-1  
(Balb/C SCID female mice, NCI)

| TOTAL DOSE (mg/kg) | % BODY WT LOSS AT NADIR | DRUG DEATHS | % T/C MASS | GROWTH DELAY (DAYS) | LOG KILL | TUMOR FREE AT DAY 179 | ACTIVITY RATING |
|--------------------|-------------------------|-------------|------------|---------------------|----------|-----------------------|-----------------|
| 0                  | +3.9%                   | -           | -          | -                   | -        | 0/5                   | -               |
| 725 <sup>a</sup>   | +3.9%                   | 0/5         | 0%         | 57                  | 2.9      | 2/5                   | ++++            |
| 500 <sup>b</sup>   | +14%                    | 0/5         | 0%         | 39                  | 2.0      | 2/5                   | ++++            |

<sup>a</sup>Drug was administered at 145 mg/kg/injection IV on days 11-13 and 19-20

<sup>b</sup>Drug was administered at 100 mg/kg/injection IV on days 11-13 and 19-20

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TABLE IX  
EARLY STAGE HUMAN OVARIAN BG-1  
(Balb/C SCID female mice, NCI)

| TOTAL<br>DOSE (mg/kg) | % BODY WT<br>LOSS AT<br>NADIR | DRUG<br>DEATHS | % T/C MASS | GROWTH<br>DELAY<br>(DAYS) | LOG KILL | TUMOR<br>FREE AT<br>DAY 176 | ACTIVITY<br>RATING |
|-----------------------|-------------------------------|----------------|------------|---------------------------|----------|-----------------------------|--------------------|
| 0                     | 0%                            | -              | -          | -                         | -        | 0/5                         | -                  |
| 870 <sup>a</sup>      | -2.0%                         | 0/5            | 0%         | 30.5                      | 3.7      | 1/5                         | ++++               |
| 600 <sup>b</sup>      | -3.0%                         | 0/5            | 0%         | 30                        | 3.6      | 0/5                         | ++++               |

<sup>a</sup>Drug was administered at 145 mg/kg/injection IV on days 3-5 and 9-11

<sup>b</sup>Drug was administered at 100 mg/kg/injection IV on days 3-5 and 9-11

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TABLE X  
EARLY STAGE MURINE COLON CARCINOMA-26  
(Balb/C female mice, NCI-Kingston-CRL)

| TOTAL DOSE (mg/kg) | % BODY WT LOSS AT NADIR | DRUG DEATHS | % T/C MASS | GROWTH DELAY (DAYS) | LOG KILL | TUMOR FREE AT DAY 31 | ACTIVITY RATING |
|--------------------|-------------------------|-------------|------------|---------------------|----------|----------------------|-----------------|
| 0                  | +1.8%                   | 0/5         | -          | -                   | -        | 0/5                  | -               |
| 1600 <sup>a</sup>  | +15%                    | 0/5         | 34%        | 15                  | 2.2      | 0/5                  | +++             |
| 1305 <sup>b</sup>  | +15%                    | 0/5         | 28%        | 6                   | 0.9      | 0/5                  | +               |
| 1740 <sup>c</sup>  | +17%                    | 0/5         | 34%        | 14                  | 2.1      | 0/5                  | +++             |

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<sup>a</sup>Drug was administered at 100 mg/kg/injection IV BID on days 1, 3, 5, 7, 13, 15, 17, and 21

<sup>b</sup>Drug was administered at 145 mg/kg/injection IV on days 1, 3, 5, 7, 9, 13, 15, 17, and 19

<sup>c</sup>Drug was administered at 145 mg/kg/injection IV on days 1, 2, 3, 7, 8, 13, 14, 16, 18, and 20-22.

TABLE XI  
EARLY STAGE HUMAN SQUAMOUS CELL LUNG CARCINOMA MRI-H165  
(Balb/C SCID female mice, NCI)

| TOTAL<br>DOSE (mg/kg) | % BODY WT<br>LOSS AT<br>NADIR | DRUG<br>DEATHS | % T/C MASS | GROWTH<br>DELAY<br>(DAYS) | LOG KILL | TUMOR<br>FREE AT<br>DAY 55 | ACTIVITY<br>RATING |
|-----------------------|-------------------------------|----------------|------------|---------------------------|----------|----------------------------|--------------------|
| 0                     | 0%                            | -              | -          | -                         | -        | 0/5                        | -                  |
| 600*                  | -2.1%                         | 0/5            | 0%         | 31                        | 3.7      | 0/5                        | +++                |

\*Drug was administered at 100 mg/kg/injection IV on days 3-5 and 10-12

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TABLE XII  
EARLY STAGE TAXOL RESISTANT HUMAN COLON ADENOCARCINOMA #15/MDR  
(Balb/C SCID female mice, NCI)

| TOTAL<br>DOSE (mg/kg) | % BODY WT<br>LOSS AT<br>NADIR | DRUG<br>DEATHS | % T/C MASS | GROWTH<br>DELAY<br>(DAYS) | LOG KILL | TUMOR<br>FREE AT<br>DAY 38 | ACTIVITY<br>RATING |
|-----------------------|-------------------------------|----------------|------------|---------------------------|----------|----------------------------|--------------------|
| 0                     | 0%                            | 0/5            | -          | -                         | -        | 0/5                        | -                  |
| 500*                  | +2.1%                         | 0/5            | 10%        | 11                        | 1.4      | 0/5                        | ++                 |

\*Drug was administered at 100 mg/kg/injection IV on days 3-5 and 13-14

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TABLE XIII  
EARLY UPSTAGED MURINE COLON ADENOCARCINOMA-38 BY IV, PO, SC, AND IP ROUTES  
(BDF1 female mice, CRL-Raleigh-NCI)

| TOTAL DOSE (mg/kg)  | % BODY WT LOSS AT NADIR | DRUG DEATHS | % T/C MASS | GROWTH DELAY (DAYS) | LOG KILL         | TUMOR FREE AT DAY 161 | ACTIVITY RATING      |
|---------------------|-------------------------|-------------|------------|---------------------|------------------|-----------------------|----------------------|
| 0                   | +6.5%                   | -           | -          | -                   | -                | 0/5                   | -                    |
| 450 IV <sup>a</sup> | +8.9%                   | 0/5         | 0%         | 18                  | 2.4 <sup>f</sup> | 2/5                   | +++                  |
| 780 PO <sup>b</sup> | +9.7%                   | 0/3         | 0%         | All cures           | >4.5             | 3/3                   | +++                  |
| 450 PO <sup>c</sup> | +6.8%                   | 0/3         | 0%         | 22.5                | 3.0 <sup>f</sup> | 2/3                   | +++                  |
| 450 SC <sup>d</sup> | +13.2%                  | 0/2         | 5.7%       | 10.5                | 1.4 <sup>f</sup> | 1/2                   | ++/++++ <sup>g</sup> |
| 450 IP <sup>e</sup> | +8.3%                   | 0/2         | 3.7%       | 17                  | 2.2 <sup>f</sup> | 1/2                   | ++/++++ <sup>g</sup> |

<sup>a</sup>Drug was administered at 150 mg/kg/injection IV on days 5, 7, and 9

<sup>b</sup>Drug was administered at 260 mg/kg/injection orally on days 5, 7, and 9

<sup>c</sup>Drug was administered at 150 mg/kg/injection orally on days 5, 7, and 9

<sup>d</sup>Drug was administered at 150 mg/kg/injection subcutaneously on days 5, 7, and 9

<sup>e</sup>Drug was administered at 150 mg/kg/injection IP on days 5, 7, and 9

<sup>f</sup>Log kill of regrowing tumors only (median)

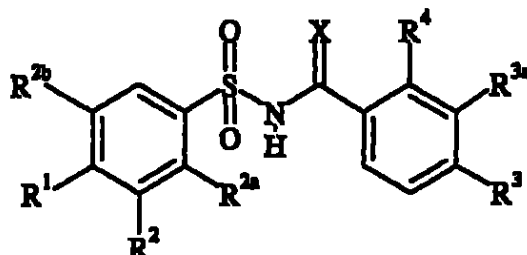
<sup>g</sup>Activity rating for each mouse in study. One mouse was cured in each study, representing a "++++" rating. The other activity rating is based on the log kill calculated for the other mouse in the study.

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## We Claim

1 A compound of Formula I.



I

5 where

X is O or NH,

10 R<sup>1</sup> is hydrogen, halo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> alkylthio, CF<sub>3</sub>, OCF<sub>3</sub>, SCF<sub>3</sub>, (C<sub>1</sub>-C<sub>4</sub> alkoxy)carbonyl, nitro, azido, O(SO<sub>2</sub>)CH<sub>3</sub>, N(CH<sub>3</sub>)<sub>2</sub>, hydroxy, phenyl, substituted phenyl, pyridinyl, thienyl, furyl, quinolynyl, or triazolyl,

R<sup>2</sup> is hydrogen, halo, cyano, CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkyl, (C<sub>1</sub>-C<sub>4</sub> alkoxy)carbonyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, phenyl, or quinolynyl,

R<sup>2a</sup> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkoxy;

15 R<sup>2b</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl provided that at least one of R<sup>2a</sup> and R<sup>2b</sup> is hydrogen,

R<sup>3</sup> is hydrogen, halo, C<sub>1</sub>-C<sub>6</sub> alkyl, CF<sub>3</sub>, or nitro,

R<sup>3a</sup> is hydrogen, halo, or C<sub>1</sub>-C<sub>6</sub> alkyl provided that when R<sup>3a</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl, R<sup>3</sup> is hydrogen and R<sup>4</sup> is halo, and

20 R<sup>4</sup> is halo, C<sub>1</sub>-C<sub>6</sub> alkyl, or CF<sub>3</sub> provided that only one of R<sup>3</sup> and R<sup>4</sup> may be C<sub>1</sub>-C<sub>6</sub> alkyl and provided that when R<sup>4</sup> is halo or C<sub>1</sub>-C<sub>6</sub> alkyl only one of R<sup>3</sup> and R<sup>3a</sup> is hydrogen, or a pharmaceutically acceptable base addition salt thereof, provided that

25 a) when R<sup>3</sup> and R<sup>4</sup> are both chloro and R<sup>2</sup> is hydrogen, R<sup>1</sup> is bromo, iodo, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> alkylthio, CF<sub>3</sub>, OCF<sub>3</sub>, nitro, azido, O(SO<sub>2</sub>)CH<sub>3</sub>, N(CH<sub>3</sub>)<sub>2</sub>, hydroxy, phenyl, substituted phenyl, pyridinyl, thienyl, furyl, or triazolyl,

b) when R<sup>3</sup> and R<sup>4</sup> are both chloro and R<sup>1</sup> is hydrogen, R<sup>2</sup> is bromo, fluoro, CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, phenyl, or quinolynyl

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x5

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2 The compound of claim 1, wherein  $R^2$ ,  $R^{2a}$ , and  $R^{2b}$  are hydrogen and  $R^1$  is selected from the group consisting of hydrogen, halo,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_4$  alkoxy,  $C_1$ - $C_4$  alkylthio,  $CF_3$ ,  $OCF_3$ ,  $SCF_3$ , ( $C_1$ - $C_4$  alkoxy)carbonyl, nitro, azido,  $O(SO_2)CH_3$ ,  $N(CH_3)_2$ , hydroxy, phenyl, substituted phenyl, pyridinyl, thienyl, furyl, quinolynyl, and triazolyl

5

3 The compound of claim 1 or 2, wherein the compound is a pharmaceutically acceptable base addition salt.

4 The compound of claim 3, wherein the pharmaceutically acceptable base addition salt is a sodium salt.

10

5 The compound of claim 1 which is *N*-[2-chloro-4-bromobenzoyl]-4-chlorophenylsulfonamide or a base addition salt thereof

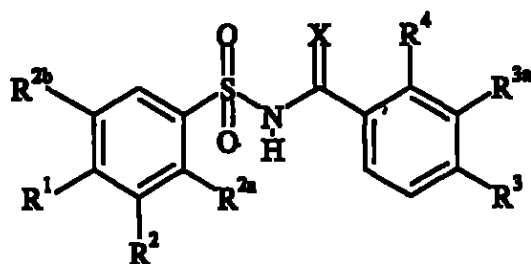
6 The compound of claim 1 which is *N*-[2,4-dichlorobenzoyl]phenylsulfonamide or a base addition salt thereof

15

7 The compound of claim 5 or 6 wherein the base addition salt is a sodium salt.

20

8 A method of treating susceptible neoplasms in a mammal comprising administering to a mammal in need of such treatment an oncolytically effective amount of a compound of Formula II



II

25

where

$X$  is O or NH,

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$R^1$  is hydrogen, halo,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_4$  alkoxy,  $C_1$ - $C_4$  alkylthio,  $CF_3$ ,  $OCF_3$ ,  $SCF_3$ ,  $(C_1$ - $C_4$  alkoxy)carbonyl, nitro, azido,  $O(SO_2)CH_3$ ,  $N(CH_3)_2$ , hydroxy, phenyl, substituted phenyl, pyridinyl, thienyl, furyl, quinoliny, or triazolyl,

$R^2$  is hydrogen, halo, cyano,  $CF_3$ ,  $C_1$ - $C_6$  alkyl,  $(C_1$ - $C_4$  alkoxy)carbonyl,  $C_1$ - $C_4$  alkoxy, phenyl, or quinoliny,

$R^{2a}$  is hydrogen or  $C_1$ - $C_4$  alkoxy,

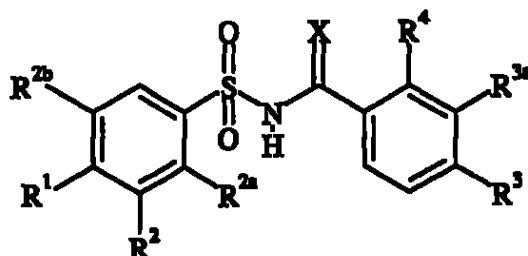
$R^{2b}$  is hydrogen or  $C_1$ - $C_6$  alkyl provided that at least one of  $R^{2a}$  and  $R^{2b}$  is hydrogen,

$R^3$  is hydrogen, halo,  $C_1$ - $C_6$  alkyl,  $CF_3$ , or nitro,

$R^{3a}$  is hydrogen, halo, or  $C_1$ - $C_6$  alkyl provided that when  $R^{3a}$  is  $C_1$ - $C_6$  alkyl,  $R^3$  is hydrogen and  $R^4$  is halo, and

$R^4$  is halo,  $C_1$ - $C_6$  alkyl, or  $CF_3$  provided that only one of  $R^3$  and  $R^4$  may be  $C_1$ - $C_6$  alkyl and provided that when  $R^4$  is halo or  $C_1$ - $C_6$  alkyl only one of  $R^3$  and  $R^{3a}$  is hydrogen, or a pharmaceutically acceptable base addition salt thereof

9 A pharmaceutical formulation comprising a compound of Formula II.



II

where.

20  $X$  is O or NH,

$R^1$  is hydrogen, halo,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_4$  alkoxy,  $C_1$ - $C_4$  alkylthio,  $CF_3$ ,  $OCF_3$ ,  $SCF_3$ ,  $(C_1$ - $C_4$  alkoxy)carbonyl, nitro, azido,  $O(SO_2)CH_3$ ,  $N(CH_3)_2$ , hydroxy, phenyl, substituted phenyl, pyridinyl, thienyl, furyl, quinoliny, or triazolyl,

$R^2$  is hydrogen, halo, cyano,  $CF_3$ ,  $C_1$ - $C_6$  alkyl,  $(C_1$ - $C_4$  alkoxy)carbonyl,  $C_1$ - $C_4$  alkoxy, phenyl, or quinoliny,

$R^{2a}$  is hydrogen or  $C_1$ - $C_4$  alkoxy,

$R^{2b}$  is hydrogen or  $C_1$ - $C_6$  alkyl provided that at least one of  $R^{2a}$  and  $R^{2b}$  is hydrogen,

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$R^3$  is hydrogen, halo,  $C_1$ - $C_6$  alkyl,  $CF_3$ , or nitro,

$R^{3a}$  is hydrogen, halo, or  $C_1$ - $C_6$  alkyl provided that when  $R^{3a}$  is  $C_1$ - $C_6$  alkyl,  $R^3$  is hydrogen and  $R^4$  is halo, and

- $R^4$  is halo,  $C_1$ - $C_6$  alkyl, or  $CF_3$  provided that only one of  $R^3$  and  $R^4$  may be  $C_1$ - $C_6$  alkyl and provided that when  $R^4$  is halo or  $C_1$ - $C_6$  alkyl only one of  $R^3$  and  $R^{3a}$  is hydrogen, or a pharmaceutically acceptable base addition salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

(12) SOLICITUD INTERNACIONAL PUBLICADA EN VIRTUD DEL TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES (PCT)

(19) Organización Mundial de la Propiedad Intelectual  
Oficina Internacional

(43) Fecha de Publicación Internacional  
12 de diciembre de 2002 (12.12.2002)

WIPO  
OMPI

(Código de Barras)  
(10) Número de Publicación Internacional  
WO 02/088848 A1

PCT

(81) Clasificación Internacional de Patente : C07C 311/81.  
321/28, C07D 213/34, 215/12, 307/38, 333/18, 521/00,  
A61K 31/18, 31/82, A61P 35/00.

(21) Número de Solicitud Internacional: PCT / US 02 / 18142

(22) Fecha de Presentación Internacional: 29 de junio de 2001 (29 . 06 . 2001)

(28) Idioma de presentación: Inglés

(26) Idioma de publicación: Inglés

(30) Datos de prioridad:

60 / 298.350 6 de junio de 2001 (06.06.2001) US

(71) Solicitante para todos los países designados excepto EE.UU.: ELI LILLY  
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(81) Estados Designados (fase nacional) : EA, AG, AL, AM, AT, (modelo de  
utilidad), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ,  
(modelo de utilidad), CZ, DE (modelo de utilidad), DE, DK(modelo de utilidad),  
DK, DM, DZ, EC, EE, (modelo de utilidad), EE, ES, FI, (modelo de utilidad) FI GB,  
GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,  
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD,  
SE, SG, SI, SK, (modelo de utilidad), SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US,  
UZ, VN, YU, ZA, ZW.

(84) Estados Designados (fase regional) : Patente ARIPO (GH, GM, KE, LS,  
MW, MZ, SD, SL, SZ, TZ, UG, ZW), Patente Euroasiática: (AM, AZ, BY, KG, KZ,  
MD, RU, TJ, TM), Patente Europea (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB,  
GR, IE, IT, LU, MC, NL, PT, SE, TR), Patente OAPI (BF, BJ, CF, CG, CI, CM, GA,  
GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaraciones bajo la regla 4.17:

-Por el poder del solicitante para solicitar y que le sea concedida una patente  
(Regla 4.17 (i)) para las siguientes designaciones: AE, AG, AL, AM, AT, AU, AZ,  
BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC,  
EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, DE, DG, DP, DR,  
DZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM,  
PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UN, UG,  
UZ, VN, YU, ZA, ZW. Patente ARIPO (GH, GM, KE, LS, MW, MZ, SD, SL, SZ,  
TZ, UG, ZW). Patente euroasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM,  
Patente Europea (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC,  
NL, PT, SE, TR) Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,  
MR, NE, SN, TD, TG).

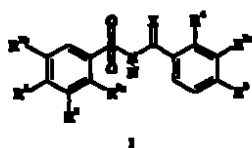
-Por el poder del solicitante para reivindicar la prioridad de una solicitud anterior  
(Regla 4.17 (ii)) por las siguientes designaciones: AE, AG, AL, AM, AT, AU, AZ,  
BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC,  
EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, DE, DG, DP, DR,  
DZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM,  
PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UN, UG,  
UZ, VN, YU, ZA, ZW. Patente ARIPO (GH, GM, KE, LS, MW, MZ, SD, SL, SZ,  
TZ, UG, ZW). Patente euroasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM,  
Patente Europea (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC,  
NL, PT, SE, TR) Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,  
MR, NE, SN, TD, TG).

Publicada:

- Con informe de búsqueda Internacional  
Para los códigos de dos letras y otras abreviaturas, véanse las "Notas Directrices  
sobre Códigos y Abreviaturas" que aparecen al principio de cada ejemplar de la  
Gaceta PCT.

(84) Título : BENZOILSULFANAMIDAS Y SULFONILBENZAMIDINAS QUE SE USAN COMO AGENTES ANTITUMORALES

(57) Resumen: La presente invención proporciona compuestos antitumorales de la Fórmula (i), y métodos antitumorales.



i

## **BENZOILSULFANAMIDAS Y SULFONILBENZAMIDINAS QUE SE USAN COMO AGENTES ANTITUMORALES**

### **ANTECEDENTES DE LA INVENCION**

5           En los últimos años se han logrado avances fundamentales en el desarrollo de agentes químicos y regímenes de terapia para combatir enfermedades neoplásicas. A pesar de estos avances continuos, los cánceres continúan ejerciendo niveles intolerables de dolor y sufrimiento humano. La necesidad de procedimientos nuevos y mejores de tratamiento de neoplasias y leucemias malignas refuerza los esfuerzos para crear nuevas clases de compuestos, especialmente en el área de tumores sólidos inoperables o metastáticos. La avalancha de información reciente con respecto a los procedimientos biológicos básicos implicados en neoplasias ha llevado a un conocimiento más profundo de la heterogeneidad de los tumores. Debido a esta heterogeneidad extrema entre poblaciones de células neoplásicas, los nuevos agentes quimioterapéuticos deberían tener un amplio espectro de actividad y un índice terapéutico aceptable. Además, dichos agentes pueden ser químicamente estables y compatibles con otros agentes. También es importante que cualquier régimen quimioterapéutico sea tan conveniente e indoloro como sea posible para el paciente.

          En el tratamiento del cáncer se usan frecuentemente quimioterapia y radiación y, aunque a menudo producen alguna respuesta en la enfermedad maligna, en muy pocas ocasiones son curativos. La mayoría de tumores sólidos aumentan de masa durante la proliferación de las células malignas y las células estromales, incluyendo células endoteliales. Para que un tumor crezca

más de 2-3 milímetros de diámetro, debe formar una vasculatura, un proceso conocido como angiogénesis. Se ha presentado que la supresión de la angiogénesis inducida por el tumor por angiostatina y endostatina da como resultado una actividad antitumoral (O'Reilly, et al., Cell, 88, 277-285 (1997)).

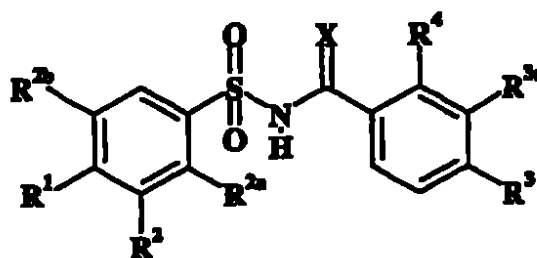
- 5 Debido a que la angiogénesis es un componente crítico de la expansión de masa de la mayoría de los tumores sólidos, el desarrollo de nuevos agentes para la inhibición de este proceso representa un planteamiento prometedor para la terapia antitumoral. Este planteamiento para la teoría antitumoral puede carecer de los efectos secundarios tóxicos o propiedades inductoras de
- 10 resistencia a fármacos de la quimioterapia convencional (Judah Folkman, Endogenous Inhibitors of Angiogenesis, The Harvey Lectures, Series 92, páginas 65-82, Wiley-Liss Inc., (1998)).

- Las *N*-[benzoi]l-fenilsulfonamidas se conocen bien en las técnicas de química agrícola como insecticidas y herbicidas (DE 2744137). El uso de *N*-
- 15 [benzoi]l-fenilsulfonamidas como agentes antitumorales en general, o como inhibidores de angiogénesis en particular, no se ha contemplado hasta ahora.

### BREVE SUMARIO DE LA INVENCION

La presente invención proporciona un compuesto de Fórmula I:

20



25

I

81

en la que:

X es O o NH;

R<sup>1</sup> es hidrógeno, halo, alquilo C<sub>1</sub>-C<sub>8</sub>, alcoxi C<sub>1</sub>-C<sub>4</sub>, alquiltio C<sub>1</sub>-C<sub>4</sub>, CF<sub>3</sub>, OCF<sub>3</sub>, SCF<sub>3</sub>, (alcoxi C<sub>1</sub>-C<sub>4</sub>)carbonilo, nitro, azido, O(SO<sub>2</sub>)CH<sub>3</sub>, N(CH<sub>3</sub>)<sub>2</sub>, hidroxi, fenilo, fenilo sustituido, piridinilo, tienilo, furilo, quinolinilo o triazolilo;

R<sup>2</sup> es hidrógeno, halo, ciano, CF<sub>3</sub>, alquilo C<sub>1</sub>-C<sub>8</sub>, (alcoxi C<sub>1</sub>-C<sub>4</sub>)carbonilo, alcoxi C<sub>1</sub>-C<sub>4</sub>, fenilo o quinolinilo;

R<sup>2a</sup> es hidrógeno o alcoxi C<sub>1</sub>-C<sub>4</sub>;

R<sup>2b</sup> es hidrógeno o alquilo C<sub>1</sub>-C<sub>8</sub>, con tal que al menos uno de R<sup>2a</sup> y R<sup>2b</sup> sea hidrógeno;

R<sup>3</sup> es hidrógeno, halo, alquilo C<sub>1</sub>-C<sub>8</sub>, CF<sub>3</sub> o nitro;

R<sup>3a</sup> es hidrógeno, halo o alquilo C<sub>1</sub>-C<sub>8</sub>, con tal que cuando R<sup>3a</sup> sea alquilo C<sub>1</sub>-C<sub>8</sub>, R<sup>3</sup> es hidrógeno y R<sup>4</sup> es halo; y

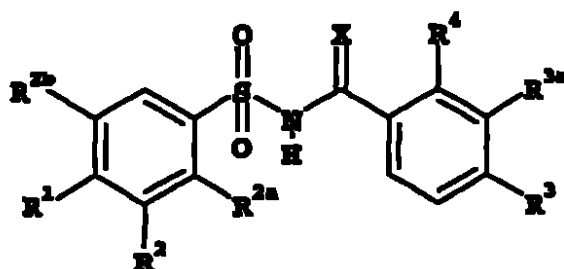
R<sup>4</sup> es halo, alquilo C<sub>1</sub>-C<sub>8</sub>, o CF<sub>3</sub> con tal que sólo uno de R<sup>3</sup> y R<sup>4</sup> puede ser alquilo C<sub>1</sub>-C<sub>8</sub>, y con tal que cuando R<sup>4</sup> es halo o alquilo C<sub>1</sub>-C<sub>8</sub>, sólo uno de R<sup>3</sup> y R<sup>3a</sup> es hidrógeno; o una sal de adición de base aceptable farmacéuticamente de los mismos, con tal que:

- a) cuando R<sup>3</sup> y R<sup>4</sup> son ambos cloro y R<sup>2</sup> es hidrógeno, R<sup>1</sup> es bromo, yodo, alcoxi C<sub>1</sub>-C<sub>4</sub>, alquiltio C<sub>1</sub>-C<sub>4</sub>, CF<sub>3</sub>, OCF<sub>3</sub>, nitro, azido, O(SO<sub>2</sub>)CH<sub>3</sub>, N(CH<sub>3</sub>)<sub>2</sub>, hidroxi, fenilo, fenilo sustituido, piridinilo, tienilo, furilo o triazolilo;
- b) cuando R<sup>3</sup> y R<sup>4</sup> son ambos cloro y R<sup>1</sup> es hidrógeno, R<sup>2</sup> es bromo, flúor, CF<sub>3</sub>, alquilo C<sub>1</sub>-C<sub>8</sub>, alcoxi C<sub>1</sub>-C<sub>4</sub>, fenilo o quinolinilo.

La presente invención proporciona también un procedimiento de

tratamiento de neoplasias susceptibles en un mamífero que comprende administrar a un mamífero que necesite dicho tratamiento una cantidad oncolíticamente eficaz de un compuesto de Fórmula II:

5



II

10 en la que:

X es O o NH;

R<sup>1</sup> es hidrógeno, halo, alquilo C<sub>1</sub>-C<sub>6</sub>, alcoxi C<sub>1</sub>-C<sub>4</sub>, alquiltio C<sub>1</sub>-C<sub>4</sub>, CF<sub>3</sub>, OCF<sub>3</sub>, SCF<sub>3</sub>, (alcoxi C<sub>1</sub>-C<sub>4</sub>)carbonilo, nitro, azido, O(SO<sub>2</sub>)CH<sub>3</sub>, N(CH<sub>3</sub>)<sub>2</sub>, hidroxil, fenilo, fenilo sustituido, piridinilo, tienilo, furilo, quinolinilo o triazolilo;

15

R<sup>2</sup> es hidrógeno, halo, clano, CF<sub>3</sub>, alquilo C<sub>1</sub>-C<sub>6</sub>, (alcoxi C<sub>1</sub>-C<sub>4</sub>)carbonilo, alcoxi C<sub>1</sub>-C<sub>4</sub>, fenilo o quinolinilo;

R<sup>2a</sup> es hidrógeno o alcoxi C<sub>1</sub>-C<sub>4</sub>,

R<sup>2b</sup> es hidrógeno o alquilo C<sub>1</sub>-C<sub>6</sub>, con tal que al menos uno de R<sup>2a</sup> y R<sup>2b</sup> sea hidrógeno;

20

R<sup>3</sup> es hidrógeno, halo, alquilo C<sub>1</sub>-C<sub>6</sub>, CF<sub>3</sub> o nitro;

R<sup>3a</sup> es hidrógeno, halo o alquilo C<sub>1</sub>-C<sub>6</sub>, con tal que cuando R<sup>3a</sup> sea alquilo C<sub>1</sub>-C<sub>6</sub>, R<sup>3</sup> sea hidrógeno y R<sup>4</sup> sea halo, y

R<sup>4</sup> es halo, alquilo C<sub>1</sub>-C<sub>6</sub>, o CF<sub>3</sub>, con tal que solo uno de R<sup>3</sup> y R<sup>4</sup> puede ser alquilo C<sub>1</sub>-C<sub>6</sub>, y con tal que cuando R<sup>4</sup> sea halo o alquilo C<sub>1</sub>-C<sub>6</sub>, sólo uno de

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R<sup>3</sup> y R<sup>3a</sup> es hidrógeno; o una sal de adición de base aceptable

farmacéuticamente del mismo.

La presente invención proporciona también un procedimiento para suprimir la angiogénesis tumoral en un mamífero que comprende administrar a un mamífero que necesite dicho tratamiento una cantidad supresora de angiogénesis de un compuesto de Fórmula II o una sal de adición de base  
5 aceptable farmacéuticamente del mismo.

La presente invención proporciona también una formulación farmacéutica que comprende un compuesto de Fórmula II o una sal de adición de base aceptable farmacéuticamente del mismo, combinado con un vehículo,  
10 diluyente o excipiente aceptable farmacéuticamente.

Esta invención proporciona también el uso de un compuesto de Fórmula II para la preparación de un medicamento para el tratamiento de neoplasias susceptibles. Adicionalmente, la invención proporciona una formulación farmacéutica concebida para el tratamiento de neoplasias susceptibles que  
15 contiene un compuesto de Fórmula II. Además, esta invención incluye un procedimiento de tratamiento de neoplasias susceptibles que comprende administrar una cantidad eficaz de un compuesto de Fórmula II.

### DESCRIPCIÓN DETALLADA DE LA INVENCION

20 Los términos químicos generales usados en las fórmulas anteriores tienen sus significados habituales. Por ejemplo, el término "alquilo C<sub>1</sub>-C<sub>8</sub>" incluye restos metilo, etilo, propilo, isopropilo, butilo, isobutilo, *sec*-butilo, *terc*-butilo, pentilo y hexilo. El término "alquilo C<sub>1</sub>-C<sub>4</sub>" se incluye en el significado de alquilo C<sub>1</sub>-C<sub>8</sub>, y se considera que significa metilo, etilo, propilo, isopropilo,  
25 butilo, isobutilo, *sec*-butilo y *terc*-butilo. El término "alcoxi C<sub>1</sub>-C<sub>4</sub>" se considera

que significa un grupo alquilo C<sub>1</sub>-C<sub>4</sub> unido a la molécula precursora mediante un átomo de oxígeno e incluye grupo metoxi, etoxi e isopropoxi. Análogamente, el término "alquiltio C<sub>1</sub>-C<sub>4</sub>" se considera que significa un grupo alquilo C<sub>1</sub>-C<sub>4</sub> unido a la molécula precursora mediante un átomo de azufre e incluye metiltio, etiltio e isobutiltio. El término "halo" se considera que significa cloro, flúor, bromo y yodo. El término "fenilo sustituido" se refiere a un fenilo monosustituido en el que las sustituciones se seleccionan del grupo constituido por alcoxi C<sub>1</sub>-C<sub>4</sub>, alquiltio C<sub>1</sub>-C<sub>4</sub>, acilo C<sub>1</sub>-C<sub>4</sub>, trifluorometilo y halo. El término "acilo" se refiere a un grupo ácido orgánico en el que el OH del grupo carboxi se sustituye por cualquier otro sustituyente (RCO-).

Cuando X=NH, la molécula puede existir en dos formas tautoméricas,



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La presente invención contempla ambas formas.

Mientras que todos los compuestos de Fórmula II son agentes antitumorales útiles, se prefieren ciertas clases de compuestos. Los siguientes párrafos describen dichas clases preferidas.

- 20 a) R<sup>1</sup> es hidrógeno y R<sup>2</sup> es bromo;
- b) R<sup>1</sup> es flúor y R<sup>2</sup> es cloro;
- c) R<sup>1</sup> es flúor;
- d) R<sup>1</sup> es cloro;
- e) R<sup>1</sup> es metilo;
- 25 f) R<sup>1</sup> es metiltio;

- g)  $R^2$  es hidrógeno;
- h)  $R^3$  es cloro, bromo o  $CF_3$ ;
- i)  $R^3$  es cloro;
- j)  $R^3$  es bromo;
- 5 k)  $R^3$  es  $CF_3$ ;
- l)  $R^{3a}$  es hidrógeno;
- m)  $R^4$  es cloro, bromo, metilo o  $CF_3$ ;
- n)  $R^4$  es cloro;
- o)  $R^4$  es bromo;
- 10 p)  $R^4$  es metilo;
- q)  $R^4$  es  $CF_3$ ;
- r)  $R^3$  y  $R^4$  son ambos cloro;
- s)  $R^3$  y  $R^4$  son ambos  $CF_3$ ;
- t)  $R^3$  es bromo y  $R^4$  es cloro;
- 15 u)  $R^{3a}$  es hidrógeno y  $R^3$  y  $R^4$  son distintos de hidrógeno;
- v) X es O;
- w) El compuesto de Fórmula II en el que el compuesto es una sal de adición de base aceptable farmacéuticamente;
- x) El compuesto de Fórmula II en el que el compuesto es una sal de sodio;
- 20 y)  $R^1$ ,  $R^{2a}$  y  $R^{2b}$  son hidrógeno y  $R^2$  se selecciona del grupo constituido por halo, alquilo  $C_1-C_4$ , alcoxi  $C_1-C_4$ , clano, trifluorometilo y quinilnilo;
- z)  $R^2$  y  $R^{2b}$  son hidrógeno,  $R^1$  es halo o alquilo  $C_1-C_4$ , y  $R^{2a}$  es alquilo  $C_1-C_4$  o alcoxi  $C_1-C_4$ ; o
- 25

aa)  $R^{2a}$  es hidrógeno,  $R^1$  es alcoxi  $C_1-C_4$ , y  $R^2$  y  $R^{2b}$  son alquilo  $C_1-C_4$ .

Adicionalmente, las siguientes clases son especialmente preferidas.

- 5 a)  $R^2$ ,  $R^{2a}$  y  $R^{2b}$  son hidrógeno y  $R^1$  se selecciona del grupo constituido por hidrógeno, halo, alquilo  $C_1-C_6$ , alcoxi  $C_1-C_4$ , alquiltio  $C_1-C_4$ ,  $CF_3$ ,  $OCF_3$ ,  $SCF_3$ , (alcoxi  $C_1-C_4$ )carbonilo, nitro, azido,  $O(SO_2)CH_3$ ,  $N(CH_3)_2$ , hidroxi, fenilo, fenilo sustituido, piridinilo, tienilo, furilo, quinolinilo y triazolilo; o
- 10 b)  $R^{2a}$  y  $R^{2b}$  son hidrógeno y  $R^1$  se selecciona del grupo constituido por halo y alquilo  $C_1-C_4$ , y  $R^2$  se selecciona del grupo constituido por halo, alquilo  $C_1-C_4$ , y alcoxi  $C_1-C_4$  carbonilo.

Debe entenderse que las clases preferidas y especialmente preferidas anteriores se pueden combinar para formar clases preferidas y especialmente preferidas adicionales.

- 15 Los compuestos de Fórmula II son agentes antineoplásicos. Por lo tanto, la presente invención proporciona un procedimiento de tratamiento de una neoplasia susceptible en un animal que comprende administrar a un mamífero que necesite dicho tratamiento una cantidad oncolíticamente eficaz de un compuesto de Fórmula II. Se cree que los presentes compuestos son útiles en
- 20 el tratamiento de carcinomas como por ejemplo neoplasias del sistema nervioso central: glioblastoma multiforme, astrocitoma, tumores oligodendrogliales, tumores del plexo endimiario y corioide, tumores pineales, tumores neuronales, meduloblastoma, schwannonma, meningioma, sarcoma meningeal; neoplasias oculares: carcinoma celular basal, carcinoma
- 25 escamoso, melanoma, rabadomiosarcoma, retinoblastoma; neoplasias de las

glándulas endocrinas: neoplasias pituitarias, neoplasias del tiroides, neoplasias del cortex adrenal, neoplasias del sistema neuroendocrino, neoplasias del sistema endocrino gastroenteropancreático, neoplasias de las gónadas; neoplasias de la cabeza y del cuello; cáncer de la cabeza y el cuello, tumores

5 en la cavidad oral, faringe, laringe, odontogénicos; neoplasias del tórax: carcinoma pulmonar de células grandes, carcinoma pulmonar de células pequeñas, carcinoma pulmonar de células no pequeñas, mesotelioma maligno, timomas, tumores celulares de germen primario del tórax; neoplasias del canal alimentario: neoplasias de esófago, neoplasias de estómago, neoplasias de

10 hígado, neoplasias de vesícula biliar, neoplasias de páncreas exocrino, neoplasias de intestino delgado, apéndice y peritoneo veriforme, adneocarcinoma de colon y recto, neoplasias de ano; neoplasias del tracto genitourinario: carcinoma de células renales, neoplasias de la pelvis renal y del uréter, neoplasias de la vejiga, neoplasias de la uretra, neoplasias de la

15 próstata, neoplasias del pene, neoplasias de los testículos; neoplasias de los órganos reproductores femeninos: neoplasias de la vulva y de la vagina, neoplasias de la cerviz, adenocarcinoma del cuerpo uterino, cáncer de ovarios, sarcomas ginecológicos; neoplasias del pecho; neoplasias de la piel: carcinoma de células basales, carcinoma escamoso, dermatofibrosarcoma, tumor celular

20 de Merkel; melanoma maligno; neoplasias de huesos y tejidos blandos: sarcoma osteogénico, histiocitoma fibroso maligno, condrosarcoma, sarcoma de Ewing, tumor neuroectodérmico primitivo, angiosarcoma; neoplasias del sistema hematopoyético; síndrome mielodisplásicos, leucemia mieloide aguda, leucemia mieloide crónica, leucemia linfática aguda, leucemia/linfoma de HTLV-

25 1 y células T, leucemia linfocítica crónica, leucemia celular en cabello,

enfermedad de Hodgkin, linfomas que no son de tipo Hodgkin, leucemia de mastocitos y neoplasias infantiles: leucemia linfoblástica aguda, leucemias mielocíticas agudas, neuroblastoma, tumores óseos, rhabdomyosarcoma, linfomas, tumores renales. En particular, se cree que los presentes compuestos  
5 son útiles en el tratamiento de tumores sólidos, especialmente tumores del colon y del recto. Es preferible que el mamífero a tratar por la administración de compuestos de Fórmula II sea humano.

Los compuestos de la presente invención son de naturaleza ácida y, como tales, pueden reaccionar con cualquier base orgánica o inorgánica,  
10 incluyendo aminas y bases de amonio cuaternarias, para formar sales de adición de base aceptables farmacéuticamente. Es preferible transformar los compuestos de Fórmula II en sus sales de adición de base aceptables farmacéuticamente para facilitar la administración cuando se necesiten disoluciones acuosas del compuesto en cuestión. Los compuestos de Fórmula  
15 II pueden reaccionar con materiales básicos como por ejemplo hidróxidos de metales alcalinos o alcalinotérreos, carbonatos y bicarbonatos incluyendo, sin limitación, hidróxido sódico, carbonato sódico, hidróxido potásico, hidróxido cálcico, hidróxido de litio, etc. para formar sales aceptables farmacéuticamente como la sal de sodio, potasio, litio o calcio correspondiente. Las sales de sodio  
20 y potasio son especialmente preferidas.

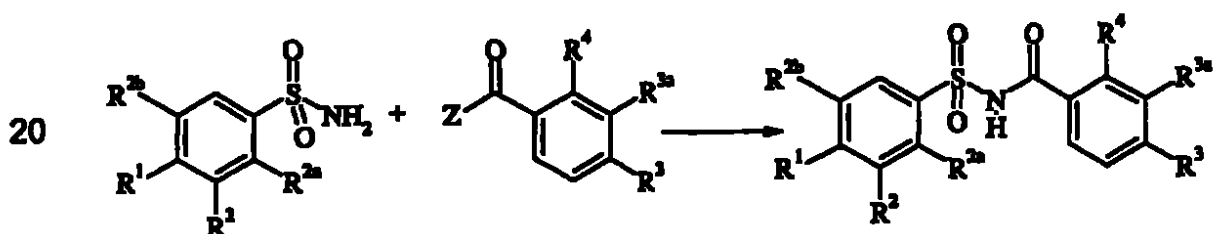
Ejemplos de aminas adecuadas para formar las sales son: aminas alifáticas y aromáticas primarias, secundarias y terciarias, como por ejemplo metilamina, etilamina, propilamina, i-propilamina, las cuatro butilaminas isoméricas, dimetilamina, dietilamina, dietanolamina, dipropilamina,  
25 diisopropilamina, di-n-butilamina, pirrodina, piperidina, morfolina,

trimetilamina, trietilamina, tripropilamina, quinuclidina, piridina, quinolina e isoquinolina, especialmente etil-, propil-, dietil- o trietilamina, aunque particularmente isopropilamina y dietanolamina.

Ejemplos de bases de amonio cuaternario son, en general, los cationes de las sales haloamonio, por ejemplo, el catión tetrametilamonio, el catión trimetilbencilamonio, el catión trietilbencilamonio, el catión tetraetilamonio o el catión trimetiletilamonio, aunque también el catión amonio.

Los compuestos de la presente invención se pueden preparar por procedimientos conocidos por un experto en la técnica. Generalmente, las *N*-[benzoyl]-fenilsulfonamidas de Fórmula II se preparan acoplando una fenilsulfonamida sustituida apropiadamente con un ácido benzoico o un derivado de ácido benzoico sustituido apropiadamente tal y como se ilustra en el siguiente esquema. Las variables  $R^1$ ,  $R^2$ ,  $R^{2a}$ ,  $R^{2b}$ ,  $R^3$  y  $R^4$  son tal y como se han definido anteriormente y Z es OH, Cl, Br, metanosulfoniloxi o trifluorometanosulfoniloxi.

#### Esquema de Síntesis I



Cuando Z es OH, el ácido benzoico correspondiente se acopla a la fenilsulfonamida en condiciones estándar de acoplamiento peptídico conocidas por los expertos en la técnica. Específicamente, la fenilsulfonamida y el ácido

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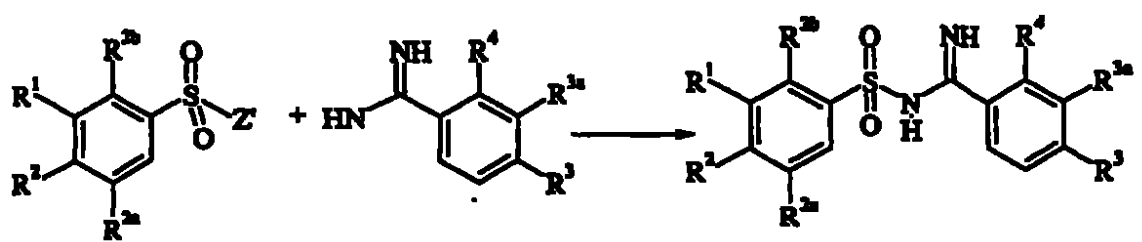
benzoico se acoplan en presencia de un reactivo de acoplamiento peptídico, opcionalmente en presencia de un catalizador. Los reactivos de acoplamiento peptídico adecuados incluyen, N,N'-carbonildiimidazol (CDI), N,N'-diciclohexilcarbodiimida (DCC), clorhidrato de 1-(3-dimetilaminopropil)-3-  
5 etilcarbodiimida (EDC) y 1-(3-(1-pirrolidinil)propil)-3-etilcarbodiimida (PEPC). Se han descrito las tres formas poliméricas soportadas de EDC (Tetrahedron Letters, 34(48), 7685 (1993) y PEPC (patente de los Estados Unidos n° 5.792.763) y son muy útiles para preparar los compuestos de la presente invención. Los catalizadores adecuados para la reacción de acoplamiento  
10 incluyen N,N-dimetil-4-aminopiridina (DMAP). Se combinaron todos los reactivos en un disolvente adecuado, típicamente diclorometano, cloroformo, tetrahidrofurano, dioxano o dietiléter y se agitaron durante 1 a 72 horas a una temperatura entre temperatura ambiente y la temperatura de reflujo del disolvente. El producto deseado se pudo aislar por técnicas estándar de  
15 extracción y cristalización y se purificó por cromatografía o cristalización según se necesite o se desee. Cuando se usan reactivos de unión a polímeros, se pueden eliminar convenientemente de la mezcla de reacción por filtración.

Alternativamente, la sulfonamida se puede hacer reaccionar con un derivado de ácido benzoico, como por ejemplo compuestos en los que Z es  
20 cloro, bromo, metanosulfonilo o trifluorometanosulfonilo, en presencia de un colector de ácido como por ejemplo piridina, trietilamina o una resina básica, opcionalmente en presencia de un catalizador. Los reactivos se combinaron y los productos se aislaron, esencialmente tal y como se ha descrito anteriormente.

25 Un experto en la técnica entenderá que los compuestos de Fórmula II en

los que X es NH se pueden preparar tal y como se ilustra en el Esquema II en el que R<sup>1</sup>, R<sup>2</sup>, R<sup>2a</sup>, R<sup>2b</sup>, R<sup>3</sup>, R<sup>3a</sup> y R<sup>4</sup> son tal y como se han definido anteriormente.

5 **Esquema de Síntesis II**



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Se hace reaccionar una benzamidina sustituida apropiadamente con derivados sulfonilo, como por ejemplo compuestos en los que Z' es cloro, bromo, metanosulfonilo o trifluorometanosulfonilo, en presencia de un colector de ácidos, como por ejemplo piridina, trietilamina o una resina básica, opcionalmente en presencia de un catalizador. Los reactivos se combinaron y los productos se aislaron, esencialmente tal y como se ha descrito anteriormente.

Los ácidos benzoicos, derivados de ácido benzoico, benzamidinas, derivados de sulfonilo y sulfonamidas requeridos están disponibles en el mercado o se pueden preparar mediante procedimientos conocidos por los expertos en la técnica.

**PREPARACIÓN 1**

**2,4-dibromobenzonitrilo**

Se agitó una disolución de cianuro de cobre (I) (2,32 g, 25,9 mmol) en

- dimetilsulfóxido anhidro (50 ml) a 60°C, y a esta disolución se añadió *terc*-butilnitrito (7,1 ml, 59,7 mmol) todo de una vez. Se añadió gota a gota a la mezcla una disolución de 2,4-dibromoanilina (5,0 g, 19,9 mmol) en dimetilsulfóxido anhidro (30 ml), mediante una cánula. Después de que
- 5 finalizara la adición, la mezcla de reacción se agitó durante 1 hora, se enfrió a 45°C y después se trató lentamente con HCl 5 N (50 ml). Cinco minutos más tarde, la mezcla de reacción se enfrió a temperatura ambiente y se extrajo con acetato de etilo:hexano 1:1 (2 x 300 ml). Las fases orgánicas combinadas se lavaron con agua (100 ml) y cloruro sódico acuoso saturado (100 ml), se secó,
- 10 se concentró a presión reducida y el residuo se sometió a cromatografía en gel de sílice, eluyendo con hexano que contenía un 0-5% de acetato de etilo. Se combinaron las fracciones que contenían el producto y se concentraron a presión reducida para proporcionar el compuesto del título (1,61 g, rendimiento del 31%).
- 15 pf = 76-78°C
- FDEM:  $m/e = 261 (M^+)$ .

## PREPARACIÓN 2

### Ácido 2,4-dibromobenzoico

- 20 Una suspensión agitada de 2,4-dibromobenzonitrilo (1,57 g, 6,0 mmol) en ácido sulfúrico (6 M, 150 ml) se calentó a reflujo durante 3 días. La mezcla de reacción se enfrió hasta temperatura ambiente y después se extrajo con acetato de etilo (2 x 75 ml). Las fases orgánicas combinadas se lavaron con agua (100 ml) y cloruro sódico acuoso saturado (50 ml), se secaron,
- 25 concentraron y después se sometieron a cromatografía en gel de sílice,

eluyendo con cloroformo que contenía un 0,5% de metanol y un 0,1% de ácido acético. Las fracciones que contenían el producto se combinaron y se concentraron a presión reducida dando el compuesto del título (0,81 g, rendimiento del 48%).

5 pf = 171-172°C

FDEM:  $m/e = 279 (M^+ - 1)$ .

### PREPARACIÓN 3

#### Ácido 2-bromo-4-clorobenzoico

- 10 Una suspensión de nitrito sódico (2,21 g) en agua (15 ml) se añadió gota a gota a una mezcla agitada enfriada en hielo de ácido 2-amino-4-clorobenzoico (5,00 g, 29,1 mmol) y ácido bromhídrico al 48% (150 ml) en agua (150 ml). La mezcla de reacción se agitó durante 2 horas a 0°C y después se trató gota a gota con una disolución de bromuro de cobre (II) (7,81 g) en agua
- 15 (20 ml). Una vez finalizada la adición, se dejó que la mezcla de reacción se calentara hasta temperatura ambiente y se agitó durante toda la noche. Después, la mezcla de reacción se extrajo con acetato de etilo:hexano 3:1 (2 x 400 ml). Las fases orgánicas combinadas se lavaron con cloruro sódico acuoso saturado (200 ml), se secaron, se concentraron a presión reducida y el residuo
- 20 se sometió a cromatografía en gel de sílice, eluyendo con cloroformo que contenía un 1% de metanol y un 0,5% de ácido acético. Las fracciones que contenían el producto se combinaron y se concentraron a presión reducida dando el compuesto del título (4,04 g, rendimiento del 59%).

pf = 154-155°C

25 FDEM:  $m/e = 233, 235 (M^+ - 1)$ .

#### PREPARACIÓN 4

##### Éster metílico del ácido 4-sulfamoilbenzoico

- Se suspendió 4-carboxifenilsulfonamida (2,0 g, 9,9 mmol) en cloroformo:metanol 3:1 (200 ml). Se añadió (trimetilsilil)-diazometano como
- 5 disolución 2,0 M en hexanos (7,4 ml, 14,8 mmol) a temperatura ambiente y se agitó durante 5 minutos. La disolución se concentró *a vacío* y el producto bruto se cromatografió en gel de sílice, con 0,5% MeOH/0,1% AcOH en CH<sub>2</sub>Cl<sub>2</sub>. El producto es un sólido blanco, 2,11 g, rendimiento del 98%.
- pf = 180°C
- 10 FDEM:  $m/e = 214 (M^+ - 1)$ .

#### PREPARACIÓN 5

##### 3,4-dibromofenilsulfonamida

- Se suspendió cloruro de 3,4-dibromo-fenilsulfonilo (20 mmol; Aldrich) en
- 15 40 ml de NH<sub>4</sub>OH acuoso al 30% y la mezcla se agitó. Se añadió acetona lentamente, de una sola vez, para formar una mezcla de reacción homogénea (5-10 ml). Esta adición es exotérmica, con burbujeo vigoroso. La reacción se agitó a temperatura ambiente y se controló por ESI-EM. La mezcla se concentró en rotavapor para eliminar la acetona y se formó un sólido. El sólido
- 20 se recogió mediante filtración por succión, se lavó con agua y se dejó secar al aire. El material se usó tal cual se obtuvo, sin mayor purificación. ESI/EM: 312, 314, 316 ( $M^+ - 1$ ); pf 169-171°C; pf lit 175-176°C Huntress, E. H.; Carten F. H. *J. Am. Chem. Soc.* 1940, 62, 511-514.

- Los compuestos de las PREPARACIONES 6-15 se prepararon
- 25 esencialmente según se describe en el procedimiento de la PREPARACIÓN 5.

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| Nº PREP. | Producto                          | Datos espectro de masas (e/m)                                                                                                                                                                     |
|----------|-----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 6        | 3-cloro-4-fluoro-fenilsulfonamida | ESIEM: 210 (M <sup>+</sup> -1)                                                                                                                                                                    |
| 7        | 4-yodo-fenilsulfonamida           | ESIEM: 284 (M <sup>+</sup> -1)                                                                                                                                                                    |
| 8        | 3,4-diclorofenilsulfonamida       | ESIEM e/m 224 (M <sup>+</sup> -1; <sup>35</sup> Cl, <sup>35</sup> Cl) y 226 (M <sup>+</sup> -1; <sup>35</sup> Cl, <sup>37</sup> Cl) y 228 (M <sup>+</sup> -1; <sup>37</sup> Cl, <sup>37</sup> Cl) |
| 9        | 4-isopropilfenilsulfonamida       | ESIEM: e/m 198 (M <sup>+</sup> -1)                                                                                                                                                                |
| 10       | 4-etilfenilsulfonamida            | ESIEM: e/m 184 (M <sup>+</sup> -1)                                                                                                                                                                |
| 11       | 3-trifluorometil-fenilsulfonamida | ESIEM: 224 (M <sup>+</sup> -1)                                                                                                                                                                    |
| 12       | 3-fluoro-fenilsulfonamida         | ESIEM: 174 (M <sup>+</sup> -1)                                                                                                                                                                    |
| 13       | tolueno-3-sulfonamida             | ESIEM: 170 (M <sup>+</sup> -1)                                                                                                                                                                    |
| 14       | 3-bromofenilsulfonamida           | ESIEM: 237 (M <sup>+</sup> -1)                                                                                                                                                                    |
| 15       | 4-gromofenilsulfonamida           | ESIEM: 237 (M <sup>+</sup> -1)                                                                                                                                                                    |

PREPARACIÓN 16

Ácido 2-cloro-4-metilbenzolco

A 4-bromo-3-clorotolueno (4,97 g, 24,2 mmol) en DMF (25 ml) se añadió  
15 Pd(Oac)<sub>2</sub> (0,54 g, 2,42 mmol), 1,3-bis(difenilfosfino)propano (0,998 g, 2,42  
mmol), trietilamina (12,5 ml) y metanol (12,5 ml). El tanque de reacción de  
evacuó y se purgó tres veces con gas monóxido de carbono. Se usó un baló  
lleno con gas monóxido de carbono para mantener la atmósfera de monóxido  
de carbono. La mezcla de reacción se calentó a 80°C durante 8 horas.  
20 Después de enfriar se añadió H<sub>2</sub>O (50 ml). La mezcla se extrajo con hexanos  
(2 x 50 ml). Las fases orgánicas combinadas se extrajeron con hexanos (2 x 50  
ml). Las fases orgánicas combinadas se secaron sobre Na<sub>2</sub>SO<sub>4</sub>, se filtraron, se  
concentraron y se cromatografiaron con EtOAc al 0-3% en hexanos. Se  
aislaron 1,24 g (28%) 2-cloro-4-metilbenzoato de metilo como un aceite  
25 incoloro. EIEM e/m 184 (M<sup>+</sup>; <sup>35</sup>Cl) y 186 (M<sup>+</sup>; <sup>37</sup>Cl).

A 2-cloro-4-metilbenzoato de metilo (1,00 g, 5,42 mmol) en THF (10 ml) MeOH (5 ml) y H<sub>2</sub>O (2,5 ml) se añadió LiOH 2 N (8,12 ml, 16,2 mmol). La mezcla de reacción se calentó a 50°C durante 2,5 horas, se enfrió a temperatura ambiente, después se apagó con HCl 5 N (3,24 ml). La mezcla se  
5 concentró para eliminar el THF y el MeOH. Se formó un precipitado blanco y se filtró. Después del secado, se aislaron 0,922 g (100%) de ácido 2-cloro-4-metilbenzoico. ESIEM *m/z* 169 (M<sup>-</sup>-1; <sup>35</sup>Cl) y 171 (M<sup>-</sup>-1; <sup>37</sup>Cl).

### PREPARACIÓN 17

#### 10 4-(*terc*-butildimetilsililo)fenilsulfonamida

Se disolvió 4-hidroxifenilsulfonamida (3,46 g, 20 mmol) en DMF (40 ml) y se trató con cloruro de *terc*-butil-dimetilsililo (3,31 g, 22,0 mmol) e imidazol (1,50 g, 22,0 mmol) a temperatura ambiente. Después de 20 horas, la mezcla de reacción se diluyó con EtOAc (100 ml) y se lavó con HCl 1,0 N (2 x 50 ml).  
15 La fase orgánica se secó (MgSO<sub>4</sub>), se filtró y se concentró dando un aceite. El aceite bruto se purificó por cromatografía en columna Biotage (columna SiO<sub>2</sub> 40 M, eluido a 75 ml/minutos con hexanos:EtOAc 1:1). Se obtuvo un sólido blanco (4,24 g, 15,4 mmol, 77%). ESI-EM *m/z* 288,1 (M<sup>+</sup>+H); pf 117-118°C; RMN <sup>1</sup>H (CDCl<sub>3</sub>) δ 7,78 (d, 2 H), 6,89 (d, 2 H), 4,86 (a s, 2 H), 0,97 (s, 9H), 0,20  
20 (s, 6 H).

### PREPARACIÓN 18

#### *N*-(2,4-diclorobenzoil)-4-(*terc*-butildimetilsililo)fenilsulfonamida

A una disolución agitada de ácido 2,4-diclorobenzoico (1,25 eq) en  
25 diclorometano seco (10 ml/mmol), se añadió 4-(*terc*-butil-

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dimetilsiloxi)fenilsulfonamida (1,0 eq) de una sola vez seguido de EDC (1,25-1,5 eq) y, finalmente, N,N-dimetil-4-aminopiridina (1,2 equiv). La mezcla se agitó vigorosamente en atmósfera de nitrógeno durante 16 horas, se concentró a presión reducida y el residuo se dividió entre acetato de etilo y agua. La fase orgánica se lavó con ácido clorhídrico 1 N (4 veces, 20 ml/mmol), después las fases acuosas combinadas se extrajeron con acetato de etilo (2 veces, 20 ml/mmol). Las fases orgánicas combinadas se lavaron finalmente con agua y cloruro sódico acuoso saturado, se secaron sobre sulfato sódico y se concentraron a presión reducida. El residuo se purificó por cromatografía en gel de sílice o cristalización, según se necesite o se desee. ESI-EM  $m/z$  458,0 ( $M^+ - H$ ); 460,0 ( $M^+ + H$ ).

Los compuestos de las PREPARACIONES 19-21 se prepararon esencialmente según se ha descrito en el procedimiento de la PREPARACIÓN 18.

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| Nº PREP. | Producto                                                  | Datos espectro de masas ( $m/z$ )  |
|----------|-----------------------------------------------------------|------------------------------------|
| 19       | 3-bromo- <i>N</i> -(2,4-dicloro-benzoyl)-fenilsulfonamida | ESI-EM: $m/z$ 409,0 ( $M^+ - H$ )  |
| 20       | 4-yodo- <i>N</i> -(2,4-dicloro-benzoyl)-fenilsulfonamida  | ESI-EM: $m/z$ 455,08 ( $M^+ - H$ ) |
| 21       | 4-bromo- <i>N</i> -(2,4-dicloro-benzoyl)-fenilsulfonamida | ESI-EM: $m/z$ 409,0 ( $M^+ - H$ )  |

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Procedimiento General de Acoplamiento

A una disolución agitada de ácido benzoico (1,25 eq) en diclorometano seco (10 ml/mmol), se añadió fenilsulfonamida (1,0 eq) de una sola vez, seguido de EDC (1,25-1,5 eq) y, finalmente, N,N-[dimetil]-4-aminopiridina (1,2 equiv). La mezcla se agitó vigorosa en atmósfera de nitrógeno durante 16

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horas, se concentró a presión reducida y el residuo se dividió entre acetato de etilo y agua. La fase orgánica se lavó con ácido clorhídrico 1 N (4 veces, 20 ml/mmol), después las fases acuosas combinadas se extrajeron con acetato de etilo (dos veces, 20 ml/mmol). Las fases orgánicas combinadas se lavaron finalmente con agua y cloruro sódico acuoso saturado, se secaron sobre sulfato sódico y se concentraron a presión reducida. El residuo se puede someter a cromatografía en gel de sílice o cristalización según se necesite o se desee.

Los compuestos de los EJEMPLOS 1-84 se prepararon esencialmente según se describe en este procedimiento general.

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| Nº DE EJ. | Producto                                                             | Datos espectro de masas (e/m)                                                  |
|-----------|----------------------------------------------------------------------|--------------------------------------------------------------------------------|
| 1         | <i>N</i> -[2,4-diclorobenzoil]-3-bromofenilsulfonamida               | EM(ES): 408 (M-H) <sup>+</sup>                                                 |
| 2         | <i>N</i> -[2,4-diclorobenzoil]-3-clorofenilsulfonamida               | EM(ES): 382 (M-H) <sup>+</sup>                                                 |
| 3         | <i>N</i> -[2,4-diclorobenzoil]-4-metoxifenilsulfonamida              | EM(ES): 380 (M-H) <sup>+</sup>                                                 |
| 4         | <i>N</i> -[2,4-dibromobenzoil]-4-metilfenilsulfonamida               | ESIES: 434 (M <sup>+</sup> +1)                                                 |
| 5         | <i>N</i> -[2,4-dibromobenzoil]-4- <i>terc</i> -butilfenilsulfonamida | ESIES: 476 (M <sup>+</sup> +1)                                                 |
| 6         | <i>N</i> -[2,4-dibromobenzoil]-4-clorofenilsulfonamida               | ESIES: 454,458 (M <sup>+</sup> +1)                                             |
| 7         | <i>N</i> -[2-bromo-4-clorobenzoil]-4-metilfenilsulfonamida           | ESIES: 388,390 (M <sup>+</sup> +1)                                             |
| 8         | <i>N</i> -[2-bromo-4-clorobenzoil]-4-clorofenilsulfonamida           | ESIES: 408,410 (M <sup>+</sup> +1)                                             |
| 9         | <i>N</i> -[2,4-diclorobenzoil]-3-cloro-4-fluorofenilsulfonamida      | ESIES: 380 (M <sup>+</sup> -2), 382(M <sup>+</sup> ), 384(M <sup>+</sup> +2)   |
| 10        | <i>N</i> -[2-cloro-4-nitrobenzoil]-4-clorofenilsulfonamida           | ESIES: 373 (M <sup>+</sup> -2), 375(M <sup>+</sup> ), 377(M <sup>+</sup> +2)   |
| 11        | <i>N</i> -[2-cloro-4-bromobenzoil]-fenilsulfonamida                  | ESIES: 372 (M <sup>+</sup> -2), 374(M <sup>+</sup> )                           |
| 12        | <i>N</i> -[2-metil-4-bromobenzoil]-fenilsulfonamida                  | ESIES: 352 (M <sup>+</sup> -2), 354(M <sup>+</sup> )                           |
| 13        | <i>N</i> -[2-cloro-4-nitrobenzoil]-fenilsulfonamida                  | ESIES: 339 (M <sup>+</sup> -2), 341(M <sup>+</sup> +1)                         |
| 14        | <i>N</i> -[2-cloro-4-bromobenzoil]-4-bromofenilsulfonamida           | ESIES: 450 (M <sup>+</sup> -3), 452(M <sup>+</sup> -1), 454(M <sup>+</sup> +1) |
| 15        | <i>N</i> -[2-cloro-4-nitrobenzoil]-4-bromofenilsulfonamida           | ESIES: 417 (M <sup>+</sup> -2), 419(M <sup>+</sup> )                           |
| 16        | <i>N</i> -[2-cloro-4-bromobenzoil]-4-fluorofenilsulfonamida          | ESIES: 390 (M <sup>+</sup> -2), 392(M <sup>+</sup> )                           |
| 17        | <i>N</i> -[2-cloro-4-bromobenzoil]-3-clorofenilsulfonamida           | ESIES: 408 (M <sup>+</sup> -3), 408(M <sup>+</sup> -1), 410(M <sup>+</sup> +1) |

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| 18 | <i>N</i> -[2-cloro-4-bromobenzoi]l-4-metoxifenilsulfonamida              | ESIEM: 402( $M^+ - 2$ ), 404( $M^+$ ), 406( $M^+ + 2$ )                                                                                                                                                           |
| 19 | <i>N</i> -[2-metil-4-bromobenzoi]l-4-metoxifenilsulfonamida              | ESIEM: 382( $M^+ - 2$ ), 384( $M^+$ )                                                                                                                                                                             |
| 20 | <i>N</i> -[2-cloro-4-nitrobenzoi]l-4-metoxifenilsulfonamida              | ESIEM: 389( $M^+ - 1$ ), 371( $M^+$ )                                                                                                                                                                             |
| 21 | <i>N</i> -[2-cloro-4-nitrobenzoi]l-3,4-diclorofenilsulfonamida           | ESIEM: 407( $M^+ - 2$ ), 409( $M^+$ ), 411( $M^+ + 2$ )                                                                                                                                                           |
| 22 | <i>N</i> -[2-metil-4-clorobenzoi]l-3-clorofenilsulfonamida               | ESIEM: 342( $M^+ - 1$ ), 344( $M^+ - 1$ ), 346( $M^+ - 1$ )                                                                                                                                                       |
| 23 | <i>N</i> -[2-metil-4-clorobenzoi]l-4-metilfenilsulfonamida               | ES Ión Negativo EM iones [M-H] <sup>-</sup> observados: $m/z$ 342 ( $^{35}\text{Cl}$ , $^{35}\text{Cl}$ ), $m/z$ 344 ( $^{35}\text{Cl}$ , $^{37}\text{Cl}$ ) y $m/z$ 346 ( $^{37}\text{Cl}$ , $^{37}\text{Cl}$ ). |
| 24 | <i>N</i> -[2,4-diclorobenzoi]l-3,4-dibromofenilsulfonamida               | ES Ión Negativo EM iones [M-H] <sup>-</sup> observados: $m/z$ 322 ( $^{35}\text{Cl}$ ) y $m/z$ 324 ( $^{37}\text{Cl}$ ).                                                                                          |
| 25 | <i>N</i> -[2,4-diclorobenzoi]l-3-trifluorometilfenilsulfonamida          | ESIEM: 395,9476/395,9489                                                                                                                                                                                          |
| 26 | <i>N</i> -[2,4-diclorobenzoi]l-3-fluorofenilsulfonamida                  | ESIEM: 345,9508/345,9515                                                                                                                                                                                          |
| 27 | <i>N</i> -[2,4-diclorobenzoi]l-3-metilfenilsulfonamida                   | ESIEM: 365,9734/365,9747                                                                                                                                                                                          |
| 28 | <i>N</i> -[2-metil-4-bromobenzoi]l-4-clorofenilsulfonamida               | ESIEM $m/e$ 386,0, 387,9 y 389,9 ( $M^+ - 1$ : $^{79}\text{Br}$ , $^{35}\text{Cl}$ ; $^{79}\text{Br}$ , $^{37}\text{Cl}$ ; $^{81}\text{Br}$ , $^{37}\text{Cl}$ )                                                  |
| 29 | <i>N</i> -[2-metil-4-bromobenzoi]l-4-metilfenilsulfonamida               | ESIEM $m/e$ 386,0 y 388,0 ( $M^+ - 1$ ; $^{79}\text{Br}$ , $^{81}\text{Br}$ )                                                                                                                                     |
| 30 | <i>N</i> -[2-bromo-4-clorobenzoi]l-4-metoxycarbonilfenilsulfonamida      | ESIEM $m/e$ 430,0, 431,9 y 433,9 ( $M^+ - 1$ : $^{35}\text{Cl}$ ; $^{79}\text{Br}$ , $^{37}\text{Cl}$ ; $^{79}\text{Br}$ , $^{37}\text{Cl}$ ; $^{81}\text{Br}$ )                                                  |
| 31 | <i>N</i> -[2,4-dibromobenzoi]l-4-metoxycarbonilsulfonamida               | ESIEM $m/e$ 473,8, 475,9 y 477,9 ( $M^+ - 1$ : $^{79}\text{Br}$ , $^{79}\text{Br}$ , $^{79}\text{Br}$ , $^{81}\text{Br}$ , $^{81}\text{Br}$ , $^{81}\text{Br}$ )                                                  |
| 32 | <i>N</i> -[2-bromo-4-clorobenzoi]l-3-metoxifenilsulfonamida              | ESIEM $m/e$ 459,9, 461,9 y 463,9 ( $M^+ - 1$ : $^{79}\text{Br}$ , $^{35}\text{Cl}$ ; $^{81}\text{Br}$ , $^{35}\text{Cl}$ ; $^{81}\text{Br}$ , $^{37}\text{Cl}$ )                                                  |
| 33 | <i>N</i> -[2-bromo-4-clorobenzoi]l-4- <i>tert</i> -butilfenilsulfonamida | ESIEM $m/e$ 428,2, 430,2 y 432,2 ( $M^+ - 1$ : $^{79}\text{Br}$ , $^{35}\text{Cl}$ ; $^{81}\text{Br}$ , $^{35}\text{Cl}$ ; $^{81}\text{Br}$ , $^{37}\text{Cl}$ )                                                  |
| 34 | <i>N</i> -[2,4-dibromobenzoi]l-3-metoxycarbonil-4-metoxifenilsulfonamida | ESIEM $m/e$ 503,9, 506,0 y 508,0; ( $M^+ - 1$ : $^{79}\text{Br}$ , $^{79}\text{Br}$ , $^{81}\text{Br}$ , $^{81}\text{Br}$ , $^{81}\text{Br}$ )                                                                    |
| 35 | <i>N</i> -[2-metil-4-bromobenzoi]l-3-cloro-4-fluorofenilsulfonamida      | ESIEM $m/e$ 404,0, 406,0 y 408,0 ( $M^+ - 1$ : $^{79}\text{Br}$ , $^{35}\text{Cl}$ ; $^{81}\text{Br}$ , $^{35}\text{Cl}$ ; $^{81}\text{Br}$ , $^{37}\text{Cl}$ )                                                  |
| 36 | <i>N</i> -[2-metil-4-bromobenzoi]l-4-yodofenilsulfonamida                | ESIEM $m/e$ 478,0 y 480,0 ( $M^+ - 1$ ; $^{79}\text{Br}$ , $^{81}\text{Br}$ )                                                                                                                                     |

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| 37 | <i>N</i> -[2-metil-4-bromobenzoil]-3-metilfenilsulfonamida          | ESIEM <i>m/e</i> 366,1 y 368,1 ( <i>M</i> <sup>-1</sup> ; <sup>79</sup> Br; <sup>81</sup> Br)                                                                                                                                 |
| 38 | <i>N</i> -[2,4-dibromobenzoil]-4-yodofenilsulfonamida               | ESIEM <i>m/e</i> 541,9, 543,9 y 545,9 ( <i>M</i> <sup>-1</sup> ; <sup>79</sup> Br, <sup>79</sup> Br, <sup>81</sup> Br, <sup>79</sup> Br, <sup>81</sup> Br, <sup>81</sup> Br)                                                  |
| 39 | <i>N</i> -[2,4-diclorobenzoil]-4-yodofenilsulfonamida               | ESIEM <i>m/e</i> 454 ( <i>M</i> <sup>-1</sup> ; <sup>35</sup> Cl, <sup>35</sup> Cl) y 456 ( <i>M</i> <sup>-1</sup> ; <sup>35</sup> Cl, <sup>37</sup> Cl) y 458 ( <i>M</i> <sup>-1</sup> ; <sup>35</sup> Cl, <sup>37</sup> Cl) |
| 40 | <i>N</i> -[2-cloro-4-bromobenzoil]-4-yodofenilsulfonamida           | ES Ión Negativo EM Iones [M-H] <sup>-</sup> observados: <i>m/z</i> 498 ( <sup>79</sup> Br, <sup>35</sup> Cl), <i>m/z</i> 500 ( <sup>81</sup> Br, <sup>35</sup> Cl) y <i>m/z</i> 502 ( <sup>81</sup> Br, <sup>37</sup> Cl).    |
| 41 | <i>N</i> -[2-metil-4-clorobenzoil]-4-metoxifenilsulfonamida         | ES Ión Negativo EM Iones [M-H] <sup>-</sup> observados: <i>m/z</i> 338 ( <sup>35</sup> Cl) y <i>m/z</i> 340 ( <sup>37</sup> Cl).                                                                                              |
| 42 | <i>N</i> -[2-metil-4-clorobenzoil]-4-fluorofenilsulfonamida         | ES Ión Negativo EM Iones [M-H] <sup>-</sup> observados: <i>m/z</i> 328 ( <sup>35</sup> Cl) y <i>m/z</i> 328 ( <sup>37</sup> Cl).                                                                                              |
| 43 | <i>N</i> -[2-metil-4-clorobenzoil]-4-bromofenilsulfonamida          | ES Ión Negativo EM Iones [M-H] <sup>-</sup> observados: <i>m/z</i> 386 ( <sup>79</sup> Br, <sup>35</sup> Cl), <i>m/z</i> 388 ( <sup>81</sup> Br, <sup>35</sup> Cl) y <i>m/z</i> 390 ( <sup>81</sup> Br, <sup>37</sup> Cl).    |
| 44 | <i>N</i> -[2-metil-4-clorobenzoil]-2-metoxi-4-metilfenilsulfonamida | ES Ión Negativo EM Iones [M-H] <sup>-</sup> observados: <i>m/z</i> 352 ( <sup>35</sup> Cl) y <i>m/z</i> 354 ( <sup>37</sup> Cl).                                                                                              |
| 45 | <i>N</i> -[2-metil-4-clorobenzoil]-3-cloro-4-metilfenilsulfonamida  | ES Ión Negativo EM Iones [M-H] <sup>-</sup> observados: <i>m/z</i> 356 ( <sup>35</sup> Cl, <sup>35</sup> Cl), <i>m/z</i> 358 ( <sup>35</sup> Cl, <sup>37</sup> Cl) y <i>m/z</i> 360 ( <sup>37</sup> Cl, <sup>37</sup> Cl).    |
| 46 | <i>N</i> -[2,4-bis-trifluorometilbenzoil]-4-fluorofenilsulfonamida  | ES Ión Negativo EM Iones [M-H] <sup>-</sup> observados: <i>m/z</i> 410                                                                                                                                                        |
| 47 | <i>N</i> -[2,4-bis-trifluorometilbenzoil]-4-metoxifenilsulfonamida  | ES Ión Negativo EM Iones [M-H] <sup>-</sup> observados: <i>m/z</i> 426                                                                                                                                                        |
| 48 | <i>N</i> -[2,4-bis-trifluorometilbenzoil]-4-metilfenilsulfonamida   | ES Ión Negativo EM Iones [M-H] <sup>-</sup> observados: <i>m/z</i> 410                                                                                                                                                        |
| 49 | <i>N</i> -[2,4-bis-trifluorometilbenzoil]-4-bromofenilsulfonamida   | ES Ión Negativo EM Iones [M-H] <sup>-</sup> observados: <i>m/z</i> 474 ( <sup>79</sup> Br) y <i>m/z</i> 476 ( <sup>79</sup> Br).                                                                                              |

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| 50 | <i>N</i> -[2,4-bis-trifluorometilbenzoi]-3-metilfenilsulfonamida          | ES Ión Negativo EM<br>iones [M-H] <sup>-</sup><br>observados: <i>m/z</i> 410.                                                                                                                                                             |
| 51 | <i>N</i> -[2-metil-4-clorobenzoi]-4-trifluorometoxifenilsulfonamida       | ES Ión Negativo EM<br>iones [M-H] <sup>-</sup><br>observados: <i>m/z</i> 392<br>( <sup>35</sup> Cl) y <i>m/z</i> 394 ( <sup>37</sup> Cl).                                                                                                 |
| 52 | <i>N</i> -[2,4-bis-trifluorometilbenzoi]-3,4-diclorofenilsulfonamida      | ES Ión Negativo EM<br>iones [M-H] <sup>-</sup><br>observados: <i>m/z</i> 464<br>( <sup>35</sup> Cl, <sup>37</sup> Cl), <i>m/z</i> 466<br>( <sup>35</sup> Cl, <sup>37</sup> Cl) y <i>m/z</i> 488<br>( <sup>37</sup> Cl, <sup>37</sup> Cl). |
| 53 | <i>N</i> -[2,4-bis-trifluorometilbenzoi]-3,4-difluorofenilsulfonamida     | ES Ión Negativo EM<br>iones [M-H] <sup>-</sup><br>observados: <i>m/z</i> 432.                                                                                                                                                             |
| 54 | <i>N</i> -[2-metil-4-clorobenzoi]-3-cloro-4-fluorofenilsulfonamida        | ES Ión Negativo EM<br>iones [M-H] <sup>-</sup><br>observados: <i>m/z</i> 360<br>( <sup>35</sup> Cl, <sup>37</sup> Cl), <i>m/z</i> 362<br>( <sup>35</sup> Cl, <sup>37</sup> Cl) y <i>m/z</i> 384<br>( <sup>37</sup> Cl, <sup>37</sup> Cl). |
| 55 | <i>N</i> -[2-metil-4-clorobenzoi]-3-metilfenilsulfonamida                 | ES Ión Negativo EM<br>iones [M-H] <sup>-</sup><br>observados: <i>m/z</i> 322<br>( <sup>35</sup> Cl) y <i>m/z</i> 324 ( <sup>37</sup> Cl).                                                                                                 |
| 56 | <i>N</i> -[2-metil-4-clorobenzoi]-4-yodofenilsulfonamida                  | ES Ión Negativo EM<br>iones [M-H] <sup>-</sup><br>observados: <i>m/z</i> 434<br>( <sup>35</sup> Cl) y <i>m/z</i> 436 ( <sup>37</sup> Cl).                                                                                                 |
| 57 | <i>N</i> -[2-metil-4-clorobenzoi]-3,4-difluorofenilsulfonamida            | ES Ión Negativo EM<br>iones [M-H] <sup>-</sup><br>observados: <i>m/z</i> 344<br>( <sup>35</sup> Cl) y <i>m/z</i> 346 ( <sup>37</sup> Cl).                                                                                                 |
| 58 | <i>N</i> -[2,4-bis-trifluorometilbenzoi]-3-cloro-4-fluorofenilsulfonamida | ES Ión Negativo EM<br>iones [M-H] <sup>-</sup><br>observados: <i>m/z</i> 448<br>( <sup>35</sup> Cl) y <i>m/z</i> 450 ( <sup>37</sup> Cl).                                                                                                 |
| 59 | <i>N</i> -[2-cloro-4-metilbenzoi]-3-cloro-4-fluorofenilsulfonamida        | ES Ión Negativo EM<br>iones [M-H] <sup>-</sup><br>observados: <i>m/z</i> 362<br>( <sup>35</sup> Cl) y <i>m/z</i> 364 ( <sup>37</sup> Cl).                                                                                                 |
| 60 | <i>N</i> -[2-metil-4-clorobenzoi]-fenilsulfonamida                        | ES Ión Negativo EM<br>iones [M-H] <sup>-</sup><br>observados: <i>m/z</i> 310<br>( <sup>35</sup> Cl) y <i>m/z</i> 312 ( <sup>37</sup> Cl).                                                                                                 |
| 61 | <i>N</i> -[2-metil-4-bromobenzoi]-4-etilfenilsulfonamida                  | ES Ión Negativo EM<br>iones [M-H] <sup>-</sup><br>observados: <i>m/z</i> 412<br>( <sup>79</sup> Br) y <i>m/z</i> 414 ( <sup>81</sup> Br).                                                                                                 |
| 62 | <i>N</i> -[2,4-diclorobenzoi]-4-etilfenilsulfonamida                      | ES Ión Negativo EM<br>iones [M-H] <sup>-</sup><br>observados: <i>m/z</i> 388<br>( <sup>35</sup> Cl, <sup>37</sup> Cl), <i>m/z</i> 390<br>( <sup>35</sup> Cl, <sup>37</sup> Cl) y <i>m/z</i> 392<br>( <sup>37</sup> Cl, <sup>37</sup> Cl). |

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| 63 | <i>N</i> -[2,4-bis-trifluorometilbenzoi]-4-isopropilfenilsulfonamida | ES Ión Negativo EM iones [M-H] <sup>-</sup> observados: <i>m/z</i> 438.                                                                                                                                                    |
| 64 | <i>N</i> -[2-cloro-4-bromobenzoi]-4-isopropilfenilsulfonamida        | ES Ión Negativo EM iones [M-H] <sup>-</sup> observados: <i>m/z</i> 414 ( <sup>79</sup> Br, <sup>35</sup> Cl), <i>m/z</i> 481 ( <sup>81</sup> Br, <sup>35</sup> Cl) y <i>m/z</i> 418 ( <sup>81</sup> Br, <sup>37</sup> Cl). |
| 65 | <i>N</i> -[2,4-dibromobenzoi]-4-etilfenilsulfonamida                 | ES Ión Negativo EM iones [M-H] <sup>-</sup> observados: <i>m/z</i> 444 ( <sup>79</sup> Br, <sup>79</sup> Br), <i>m/z</i> 446 ( <sup>79</sup> Br, <sup>81</sup> Br) y <i>m/z</i> 448 ( <sup>81</sup> Br, <sup>81</sup> Br). |
| 66 | <i>N</i> -[2-metil-4-bromobenzoi]-4-etilfenilsulfonamida             | ES Ión Negativo EM iones [M-H] <sup>-</sup> observados: <i>m/z</i> 380 ( <sup>79</sup> Br) y <i>m/z</i> 382 ( <sup>81</sup> Br).                                                                                           |
| 67 | <i>N</i> -[2,4-dibromobenzoi]-4-isopropilfenilsulfonamida            | ES Ión Negativo EM iones [M-H] <sup>-</sup> observados: <i>m/z</i> 460 ( <sup>79</sup> Br, <sup>79</sup> Br), <i>m/z</i> 482 ( <sup>79</sup> Br, <sup>81</sup> Br) y <i>m/z</i> 484 ( <sup>81</sup> Br, <sup>81</sup> Br). |
| 68 | <i>N</i> -[2,4-diclorobenzoi]-4-isopropilfenilsulfonamida            | ES Ión Negativo EM iones [M-H] <sup>-</sup> observados: <i>m/z</i> 370 ( <sup>35</sup> Cl, <sup>35</sup> Cl), <i>m/z</i> 372 ( <sup>35</sup> Cl, <sup>37</sup> Cl) y <i>m/z</i> 374 ( <sup>37</sup> Cl, <sup>37</sup> Cl). |
| 69 | <i>N</i> -[2,4-diclorobenzoi]-4-etilfenilsulfonamida                 | ES Ión Negativo EM iones [M-H] <sup>-</sup> observados: <i>m/z</i> 356 ( <sup>35</sup> Cl, <sup>35</sup> Cl), <i>m/z</i> 358 ( <sup>35</sup> Cl, <sup>37</sup> Cl) y <i>m/z</i> 370 ( <sup>37</sup> Cl, <sup>37</sup> Cl). |
| 70 | <i>N</i> -[2-metil-4-clorobenzoi]-4-etilfenilsulfonamida             | ES Ión Negativo EM iones [M-H] <sup>-</sup> observados: <i>m/z</i> 366 ( <sup>35</sup> Cl) y <i>m/z</i> 338 ( <sup>37</sup> Cl).                                                                                           |
| 71 | <i>N</i> -[2-cloro-4-bromobenzoi]-4-etilfenilsulfonamida             | ES Ión Negativo EM iones [M-H] <sup>-</sup> observados: <i>m/z</i> 400 ( <sup>79</sup> Br, <sup>35</sup> Cl), <i>m/z</i> 402 ( <sup>81</sup> Br, <sup>35</sup> Cl) y <i>m/z</i> 404 ( <sup>81</sup> Br, <sup>37</sup> Cl). |
| 72 | <i>N</i> -[2-bromo-4-clorobenzoi]-4-etilfenilsulfonamida             | ES Ión Negativo EM iones [M-H] <sup>-</sup> observados: <i>m/z</i> 400 ( <sup>79</sup> Br, <sup>35</sup> Cl), <i>m/z</i> 402 ( <sup>81</sup> Br, <sup>35</sup> Cl) y <i>m/z</i> 404 ( <sup>81</sup> Br, <sup>37</sup> Cl). |
| 73 | <i>N</i> -[2-bromo-4-clorobenzoi]-4-isopropilfenilsulfonamida        | ES Ión Negativo EM iones [M-H] <sup>-</sup> observados: <i>m/z</i> 414 ( <sup>79</sup> Br, <sup>35</sup> Cl), <i>m/z</i> 416 ( <sup>81</sup> Br, <sup>35</sup> Cl) y <i>m/z</i> 418 ( <sup>81</sup> Br, <sup>37</sup> Cl). |

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| 74 | <i>N</i> -[2-cloro-4-yodobenzoil]-4-azidofenilsulfonamida            | ESIEM <i>a/m</i> 480,9 (M-1).                                                                                                                                                                                              |
| 75 | <i>N</i> -[2-metil-4-clorobenzoil]-4-metilfenilsulfonamida           | ES Ión Positivo EM Iones [M+H] <sup>+</sup> observados: <i>m/z</i> 356 ( <sup>35</sup> Cl) y <i>m/z</i> 358 ( <sup>37</sup> Cl).                                                                                           |
| 76 | <i>N</i> -[2-metil-4-clorobenzoil]-4-trifluorometilfenilsulfonamida  | ES Ión Negativo EM Iones [M-H] <sup>-</sup> observados: <i>m/z</i> 408 ( <sup>79</sup> Br, <sup>35</sup> Cl), <i>m/z</i> 410 ( <sup>81</sup> Br, <sup>35</sup> Cl) y <i>m/z</i> 412 ( <sup>81</sup> Br, <sup>37</sup> Cl). |
| 77 | <i>N</i> -[2-metil-4-clorobenzoil]-3-trifluorometilfenilsulfonamida  | ES Ión Positivo EM Iones [M+H] <sup>+</sup> observados: <i>m/z</i> 378 ( <sup>35</sup> Cl) y <i>m/z</i> 380 ( <sup>37</sup> Cl).                                                                                           |
| 78 | <i>N</i> -[2-metil-4-bromobenzoil]-3-trifluorometilfenilsulfonamida  | ES Ión Positivo EM Iones [M+H] <sup>+</sup> observados: <i>m/z</i> 422 ( <sup>79</sup> Br) y <i>m/z</i> 424 ( <sup>81</sup> Br).                                                                                           |
| 79 | <i>N</i> -[2-trifluorometil-4-metilbenzoil]-4-metilfenilsulfonamida  | ES Ión Positivo EM Iones [M+H] <sup>+</sup> observados: <i>m/z</i> 358.                                                                                                                                                    |
| 80 | <i>N</i> -[2,4-diclorobenzoil]-3-metoxifenilsulfonamida              | RMN <sup>1</sup> H (CDCl <sub>3</sub> ) δ 7,68-7,15 (m, 7H); 3,80 (s, 3H).                                                                                                                                                 |
| 81 | <i>N</i> -[2,4-diclorobenzoil]-4-trifluorometilfenilsulfonamida      | ESI-EM <i>a/m</i> 395,9 (M <sup>+</sup> -H)                                                                                                                                                                                |
| 82 | <i>N</i> -[2,4-diclorobenzoil]-4-hidroxifenilsulfonamida             | Pf 155-157°C; ESI-EM <i>a/m</i> 344,0 (M <sup>+</sup> -H)                                                                                                                                                                  |
| 83 | <i>N</i> -[4-bromo-2-metil-benzoil]-3,4-dimetil-fenilsulfonamida     | EM(ES): [M-H] <sup>-</sup> 379,9943                                                                                                                                                                                        |
| 84 | <i>N</i> -[2,4-bis-trifluorometil-benzoil]-3-fluoro-fenilsulfonamida | EM(ES): [M-H] <sup>-</sup> 414,049                                                                                                                                                                                         |

EJEMPLO 85

*N*-[2-cloro-4-bromobenzoil]-4-clorofenilsulfonamida

20            Se cargó un vial de reacción con 8 ml de ácido 2-cloro-4-benzoico (0,39 mmol, 1,5 eq) y 2,0 ml de diclorometano. Se añadió una disolución madre (4,0 ml) que contenía 4-clorofenilsulfonamida (0,26 mmol, 1 eq) y N,N-[dimetil]-4-aminopiridina (48 mg, 0,39 mmol, 1,5 eq) en diclorometano, seguida de 0,261 g de resina de poliestireno carbodilimida (2,0 mmol/g, 0,52 mmol, 2,0 eq, Novabiochem) y el vial se tapó y se giró. Después de 72 horas, se añadieron

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0,77 g de resina de poliestireno sulfonatada (MP-TsOH) (1,53 mmol/g, 1,17 mmol, Argonaut). Después de 18 horas la mezcla de reacción se filtró y se concentró bajo una corriente de nitrógeno. El residuo se sometió a HPLC en fase inversa en una columna CombiPrep, columna YMC ODS-A 20 x 50 mm de 5 micras, C18, tamaño de poro de 120 Angstrom, gradiente: del 5% al 95% CH<sub>3</sub>CN/disolución acuosa de HCl 0,01. Las fracciones que contenían el producto se combinaron y concentraron a presión reducida dando el compuesto del título.

ESIEM:  $m/z = 408(M^+ + 1)$ ,  $406(M^+ - 1)$ ,  $408(M^+ + 3)$ .

10 Los compuestos de los Ejemplos 86-107 se prepararon, básicamente, según se describe en el Ejemplo 85.

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| Nº DE EJ. | Producto                                                            | Datos espectro de masas (e/m)                           |
|-----------|---------------------------------------------------------------------|---------------------------------------------------------|
| 86        | <i>N</i> -[2,4-diclorobenzol]-4-metilfenilsulfonamida               | ESIEM: $342(M^+ - 1)$ , $344(M^+ + 1)$                  |
| 87        | <i>N</i> -[2,4-diclorobenzol]-4-metiltofenilsulfonamida             | ESIEM: $374(M^+ - 1)$ , $376(M^+ + 1)$                  |
| 88        | <i>N</i> -[2,4-diclorobenzol]-4- <i>tert</i> -butilfenilsulfonamida | ESIEM: $384(M^+ - 1)$ , $386(M^+ + 1)$                  |
| 89        | <i>N</i> -[2,4-diclorobenzol]-3-cloro-4-metilfenilsulfonamida       | ESIEM: $378(M^+ + 1)$ , $376(M^+ - 1)$ , $380(M^+ + 3)$ |
| 90        | <i>N</i> -[2-metil-4-clorobenzol]-3-bromofenilsulfonamida           | ESIEM: $388(M^+ + 1)$ , $386(M^+ - 1)$ , $390(M^+ + 3)$ |
| 91        | <i>N</i> -[2,4-diclorobenzol]-4-fluorofenilsulfonamida              | ESIEM: $346(M^+ - 1)$ , $348(M^+ + 1)$                  |
| 92        | <i>N</i> -[2,4-diclorobenzol]-3,4-diclorofenilsulfonamida           | ESIEM: $398(M^+ + 1)$ , $396(M^+ - 1)$ , $400(M^+ + 3)$ |
| 93        | <i>N</i> -[2-metil-4-clorobenzol]-4-clorofenilsulfonamida           | ESIEM: $342(M^+ - 1)$ , $344(M^+ + 1)$                  |
| 94        | <i>N</i> -[2,4-diclorobenzol]-4-bromofenilsulfonamida               | ESIEM: $408(M^+ + 1)$ , $406(M^+ - 1)$ , $410(M^+ + 3)$ |
| 95        | <i>N</i> -[2,4-diclorobenzol]-3-metilsulfoniloxifenilsulfonamida    | ESIEM: $422(M^+ - 2)$ , $424(M^+)$ , $426(M^+ + 2)$     |

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|-----|-------------------------------------------------------------------------|--------------------------------------|
| 96  | <i>N</i> -[2,4-diclorobenzoi]-4-trifluorometoxifenilsulfonamida         | ESIEM: 412(M-2), 414 (M), 416(M+2)   |
| 97  | <i>N</i> -[2,4-diclorobenzoi]-4-metoxi-3,5-dimetilfenilsulfonamida      | ESIEM: 368(M-2), 370 (M), 372(M+2)   |
| 98  | <i>N</i> -[2,4-diclorobenzoi]-4-dimetilaminofenilsulfonamida            | ESIEM: 371(M-2), 373(M)              |
| 99  | <i>N</i> -[2,4-bis-trifluorometilbenzoi]-4-clorofenilsulfonamida        | ESIEM: 430(M-1), 432(M+1)            |
| 100 | <i>N</i> -[2-metil-4-bromobenzoi]-4-bromofenilsulfonamida               | ESIEM: 430(M-3), 432 (M-1), 434(M+1) |
| 101 | <i>N</i> -[2-cloro-4-nitrobenzoi]-4-fluorofenilsulfonamida              | ESIEM: 357(M-1)                      |
| 102 | <i>N</i> -[2-cloro-3-metilbenzoi]-4-clorofenilsulfonamida               | ESIEM: 342(M-1), 344 (M+1)           |
| 103 | <i>N</i> -[2,4-diclorobenzoi]-4-nitrofenilsulfonamida                   | ESIEM: 373(M-1), 375 (M+1)           |
| 104 | <i>N</i> -[2-metil-4-clorobenzoi]-3,4-diclorofenilsulfonamida           | ESIEM: 378(M+1), 378 (M-1), 380(M+3) |
| 105 | <i>N</i> -[2-metil-4-clorobenzoi]-4- <i>tert</i> -butilfenilsulfonamida | ESIEM: 364(M-1), 366 (M+1)           |
| 106 | <i>N</i> -[2-metil-4-clorobenzoi]-3-clanofenilsulfonamida               | ESIEM: 333(M-1)                      |
| 107 | <i>N</i> -[2,4-diclorobenzoi]-4-[1,2,4]triazol-4-il-fenilsulfonamida    | 395 (M)                              |

EJEMPLO 108

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*N*-[2,4-diclorobenzoi]-4-(1-metilsulfanil-fen-4-il)fenilsulfonamida

Etapas A: Procedimiento de activación de la resina

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La resina de amida Rink (CA Novabiochem, 0,53 mmol/g) se suspendió en una disolución de piridina al 30% en DMF y se agitó a temperatura ambiente durante 3 horas. La mezcla se filtró y la resina se lavó dos veces con DMF y después, alternativamente con CH<sub>2</sub>Cl<sub>2</sub> y MeOH. La resina activada que tiene un grupo amino libre se secó y se usó sin mayor purificación.

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La resina de amida Rink (0,53 mmol/g) se suspendió en una mezcla 1:1 de CH<sub>2</sub>Cl<sub>2</sub>/THF y Et<sub>3</sub>N (4 eq), 4-yodofenilsulfonamida (3 eq) y DMAP (cantidad catalítica). La disolución se agitó durante toda la noche a temperatura ambiente. La mezcla se filtró y la resina se lavó alternativamente con CH<sub>2</sub>Cl<sub>2</sub> y

MeOH. La resina de 4-yodofenilsulfonamida de Rink se secó a vacío.

La resina de 4-yodofenilsulfonamida de Rink (0,26 mmol, 0,53 mmol/g), ácido metilsulfanil-fenilo (2 eq), carbonato potásico (6 eq) y acetato de paladio (0,5 eq) se mezclaron todos juntos y se suspendieron en 7 ml de una mezcla de dioxano y agua 6:1. Esta mezcla se calentó en un Argovant® QUEST® 210 a 100° durante 24 horas. Después, la resina se lavó dos veces con 5 ml de una mezcla de dioxano/agua 6:1 y después seis veces con CH<sub>2</sub>Cl<sub>2</sub> (7 ml) seguido cada vez de MeOH (7 ml).

Se añadieron 3 ml de una disolución acuosa al 95% de ácido trifluoroacético a la resina, disueltos previamente en 3 ml de CH<sub>2</sub>Cl<sub>2</sub>. La mezcla se agitó durante 30 minutos a temperatura ambiente y se filtró como se ha descrito anteriormente. Se utilizó la 4'-metilsulfanil-bifenil-4-sulfonamida sin mayor purificación.

A una disolución agitada de ácido 2,4-dicloro-benzoico (1,25 eq) en CH<sub>2</sub>Cl<sub>2</sub> seco (10 ml/mmol) se añadió 4'-metilsulfanil-bifenil-4-sulfonamida (1,0 eq) de una sola vez mediante EDC (1,25 o 1,5 eq) y, finalmente, DMAP (1,2 equiv). La mezcla se agitó vigorosamente en atmósfera de nitrógeno durante 16 horas, después se vaporó a vacío y el residuo se dividió entre EtOAc y agua. La fase orgánica se lavó con HCl 1 N (4 veces, 20 ml/mmol), después la fase acuosa se extrajo con EtOAc (dos veces, 20 ml/mmol). Las fases orgánicas combinadas se lavaron finalmente con agua y salmuera, se secaron sobre Na<sub>2</sub>SO<sub>4</sub>, y se concentraron a vacío. El producto bruto se purificó por cromatografía en gel de sílice usando el efluente apropiado, dando el compuesto del título.

ESI-EM (M<sup>+</sup>-H) 450,9870/450,0.

## EJEMPLO 109

*N*-[2,4-diclorobenzoi]-4-3'-acetil-bifenilsulfonamida

Se usó una suspensión de resina de 4-yodofenilsulfonamida de Rink (0,26 mmol, 0,53 mmol/g), ácido 3-acetilfenil borónico (2 eq) y ácido 2,4-diclorobenzoico (1,25 eq), básicamente, como se describe en el Ejemplo 108 para preparar el compuesto del título.

ESI-EM ( $M^+-H$ ) 447,0099/446,0.

## EJEMPLO 110

10 *N*-[2,4-diclorobenzoi]-fenilsulfonamida

A una mezcla de fenilsulfonamida (0,16 mol; 25,12 g) y carbonato potásico (0,2 mol; 27,6 g) en 500 ml de dioxano se añadió, gota a gota, cloruro de 2,4-diclorobenzoi (0,13 mol, 18,0 ml). La mezcla se calentó a reflujo en atmósfera de nitrógeno durante 16 horas. La reacción se diluyó entonces con agua (500 ml), se neutralizó a pH 5 con ácido clorhídrico concentrado y se extrajo 3 veces con acetato de etilo. Las fases de acetato de etilo combinadas se lavaron con cloruro sódico acuoso saturado. El residuo sólido se sometió a cromatografía en gel de sílice, eluyendo con diclorometano que contenía un 0-5% de metanol. Se combinaron las fracciones que contenían el producto y se concentraron a presión reducida dando el compuesto del título.

MS(EM):  $m/z$  = 329,9 ( $M^++1$ ), 327,9 ( $M^+-1$ ).

## EJEMPLO 111

*N*-[2,4-diclorobenzoi]-4-clorofenilsulfonamida

25 Una mezcla de 4-clorofenilsulfonamida (0,1 mol; 19,0 g) y cloruro de 2,4-

diclorobenzolillo (0,12 mol; 16,8 ml); el compuesto del título se preparó básicamente según se ha descrito en el Ejemplo 110.

MS(ES):  $m/z = 363,9$  (M<sup>+</sup>)

EA: Calculada para C<sub>13</sub>H<sub>8</sub>Cl<sub>3</sub>NO<sub>3</sub>S: Teoría: C, 42,82; H, 2,21; N, 3,84. Hallado:

5 C, 42,56; H, 2,14; N, 3,76.

## EJEMPLO 112

### *N*-[2-cloro-4-bromobenzoil]-4-clorofenilsulfonamida

A una mezcla de reacción de 4-clorofenilsulfonamida (15,6 g, 81,4  
10 mmol), CDI (15,82 g, 97,7 mmol) y acetato de etilo (300 ml) a temperatura ambiente se añadió una suspensión de ácido 2-cloro-4-bromobenzoico (23,0 g, 97,7 mmol) en acetato de etilo (100,0 ml) durante un periodo de 15,0 minutos (nótese: se observó desprendimiento de gas que se pudo controlar por la velocidad de adición de la suspensión; la mezcla de reacción entró en  
15 disolución hacia el final de la adición de la suspensión; la reacción se pudo controlar por HPLC o TLC con acetato de etilo/heptano 1:1 como eluyente. Después la mezcla de reacción se agitó a temperatura ambiente durante 30 minutos y después se calentó a 60°C durante 90 minutos o hasta que no se observe desprendimiento de gas. La reacción se enfrió a 40°C y se añadió (de  
20 una sola vez) 1,8-diazabicyclo[5.4.0]undec-7-eno (14,63 ml). La temperatura de reacción pasó de 40°C a 45°C. La mezcla se agitó hasta que alcanzó temperatura ambiente antes de apagarla con agua desionizada (400 ml). La fase orgánica superior se separó, se lavó con HCl 1 N (300,0 ml), se secó con MgSO<sub>4</sub> anhidro, se filtró y la torta se lavó con acetato de etilo (20,0 ml). El  
25 filtrado se concentró a 50,0 g de disolución de jarabe, después se añadió

heptano (250,0 ml) con agitación vigorosa. Calentando, se formó una suspensión blanca y se sometió a reflujo y después se dejó equilibrar a temperatura ambiente. El precipitado blanco se filtró y la torta se lavó con heptano (20,0 ml). El precipitado se secó a vacío a 55°C durante 18 horas.

5 (masa = 29,12 g, rendimiento del 87,4%).

Se calentó a reflujo una mezcla de 19,17 g del producto y acetato de etilo/heptano 1:2 (150,0 ml) durante 30 minutos, y después se enfrió a temperatura ambiente. El precipitado blanquecino se filtró y la torta se lavó con heptano (50,0 ml). El precipitado se secó a vacío a 50°C durante 18 horas.

10 (masa = 14,93 g; recuperación del 78%).

ESI EM:  $m/z$  = 408 ( $M^+ + 1$ ), 406 ( $M^+ - 1$ ), 410 ( $M^+ + 3$ ).

### EJEMPLO 113

Sal sódica de *N*-[2-cloro-4-bromobenzoil]-4-clorofenilsulfonamida

15 A una disolución de *N*-[2-cloro-4-bromobenzoil]-4-clorofenilsulfonamida (5,2 g, 12,72 mmol) y éter metílico de *tert*-butiléter (88,0 ml) a temperatura ambiente se añadió metóxido sódico (0,69 g, 12,72 mmol) de una sola vez. Después, la reacción se agitó durante 5 horas, después de las cuales se añadió heptano (88,0 ml) seguido de agitación vigorosa durante 60 minutos. Se formó un

20 precipitado blanco, se filtró en una atmósfera positiva de nitrógeno y la torta se lavó posteriormente con heptano (2 x 44,0 ml). La torta se secó hasta semisequedad, seguida por secado en horno a vacío a 130°C durante 18 horas (masa = 4,4 g, 80% en peso. rendimiento; RMN  $^1H$  (DMSO  $d_6$ ) 7,8-7,85 (m, 1H), 7,81-7,82 (m, 1H), 7,58-7,59 (d, 1H,  $J$  = 1,76 Hz), 7,51-7,52 (m, 1H), 7,48-7,49

25 (m, 1H), 7,44-7,45 (d, 1H,  $J$  = 1,76) 7,37-7,4 (d, 1H).

## EJEMPLO 114

*N*-[3-cloro-4-fluorofenilsulfonil]-3-fluoro-4-metilbenzamidina

Se añade clorhidrato de 3-fluoro-4-metilbenzamidina (0,025 g, 0,133 mmol) en THF (0,5 ml) a cloruro de sulfonilo de 3-cloro-4-fluorofenilo (0,0304 g, 0,133 mmol) seguido de *N*-metilmorfolina (0,2 ml). La mezcla de reacción se concentró y se cromatografió usando cromatografía en fase inversa (gradiente del 5-95% (0,1% TFA en CH<sub>3</sub>CN) en ((0,1% TFA en H<sub>2</sub>O). Se aisló un sólido blanco (16,4 mg, 36%). ES EM Ión Positivo iones [M+H]<sup>+</sup> observada: *m/z* 345 (<sup>35</sup>Cl) y *m/z* 347 (<sup>37</sup>Cl).

## EJEMPLO 115

*N*-[3-cloro-4-fluorofenilsulfonil]-4-clorobenzamidina

Se usó clorhidrato de 4-clorobenzamidina (0,025 g, 0,133 mmol) y cloruro de sulfonilo de 3-cloro-4-fluorofenilo (0,0304 g, 0,133 mmol), básicamente según se describe en el Ejemplo 114 para preparar el compuesto del título. ES EM Ión Positivo iones [M+H]<sup>+</sup> observada: *m/z* 347 (<sup>35</sup>Cl, <sup>35</sup>Cl), 349 (<sup>35</sup>Cl, <sup>37</sup>Cl) y 351 (<sup>37</sup>Cl, <sup>37</sup>Cl).

## EJEMPLO 116

*N*-[3-cloro-4-fluorofenilsulfonil]-3-cloro-4-fluorobenzamidina

Una mezcla de clorhidrato de 3-cloro-4-fluorobenzamidina (0,025 g, 0,133 mmol) y cloruro de sulfonilo de 3-cloro-4-fluorofenilo (0,0304 g, 0,133 mmol); el compuesto del título se preparó, básicamente, según se describe en el Ejemplo 115. ES EM Ión Positivo iones [M+H]<sup>+</sup> observada: *m/z* 365 (<sup>35</sup>Cl,

HS  
111

<sup>35</sup>Cl), 367 (<sup>35</sup>Cl, <sup>37</sup>Cl) y 369 (<sup>37</sup>Cl, <sup>37</sup>Cl).

#### EJEMPLO 117

##### *N*-[2,4-diclorobenzoi]-4-hidroxifenilsulfonamida

- 5 Se disolvió 4-metoxi-fenil-4-sulfonamida (0,0608 g, 0,132 mmol) en THF (1,25 ml) y se trató con fluoruro de tetrabutilamonio (THF/1,0 N; 200  $\mu$ l, 2,0 mmol) a temperatura ambiente con agitación, durante 18 horas. La mezcla de reacción se diluyó con EtOAc (10 ml) y se lavó con NH<sub>4</sub>Cl ac. Saturado (1 ml), H<sub>2</sub>O (2 x 1 ml) y salmuera (1 ml). La fase orgánica se secó sobre MgSO<sub>4</sub>, se filtró y se
- 10 concentró en rotavapor. (Se liofilizó en H<sub>2</sub>O/MeOH para obtener un sólido cristalino, 20 mg (0,058 mmol, 58%). Se purificó por HPLC) pf 155-157°C; ESI-EM e/m 344,0 (M+ - H); RMN <sup>1</sup>H (d<sub>6</sub>-DMSO) 7,90 (d, 2 H); 7,68 (s, 1 H); 7,44 (s, 2 H); 6,90 (d, 2H); 3,43 (a s, 3 H).

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#### EJEMPLO 118

##### *N*-[2,4-diclorobenzoi]-4-(tien-3-il)-fenilsulfonamida

- A una disolución de *N*-(2,4-diclorobenzoi)-4-yodo-fenilsulfonamida (0,10 mmol) en tolueno/etanol 20/1 (3 ml) se añadió ácido 3-tiofenoborónico (0,18 mmol, 0,18 ml, disolución 1,0 M en DMF) y tetrakis-(trifenilfosfina) de paladio
- 20 (0) (10% mol). Después, se añadió Na<sub>2</sub>CO<sub>3</sub> acuoso 2 M (0,3 ml) y la mezcla agitada se calentó a 100°C durante toda la noche (17 h) (sistema Buchi Syncore). La mezcla de reacción se concentró (aparato Genevac), después se añadió agua (2,5 ml) y acetato de etilo (5 ml). Las fases se separaron y la fase acuosa se extrajo con acetato de etilo (3 x 5 ml). Este procedimiento se llevó a
- 25 cabo automáticamente usando un sistema Tecan. Los disolventes se

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evaporaron y el producto bruto correspondiente se purificó por HPLC dando el compuesto del título.

ESI EM *a/m* 410,96/410,0 [M<sup>+</sup>-H]<sup>+</sup>

5 Los compuestos de los EJEMPLOS 119-130 se prepararon, básicamente, según se describe en el procedimiento del EJEMPLO 118.

| Nº de ejemplo | Producto                                                                         | Datos espectro de masas (e/m)     |                     |
|---------------|----------------------------------------------------------------------------------|-----------------------------------|---------------------|
|               |                                                                                  | ESI-EM                            | <i>e/m</i>          |
| 10            | 119 <i>N</i> -[2,4-diclorobenzoil]-4-(1-trifluorometilfen-4-il)fenilsulfonamida  | ESI-EM: <i>e/m</i> 472,99 / 472,2 | [M <sup>+</sup> -H] |
|               | 120 <i>N</i> -[2,4-diclorobenzoil]-4-(1-fluoro-fen-3-il)-fenilsulfonamida        | ESI-EM: <i>e/m</i> 422,99 / 422,0 | [M <sup>+</sup> -H] |
|               | 121 <i>N</i> -[2,4-dicloro-benzoil]-4-furan-2-il-fenilsulfonamida                | ESI-EM: <i>e/m</i> 394,98 / 394,2 | [M <sup>+</sup> -H] |
|               | 122 <i>N</i> -[2,4-diclorobenzoil]-4-(1-metoxi-fen-2-il)fenilsulfonamida         | ESI-EM: <i>e/m</i> 435,01 / 434,0 | [M <sup>+</sup> -H] |
|               | 123 <i>N</i> -[2,4-diclorobenzoil]-4-(1-metoxycarbonil-fen-4-il)fenilsulfonamida | ESI-EM: <i>e/m</i> 447,07 / 446,0 | [M <sup>+</sup> -H] |
| 15            | 124 <i>N</i> -[2,4-diclorobenzoil]-4-quinolin-8-il-fenilsulfonamida              | ESI-EM: <i>e/m</i> 456,01 / 455,1 | [M <sup>+</sup> -H] |
|               | 125 <i>N</i> -[2,4-diclorobenzoil]-3-quinolin-8-il-fenilsulfonamida              | ESI-EM: <i>e/m</i> 456,01 / 457,2 | [M <sup>+</sup> +H] |
|               | 126 <i>N</i> -[2,4-diclorobenzoil]-4-fur-3-il-fenilsulfonamida                   | ESI-EM: <i>e/m</i> 394,98 / 394,0 | [M <sup>+</sup> -H] |
|               | 127 <i>N</i> -[2,4-diclorobenzoil]-4-piridin-3-il-fenilsulfonamida               | ESI-EM: <i>e/m</i> 406,0          | [M <sup>+</sup> -H] |
|               | 128 <i>N</i> -[2,4-diclorobenzoil]-3-bifenilsulfonamida                          | ESI-EM: <i>e/m</i> 405,1          | [M <sup>+</sup> -H] |
| 20            | 129 <i>N</i> -[2,4-diclorobenzoil]-4'-metoxi-4-bifenilsulfonamida                | ESI-EM: <i>e/m</i> 435,2          | [M <sup>+</sup> -H] |
|               | 130 <i>N</i> -[2,4-diclorobenzoil]-4-bifen-2-il-fenilsulfonamida                 | ESI-EM: <i>e/m</i> 411,1          | [M <sup>+</sup> -H] |

Todos los compuestos relacionados están disponibles oralmente y normalmente se administran oralmente, por lo que la administración oral es la preferida. Sin embargo, la administración oral no es la única vía o incluso la

única vía preferida. Por ejemplo, la administración transdérmica puede ser muy deseable para pacientes que sean olvidadizos o irritables a la hora de tomar medicinas orales y, de hecho, puede preferirse la vía intravenosa por conveniencia para evitar complicaciones potenciales relacionadas con la administración oral. Los compuestos de Fórmula II se pueden administrar también por vía percutánea, Intramuscular, Intranasal o intrarectal en circunstancias particulares. La vía de administración se puede variar de cualquier manera, limitada sólo por las propiedades físicas de los fármacos, la conveniencia del paciente y del cuidador, y otras circunstancias relevantes (Remington's Pharmaceutical Sciences, 18ª Edición, Mack Publishing Co. (1990)).

Las composiciones farmacéuticas se preparan de una manera que el experto en la técnica conoce. El vehículo o excipiente puede ser un material sólido, semisólido o líquido que puede servir como vehículo o medio para el ingrediente activo. Los vehículos o excipientes adecuados son bien conocidos en la técnica. La composición farmacéutica se puede adaptar para uso oral, por inhalación, parenteral o tópico y se pueden administrar al paciente en forma de comprimidos, cápsulas, aerosoles, Inhaladores, supositorios, disoluciones, suspensiones o similares.

Los compuestos de la presente invención se pueden administrar oralmente, por ejemplo, con un diluyente inerte para cápsulas o comprimido en comprimidos. Con el fin de administración terapéutica oral, los compuestos se pueden incorporar con excipientes y se pueden usar en forma de comprimidos, comprimidos medicinales, cápsulas, elixires, suspensiones, jarabes, obleas, chicles y similares. Estas preparación deberían contener, al menos, un 45% del

compuesto de la presente invención, el ingrediente activo, aunque esto puede variar dependiendo de la forma particular y, convenientemente, está entre el 4% y el 70% del peso de la unidad. La cantidad del compuesto presente en las composiciones es la que permite obtener una dosificación adecuada. Las composiciones y preparaciones preferidas de la presente invención se pueden determinar por procedimientos bien conocidos por los expertos en la técnica.

Las pastillas, píldoras, cápsulas, comprimidos y similares pueden contener también uno o más de los siguientes adyuvantes: aglutinantes como por ejemplo povidona, hidroxipropilcelulosa, celulosa microcristalina o gelatina; excipientes o diluyentes como por ejemplo almidón, lactosa, celulosa microcristalina o fosfato dicálcico; agentes disgregantes como por ejemplo croscarmelosa, crospovidona, almidón glicolato sódico, almidón de maíz y similares; lubricantes como por ejemplo estearato magnésico, ácido esteárico, talco o aceite vegetal hidrogenado; glidantes como por ejemplo dióxido de silicio coloidal; agentes humectantes como por ejemplo lauril sulfato sódico y polisorbato 80 (CAS nº 9005-65-6); y agentes edulcorantes como por ejemplo sacarosa, aspartamo o sacarina o un agente aromatizante como por ejemplo menta, salicilato de metilo o aroma de naranja. Cuando la forma de dosificación unitaria es una cápsula, puede contener además de los materiales del tipo anterior, un vehículo líquido como por ejemplo polietilenglicol o un aceite graso. Otras formas de dosificación unitaria pueden contener diversos materiales que modifican la forma física de la unidad de dosificación, por ejemplo, recubrimientos. Por lo tanto, los comprimidos o píldoras se pueden recubrir con azúcar, hidroxipropilmetilcelulosa, polimetacrilatos u otros agentes de recubrimiento. Los jarabes pueden contener, además de los presentes

compuestos, sacarosa como agente edulcorante y ciertos conservantes, tintes y colorantes y aromatizantes. Los materiales usados en la preparación de estas composiciones diversas debería ser farmacéuticamente puro e inocuo en las cantidades utilizadas.

- 5 Las inyecciones para administración parenteral incluyen disoluciones, suspensiones y emulsiones estériles acuosas y no acuosas. Las disoluciones y suspensiones acuosas pueden incluir agua destilada para inyección o una disolución de sal fisiológica. Las disoluciones y suspensiones no acuosas pueden incluir propilenglicol, polietilenglicol, aceites vegetales como por
- 10 ejemplo aceite de oliva, alcohol como por ejemplo etanol o polisorbato 80. Las inyecciones pueden comprender ingredientes adicionales distintos de diluyentes inertes: por ejemplo, agentes conservantes, agentes humectantes, agentes emulgentes, agentes dispersantes, agentes estabilizantes (como por ejemplo lactosa), agentes ayudantes como por ejemplo agentes que ayudan en
- 15 la disolución (por ejemplo, ácido glutámico o aspártico). Se pueden esterilizar, por ejemplo, por filtración a través de un filtro que retiene bacteria, incorporando agentes esterilizantes en las composiciones o por irradiación. Se pueden preparar también en forma de composiciones sólidas estériles que se pueden disolver en agua estéril o en otro diluyente estéril para inyección
- 20 Inmediatamente antes de su uso.

Los compuestos de Fórmula II son eficaces, en general, en un amplio intervalo de dosificación. Por ejemplo, las dosificaciones por día caen, normalmente, en el intervalo de aproximadamente 10 a aproximadamente 300 mg/kg de peso corporal. En algunos casos los niveles de dosificación por

25 debajo del límite inferior del intervalo mencionado anteriormente pueden ser

carbono/aire humidificado al 5%. Se añadió el reactivo de proliferación celular WST-1 (20  $\mu$ l; Boehringer Mannheim, Indianápolis, IN) a los pocillos y las placas se devolvieron a la incubadora durante 1 hora. Se midió la absorbancia de cada pocillo a 440 nm. Se determinó la fracción de crecimiento a partir de la absorbancia de los pocillos tratados con y sin VEGF dividido por la absorbancia obtenida a partir de pocillos de control ajustados a cero y 1,0. Los compuestos ejemplares se ensayaron en este ensayo y todos presentaron una  $CI_{50} \leq 1,0$   $\mu$ M.

#### 10 Ensayo de Microcavidad Corneal en Rata

Se anestesiaron ratas hembra Fisher 344 (145-155 gramos; Taconic, Inc., Germantown, NY) con acepromazina (2,5 mg/kg, ip) 20 minutos antes de comenzar la inhalación de un 2-3% de Isoflurano/oxígeno. Se mantuvo la temperatura corporal con una almohadilla de agua caliente circulante. La cirugía se llevó a cabo usando un microscopio oftálmico de operación (Microscopio de Operación OMS.75, TopCon Corporation, Japón). Se usó un escalpelo (nº 15) para hacer una incisión corneal lineal vertical de grosor medio justo al lado del centro del ojo. Se usó la punta del escalpelo para extraer suavemente la capa corneal superior más próxima al limbus. Se formó una cavidad en la córnea usando disección roma con unas tijeras corneales (Roboz, Rockville, MD). Se cortaron filtros de nitrocelulosa (0,45  $\mu$ m, Millipore, Bedford, MA) en pequeños discos usando una aguja de punción de 5,06  $\mu$ m. Los discos se empaparon en 2  $\mu$ l de disolución de VEGF humana (0,82  $\mu$ g/ $\mu$ l; R&D Systems) o factor de crecimiento de fibroblastos básico (0,20  $\mu$ g/ $\mu$ l; R&D Systems) durante 10 minutos en hielo. Usando un fórceps, se insertaron los discos impregnados con el factor angiogénico (VEGF o bFGF) en las cavidades

comeales de manera que el disco cubría firmemente el epitelio corneal. Los animales se trataron con el compuesto del Ejemplo 110 (160 mg/kg) administrado oralmente mediante administración forzada en suero fisiológico tamponado con fosfato una vez al día en los días 1 a 10 después de la  
5 implantación de los discos. Los ojos se fotografiaron en los días 7 y 14 después de la implantación de los discos. Para la fotografía, los animales se trataron típicamente, con sulfato de atropina (AmTech Group, Inc., Phoenix Scientific, Inc., St. Joseph, MO) para midriasis, y se anestesiaron con un 2-3% de isoflurano/oxígeno. Los ojos se fotografiaron usando el microscopio oftálmico y  
10 las imágenes se guardaron usando el software Image Pro-Plus. Las imágenes se analizaron convirtiendo el área de interés en una imagen invertida de alto contraste en blanco y negro y contando los píxeles brillantes como determinación del área vascular. Los datos son imágenes de al menos 6 ojos. El compuesto del Ejemplo 110 fue un inhibidor muy eficaz de la  
15 neoangiogénesis inducida por VEGF, aunque no fue un inhibidor eficaz de la neoangiogénesis inducida por bFGF.

#### Inhibición del crecimiento celular del carcinoma de colon HCT116

Se desarrolló un cultivo monocapa de células de carcinoma de colon  
20 HCT116 humanas en un medio RPMI 1640 suplementado con un 10% de suero bovino fetal y un 1% de penicilina-estreptomicina (GibcoBRL, Grand Island, NY). Las células HCT116 en fase de crecimiento exponencial se expusieron a diversas concentraciones de los compuestos de ensayo a 37°C durante 72 horas en dióxido de carbono/aire al 5%. Después de la exposición al  
25 agente, las células se lavaron con suero fisiológico tamponado con fosfato al

0,9%. Se determinó la inhibición del crecimiento usando un reactivo de proliferación celular WST-1 tal y como se ha descrito anteriormente. Los resultados se expresan como el fracción de crecimiento de las células tratadas comparadas con los cultivos de control. Se ensayó la eficacia de los

5 compuestos representativos de la presente invención contra células tumorales HCT116 de colon humano. Los datos a partir de estos experimentos se resumen en la TABLA I.

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TABLA I

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| EJEMPLO | Cl <sub>50</sub> (μM) | EJEMPLO | Cl <sub>50</sub> (μM) |
|---------|-----------------------|---------|-----------------------|
| 1       | 4,2                   | 82      | 19,3                  |
| 3       | 2,5                   | 83      | 24,7                  |
| 5       | 3,8                   | 84      | 18,2                  |
| 6       | 4,0                   | 70      | 16,9                  |
| 9       | 1,7                   | 73      | 8,3                   |
| 10      | 12,1                  | 79      | 5,2                   |
| 11      | 5,5                   | 80      | 12,3                  |
| 14      | 40,0                  | 81      | 11,3                  |
| 15      | 10,4                  | 82      | 12,4                  |
| 16      | 3,8                   | 86      | 1,6                   |
| 17      | 15,8                  | 87      | 5,5                   |
| 18      | 9,3                   | 88      | 4,8                   |
| 20      | 2,4                   | 89      | 4,8                   |
| 21      | 30,4                  | 90      | 4,5                   |
| 23      | 15,9                  | 92      | 17,4                  |
| 24      | 37,1                  | 93      | 18,1                  |
| 25      | 9,6                   | 94      | 3,6                   |
| 26      | 6,1                   | 95      | 4,3                   |
| 30      | 10,1                  | 96      | 34,7                  |
| 32      | 7,8                   | 97      | 7,0                   |
| 33      | 7,8                   | 98      | 13,0                  |
| 34      | 16,5                  | 99      | 33,5                  |
| 35      | 17,0                  | 100     | 9,2                   |
| 36      | 28,4                  | 101     | 12,4                  |
| 37      | 15,5                  | 102     | 6,3                   |
| 38      | 13,9                  | 103     | 11,9                  |
| 41      | 14,5                  | 104     | 22,2                  |
| 42      | 3,3                   | 105     | 14,8                  |
| 44      | 18,7                  | 106     | 4,6                   |
| 45      | 20,7                  | 108     | 16,0                  |
| 46      | 4,8                   | 109     | 25,1                  |
| 47      | 8,7                   | 110     | 3,5                   |
| 49      | 14,7                  | 111     | 15,0                  |
| 50      | 10,5                  | 112     | 2,8                   |
| 51      | 26,7                  | 115     | 33,6                  |
| 53      | 11,2                  | 116     | 5,9                   |
| 55      | 9,5                   | 117     | 12,4                  |
| 56      | 16,8                  | 121     | 24,5                  |
| 57      | 5,0                   | 122     | 25,8                  |
| 59      | 15,0                  | 123     | 37,7                  |
| 60      | 6,6                   | 124     | 5,6                   |
| 61      | 14,2                  | 126     | 18,5                  |

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### Ensayos Convencionales de Tumor Murino y Xenoinjerto Humano

La inhibición de los tumores transplantados en ratones es un procedimiento aceptado para estudiar la eficacia de los agentes antitumorales (Corbett, et al., In vivo Methods for Screening and Preclinical Testing; Use of rodent solid tumors for drug discovery., En: Anticancer Drug Development Guide: Preclinical Screening, Clinical Trials, and Approval, B. Teicher (ed), Humana Press Inc., Totowa, NJ, Capítulo 5, páginas 75-99 (1997); (Corbett, et al., Int. J. Pharmacog., **33**, Supplement, 102-122 (19995)). Los tumores de murina o xenoinjertos humanos se implantaron, esencialmente, según describe Corbett en In vivo Methods for Screening and Preclinical Testing; Use of rodent solid tumors for drug discovery. Brevemente, el tumor de murina o xenoinjerto humano se implantó subcutáneamente usando implantes trocar de 3,04  $\mu\text{m}$  o un número de células contadas. La localización de la inserción trocar está a medio camino entre las regiones axilar e inguinal a lo largo del costado del ratón. El trocar se desliza aproximadamente  $\frac{3}{4}$  de pulgada subcutáneamente hacia la axila antes de descargar el fragmento tumoral, y pinzando la piel cuando se elimina el trocar. Alternativamente, las células tumorales humanas preparadas a partir de un conjunto de tumores del donante ( $5 \times 10^6$  células) se implantaron subcutáneamente en la pata trasera de un ratón hembra o macho (Charles River). Se administró el compuesto de ensayo en un vehículo o el vehículo solo por inyección de bolo intravenoso (iv), inyección intraperitoneal (ip) o por administración forzada oral (po). Cada grupo de tratamiento, así como un grupo de animales de control sin tratar, que consistía en cinco animales por grupo en cada experimento. Se controló la respuesta tumoral subcutánea midiendo el volumen tumoral, que se llevó a cabo dos veces cada semana

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durante el transcurso del experimento (60-120 días). Los pesos corporales se tomaron como una medida general de la toxicidad. Los datos de tumores subcutáneos se analizaron determinando el peso medio del tumor para cada grupo de tratamiento en el curso del experimento y calculando el retraso del crecimiento tumoral como la diferencia en días para el tratamiento frente a los tumores de control para alcanzar un volumen de 500 o 1000 mm<sup>3</sup>.

El compuesto del Ejemplo 110 se ensayó contra diversos tumores humanos y de murina, sustancialmente, según se ha descrito anteriormente. Los datos de estos ensayos se resumen en las TABLAS II-XIII. Los parámetros medidos en cada experimento se resumen en los siguientes párrafos.

Peso del tumor (mg) =  $(a \times b^2)/2$  en la que a = longitud del tumor (mm) y b anchura del tumor (mm).

Retraso del crecimiento tumoral = T - C en la que T es el tiempo medio (días) necesario para que los tumores del grupo de tratamiento alcancen un tamaño predeterminado y C es el tiempo medio (días) para que los tumores del grupo de control alcancen el mismo tamaño. Los supervivientes exentos de tumores se excluyen de este cálculo y se tabulan por separado (exento de tumor).

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Log destrucción = retraso del crecimiento tumoral  
(3,32)(Td)

en la que retraso del crecimiento tumoral es tal y como se ha definido anteriormente y Td es el volumen tumoral al doblarse el tiempo (días), estimado a partir del mejor ajuste lineal de una representación lineal del crecimiento

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123

logarítmico del grupo de control de tumores en crecimiento exponencial (100-800 mg de intervalo).

**% de masa T/C.** Los grupos de tratamiento y de control se midieron cuando los tumores del grupo de control alcanzaron, aproximadamente 700 o 1200 mg de tamaño (grupo medio). El peso medio del tumor de cada grupo se determinó (incluyendo ceros). El valor de T/C en porcentaje es una indicación de la eficacia antitumoral. Un  $T/C \leq 42\%$  se considera una actividad antitumoral significativa. Un  $T/C < 10\%$  se considera que indica una actividad antitumoral significativamente mayor.

**Pérdida de Peso Corporal Nadir.** Una pérdida de peso corporal nadir (media de un grupo) mayor del 20% o muertes con fármaco mayores del 20% se considera que indican una dosificación tóxica excesiva en experimentos unitarios.

**Índice de Actividad.** El Índice de Actividad se deriva de Log de destrucción según la siguiente tabla.

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| ACTIVIDAD ANTITUMORAL | LOG DE DESTRUCCIÓN | INDICE DE ACTIVIDAD |
|-----------------------|--------------------|---------------------|
| MUY ACTIVO            | > 2,8              | ++++                |
|                       | 2,0 - 2,8          | +++                 |
|                       | 1,3 - 1,9          | ++                  |
|                       | 0,7 - 1,2          | +                   |
| INACTIVO              | < 0,7              | -                   |

TABLA II  
FASE TEMPRANA DEL ADENOCARCINOMA-38 DE COLON MURINO  
(ratones macho BDF1, CRL-Raleigh)

| DOSIS<br>TOTAL<br>(mg/kg) | % DE<br>PÉRDIDA<br>DE PESO<br>CORPORAL<br>A NADIR | MUERTES<br>CON<br>FÁRMACO | % DE<br>MASA<br>T/C | RETRASO<br>DEL<br>CRECIMIENTO<br>(DÍAS) | LOG DE<br>DESTRUCCIÓN | TUMOR<br>LIBRE EN<br>EL DÍA<br>144 | INDICE DE<br>ACTIVIDAD |
|---------------------------|---------------------------------------------------|---------------------------|---------------------|-----------------------------------------|-----------------------|------------------------------------|------------------------|
| 0                         | +6,3%                                             | 0/5                       | -                   | -                                       | -                     | 0/5                                | -                      |
| 1200 <sup>a</sup>         | -5,2%                                             | 0/6                       | 0%                  | Se curan todos                          | > 4,5                 | 6/6                                | ++++                   |
| 920 <sup>b</sup>          | +7,7%                                             | 0/5                       | 0%                  | Se curan todos                          | > 4,5                 | 5/5                                | ++++                   |
| 272 <sup>c</sup>          | +3,1%                                             | 0/5                       | 0%                  | Se curan todos                          | > 4,5                 | 5/5                                | ++++                   |

5

- <sup>a</sup> El fármaco se administró por vía intravenosa a 80 mg/kg en el día 3, 160 mg/kg en el día 4, 240 mg/kg en el día 5 y 120 mg/kg/inyección BID en los días 7-9
- <sup>b</sup> El fármaco se administró por vía intravenosa a 40 mg/kg en el día 3, 80 mg/kg en el día 4 y 160 mg/kg/inyección QD en los días 5-9
- <sup>c</sup> El fármaco se administró por vía intravenosa a 20 mg/kg en el día 3, 40 mg/kg en el día 4 y 106 mg/kg/inyección QD en los días 5-8

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TABLA III  
FASE TEMPRANA DEL ADENOCARCINOMA-16/C DE MAMA MURINO  
(ratones hembra C3H, CRL-Kingston)

| DOSIS<br>TOTAL<br>(mg/kg)   | % DE<br>PÉRDIDA<br>DE PESO<br>CORPORAL<br>NADIR | MUERTES<br>CON<br>FÁRMACO | % DE<br>MASA<br>T/C | RETRASO<br>DEL<br>CRECIMIENTO<br>(DÍAS) | LOG DE<br>DESTRUCCIÓN | TUMOR<br>LIBRE EN<br>EL DÍA 14 | INDICE DE<br>ACTIVIDAD |
|-----------------------------|-------------------------------------------------|---------------------------|---------------------|-----------------------------------------|-----------------------|--------------------------------|------------------------|
| 0                           | +0,0%                                           | 0/5                       | -                   | -                                       | -                     | 0/5                            | -                      |
| INFUSIÓN<br>DE<br>DILUYENTE | +10,8%                                          | 0/4                       | 80%                 | 0,7                                     | 0,22                  | 0/4                            | -                      |
| 560 <sup>a</sup>            | MUERTE                                          | 5/5                       | -                   | MUERTE                                  | -                     | 0/5                            | MUERTE                 |
| 560 <sup>b</sup>            | +10,9%                                          | 0/4                       | 37%                 | 2,0                                     | 0,6                   | 0/4                            | ±                      |
| 680 <sup>c</sup>            | +7,6%                                           | 0/5                       | 39%                 | 2,5                                     | 0,75                  | 0/5                            | ±                      |

<sup>a</sup> El fármaco se administró a 560 mg/kg por infusión intravenosa durante 3 horas en el día 3  
<sup>b</sup> El fármaco se administró a 280 mg/kg por infusión intravenosa en los días 3 y 7  
<sup>c</sup> El fármaco se administró por vía intravenosa a 80 mg/kg/inyección en los días 3-6, 120 mg/kg/inyección en los días 7-9

125

TABLA IV  
FASE TEMPRANA DEL ADENOCARCINOMA-HCT116 DE COLON HUMANO  
(ratones hembra Balb/C SCID, NCI)

| DOSIS<br>TOTAL<br>(mg/kg) | % DE<br>PÉRDIDA<br>DE PESO<br>CORPORAL<br>NADIR | MUERTES<br>CON<br>FÁRMACO | % DE<br>MASA<br>T/C | RETRASO<br>DEL<br>CRECIMIENTO<br>(DÍAS) | LOG DE<br>DESTRUCCIÓN | TUMOR<br>LIBRE EN<br>EL DÍA<br>144 | INDICE DE<br>ACTIVIDAD |
|---------------------------|-------------------------------------------------|---------------------------|---------------------|-----------------------------------------|-----------------------|------------------------------------|------------------------|
| 0                         | -4,2%                                           | -                         | -                   | -                                       | -                     | 0/5                                | -                      |
| 580 <sup>a</sup>          | -4,0%                                           | 0/5                       | 0%                  | 56                                      | 6,7                   | 2/5                                | ++++                   |
| 280 <sup>b</sup>          | 0%                                              | 0/5                       | 0%                  | 28                                      | 3,4                   | 2/5                                | ++++                   |

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<sup>a</sup> El fármaco se administró a 140 mg/kg/inyección por vía intravenosa en los días 3, 4, 5 y 9  
<sup>b</sup> El fármaco se administró a 70 mg/kg/inyección por vía intravenosa en los días 3, 4, 5 y 9

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TABLA V  
FASE TEMPRANA DEL ADENOCARCINOMA nº 15/0 DE COLON HUMANO QUE RESPONDE A TAXOL  
(ratones hembra Balb/C SCID, NCI)

| DOSIS<br>TOTAL<br>(mg/kg) | % DE<br>PÉRDIDA<br>DE PESO<br>CORPORAL<br>NADIR | MUERTES<br>CON<br>FÁRMACO | % DE<br>MASA<br>T/C | RETRASO<br>DEL<br>CRECIMIENTO<br>(DÍAS) | LOG DE<br>DESTRUCCIÓN | TUMOR<br>LIBRE EN<br>EL DÍA<br>144 | INDICE DE<br>ACTIVIDAD |
|---------------------------|-------------------------------------------------|---------------------------|---------------------|-----------------------------------------|-----------------------|------------------------------------|------------------------|
| 0                         | +4,3%                                           | 0/5                       | -                   | -                                       | -                     | 0/5                                | -                      |
| 420 <sup>a</sup>          | 0%                                              | 0/5                       | 0%                  | 33,5                                    | 5,0                   | 1/5                                | ++++                   |

<sup>a</sup> El fármaco se administró a 140 mg/kg por vía intravenosa en los días 3, 5 y 7

X  
6

TABLA VI  
FASE TEMPRANA DE LC-12 DE PULMÓN ESCAMOSO MURINO  
(ratones hembra Balb/C, NCI-Kingston)

| DOSIS<br>TOTAL<br>(mg/kg) | % DE<br>PÉRDIDA<br>DE PESO<br>CORPORAL<br>NADIR | MUERTES<br>CON<br>FÁRMACO | % DE<br>MASA<br>T/C | RETRASO<br>DEL<br>CRECIMIENTO<br>(DÍAS) | LOG DE<br>DESTRUCCIÓN | TUMOR<br>LIBRE EN<br>EL DÍA<br>144 | INDICE DE<br>ACTIVIDAD |
|---------------------------|-------------------------------------------------|---------------------------|---------------------|-----------------------------------------|-----------------------|------------------------------------|------------------------|
| 0                         | +6,5%                                           | 0/5                       | -                   | -                                       | -                     | 0/5                                | -                      |
| 640 <sup>a</sup>          | 0%                                              | 0/4                       | 14%                 | 12,5                                    | 1,7                   | 0/4                                | ++                     |
| 1391 <sup>b</sup>         | +1,6%                                           | 0/5                       | 20%                 | 15,5                                    | 2,1                   | 0/5                                | +++                    |

50

<sup>a</sup> El fármaco se administró a 160 mg/kg/inyección por vía intravenosa en los días 4, 6, 8 y 10  
<sup>b</sup> El fármaco se administró a 107 mg/kg/inyección por vía intravenosa en los días 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 y 28

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TABLA VII  
FASE TEMPRANA DE LNCaP DE PRÓSTATA HUMANO  
(ratones hembra Balb/C SCID, NCI)

| DOSIS<br>TOTAL<br>(mg/kg) | % DE<br>PÉRDIDA<br>DE PESO<br>CORPORAL<br>NADIR | MUERTES<br>CON<br>FÁRMACO | % DE<br>MASA<br>T/C | RETRASO<br>DEL<br>CRECIMIENTO<br>(DÍAS) | LOG DE<br>DESTRUCCIÓN | TUMOR<br>LIBRE EN<br>EL DÍA<br>144 | INDICE DE<br>ACTIVIDAD |
|---------------------------|-------------------------------------------------|---------------------------|---------------------|-----------------------------------------|-----------------------|------------------------------------|------------------------|
| 0                         | +3,9%                                           | -                         | -                   | -                                       | -                     | 0/5                                | -                      |
| 840 <sup>a</sup>          | +5,6%                                           | 0/5                       | 0                   | 60 <sup>a</sup>                         | 7,2 <sup>a</sup>      | 4/5                                | ++++                   |

<sup>a</sup> El fármaco se administró a 140 mg/kg/inyección por vía intravenosa en los días 3, 5, 7, 9, 10 y 11

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TABLA VIII  
WSU-Br-1 DE MAMA HUMANO EN FASE TERMINAL  
(ratones hembra Balb/C SCID, NCI)

| DOSIS<br>TOTAL<br>(mg/kg) | % DE<br>PÉRDIDA<br>DE PESO<br>CORPORAL<br>NADIR | MUERTES<br>CON<br>FÁRMACO | % DE<br>MASA<br>T/C | RETRASO<br>DEL<br>CRECIMIENTO<br>(DÍAS) | LOG DE<br>DESTRUCCIÓN | TUMOR<br>LIBRE EN<br>EL DÍA<br>144 | INDICE DE<br>ACTIVIDAD |
|---------------------------|-------------------------------------------------|---------------------------|---------------------|-----------------------------------------|-----------------------|------------------------------------|------------------------|
| 0                         | +3.9%                                           | -                         | -                   | -                                       | -                     | 0/5                                | -                      |
| 725 <sup>a</sup>          | -3.9%                                           | 0/5                       | 0%                  | 57                                      | 2.9                   | 2/5                                | ++++                   |
| 500 <sup>b</sup>          | +14%                                            | 0/5                       | 0%                  | 39                                      | 2.0                   | 2/5                                | ++++                   |

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<sup>a</sup> El fármaco se administró a 145 mg/kg por vía intravenosa en los días 11-13 y 19-20

<sup>b</sup> El fármaco se administró a 100 mg/kg por vía intravenosa en los días 11-13 y 19-20

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TABLA IX  
FASE TEMPRANA BG-1 DE OVARIO HUMANO  
(ratones hembra Balb/C SCID, NCI)

| DOSIS<br>TOTAL<br>(mg/kg) | % DE<br>PÉRDIDA<br>DE PESO<br>CORPORAL<br>NADIR | MUERTES<br>CON<br>FÁRMACO | % DE<br>MASA<br>T/C | RETRASO<br>DEL<br>CRECIMIENTO<br>(DÍAS) | LOG DE<br>DESTRUCCIÓN | TUMOR<br>LIBRE EN<br>EL DÍA<br>144 | INDICE DE<br>ACTIVIDAD |
|---------------------------|-------------------------------------------------|---------------------------|---------------------|-----------------------------------------|-----------------------|------------------------------------|------------------------|
| 0                         | 0%                                              | -                         | -                   | -                                       | -                     | 0/5                                | -                      |
| 870 <sup>a</sup>          | -2,0%                                           | 0/5                       | 0%                  | 30,5                                    | 3,7                   | 1/5                                | ++++                   |
| 600 <sup>b</sup>          | -3,0%                                           | 0/5                       | 0%                  | 30                                      | 3,6                   | 0/5                                | ++++                   |

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<sup>a</sup> El fármaco se administró a 145 mg/kg/inyección por vía intravenosa en los días 3-5 y 9-11

<sup>b</sup> El fármaco se administró a 100 mg/kg por vía intravenosa en los días 3-5 y 9-11

X  
53

TABLA X  
FASE TEMPRANA DEL CARCINOMA-26 DE COLON MURINO  
(ratones hembra Balb/C, NCI-Kinston-CRL)

| DOSIS<br>TOTAL<br>(mg/kg) | % DE<br>PÉRDIDA<br>DE PESO<br>CORPORAL<br>NADIR | MUERTES<br>CON<br>FÁRMACO | % DE<br>MASA<br>T/C | RETRASO<br>DEL<br>CRECIMIENTO<br>(DÍAS) | LOG DE<br>DESTRUCCIÓN | TUMOR<br>LIBRE EN<br>EL DÍA<br>144 | INDICE DE<br>ACTIVIDAD |
|---------------------------|-------------------------------------------------|---------------------------|---------------------|-----------------------------------------|-----------------------|------------------------------------|------------------------|
| 0                         | +1,8%                                           | 0/5                       | -                   | -                                       | -                     | 0/5                                | -                      |
| 1600 <sup>a</sup>         | +15%                                            | 0/5                       | 34%                 | 15                                      | 2,2                   | 0/5                                | +++                    |
| 1305 <sup>b</sup>         | +15%                                            | 0/5                       | 28%                 | 6                                       | 0,9                   | 0/5                                | +                      |
| 1740 <sup>c</sup>         | +17%                                            | 0/5                       | 34%                 | 14                                      | 2,1                   | 0/5                                | +++                    |

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<sup>a</sup> El fármaco se administró a 100 mg/kg/inyección por vía intravenosa BID en los días 1, 3, 5, 7, 13, 15, 17 y 21  
<sup>b</sup> El fármaco se administró a 145 mg/kg/inyección por vía intravenosa en los días 1, 2, 5, 7, 9, 13, 15, 17 y 19  
<sup>c</sup> El fármaco se administró a 1450 mg/kg/inyección por vía intravenosa en los días 1, 2, 3, 7, 8, 13, 14, 16, 18 y 20-  
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TABLA XI  
FASE TEMPRANA DEL CARCINOMA MRI-H165 DE PULMÓN ESCAMOSO  
(ratones hembra Balb/C, NCI)

| DOSIS<br>TOTAL<br>(mg/kg) | % DE<br>PÉRDIDA<br>DE PESO<br>CORPORAL<br>NADIR | MUERTES<br>CON<br>FÁRMACO | % DE<br>MASA<br>T/C | RETRASO<br>DEL<br>CRECIMIENTO<br>(DÍAS) | LOG DE<br>DESTRUCCIÓN | TUMOR<br>LIBRE EN<br>EL DÍA<br>144 | INDICE DE<br>ACTIVIDAD |
|---------------------------|-------------------------------------------------|---------------------------|---------------------|-----------------------------------------|-----------------------|------------------------------------|------------------------|
| 0                         | 0%                                              | -                         | -                   | -                                       | -                     | 0/5                                | -                      |
| 600 <sup>a</sup>          | -2,1%                                           | 0/5                       | 0%                  | 31                                      | 3,7                   | 0/5                                | ++++                   |

<sup>a</sup> El fármaco se administró a 100 mg/kg/inyección por vía intravenosa en los días 3-5 y 10-12

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TABLA XII  
FASE TEMPRANA DEL ADENOCARCINOMA n°15/MDR DE COLON DE HUMANO RESISTENTE A TAXOL  
(ratones hembra Balb/C, NCI)

| DOSIS<br>TOTAL<br>(mg/kg) | % DE<br>PÉRDIDA<br>DE PESO<br>CORPORAL<br>NADIR | MUERTES<br>CON<br>FÁRMACO | % DE<br>MASA<br>T/C | RETRASO<br>DEL<br>CRECIMIENTO<br>(DÍAS) | LOG DE<br>DESTRUCCIÓN | TUMOR<br>LIBRE EN<br>EL DÍA<br>144 | INDICE DE<br>ACTIVIDAD |
|---------------------------|-------------------------------------------------|---------------------------|---------------------|-----------------------------------------|-----------------------|------------------------------------|------------------------|
| 0                         | 0%                                              | 0/5                       | -                   | -                                       | -                     | 0/5                                | -                      |
| 500 <sup>a</sup>          | +2,1%                                           | 0/5                       | 10%                 | 11                                      | 1,4                   | 0/5                                | ++                     |

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<sup>a</sup> El fármaco se administró a 100 mg/kg/inyección por vía intravenosa en los días 3-5 y 13-14

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TABLA XIII  
ETAPA TEMPRANA TERMINAL DEL ADENOCARCINOMA-38 DE COLON MURINO POR VÍAS IV, PO, SC E IP  
(ratones hembra Balb/C, CRL-Raleigh-NCI)

| DOSIS<br>TOTAL<br>(mg/kg) | % DE<br>PÉRDIDA<br>DE PESO<br>CORPORAL<br>NADIR | MUERTES<br>CON<br>FÁRMACO | % DE<br>MASA<br>T/C | RETRASO<br>DEL<br>CRECIMIENTO<br>(DÍAS) | LOG DE<br>DESTRUCCIÓN | TUMOR<br>LIBRE EN<br>EL DÍA<br>144 | INDICE DE<br>ACTIVIDAD |
|---------------------------|-------------------------------------------------|---------------------------|---------------------|-----------------------------------------|-----------------------|------------------------------------|------------------------|
| 0                         | +6,5%                                           | -                         | -                   | -                                       | -                     | 0/5                                | -                      |
| 450 IV <sup>a</sup>       | +8,9%                                           | 0/56                      | 0%                  | 18                                      | 2,4 <sup>f</sup>      | 2/5                                | ++++                   |
| 780 PO <sup>b</sup>       | +9,7%                                           | 0/3                       | 0%                  | Se curan todos                          | > 4,5                 | 3/3                                | ++++                   |
| 450 PO <sup>c</sup>       | +6,8%                                           | 0/3                       | 0%                  | 22,5                                    | 3,0 <sup>f</sup>      | 2/3                                | ++++                   |
| 450 SC <sup>d</sup>       | +13,2%                                          | 0/2                       | 5,7%                | 10,5                                    | 1,4 <sup>f</sup>      | 1/2                                | ++/++++ <sup>g</sup>   |
| 450 IP <sup>e</sup>       | +8,3%                                           | 0/2                       | 3,7%                | 17                                      | 2,2 <sup>f</sup>      | 1/2                                | +++/++++ <sup>g</sup>  |

<sup>a</sup> El fármaco se administró a 150 mg/kg/inyección por vía intravenosa en los días 5, 7 y 9  
<sup>b</sup> El fármaco se administró a 260 mg/kg/inyección, oralmente, en los días 5, 7 y 9  
<sup>c</sup> El fármaco se administró a 150 mg/kg/inyección en los días 5, 7 y 9  
<sup>d</sup> El fármaco se administró a 150 mg/kg/inyección, subcutáneamente, en los días 5, 7 y 9  
<sup>e</sup> El fármaco se administró a 150 mg/kg/inyección por vía intrapertoneal en los días 5, 7 y 9  
<sup>f</sup> Log de destrucción de tumores que vuelven a crecer (media)  
<sup>g</sup> Índice de actividad para cada ratón en estudio Se curó un ratón en cada estudio, representando un índice "++++" El otro índice de actividad se basa en el log de destrucción para los otros ratones del estudio

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140  
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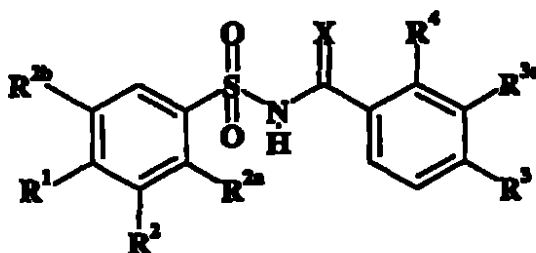
Habiendo descrito la invención como antecede, se declara como propiedad lo contenido en las siguientes

### Reivindicaciones

5

1 Un compuesto de Fórmula I

10



I

en la que

X es O o NH,

15

R<sup>1</sup> es hidrógeno, halo, alquilo C<sub>1</sub>-C<sub>6</sub>, alcoxi C<sub>1</sub>-C<sub>4</sub>, alquilito C<sub>1</sub>-C<sub>4</sub>, CF<sub>3</sub>, OCF<sub>3</sub>, SCF<sub>3</sub>, (alcoxi C<sub>1</sub>-C<sub>4</sub>)carbonilo, nitró, azido, O(SO<sub>2</sub>)CH<sub>3</sub>, N(CH<sub>3</sub>)<sub>2</sub>, hidroxilo, fenilo, fenilo sustituido, piridinilo, tienilo, furilo, quinolinilo o triazolilo,

R<sup>2</sup> es hidrógeno, halo, ciano, CF<sub>3</sub>, alquilo C<sub>1</sub>-C<sub>6</sub>, (alcoxi C<sub>1</sub>-C<sub>4</sub>)carbonilo, alcoxi C<sub>1</sub>-C<sub>4</sub>, fenilo o quinolinilo,

20

R<sup>2a</sup> es hidrógeno o alcoxi C<sub>1</sub>-C<sub>4</sub>,

R<sup>2b</sup> es hidrógeno o alquilo C<sub>1</sub>-C<sub>6</sub>, con tal que al menos uno de R<sup>2a</sup> y R<sup>2b</sup> sea hidrógeno,

R<sup>3</sup> es hidrógeno, halo, alquilo C<sub>1</sub>-C<sub>6</sub>, CF<sub>3</sub> o nitró,

R<sup>3a</sup> es hidrógeno, halo o alquilo C<sub>1</sub>-C<sub>6</sub>, con tal que cuando R<sup>3a</sup> sea

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alquilo C<sub>1</sub>-C<sub>6</sub>, R<sup>3</sup> es hidrógeno y R<sup>4</sup> es halo, y

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$R^4$  es halo, alquilo  $C_1-C_6$ , o  $CF_3$  con tal que sólo uno de  $R^3$  y  $R^4$  puede ser alquilo  $C_1-C_6$ , y con tal que cuando  $R^4$  es halo o alquilo  $C_1-C_6$ , sólo uno de  $R^3$  y  $R^{3a}$  es hidrógeno; o una sal de adición de base aceptable farmacéuticamente de los mismos, con tal que:

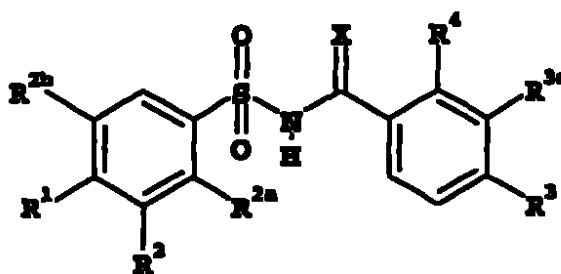
- 5                      a)              cuando  $R^3$  y  $R^4$  son ambos cloro y  $R^2$  es hidrógeno,  $R^1$  es bromo, yodo, alcoxi  $C_1-C_4$ , alquiltio  $C_1-C_4$ ,  $CF_3$ ,  $OCF_3$ , nitro, azido,  $O(SO_2)CH_3$ ,  $N(CH_3)_2$ , hidroxil, fenilo, fenilo sustituido, piridinilo, tienilo, furilo o triazolilo;
- 10                     b)              cuando  $R^3$  y  $R^4$  son ambos cloro y  $R^1$  es hidrógeno,  $R^2$  es bromo, flúor,  $CF_3$ , alquilo  $C_1-C_6$ , alcoxi  $C_1-C_4$ , fenilo o quinolinilo.

2.      El compuesto de la reivindicación 1, en el que  $R^2$ ,  $R^{2a}$  y  $R^{2b}$  son hidrógeno y  $R^1$  se selecciona del grupo constituido por halo, alquilo  $C_1-C_6$ , alcoxi  $C_1-C_4$ , alquil  $C_1-C_4$  tio,  $CF_3$ ,  $OCF_3$ ,  $SCF_3$ , (alcoxi  $C_1-C_4$ )carbonilo, nitro, azido,  $O(SO_2)CH_3$ ,  $N(CH_3)_2$ , hidroxil, fenilo, fenilo sustituido, piridinilo, tienilo, furilo, quinolinilo y triazolilo.

20      3.      El compuesto de las reivindicaciones 1 ó 2, en el que el compuesto es una sal de adición de base aceptable farmacéuticamente.

4.      El compuesto de la reivindicación 3, en el que la sal de adición de base aceptable farmacéuticamente es una sal de sodio.

5. El compuesto de la reivindicación 1 que es *N*-[2-cloro-4-bromobenzoi]-4-clorofenilsulfonamida o una sal de adición de base del mismo.
6. El compuesto de la reivindicación 1 que es *N*-[2,4-diclorobenzoi]-fenilsulfonamida o una sal de adición de base del mismo.
7. El compuesto de las reivindicaciones 5 ó 6 en el que la sal de adición de base es una sal sódica.
8. Un procedimiento de tratamiento de neoplasias susceptibles en un mamífero que comprende administrar a un mamífero que necesite dicho tratamiento una cantidad oncolíticamente eficaz de un compuesto de Fórmula II:



II

en la que:

X es O o NH;

R¹ es hidrógeno, halo, alquilo C<sub>1</sub>-C<sub>8</sub>, alcoxi C<sub>1</sub>-C<sub>4</sub>, alquiltio C<sub>1</sub>-C<sub>4</sub>, CF<sub>3</sub>, OCF<sub>3</sub>, SCF<sub>3</sub>, (alcoxi C<sub>1</sub>-C<sub>4</sub>)carbonilo, nitro, azido, O(SO<sub>2</sub>)CH<sub>3</sub>, N(CH<sub>3</sub>)<sub>2</sub>, hidroxí, fenilo, fenilo sustituido, piridinilo, tienilo, furilo, quinolinilo o triazolilo;

R² es hidrógeno, halo, ciano, CF<sub>3</sub>, alquilo C<sub>1</sub>-C<sub>8</sub>, (alcoxi C<sub>1</sub>-C<sub>4</sub>)carbonilo,

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alcoxi C<sub>1</sub>-C<sub>4</sub>, fenilo o quinolinilo;

R<sup>2a</sup> es hidrógeno o alcoxi C<sub>1</sub>-C<sub>4</sub>,

R<sup>2b</sup> es hidrógeno o alquilo C<sub>1</sub>-C<sub>6</sub>, con tal que al menos uno de R<sup>2a</sup> y R<sup>2b</sup> sea hidrógeno;

5 R<sup>3</sup> es hidrógeno, halo, alquilo C<sub>1</sub>-C<sub>6</sub>, CF<sub>3</sub> o nitro;

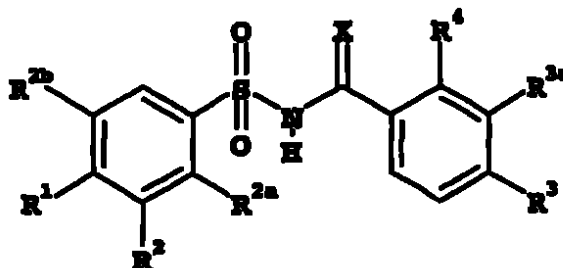
R<sup>3a</sup> es hidrógeno, halo o alquilo C<sub>1</sub>-C<sub>6</sub>, con tal que cuando R<sup>3a</sup> sea alquilo C<sub>1</sub>-C<sub>6</sub>, R<sup>3</sup> sea hidrógeno y R<sup>4</sup> sea halo, y

R<sup>4</sup> es halo, alquilo C<sub>1</sub>-C<sub>6</sub>, o CF<sub>3</sub>, con tal que solo uno de R<sup>3</sup> y R<sup>4</sup> puede ser alquilo C<sub>1</sub>-C<sub>6</sub>, y con tal que cuando R<sup>4</sup> sea halo o alquilo C<sub>1</sub>-C<sub>6</sub>, sólo uno de

10 R<sup>3</sup> y R<sup>3a</sup> es hidrógeno; o una sal de adición de base aceptable farmacéuticamente del mismo.

9. Una formulación farmacéutica que comprende un compuesto de Fórmula II:

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II

en la que

X es O o NH;

R<sup>1</sup> es hidrógeno, halo, alquilo C<sub>1</sub>-C<sub>6</sub>, alcoxi C<sub>1</sub>-C<sub>4</sub>, alquiltio C<sub>1</sub>-C<sub>4</sub>, CF<sub>3</sub>, OCF<sub>3</sub>, SCF<sub>3</sub>, (alcoxi C<sub>1</sub>-C<sub>4</sub>)carbonilo, nitro, azido, O(SO<sub>2</sub>)CH<sub>3</sub>, N(CH<sub>3</sub>)<sub>2</sub>, hidroxil,

25 fenilo, fenilo sustituido, piridinilo, tienilo, furilo, quinolinilo o triazolilo;

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$R^2$  es hidrógeno, halo, ciano,  $CF_3$ , alquilo  $C_1-C_6$ , (alcoxi  $C_1-C_4$ )carbonilo, alcoxi  $C_1-C_4$ , fenilo o quinolinilo;

$R^{2a}$  es hidrógeno o alcoxi  $C_1-C_4$ ,

$R^{2b}$  es hidrógeno o alquilo  $C_1-C_6$ , con tal que al menos uno de  $R^{2a}$  y  $R^{2b}$

5 sea hidrógeno;

$R^3$  es hidrógeno, halo, alquilo  $C_1-C_6$ ,  $CF_3$  o nitró;

$R^{3a}$  es hidrógeno, halo o alquilo  $C_1-C_6$ , con tal que cuando  $R^{3a}$  sea alquilo  $C_1-C_6$ ,  $R^3$  sea hidrógeno y  $R^4$  sea halo, y

10  $R^4$  es halo, alquilo  $C_1-C_6$ , o  $CF_3$ , con tal que solo uno de  $R^3$  y  $R^4$  puede ser alquilo  $C_1-C_6$ , y con tal que cuando  $R^4$  sea halo o alquilo  $C_1-C_6$ , sólo uno de  $R^3$  y  $R^{3a}$  es hidrógeno; o una sal de adición de base aceptable farmacéuticamente del mismo y un vehículo, diluyente o excipiente aceptable farmacéuticamente.

MAY 28 2003

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITYELI LILLY & COMPANY  
PATENT DEPT

PCT

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT  
(PCT Rule 71.1)

|                                                                                                                            |
|----------------------------------------------------------------------------------------------------------------------------|
| To: <i>T. Tucker</i>                                                                                                       |
| <del>Ivan BURNSTIDE</del><br>Eli Lilly And Company<br>P O Box 6288<br>Indianapolis, IN 46206-6288<br>ETATS-UNIS D'AMERIQUE |

|                                     |              |
|-------------------------------------|--------------|
| Date of mailing<br>(day/month/year) | 21.05.2003 ✓ |
|-------------------------------------|--------------|

|                                                  |                        |
|--------------------------------------------------|------------------------|
| Applicant's or agent's file reference<br>X-14776 | IMPORTANT NOTIFICATION |
|--------------------------------------------------|------------------------|

|                                                 |                                                          |                                              |
|-------------------------------------------------|----------------------------------------------------------|----------------------------------------------|
| International application No.<br>PCT/US02/15142 | International filing date (day/month/year)<br>24/05/2002 | Priority date (day/month/year)<br>08/08/2001 |
|-------------------------------------------------|----------------------------------------------------------|----------------------------------------------|

|                                    |
|------------------------------------|
| Applicant<br>ELI LILLY AND COMPANY |
|------------------------------------|

- 1 The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the International preliminary examination report and its annexes, if any, established on the International application
- 2 A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
- 3 Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices
- 4 REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301)

Where a translation of the International application must be furnished to an elected Office, that translation must contain a translation of any annexes to the International preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide

For the purpose of deciding whether the claimed invention is patentable or not, the elected Offices may apply criteria additional to or different from the criteria on which the International preliminary examination report is based (see Articles 27(5) 33(5)) Additional criteria may include e.g. exemptions from patentability and the requirements of enabling disclosure and of clarity and support of claims.

|                                                                                                                                                                                                                                       |                                                                                                                                                 |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| Name and mailing address of the IPEA/<br> European Patent Office<br>D-80289 Munich<br>Tel +49 89 2369 0 Tx: 523656 apmu d<br>Fax: +49 89 2369 4485 | Authorized officer<br>Roche, S<br><br>Tel +49 89 2369-8031 |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                   |                                                     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
| Applicant's or agent's file reference<br><b>X-14776</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | <b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)                                      |                                                     |
| International application No.<br><b>PCT/US02/15142</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | International filing date (day/month/year)<br><b>24/05/2002</b>                                                                                                   | Priority date (day/month/year)<br><b>06/06/2001</b> |
| International Patent Classification (IPC) or national classification and IPC<br><b>C07C311/51</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                   |                                                     |
| Applicant<br><b>ELI LILLY AND COMPANY</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                   |                                                     |
| <p>1 This International preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2 This REPORT consists of a total of 6 sheets, including this cover sheet</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 807 of the Administrative Instructions under the PCT)</p> <p>These annexes consist of a total of sheets.</p> <p>3. This report contains indications relating to the following items.</p> <ul style="list-style-type: none"><li>I <input checked="" type="checkbox"/> Basis of the report</li><li>II <input type="checkbox"/> Priority</li><li>III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty inventive step and industrial applicability</li><li>IV <input type="checkbox"/> Lack of unity of invention</li><li>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty inventive step or industrial applicability citations and explanations supporting such statement</li><li>VI <input type="checkbox"/> Certain documents cited</li><li>VII <input type="checkbox"/> Certain defects in the international application</li><li>VIII <input type="checkbox"/> Certain observations on the international application</li></ul> |                                                                                                                                                                   |                                                     |
| Date of submission of the demand<br><b>19/12/2002</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Date of completion of this report<br><b>21.05.2003</b>                                                                                                            |                                                     |
| Name and mailing address of the international preliminary examining authority<br> <b>European Patent Office<br/>D-80289 Munich<br/>Tel. +49 89 2369 0 Tlx 523656 epmu d<br/>Fax: +49 89 2369 4465</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Authorized officer<br><b>Herzog, A</b><br>Telephone No. +49 89 2369 8033<br> |                                                     |

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US02/15142

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**I Basis of the report**

- 1 With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed", and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):-

Description, pages  
1-51 as originally filed

Claims, No.

1-9 as originally filed

- 2 With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed unless otherwise indicated under this item

These elements were available or furnished to this Authority in the following language, which is

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b))  
☐ the language of publication of the international application (under Rule 48.3(b))  
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3)

- 3 With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing

- ☐ contained in the international application in written form  
☐ filed together with the international application in computer readable form  
☐ furnished subsequently to this Authority in written form  
☐ furnished subsequently to this Authority in computer readable form  
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished  
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:-

- ☐ the description, pages.  
☐ the claims, Nos.  
☐ the drawings, sheets.

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c))

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US02/15142

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report)

6 Additional observations, if necessary

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1 The questions whether the claimed invention appears to be novel to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 8.

because

☒ the said international application, or the said claims Nos. 8 relate to the following subject matter which does not require an international preliminary examination (specify)  
see separate sheet

☐ the description, claims or drawings (indicate particular elements below) or said claims Nos. are so unclear that no meaningful opinion could be formed (specify)

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed

☐ no international search report has been established for the said claims Nos.

2 A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions

☐ the written form has not been furnished or does not comply with the standard

☐ the computer readable form has not been furnished or does not comply with the standard

**V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement**

1 Statement

|                               |     |              |
|-------------------------------|-----|--------------|
| Novelty (N)                   | Yes | Claims 1-9   |
|                               | No  | Claims       |
| Inventive step (IS)           | Yes | Claims 1-9   |
|                               | No  | Claims       |
| Industrial applicability (IA) | Yes | Claims 1-7,9 |

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**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US02/15142

No.      Claims

2 Citations and explanations  
see separate sheet

**Re Item III****Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claim 8 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67 1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT)

For the assessment of present claim 8 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Re Item V****Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement**

- D1 EP-A-0 602 878
- D2 US-A-5 110 830
- D3 EP-A-0 927 716
- D4 US-A-5 929 097
- D5 XP002212204 (Greenidge, P A et al, J Med Chem, vol 41, no 14 (1998), p 2503-2512)

Due to the provisos in claim 1, the subject-matter of present claims 1-9 appears to be new.

D1 and D2 are considered to be the closest prior art. The compounds disclosed therein are also useful as antitumour agents. The structure of said compounds differs from the

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No PCT/US02/15142

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presently claimed compounds in that an additional nitrogen atom is present in the chain connecting the two phenyl rings, i.e. the compounds are diarylsulfonylureas whereas the present compounds are either N-benzoylsulfonamides or sulfonylbenzamidines. The compounds in D1 and D2 also show a different substitution pattern at the phenyl rings

The problem to be solved by the present application can be seen in the provision of new antitumour agents, specifically new inhibitors of angiogenesis

The suggested solution is not considered obvious since the person skilled in the art knows that already small changes in the structure of a pharmacophore can lead to a change in or even loss of activity

The subject-matter of claims 1-9 is therefore considered novel and inventive

Industrial applicability is acknowledged for claims 1-7 and 9

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|                                                                                                                                                                                                                                                                                                       |                                                                                                               |                                                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|------------------------------------------------------|
| A. CLASIFICACIÓN DEL OBJETO DE SOLICITUD                                                                                                                                                                                                                                                              |                                                                                                               |                                                      |
| IPC 7 C07C311/51 C07C321/28 C07D213/34 C07D215/12 C07D307/38<br>C07D333/18 C07D521/00 A81K31/18 A81K31/83 A81P35/00                                                                                                                                                                                   |                                                                                                               |                                                      |
| Según la clasificación internacional de Patentes (IPC) o tanto clasificación nacional e IPC                                                                                                                                                                                                           |                                                                                                               |                                                      |
| B. CAMPOS INVESTIGADOS                                                                                                                                                                                                                                                                                |                                                                                                               |                                                      |
| Material mínimo comprobado en la búsqueda (sistema de clasificación y símbolos de clasificación)                                                                                                                                                                                                      |                                                                                                               |                                                      |
| IPC 7 C07C C07D A81K                                                                                                                                                                                                                                                                                  |                                                                                                               |                                                      |
| Publicaciones investigadas que, sin embargo, no forman parte del material mínimo comprobado, en la medida que pertenezcan a los campos de la búsqueda                                                                                                                                                 |                                                                                                               |                                                      |
| Base de datos electrónica consultada en la búsqueda internacional (nombre de la base de datos y conceptos de búsqueda eventualmente utilizados)                                                                                                                                                       |                                                                                                               |                                                      |
| EPO-Internal, WPI Data, MEDLINE, BIOSIS, BEILSTEIN Data, CHEM ABS Data.                                                                                                                                                                                                                               |                                                                                                               |                                                      |
| C. DOCUMENTOS CONSIDERADOS FUNDAMENTALES                                                                                                                                                                                                                                                              |                                                                                                               |                                                      |
| Categoría*                                                                                                                                                                                                                                                                                            | Denominación de la publicación, si es necesario, indicándose las partes relevantes                            | Resp. a reivindicación Nº                            |
| A                                                                                                                                                                                                                                                                                                     | EP 0 602 878 A (JILLY CO ELI)<br>22 de junio de 1994 (1994-06-22)<br>Resumen; reivindicaciones.               | 1-9                                                  |
| A                                                                                                                                                                                                                                                                                                     | —<br>US 5 110 830 A (HARPER RICHARD W ET AL)<br>5 de mayo de 1992 (1992-05-05)<br>Reivindicaciones; ejemplos. | 1-9                                                  |
| A                                                                                                                                                                                                                                                                                                     | —<br>EP 0 927 716 A (SENJU PHARMA CO)<br>7 de julio de 1999 (1999-07-07)<br>Página 3, reivindicaciones.       | 1-9                                                  |
| A                                                                                                                                                                                                                                                                                                     | —<br>US 562 067 A (DU MILA T ET AL)<br>27 de julio de 1999 (1999-07-27)<br>Resumen; reivindicaciones.         | 1-9                                                  |
| X Otras publicaciones se indican en la continuación del campo C X Véase el anexo Familia de patentes                                                                                                                                                                                                  |                                                                                                               |                                                      |
| * Categorías especiales de las publicaciones indicadas                                                                                                                                                                                                                                                |                                                                                                               |                                                      |
| "A" Publicación que define el estado general de la técnica, pero que no debe considerarse especialmente relevante                                                                                                                                                                                     |                                                                                                               |                                                      |
| "E" Documento anterior que, sin embargo, no se ha publicado antes de la fecha de solicitud internacional o incluso posteriormente a ésta.                                                                                                                                                             |                                                                                                               |                                                      |
| "L" Publicación que hace dudosos la reivindicación de la prioridad o con la que se pretende comprobar la fecha de publicación de otra publicación indicada en el Informe de búsqueda o que se indica por otra razón especial (según se indique).                                                      |                                                                                                               |                                                      |
| "O" Publicación que se refiere a una descripción oral, un uso, una exposición u otras medidas                                                                                                                                                                                                         |                                                                                                               |                                                      |
| "P" Publicación que se ha publicado antes de la fecha de solicitud internacional, pero después de la fecha de prioridad reivindicada.                                                                                                                                                                 |                                                                                                               |                                                      |
| "T" Publicación posterior, que se ha publicado después de la fecha de solicitud internacional o después de la fecha de prioridad y con la que no colisiona la solicitud, indicándose sólo para la comprensión del principio en el que se basa la invención o de la teoría en la que se basa la misma. |                                                                                                               |                                                      |
| "X" Publicación de importancia especial; solamente en base a esta publicación, la invención reivindicada no puede considerarse nueva ni puede considerarse que la misma esté basada en una actividad inventiva.                                                                                       |                                                                                                               |                                                      |
| "Y" Publicación de importancia especial; no puede considerarse que la invención reivindicada esté basada en una actividad inventiva, si la publicación se asocia a una o a varias otras publicaciones de esta categoría y si esta asociación es evidente para un experto.                             |                                                                                                               |                                                      |
| "Z" Publicación que es miembro de la misma familia de patentes                                                                                                                                                                                                                                        |                                                                                                               |                                                      |
| Fecha de la finalización de la búsqueda internacional                                                                                                                                                                                                                                                 |                                                                                                               | Fecha de envío del Informe internacional de búsqueda |
| 4 de septiembre de 2002                                                                                                                                                                                                                                                                               |                                                                                                               | 30/09/2002                                           |
| Nombre y dirección postal de la Autoridad Internacional de Búsqueda                                                                                                                                                                                                                                   |                                                                                                               | Empleado autorizado                                  |
| European Patent Office (Oficina Europea de Patentes)<br>NL - 2280 HV Rijswijk<br>Tel (+31-70) 340-2040, Tx. 31 651 epo nl.<br>Fax (+31-70) 340-3018                                                                                                                                                   |                                                                                                               | Herzog, A.                                           |

INFORME INTERNACIONAL DE BÚSQUEDA

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Datos respecto a publicaciones que forman parte de la misma familia de patentes

Nº de expediente internacional  
PCT/US 02/15142

| Documento de patente indicado en el Informe de búsqueda |   | Fecha de publicación | Miembro(s) de la familia de patentes |           |     | Fecha de publicación |
|---------------------------------------------------------|---|----------------------|--------------------------------------|-----------|-----|----------------------|
| EP 06287                                                | A | 22-08-1994           | CA                                   | 2110834   | A1  | 11-08-1994           |
|                                                         |   |                      | EP                                   | 062878    | A1  | 22-08-1994           |
|                                                         |   |                      | JP                                   | 8211777   | A   | 02-08-1994           |
|                                                         |   |                      | US                                   | 5585484   | A   | 15-10-1998           |
| US 5110830                                              | A | 05-05-1992           | US                                   | 5280388   | A   | 09-11-1993           |
|                                                         |   |                      | AR                                   | 240918    | A1  | 27-03-1991           |
|                                                         |   |                      | AT                                   | 88739     | T   | 15-08-1993           |
|                                                         |   |                      | AU                                   | 571706    | B2  | 21-04-1988           |
|                                                         |   |                      | AU                                   | 4418255   | A   | 02-01-1998           |
|                                                         |   |                      | CA                                   | 1281183   | A1  | 22-10-1991           |
|                                                         |   |                      | DE                                   | 3587359   | D1  | 01-07-1993           |
|                                                         |   |                      | DE                                   | 3587359   | T2  | 04-11-1993           |
|                                                         |   |                      | DK                                   | 288785    | A   | 28-12-1985           |
|                                                         |   |                      | EP                                   | 0188815   | A2  | 02-01-1988           |
|                                                         |   |                      | ES                                   | 044028    | D0  | 18-01-1988           |
|                                                         |   |                      | ES                                   | 8804128   | A1  | 01-08-1988           |
|                                                         |   |                      | GR                                   | 851538    | A1  | 28-11-1985           |
|                                                         |   |                      | HU                                   | 28083     | A2  | 28-04-1988           |
|                                                         |   |                      | JP                                   | 1984582   | C   | 25-10-1995           |
|                                                         |   |                      | JP                                   | 7014881   | B   | 22-02-1995           |
|                                                         |   |                      | JP                                   | 81018754  | A   | 27-01-1988           |
|                                                         |   |                      | KR                                   | 8700741   | B1  | 13-04-1987           |
|                                                         |   |                      | NZ                                   | 212621    | A   | 24-02-1989           |
|                                                         |   |                      | PH                                   | 22825     | A   | 19-01-1989           |
|                                                         |   |                      | PT                                   | 80708     | A,B | 01-07-1985           |
|                                                         |   |                      | US                                   | 4848126   | A   | 04-07-1989           |
|                                                         |   |                      | ZA                                   | 8504744   | A   | 25-02-1987           |
| EP 0827718                                              | A | 07-07-1994           | EP                                   | 0827718   | A1  | 07-07-1999           |
|                                                         |   |                      | AU                                   | 71895     | B2  | 24-02-2000           |
|                                                         |   |                      | AU                                   | 7038486   | A   | 01-05-1997           |
|                                                         |   |                      | BR                                   | 9805287   | A   | 21-07-1998           |
|                                                         |   |                      | CA                                   | 2188817   | A1  | 28-04-1997           |
|                                                         |   |                      | EP                                   | 0771885   | A2  | 07-06-1987           |
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|                                                         |   |                      | HU                                   | 8802843   | A2  | 28-08-1987           |
|                                                         |   |                      | JP                                   | 10147586  | A   | 02-08-1998           |
|                                                         |   |                      | NO                                   | 884814    | A   | 28-04-1987           |
|                                                         |   |                      | PL                                   | 318889    | A1  | 28-04-1987           |
|                                                         |   |                      | US                                   | 8214800   | B1  | 10-04-2001           |
|                                                         |   |                      | US                                   | 8087280   | A   | 02-05-2000           |
|                                                         |   |                      | ZA                                   | 9808847   | A   | 28-05-1987           |
|                                                         |   |                      | JP                                   | 3185700   | B2  | 11-07-2001           |
|                                                         |   |                      | JP                                   | 10147584  | A   | 02-08-1998           |
|                                                         |   |                      | JP                                   | 200123847 | A   | 28-08-2001           |
| US 5928087                                              | A | 27-07-1999           | NINGUNO                              |           |     |                      |

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| C. (continuación) DOCUMENTOS CONSIDERADOS RELEVANTES |                                                                                                                                                                                                                                                                                                                                                                                           |                           |
|------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| Categoría <sup>a</sup>                               | Denominación de la publicación, si es necesario, indicándose las partes relevantes                                                                                                                                                                                                                                                                                                        | Resp. a reivindicación Nº |
| A                                                    | <p>GREENIDGE, P.A. ET AL.: "Pharmacophores incorporating numerous excluded volumes defined by X-ray crystallographic structure in three dimensional database searching: application to the thyroid hormone receptor"</p> <p>J. MED. CHEM.</p> <p>Vol. 41 no. 14 1998, páginas 2503-2512,</p> <p>XP002212204</p> <p>Página 2503, column 1</p> <p>Página 2511; figura 6; table</p> <p>—</p> | 1-9                       |

INFORME INTERNACIONAL DE BÚSQUEDA

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Datos respecto a publicaciones que forman parte de la misma familia de patentes

Nº de expediente internacional  
PCT/US 01/45857

Cañilla I Observaciones donde ciertas reivindicaciones se encontraron no susceptibles de búsqueda.

El informe de búsqueda internacional no ha sido establecido respecto a ciertas reivindicaciones bajo el Artículo 17(2)(a) por las siguientes razones.

- 1. ☒ Reivindicaciones número:  
Puesto que se refieren a un asunto no solicitado para ser buscado por la autoridad, literalmente:  
Aunque la reivindicación 8 está dirigida a un procedimiento para el tratamiento humano/animal, la búsqueda se ha llevado a cabo y se ha basado en los efectos del compuesto.
- 2. Reivindicaciones número: Porque se refieren a partes de la Solicitud Internacional que no cumplen con los requisitos prescritos a esta extensión que ninguna búsqueda significativa puede ser llevada a cabo, específicamente:
- 3. ☐ Reivindicaciones número:  
Porque son reivindicaciones dependientes y no están redactada de acuerdo con las sentencias segunda y tercera de la regla 6.4 (a)

Cañilla II Observaciones donde la unidad de invención es carente (continuación del punto 2 de la primera página)

La Autoridad de Búsqueda Internacional encuentra múltiples invenciones en esta solicitud internacional, como a continuación se describe

- 1 ☐ Todas las tasas adicionales de búsqueda fueron pagadas a tiempo por el solicitante por lo que el Informe de Búsqueda cubre todas las reivindicaciones susceptibles de búsqueda.
- 2 ☐ Todas las reivindicaciones susceptibles de búsqueda pueden ser buscadas sin esfuerzo que justifique una tasa adicional , Esta Autoridad no requiere el pago de cualquier tasa adicional.
- 3 ☐ Sólo algunas de las tasas adicionales de la búsqueda fueron pagadas a tiempo por el solicitante por lo que este informe de Búsqueda cubre sólo aquellas reivindicaciones por las cuales las tasas fueron pagadas específicamente:
- 4 ☐ Ninguna de las tasas adicionales requeridas fueron pagadas a tiempo. Como consecuencia, este Informe de Búsqueda Internacional esta restringido a la invención primeramente mencionada en las reivindicaciones, y esta cubierto por las reivindicaciones número:

Comentarios como protesta

- ☐ Las tasas de búsqueda adicionales fueron acompañadas por la protesta del solicitante
- ☐ Ninguna protesta acompañaba el pago de las tasas adicionales.

## REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

|                                                                                       | USUARIO | RADICADOR |
|---------------------------------------------------------------------------------------|---------|-----------|
| <b>PATENTE DE INVENCION</b> ✓                                                         | ( )     | ( ) ✓     |
| Indicacion de que se solicita la concesion de una patente                             | ( )     | ( ) ✓     |
| Datos de Identificación del solicitante o de la persona que se presenta la solicitud. | ( )     | ( ) ✓     |
| - Descripción de la invención                                                         | ( )     | ( ) ✓     |
| Dibujos de ser estos pertinentes.                                                     | ( )     | ( ) ✓     |
| Comprobante de Pago de las tasas establecidas                                         |         |           |

COMPLETA ( ) INCOMPLETA ( )

### DISEÑO INDUSTRIAL ( )

- |                                                                                                             |     |     |
|-------------------------------------------------------------------------------------------------------------|-----|-----|
| - Indicación de que se solicita el registro de Diseño Industrial                                            | ( ) | ( ) |
| - Datos de identificación del solicitante o de la persona que presenta la solicitud                         | ( ) | ( ) |
| - Representación gráfica y fotografica del Diseño Industrial o muestra del Material que incorpora el diseño | ( ) | ( ) |
| Comprobante de pago de las tasas establecidas                                                               | ( ) | ( ) |

COMPLETA ( ) INCOMPLETA ( )

### ESQUEMA DE TRAZADO ( )

- |                                                                                     |     |     |
|-------------------------------------------------------------------------------------|-----|-----|
| - Indicacion de que solicita el registro de un Esquema de trazado                   | ( ) | ( ) |
| - Datos de Identificación del solicitante o de la persona que presenta La solicitud | ( ) | ( ) |
| Representación grafica del esquema de trazado                                       | ( ) | ( ) |
| Comprobante de pago de las tasas establecidas                                       | ( ) | ( ) |

COMPLETA ( ) INCOMPLETA ( )

Firma Responsable

Fecha



Folio 158

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2020  
Bogotá DC

Doctor(a)  
CARLOS R OLARTE  
Apoderado(a)  
ELI LILLY AND COMPANY

|                    |                            |                  |
|--------------------|----------------------------|------------------|
| <b>REFERENCIA:</b> | Radicación No.             | 03 107114        |
|                    | Solicitud Internacional    | PCT/US2002/15142 |
|                    | Fecha inicio fase nacional | 08/01/2004       |
|                    | Trámite                    | 011              |
|                    | Evento                     | 379              |
|                    | Actuación                  | 416              |
|                    | Oficio No.                 | 39               |
|                    | Folios                     | 001              |

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Unica de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase  
Dado en Bogotá DC, 06 FEB. 2004

  
**ALIX CARMENZA CESPEDES DE VERGEL**  
Jefe de la División de Nuevas Creaciones

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