



No. 07-128249-00000-0000

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Tra. 11. PATENTEIYI E. 373. FASENACIONALI
Act. 411. PRESENTACION. Folios. 202

**FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL**

P2007/000172

SOLICITUD DE:

1

☒

Patente de Invención.

☐

Patente de Modelo de Utilidad.

☒

Capítulo I.

☐

Capítulo II.

2

**SOLICITANTE
(71)**

Nombre: ELI-LILLY AND COMPANY

Dirección: Lilly Corporate Center, Indianapolis
Indiana 46285 E.U.A.

Nacionalidad o Domicilio: ESTADOUNIDENSE

Lugar de Constitución: ESTADOS UNIDOS
DE AMERICA

Teléfono: _____ Fax: _____

E-mail: _____

IDENTIFICACIÓN

C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número _____

3

**REPRESENTANTE
O APODERADO**

Nombre: CARLOS R. OLARTE

Dirección: World Trade Center Torre A, Calle
100 N°. 8A-37 Piso 10

Teléfono: 601-7700 Fax: 601-7799

E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número 79.782.747 Btá
TP 74.295

4

**INVENTOR (ES)
(72)**

Nombre: VER PAGINA ADJUNTA

Dirección: VER PAGINA ADJUNTA

Nacionalidad o Domicilio: VER PAGINA ADJUNTA

5

PCT (86)

Solicitud Internacional No. PCT/US2006/020204 Fecha Mayo 25, 2006

Publicación Internacional No. WO 2006/132811 Fecha Diciembre 14, 2006

6

Título (54) POTENCIADORES DEL RECEPTOR AMPA

7

Clasificación Internacional (51) C07D 333/06, C07D 213/75, C07D 237/04, C07D
409/10, C07D 257/04, C07C 311/00, A61K 31/381, A61K 31/44, A61P 25/00

8

Prioridad

SI ☒ NO ☐

(33) País de Origen

EP

EP

US

(32) Fecha

Junio 06, 2005

Agosto 18, 2005

Octubre 06, 2005

(31) Número de Solicitud

05380117.1

05380187.4

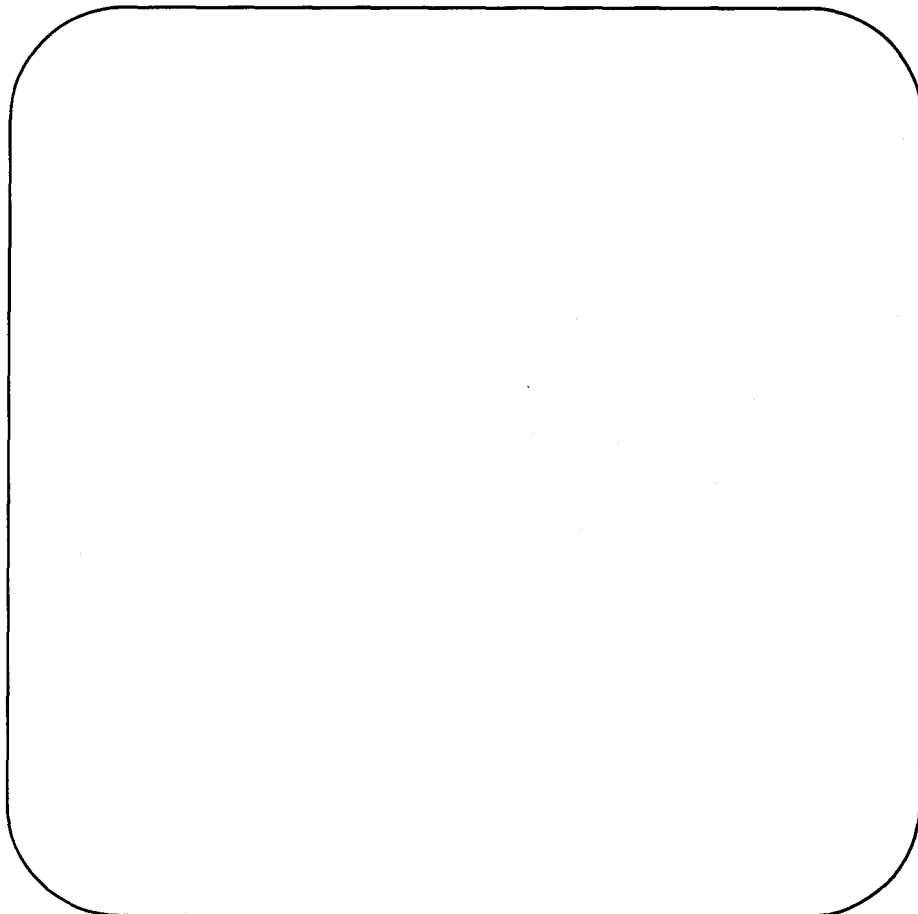
60/724.206

10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud.
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. **Ver Exn 06-021.173**
- ☒ Documento de cesión del interventor 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. Búsqueda Internacional

11

FIGURA CARACTERÍSTICA:

3
27

ANA MARIA CASTANO MANSANET,
Lilly, S. A., Avenida De La Industria 30,
E-28100 Alcobendas
España
Nacionalidad: Española

FREDERIC LAURENT CORDIER,
Lilly, S. A., Avenida De La Industria 30,
E-28100 Alcobendas
Francia
Nacionalidad: Española

ESTEBAN DOMINGUEZ-MANZANARES,
Lilly, S. A., Avenida De La Industria 30,
E-28100 Alcobendas
España
Nacionalidad: Española

JIAN ERIC HONG,
881 Ursa Lane, Foster City,
California 94404
Estados Unidos de America
Nacionalidad: China

WILLIAM JOSEPH HORNBACK,
10063 Bent Tree Lane,
Fishers, Indiana 46037
Estados Unidos de América
Nacionalidad: Estaunidense

DELU JIANG,
14438 Chariot Whisper Drive,
Westfield, Indiana 46074
Estados Unidos de América
Nacionalidad: China

4



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 96,110
FECHA : NOVIEMBRE 26 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PAGO	VR. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO POPULAR	050-00110-6	67993475	26/11/2007	5.090.000.00

C O N C E P T O

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		1 TRAMITES DE SOL. DE PATENTE DE IN	482,000.00
		TOTAL ;	\$ 482,000.00

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

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

6
2/6
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 CASTRO

Traductor e Intérprete Oficial

Inglés - Español - Inglés

Resolución No. 2117 del 7 Oct 1987

OLARTE RAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER - TORRE C
CALLIE 100 No. 8A-55 Piso 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
Fax: +57-1 638-6201

www.olarteraisbeck.com

Power of Attorney

The undersigned,

domiciled in

ELI LILLY AND COMPANY

El suscrito,

domiciliado en

Lilly Corporate Center, Indianapolis, Indiana 46285 US

by means of these presents hereby grants to **Carlos R. Olarte, J. Ian Raisbeck and Ana María Frieri** 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.

por medio del presente otorga a **Carlos R. Olarte, J. Ian Raisbeck y Ana María Frieri** 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, desistir 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 asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma

Date/Fecha: /7 July 2003

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



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

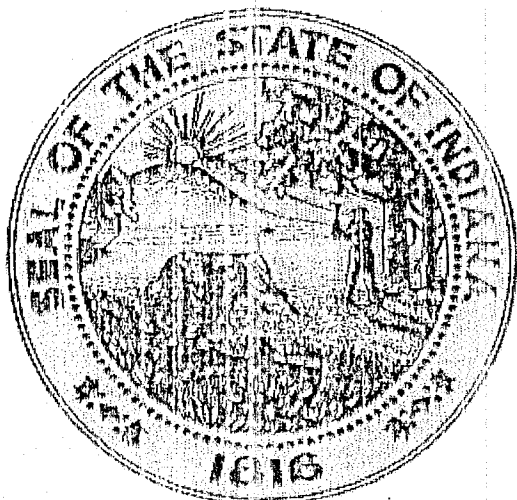
Certified

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

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

OLARTE RAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER - TORRE C
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BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
Fax: +57-1 638-6201

www.olarteraisbeck.com

Notarial Certification

Certificación Notarial

On this date,
17 July 2003

The undersigned Notary Public certifies:

1. That

of legal age and domiciled in

7620 Castleton Farms, West Drive, Indianapolis, Indiana 46256 US
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

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
suscibir 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, reading "Catherine Michel".

Catherine Michel

My Commission Expires October 21, 2008

Resident of Johnson County

Secretaria de Estado

Estado de Indiana

APOSTILLA

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

1. País: Estados Unidos de América
2. El presente documento público fue firmado por: Catherine Michel
3. Que actuó en su calidad de Notario Público en y para el condado de Johnson
4. Y lleva el sello del Notario Público en y para el estado de Indiana

Se certifico

5. En Indianápolis, Indiana
6. El 23 de octubre de 2007
7. Por el secretario de Estado, Estado de Indiana.
8. Bajo el Número **A2007 - 014853**
9. Lleva el Sello del Estado de Indiana.
10. Firmado por Todd Rokita, Secretario de Estado

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X

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X

CERTIFICADO DE CONFORMIDAD

ESTADO DE INDIANA

CONDADO DE MARION

Yo, Catherine Michel, un Notario Público debidamente autorizado comisionado en el condado de Johnson, Estado de Indiana, Estados Unidos de América, por medio del presente certifico que el documento adjunto es una fiel copia del documento de cesión original entre Ana Maria Castano Mansañet, Frederic Lauren Cordier, Esteban Domínguez-Manzanares, Jian Eric Hong, William Joseph Hornback, Delu Jiang y ELI LILLY AND COMPANY, es una copia exacta del documento original.

Firmado el 22 de octubre de 2007

(sello)

(firmado: Catherine Michel)
Notario Público
Catherine Michel
Mi comisión vence el 21 de octubre de 2008.
Residente del condado de Jonson

CESIÓN

Considerando que:

Ana Maria Castano Mansañet, Lilly S.A., Avenida de la industria 30, 28108 Alcobendas, Madrid, España, Nacionalidad: ES

Frederic Lauren Cordier, Lilly S.A., Avenida de la industria 30, 28108 Alcobendas, Madrid, España, Nacionalidad: FR

Esteban Domínguez-Manzanares, Lilly S.A., Avenida de la industria 30, 28108 Alcobendas, Madrid, España, Nacionalidad: ES

Jian Eric Hong, 881 Ursa Lane, Foster City, California 94404, Nacionalidad: CN

William Joseph Hornback, 10063 Bent Tree Lane, Fishers, Indiana 46037, Nacionalidad: US

Delu Jiang, 14438 Chariot Whisper Drive, Whetstfield, IN 46074, Nacionalidad: CN

Somos inventores o co-inventores (con las personas listadas abajo) de un invento que es objeto de una solicitud de patente ("Solicitud") el cual se denomina "POTENCIADORES DEL RECEPTOR AMPA" que contiene 64 páginas y 0 dibujos, la cual:

(X) Fue radicada.

(X) En la oficina de marcas y patentes de los Estados Unidos

el 5 de Junio de 2006 con el número serial acordado 11/446,840; y

Considerando que **ELI LILLY AND COMPANY**, una corporación organizada y existente bajo las leyes del estado de Indiana, cuya oficina comercial es Lilly Corporate Center, Indianápolis, Indiana 46285, desea adquirir la totalidad del derecho, título e interés de todo el invento revelado en dicha Solicitud;

13
✓

ENTONCES Y POR LO TANTO, en consideración de mi empleo, cualquier acuerdo relacionado con eso u otra consideración buena y valiosa, recibo de la cual se está acusando, yo, por medio del presente documento cedo a Eli Lilly and Company., sus sucesores y beneficiarios (colectivamente "Lilly") la totalidad de mi derecho, título e interés en, y con respecto a la solicitud, incluyendo todos los derechos de prioridad para otros países que se generen a partir de allí, todos los inventos allí revelados y cualquiera y todas las solicitudes de Patente presentes o futuras de tales inventos que pudieran ser radicadas en cualquier país, inclusive, pero no solamente con respecto a continuaciones, continuaciones parciales, divisiones, sustituciones, re-exámenes, re-expediciones, solicitudes internacionales radicadas según el PCT, solicitudes provisionales de Patentes en los Estados Unidos solicitudes de Patentes provisionales subsiguientes en los Estados Unidos que reclamen algo o la totalidad de este invento, certificados de adición, modelos de utilidades, patentes menores, así como toda la demás propiedad intelectual relacionada con la Solicitud, inclusive, pero no exclusivamente a certificados suplementarios de protección; y a cualquier prórroga de plazo de patente relacionado que pueda otorgarse para Cartas de Patente con respecto a la Solicitud; todo lo anterior para ser llevado a cabo y disfrutado por Lilly para su propio uso y provecho hasta el final del término o términos para los cuales dichas Cartas de Patente y derechos de propiedad intelectual relacionados puedan otorgarse, tan completamente como los mismos hubieran sido llevados a cabo y disfrutados por mí si esta Cesión y venta a Lilly no se hubiera realizado.

Por mi mismo y por mis herederos, sucesores y representantes legales, convengo que no se ha hecho o se hará ninguna cesión, venta acuerdo o afectación que pudiera entrar en conflicto con esta cesión.

Además por mi mismo y por mis herederos, sucesores y representantes legales, convengo y acuerdo con Lilly según solicito yo y ellos, sin mayor consideración que será pagada ahora a costa de Lilly: (i) dispondré la ejecución de las solicitudes originales, provisionales sustitutas, de continuación, divisionales, de continuación parcial, re-examinadas o reexpedidas, las especificaciones enmendadas o las declaraciones legítimas o declaraciones

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~~XX~~

juramentadas para dicha solicitud; (ii) comunicare a Lilly cualquier hecho conocido por mi o por ellos con relación a dichos inventos o la historia de los mismos; (iii) dispondré la ejecución de las declaraciones preliminares y el testimonio en cualquier procedimiento de interferencia, procedimientos de descubrimiento de litigio y declaraciones, oposiciones, procedimientos de cancelación, con cursos de prioridad, procedimientos de uso público, procedimientos de entidad administrativa, litigio y otras acciones procesales y similares; (iv) dispondré a ejecutar y entregar cualquier documento de solicitud, declaraciones juramentadas, declaraciones, cesiones u otros instrumentos; y (v) haré todas las demás acciones que, en opinión razonable del asesor jurídico de Lilly, puedan ser necesarias ó deseables para asegurar el otorgamiento de Cartas de Patente y propiedad intelectual relacionada con Lilly o sus delegados, en los Estados Unidos y en todos los demás países donde Lilly desee tener dichos inventos, o cualquiera de ellos, patentados, con especificaciones y pretensiones de tal forma como sean aprobadas por el asesor jurídico de Lilly y para investir y confirmar a Lilly o sus delegados con el título completo, legal y equitativo para todas las dichas Cartas de Patente y propiedad intelectual relacionada.

He ejecutado este documento de cesión en la fecha indicada más adelante.

Fecha: 10 de julio de 2006.

(Fdo) Ana Maria Castano Mansañet

Fecha: 10 de julio de 2006.

(Fdo) Frederic Lauren Cordier

Fecha: 10 de julio de 2006.

(Fdo) Esteban Domínguez-Manzanares

Fecha: 1 de Julio de 2006

(Fdo) Jian Eric Hong

ESTADOS UNIDOS DE AMERICA

ESTADO: California

CONDADO: San Mateo

15
✓
Ccompareció ante mí, un Notario Público del Condado de San Mateo, Estado de California, personalmente apareció Jian Eric Hong y reconoció que ejecuto el anterior instrumento el día 1 del Julio de 2006.

(sello)

(firmado: Jose J. San Gabriel)
Notario Público California
Condado de San Mateo
Mi comisión vence el 28 de julio de 2007.
Residente del condado de Jonson

Fecha: 7 de Junio de 2006

(Fdo) William Joseph Hornback

ESTADOS UNIDOS DE AMERICA

ESTADO: Indiana
CONDADO: Marion

Ccompareció ante mí, un Notario Público del Condado de Johnson, Estado de Indiana, personalmente apareció William Joseph Hornback y reconoció que ejecuto el anterior instrumento el día 6 del Julio de 2006.

(sello)

(firmado: Laura Waltz)
Notario Público
Mi comisión vence el 20 de Mayo de 2008.
Residente del condado de Jonson

Fecha: 7 de Junio de 2006

(Fdo) Delu Jiang

ESTADOS UNIDOS DE AMERICA

ESTADO: Indiana
CONDADO: Marion

Ccompareció ante mí, un Notario Público del Condado de Johnson, Estado de Indiana, personalmente apareció Delu Jiang y reconoció que ejecuto el anterior instrumento el día 6 del Julio de 2006.

(sello)

(firmado: Laura Waltz)
Notario Público
Mi comisión vence el 20 de Mayo de 2008.
Residente del condado de Jonson

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16

SECRETARY OF STATE
STATE OF INDIANA



Todd Rokita
Secretary of State

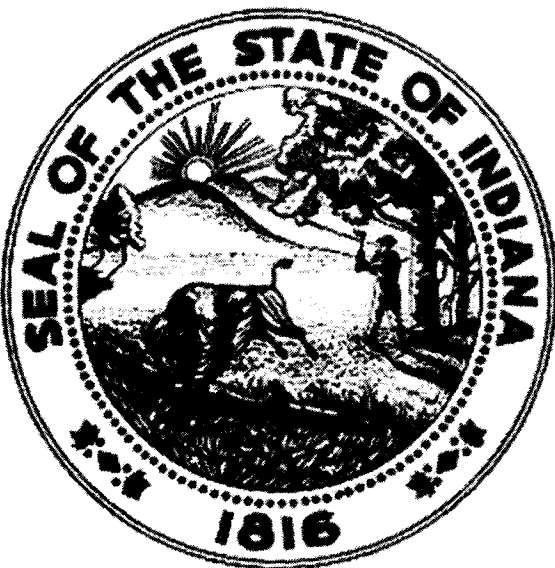
APOSTILLE

(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 notary public in & for *Johnson County*
4. and bears the seal/stamp of notary public in & for the State of Indiana
- Certified**
5. at Indianapolis, Indiana
6. this *Twenty-third* day of *October, 2007*
7. by Secretary of State of Indiana
8. No. A2007 - 014853

9. Seal/Stamp:

10. Signature:



Todd Rokita
Indiana Secretary of State

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

taove

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
14 December 2006 (14.12.2006)

PCT

(10) International Publication Number
WO 2006/132811 A2

(51) International Patent Classification:

C07D 333/36 (2006.01) C07C 311/00 (2006.01)
C07D 213/75 (2006.01) A61K 31/381 (2006.01)
C07D 237/04 (2006.01) A61K 31/44 (2006.01)
C07D 409/10 (2006.01) A61P 25/00 (2006.01)
C07D 257/04 (2006.01)

(74) Agents: COMBS, Tonya, L. et al.; ELI LILLY AND COMPANY, P. O. Box 6288, Indianapolis, Indiana 46206-6288 (US).

(21) International Application Number:

PCT/US2006/020204

(22) International Filing Date: 25 May 2006 (25.05.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

05380117.1 6 June 2005 (06.06.2005) EP
05380187.4 18 August 2005 (18.08.2005) EP
60/724,206 6 October 2005 (06.10.2005) US

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

(72) Inventors; and

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

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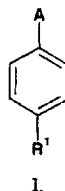
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(54) Title: AMPA RECEPTOR POTENTIATORS



(I)

(57) Abstract: The present invention relates to AMPA receptor potentiators of Formula (I), formulations comprising them, methods for their use, and intermediates useful for their preparation.

AMPA RECEPTOR POTENTIATORS

BACKGROUND OF THE INVENTION

5 Glutamate is the major excitatory neurotransmitter in the central nervous system. Three glutamate receptor ion channel subtypes have been identified based on their sensitivity to the selective activators (agonists) N-methyl-D-aspartate (NMDA), α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), and kainate.

10 AMPA receptors mediate cellular responses to glutamate by direct and indirect mechanisms. When activated by glutamate or AMPA, AMPA receptor ion channels allow sodium ions (Na^+) and calcium ions (Ca^{2+}) to pass directly through the channel pore. In addition, AMPA receptor ion channels can facilitate the activation of NMDA receptors by initiating cellular depolarization that relieves magnesium ion (Mg^{2+})-dependent block of NMDA receptors.

15 Multiple AMPA receptor subtypes have been identified and cloned: GluR1, GluR2, GluR3, and GluR4 as disclosed by Hollmann and Heinemann, *Ann. Rev. Neurosci.*, 17, 31-108 (1994). Each subunit consists of a sequence of approximately 900 amino acids. Four subunits are thought to assemble to form a tetrameric ion channel complex with the functional properties of this ion channel most likely being determined
20 by its subunit composition.

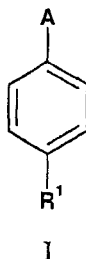
 Ion channel currents activated by glutamate via AMPA receptors are transient. The time course of currents is modified by refractory states caused during glutamate binding which is referred to as desensitization and by the rate of glutamate removal from the ion channel binding site which results in deactivation. Ion influx through AMPA
25 receptors may be enhanced by compounds that either prevent desensitization or by compounds that slow deactivation rates. Compounds that enhance glutamate-stimulated ion influx at AMPA receptors are known as positive AMPA receptor allosteric modulators or AMPA receptor potentiators. One such compound, which selectively potentiates AMPA receptor function, is cyclothiazide. Since AMPA receptors play a
30 pivotal role in mediating fast excitatory transmission in the central nervous system, molecules that enhance AMPA receptor function have multiple therapeutic targets.

Compounds that allosterically potentiate AMPA receptors have been shown to enhance synaptic activity *in vitro* and *in vivo* as disclosed, for example, by I. Ito, et al., *J. Physiol.*, **424**, 533-543 (1990) and A. Copani, et al., *Journal of Neurochemistry*, **58**, 1199-1204 (1992). Such compounds have also been shown to enhance learning and memory in rats, monkeys, and humans, and are reviewed by Gouliaev and Senning, *Brain Research Reviews*, **19**, 180-222 (1994).

International Patent Application Publication WO 98/33496 published August 6, 1998 discloses certain sulfonamide derivatives which are useful, for example, for treating psychiatric and neurological disorders, for example cognitive disorders, Alzheimer's disease, age-related dementias, age-induced memory impairment, tardive dyskinesia, Huntington's chorea, myoclonus, Parkinson's disease, reversal of drug-induced states (such as cocaine, amphetamines, alcohol-induced states), depression, attention deficit disorder, attention deficit hyperactivity disorder, psychosis, cognitive deficits associated with psychosis, and drug-induced psychosis. P.L. Ornstein, et al. *J. Med. Chem.*, **43**, 4354 (2000) further disclose biarylpropylsulfonamides which are potent potentiators of AMPA receptors. In addition, X. Li, et al., *Neuropharmacology*, **40**, 1028 (2001) disclose antidepressant-like actions of an AMPA receptor potentiators. D.D. Schoepp, et al. and Tizzano, et al., *Society for Neuroscience Abstracts*, 26(1-2), 528.19 and 528.20, 30th Annual Meeting, New Orleans, (November 4-9, 2000) disclose an orally active AMPA receptor potentiator that enhances spatial learning and memory performance in rats, and reverses both pharmacologically and age-associated learning and memory deficit in rats. New AMPA receptor potentiators are needed to treat these neurological disorders.

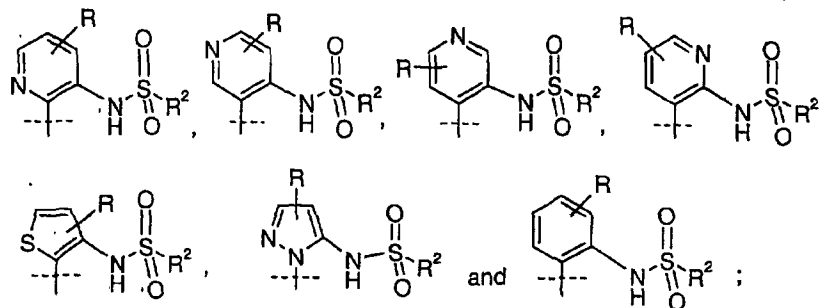
SUMMARY OF THE INVENTION

The present invention provides compounds of Formula I:



where:

A is selected from the group consisting of

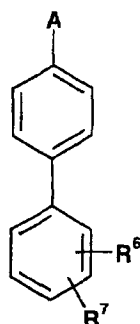


R is H, halo, $-\text{COOH}$, or $-\text{CH}_2\text{COOH}$;

- 5 R^1 is phenyl optionally substituted with a first substituent selected from the group consisting of halo, cyano, $\text{C}_1\text{-C}_4$ acyl, $-\text{COOH}$, $-\text{NHR}^3$, $\text{C}_1\text{-C}_2$ alkyl substituted with $-\text{NHCH}_3$, $-\text{N}(\text{SO}_2(\text{C}_1\text{-C}_3 \text{ alkyl}))_2$, $-\text{COOH}$, $-\text{CONH}_2$, cyano, hydroxy, or tetrazol-5-yl, $-\text{OCH}_2\text{COOH}$, $-\text{SCH}_2\text{COOH}$, $-\text{C}(\text{O})\text{CH}_2\text{CH}_2\text{COOH}$, $-\text{SO}_2\text{NH}_2$, tetrazol-5-yl, and 1,2,4-triazol-1-yl; optionally further substituted with a second substituent selected from
- 10 the group consisting of: halo, trifluoromethyl, cyano, nitro, $\text{C}_1\text{-C}_4$ alkoxy, hydroxy, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ alkylthio, $-\text{NHCH}_2\text{CN}$, $-\text{OCH}_2\text{CN}$, $-\text{NHSO}_2\text{CH}(\text{CH}_3)_2$, and $-\text{C}(\text{O})\text{NHR}^4$; optionally further substituted with a third substituent selected from the group consisting of halo and cyano; optionally further substituted with a fourth substituent selected from the group consisting of halo;

- 15 R^2 is $\text{C}_1\text{-C}_4$ alkyl or dimethylamino;
 R^3 is $-\text{SO}_2(\text{C}_1\text{-C}_3 \text{ alkyl})$, $\text{C}_1\text{-C}_4$ acyl, $\text{C}_1\text{-C}_4$ alkyl, or hydrogen;
 R^4 is hydrogen, $\text{C}_1\text{-C}_4$ alkyl, or $-\text{SO}_2(\text{C}_1\text{-C}_4 \text{ alkyl})$; or a pharmaceutically acceptable
salt thereof.

- 20 The present invention also provides intermediates of Formula II:

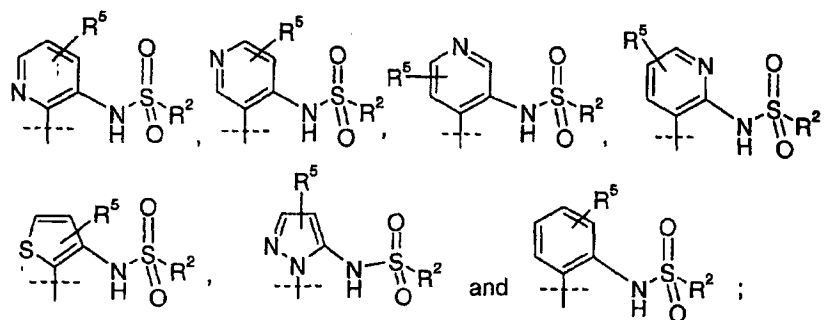


II

where:

A is selected from the group consisting of

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R^2 is C_1 - C_4 alkyl or dimethylamino;

R^5 is H, halo, $-COOR^8$, or $-CH_2COOR^8$;

R^6 is H, cyano, C_1 - C_4 alkoxy, halo, hydroxy, trifluoromethyl, or methylthio;

10 R^7 is $-COOR^9$, $-C(O)CH_2CH_2COOR^9$, $-OCH_2COOR^9$, $-SCH_2COOR^9$, or C_1 - C_2 alkyl substituted with $-COOR^9$;

R^8 and R^9 are each independently selected from the group consisting of hydrogen and C_1 - C_4 alkyl provided that at least one of R^8 and R^9 is other than hydrogen; or a base addition salt thereof.

15 The present invention provides a compound of Formula I for use as a pharmaceutical. The present invention further provides a method of potentiating glutamate receptor function in a patient, which comprises administering to said patient in need of such treatment an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof.

In addition, the present invention further provides a method of treating schizophrenia, cognitive deficits associated with schizophrenia, Alzheimer's disease, dementia of the Alzheimer's type, mild cognitive impairment, Parkinson's disease, or depression in a patient, which comprises administering to a patient in need of such treatment an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof.

According to another aspect, the present invention provides the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating schizophrenia, cognitive deficits associated with schizophrenia, Alzheimer's disease, dementia of the Alzheimer's type, mild cognitive impairment, Parkinson's disease, or depression.

In addition, the present invention provides the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for treating schizophrenia, cognitive deficits associated with schizophrenia, Alzheimer's disease, dementia of the Alzheimer's type, mild cognitive impairment, Parkinson's disease, or depression.

The invention further provides pharmaceutical compositions comprising, a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

Additionally, the use of compounds of Formula I in conjunction with antipsychotics, antidepressants, and drugs useful in treating cognitive disorder are contemplated within the scope of the present invention. WO 2005/040110 teaches the use of compounds that potentiate glutamate receptor function in conjunction with antipsychotics, antidepressants and drugs useful in treating cognitive disorder.

DETAILED DESCRIPTION OF THE INVENTION

As used herein the term "potentiating glutamate receptor function" refers to any increased responsiveness of glutamate receptors, for example AMPA receptors, to glutamate or an agonist, and includes but is not limited to inhibition of rapid desensitization or deactivation of AMPA receptors to glutamate.

A wide variety of conditions may be treated or prevented by compounds of Formula I and their pharmaceutically acceptable salts through their action as potentiators

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of glutamate receptor function. Such conditions include those associated with glutamate hypofunction, such as psychiatric and neurological disorders, for example cognitive disorders and neuro-degenerative disorders such as Alzheimer's disease; dementia of the Alzheimer's type, age-related dementias; age-induced memory impairment; cognitive

5 deficits due to autism, Down's syndrome and other central nervous system disorders with childhood onset, cognitive deficits post electroconvulsive therapy, movement disorders such as tardive dyskinesia, Huntington's chorea, myoclonus, dystonia, spasticity, Parkinson's disease; reversal of drug-induced states (such as cocaine, amphetamines, alcohol-induced states); depression; attention deficit disorder; attention deficit

10 hyperactivity disorder; psychosis such as schizophrenia; cognitive deficits associated with psychosis such as schizophrenia, drug-induced psychosis, stroke, and sexual dysfunction. Compounds of Formula I may also be useful for improving memory (both short term and long term) and learning ability. The present invention provides the use of compounds of Formula I for the treatment of each of these conditions.

15 It is understood by one of ordinary skill in the art that cognition includes various "domains". These domains include short-term memory, long term memory, working memory, executive function, and attention. As used herein the term "cognitive disorder" is meant to encompass any disorder characterized by a deficit in one or more of the cognitive domains, including but not limited to short term memory, long term memory,

20 working memory, executive function, and attention. It is further understood that the term "cognitive disorder" includes, but is not limited to the following specific disorders: age-related cognitive decline, mild cognitive impairment, Alzheimer's disease, dementia, dementia of the Alzheimer's type, Parkinson's dementia, Lewy Body dementia, substance-induced persisting dementia, alcohol-induced persisting dementia, alcohol-

25 induced cognitive impairment, AIDS-induced dementia, learning disorders, cognitive deficits subsequent to cardiac bypass surgery and grafting, stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, and hypoglycemic neuronal damage, vascular dementia, multi-infarct dementia, cognitive deficits associated with amyotrophic lateral sclerosis, and cognitive deficits associated with multiple

30 sclerosis. Mild cognitive impairment has been defined as a potential prodromal phase of dementia associated with Alzheimer's disease based on clinical presentation and on

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progression of patients exhibiting mild cognitive impairment to Alzheimer's dementia over time. (Morris, et al., Arch. Neurol., 58, 397-405 (2001); Petersen, et al., Arch. Neurol., 56, 303-308 (1999)).

5 The fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (1994, American Psychiatric Association, Washington, D.C.) provides a diagnostic tool for identifying many of the disorders described herein. The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for disorders described herein, including those as described in the International Statistical Classification of Diseases and Related Health Problems, tenth revision (ICD-10) (1992, World Health Organization, Geneva) and that terminology and classification systems evolve with medical scientific progress.

15 The present invention includes the pharmaceutically acceptable salts of the compounds defined by Formula I. A compound of this invention can possess a sufficiently acidic group, and accordingly react with any of a number of organic and inorganic bases to form a pharmaceutically acceptable salt. The term "pharmaceutically acceptable salt" as used herein, refers to salts of the compounds of Formula I which are substantially non-toxic to living organisms. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a pharmaceutically acceptable organic or inorganic base. Such salts are known as base addition salts. Such salts include the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66, 2-19 (1977), which are known to the skilled artisan.

20 Magnesium, diethylamine, hemipiperazine, and tert-butylamine salts are preferred. The tert-butylamine salts are most preferred.

25 Some of the compounds of the present invention have one or more chiral centers and may exist in a variety of stereoisomeric configurations. As a consequence of these chiral centers, the compounds of the present invention occur as racemates, mixtures of enantiomers and as individual enantiomers, as well as diastereomers and mixtures of diastereomers. All such racemates, enantiomers, and diastereomers are within the scope of the present invention. The specific stereoisomers and enantiomers of compounds of Formula I can be prepared by one of ordinary skill in the art utilizing well known techniques and processes, such as those disclosed by J. Jacques, et al., "Enantiomers,

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Racemates, and Resolutions", John Wiley and Sons, Inc., 1981, and E.L. Eliel and S.H. Wilen, " Stereochemistry of Organic Compounds", (Wiley-Interscience 1994), and European Patent Application No. EP-A-838448, published April 29, 1998. Examples of resolutions include recrystallization techniques or chiral chromatography.

5 As used herein, the terms "Halo", "Halide" or "Hal" refers to a chlorine, bromine, iodine or fluorine atom, unless otherwise specified herein.

As used herein the term "C₁-C₄ alkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of one to four carbon atoms and includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and t-butyl. The term "C₁-C₄ alkyl "

10 includes within its definition the term "C₁-C₃ alkyl".

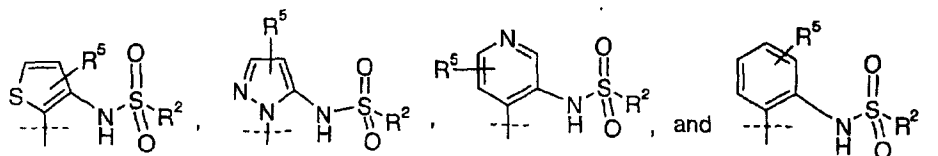
As used herein the term "C₁-C₄ alkoxy" refers to a straight or branched alkyl chain having from one to four carbon atoms attached to an oxygen atom. Typical C₁-C₄ alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy and the like. The term "C₁-C₄ alkoxy" includes within its definition the term

15 "C₁-C₃ alkoxy".

As used herein the term "C₁-C₄ acyl" refers to a straight or branched alkyl chain having from one to three carbon atoms attached to a carbonyl group. Examples include, but are not limited to acetyl, propionyl, butyryl, 2-methylpropionyl and the like. The term "C₁-C₄ acyl" includes within its definition the term "C₁-C₃ acyl".

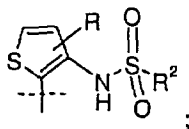
20 As used herein the term "C₁-C₄ alkylthio" refers to a straight or branched alkyl chain having from one to four carbon atoms attached to an sulfur atom. Typical C₁-C₄ alkylthio groups include methylthio, ethylthio, propylthio, isopropylthio, butylthio, tert-butylthio and the like. The term "C₁-C₄ alkylthio" includes within its definition the term "C₁-C₃ alkylthio".

25 An further embodiment of the present invention is compounds of Formula I where A is selected from the group consisting of:



Certain classes of compounds of Formula I are preferred AMPA potentiators. The following paragraphs describe such preferred classes:

a) A is

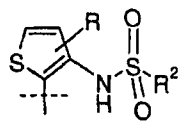


- 5 b) R is hydrogen;
- c) R¹ is phenyl substituted with a single substituent;
- d) R¹ is phenyl substituted with a single substituent selected from the group consisting of cyano, tetrazol-5-yl, C₁-C₂ alkyl substituted with -COOH or tetrazol-5-yl, -SO₂NH₂, -OCH₂COOH, and -SCH₂COOH;
- 10 e) R¹ is phenyl mono-substituted in the 4-position with a substituent selected from the group consisting of tetrazol-5-yl, -OCH₂COOH, -SCH₂COOH, and C₁-C₂ alkyl substituted with -COOH, in the 3-position with a substituent selected from the group consisting of -SONH₂ and C₁-C₂ alkyl substituted with tetrazol-5-yl, or in the 2-position with cyano;
- 15 f) R¹ is phenyl substituted with two substituents;
- g) R¹ is phenyl substituted with a first substituent selected from the group consisting of C₁-C₄ alkoxy, hydroxy, halo, cyano, -COOH, and -NHSO₂CH(CH₃)₂, and with a second substituent selected from the group consisting of amino, trifluoromethyl, -COOH, -C(O)NHR³, tetrazol-5-yl, -OCH₂COOH, and C₁-C₂ alkyl substituted with -COOH;
- 20 h) R¹ is phenyl substituted in the 2-position with a substituent selected from the group consisting of C₁-C₄ alkoxy, hydroxy, halo, cyano, -COOH, and -NHSO₂CH(CH₃)₂, and further substituted in the 4-position with tetrazol-5-yl, -COOH, -C(O)NHR³, or C₁-C₂ alkyl substituted with -COOH, in the 5-position with amino, -COOH, or -OCH₂COOH, or in the 6-position with -COOH;
- 25 i) R¹ is 2-cyano-3-fluoro-4-hydroxy-5-fluorophenyl;
- j) R¹ is 2-cyano-4-carboxyphenyl;
- k) R¹ is 2-ethoxy-4-carboxyphenyl;

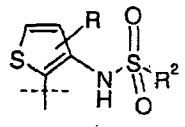
- l) R^2 is C_1 - C_4 alkyl;
m) R^2 is isopropyl;
n) The compound of Formula I is a free acid;
o) The compound of Formula I is a salt;
5 p) The compound of Formula I is a hydrate;
q) The compound of Formula I is an anhydrate;
r) The compound of Formula I is the hemipiperazine salt;
s) The compound of Formula I is the diethylamine salt;
t) The compound of Formula I is the tert-butylamine salt.

10 Preferred embodiments of the invention include all combinations of paragraphs a)

- t). Especially preferred compounds of Formula I are those where A is

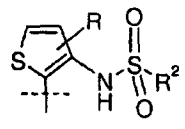


R is hydrogen; R^1 is as described in paragraph h); and R^2 is C_1 - C_4 alkyl. It is also preferred that A is

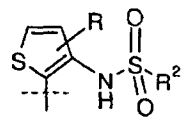


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R is hydrogen; R^1 is as described in paragraph h); and R^2 is isopropyl. It is particularly preferred that A is



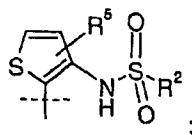
20 R is hydrogen; R^1 is phenyl substituted in the 2-position with C_1 - C_4 alkoxy or cyano and in the 4-position with $-COOH$; and R^2 is isopropyl. It is most preferred that A is



R is hydrogen; R¹ is 2-cyano-4-carboxyphenyl or 2-ethoxy-4-carboxyphenyl; and R² is isopropyl.

Although all of the intermediates of Formula II are useful for preparing compounds of the present invention, certain classes are preferred:

5 u) A is



v) R² is C₁-C₄ alkyl;

w) R² is isopropyl;

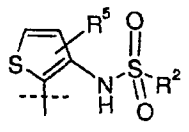
x) R⁵ is hydrogen;

10 y) R⁶ is in the 2-position of the phenyl ring to which it is attached;

z) R⁶ is in the 2-position of the phenyl ring to which it is attached and is selected from the group consisting of hydrogen, cyano, and C₁-C₄ alkoxy;

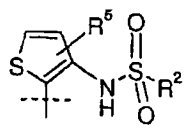
aa) R⁹ is C₁-C₄ alkyl.

Especially preferred compounds of Formula II are those where A is



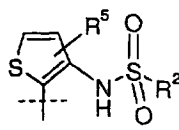
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R⁵ is hydrogen; R² is C₁-C₄ alkyl; R⁶ is in the 2-position of the phenyl to which it is attached and is selected from the group consisting of cyano and C₁-C₄ alkoxy; R⁷ is in the 4-position of the phenyl ring to which it is attached and is -COOR⁹, and R⁹ is C₁-C₄ alkyl. It is also preferred that A is



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R⁵ is hydrogen; R² is isopropyl; R⁶ is in the 2-position of the phenyl to which it is attached and is selected from the group consisting of cyano and C₁-C₄ alkoxy; R⁷ is in the 4-position of the phenyl ring to which it is attached and is -COOR⁹, and R⁹ is C₁-C₄ alkyl. It is most preferred that A is

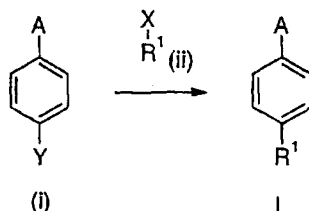


R⁵ is hydrogen; R² is isopropyl; R⁶ is in the 2-position of the phenyl to which it is attached and is selected from the group consisting of cyano, methoxy, and ethoxy; R⁷ is in the 4-position of the phenyl ring to which it is attached and is -COOR⁹, and R⁹ is methyl or ethyl.

The compounds of Formula I can be prepared by one of ordinary skill in the art following art recognized techniques and procedures. More specifically, compounds of Formula I can be prepared as set forth in the schemes, methods, and examples set forth below. The reagents and starting materials are readily available to one of ordinary skill in the art. All substituents, unless otherwise specified, are as previously defined.

The compounds of Formula I where A and R¹ are as previously defined may be prepared as illustrated in the following scheme where (i) is a suitable aryl boronic acid, aryl trimethylstannyl, or aryl boronic ester, and X is bromo, iodo, chloro, or trifluoromethane-sulfoxy.

Scheme I



The compound of structure (ii) is coupled to a suitable phenyl boronic acid, suitable phenyl boronic ester, or suitable phenyl trimethylstannane (i), under Suzuki-Type or Stille-Type coupling reaction conditions well known to one of ordinary skill in the art to provide the compound of Formula I. See Suzuki, A., *Journal of Organometallic Chemistry*, 576, 147-168 (1999), and Miyaura and Suzuki, *Chemical Reviews*, 95, 2457-2483 (1995) for examples of general cross-coupling techniques and for methods for preparing suitable starting materials and reagents.

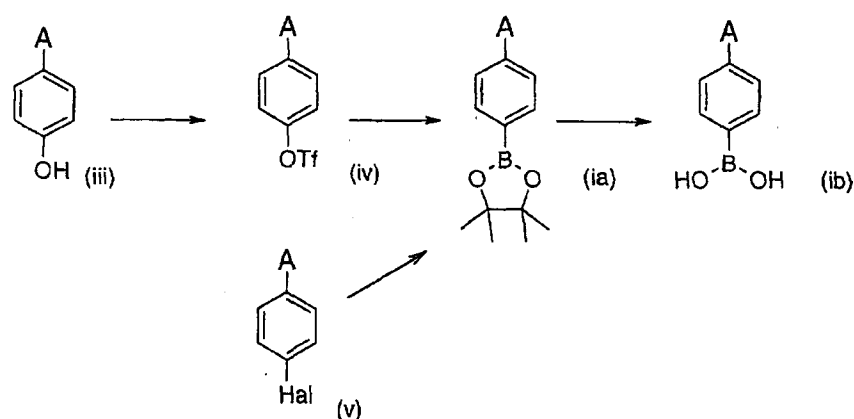
More specifically, the compound of structure (ii) is combined with about 1.0 to 1.5 equivalents of the suitable phenyl boronic acid or ester (i) in a suitable organic solvent or a suitable mixture of solvents. Examples of suitable organic solvents include 1,4-dioxane, dimethoxyethane (DME), DMF, benzene, toluene, acetone, ethanol (EtOH), and the like.

5 Examples of suitable solvent mixtures include DME/EtOH, THF:Water, and the like. A suitable catalyst, such as tetrakis(triphenylphosphine)palladium, dichlorobis(triphenylphosphine)-palladium (II), $\text{Pd}(\text{PCy}_3)_2\text{Cl}_2$, or [1,1-bis(diphenylphosphino)ferrocene] dichloro-palladium(II) or palladium black and a suitable base, for example sodium carbonate, are added to the reaction mixture with stirring.

10 Alternatively, the skilled artisan appreciates that compounds of Formula (I) may also be prepared by coupling a suitable aryl halide with a suitable aryl boronic acid, suitable aryl boronic ester, or suitable aryl trimethylstannyl compound under Suzuki-Type or Stille-Type coupling reaction conditions well known to one of ordinary skill in the art to provide the compound of Formula (I).

15 The requisite boronic acids and esters can be prepared as illustrated in the following scheme where A is as previously defined, and Hal is bromo or iodo.

Scheme II



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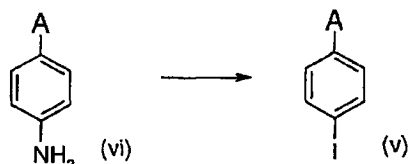
An appropriately substituted phenol (iii) is reacted with a triflating reagent, such as triflic anhydride or N-phenyltrifluoromethanesulphonimide, in the presence of base, for example DMAP or sodium hydroxide in a suitable solvent, such as methylene chloride or

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tetrahydrofuran to give the triflate (iv). The resulting triflate is dissolved in a suitable solvent such as acetonitrile or dimethylsulfoxide and reacted in the presence of a base such as triethylamine or potassium acetate, catalyst such as [1,1'-bis(disphenylphosphino)-ferrocene]dichloropalladium(II) complex, and a borane such as bis(pinacolato)borane to form the requisite boronic ester (ia). Alternatively, PdCl₂ (dppf) and the base potassium acetate in dimethylformamide may be employed if necessary or desired. The boronic acid ester may also be prepared by reacting the phenyl halide (v) in an appropriate solvent such as acetonitrile or dimethylsulfoxide and a base such as triethylamine or potassium acetate is added. A catalyst such as [1,1'-bis(disphenylphosphino)-ferrocene]dichloropalladium(II) complex and a borane such as bis(pinacolato)borane are added. The skilled artisan appreciates that the resultant borate ester can be hydrolyzed under conditions well known in the art, with an acid such as hydrochloride acid or in a suitable solvent such as acetone and in the presence of an oxidizing agent such as sodium periodate and an ammonium acetate solution to provide the boronic acid (ib).

The requisite phenyl halides (v) may be prepared as shown in Scheme III, wherein A is as previously defined.

Scheme III



The aniline (vi) is reacted with a suitable oxidizing reagent, such as isoamyl nitrite in a suitable solvent, such as acetonitrile, in the presence of a source of halide, such as diiodomethane, to provide compounds of formula (v).

Certain compounds of Formula I may be serve as intermediates to further compounds of Formula I via reactions and functional group transformations familiar to those skilled in the art. See Larock, R., "Comprehensive Organic Transformations," VCH Publishing, Inc., New York, 1989. For example. an amino group is reacted with a

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suitable sulfonyl chloride in the presence of pyridine or aqueous base, such as triethylamine, under conditions well known in the art to provide the corresponding sulfonamide. Furthermore, nitro substituents are readily converted to amines by reacting the nitro-containing compound with a suitable reducing agent, such as tin chloride, in an appropriate solvent, for example, ethanol. In addition, carboxylic esters of Formula II are converted to carboxylic acids of Formula I under conditions well known to the skilled artisan, for example by treating an ester of Formula II in a suitable solvent or solvent mixture such as THF, methanol, ethanol, and the like with water and a slight excess of suitable base, such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like. The resultant carboxylic acid can then be converted to the primary amide under well known conditions. For example, the carboxylic acid compound of Formula I is dissolved in a suitable organic solvent, such as methylene chloride or THF and treated with oxalyl chloride optionally followed by addition of a catalytic amount of DMF with stirring. The reaction mixture is stirred and concentrated then dissolved in a suitable organic solvent, such as methylene chloride or THF, and treated with a slight excess of an ammonia hydroxide or ammonia/methanol or ammonia/dioxane solution with stirring. Primary amide compounds of Formula I can be converted to tetrazolyl compounds of Formula I under standard conditions. For example, the primary amide compound of Formula I is reacted with silicon tetrachloride and sodium azide in the presence of a suitable organic solvent, such as acetonitrile. Alternatively, tetrazolyl compounds Formula I are formed by reacting a cyano compound of Formula I with sodium azide and triethylamine in a suitable organic solvent.

The examples set forth herein represent typical syntheses of the compounds of the present invention. The reagents and starting materials are readily available to one of ordinary skill in the art. Nomenclature for examples set forth herein with AutoNom 2000 Add-in for MDL® ISIS/Desktop. As used herein, the terms listed in the following table have the corresponding meanings as indicated:

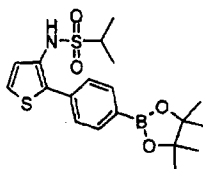
TERM	MEANING
MS(ES)	Electron spray mass spectrometry

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TERM	MEANING
$^1\text{H NMR}$	Proton nuclear magnetic resonance spectrometry
J/g	joules per gram
TLC	thin layer chromatography
HPLC	high performance liquid chromatography
R_f	retention factor
R_t	retention time
AcOH	Acetic acid
RT	room temperature
DCM	dichloromethane
DMF	N,N-dimethylformamide
DMSO	methyl sulfoxide
LDA	lithium diisopropylamide
EtOAc	ethyl acetate
THF	tetrahydrofuran
iPrOAc	isopropyl acetate
DMAP	4-dimethylaminopyridine
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
Et_3N	triethylamine
$(\text{Boc})_2\text{O}$	di-tert-butyl dicarbonate
MeOH	methanol
Triflate	$-\text{SO}_3\text{CF}_3$ functional group
(dppf)	1,1'-bis(diphenylphosphino)ferrocene
S.M.	starting material
SCX	strong cation-exchange cartridge
$\text{Pd}(\text{PCy}_3)_2\text{Cl}_2$	dichlorobis(tricyclohexylphosphine) palladium (II)
$\text{Pd}_2(\text{dba})_3$	tris(dibenzylideneacetone)-dipalladium(0)
EDCI	1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide HCl

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38Preparation 1

Propane-2-sulfonic acid{2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-thiophen-3-yl}-amide



- 5 In a manner analogous to the method of Barker, J. M.; et al., *Synthetic Communications*, 25(23), 3729-3734 (1995), reflux (120°C) methyl-3-aminothiophene-2-carboxylate (42.8 g, 0.27 mol) with 2M sodium hydroxide aqueous solution (270 mL) for 30 min. Cool the reaction mixture to 0°C and acidify to pH 5.0 (Congo red) with concentrated hydrochloric acid. Filter the thick precipitate. Dry the solid and dissolve in
- 10 acetone (300 mL) and dry the resulting solution (MgSO₄), filter, and evaporate at 20°C. Treat the resulting thick oil instantly with oxalic acid dihydrate (26.7 g) in 2-propanol (100 mL) at 38°C for 45 min. Allow the mixture to reach room temperature and dilute with diethyl ether (40 mL). Filter the solid and wash with diethyl ether. The resulting white solid (33.1 g) becomes pale lilac on exposure to light and air. Dissolve the resulting
- 15 salt (33.1 g) in water (400 mL) and basify with concentrated ammonium hydroxide. Extract the mixture with methylene chloride (3 x 200 mL) and combine the extract and dry (MgSO₄), filter, and evaporate to give a brown oil (15 g, 56%). Dissolve this material (15 g, 0.15 mol) in methylene chloride (300 mL) and add Et₃N (42.2 mL, 0.3 mol) at 0°C. Add a solution of (Boc)₂O (39.3 g, 0.18 mol) in methylene chloride (100 mL) dropwise at
- 20 0°C and stir the mixture overnight at room temperature. Monitor TLC (Hexane/EtOAc 9:1) for complete disappearance of starting material. Quench the reaction by addition of water (200 mL). Extract the mixture with methylene chloride (2 x 200 mL) and combine the extracts, dry (MgSO₄), filter, and evaporate. Purify the crude by flash chromatography (Silica gel -Hexane /EtOAc 9:1) to obtain 20.1 g (67%) of (*tert*-butoxy)-N-(3-
- 25 thiophenyl)carboxamide as a white solid.

In a manner analogous to Campaigne, E. and Monroe, P. A. *J.A.C.S.*, 76, 2447-2450 (1954), to a boiling solution of (*tert*-butoxy)-N-(3-thiophenyl)carboxamide (21.0 g, 0.1 mol) in methylene chloride (400 mL) add N-iodosuccinimide (23.7 g, 0.1 mol) in

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small portions. Set the heating bath to 65°C for 20 min. Take the reaction to room temperature, evaporate the solvent and purify the crude by flash chromatography (Silica gel–Hexane /EtOAc 9:1) to obtain 30.0 g (88%) of (tert-Butoxy)-N-(2-iodo(3-thiophenyl))carboxamide as a white solid.

- 5 Heat (tert-Butoxy)-N-(2-iodo(3-thiophenyl))carboxamide (16.88 g, 0.52 mol), 4-bromophenylboronic acid (15.65 g, 0.78 mol), Na₂CO₃ (1.01 g, 1.04 mol) and Pd(PPh₃)₄ (5.79 g, 0.052 mol) in 375 ml of an anhydrous and deoxygenated 2:1 DME/EtOH mixture to 80°C under nitrogen atmosphere for 24 h. Evaporate the organic solvents prior to the addition of water (200 mL). Extract the mixture with methylene chloride (3 x 150 mL)
- 10 and combine the organic phases, dry (anh MgSO₄), filter, and concentrate to furnish a crude mixture as a yellowish solid. Purification by flash chromatography (Silica gel–Hexane /EtOAc 49:1) yields 10.8 g (60%) of (tert-butoxy)-N-[2-(4-bromophenyl)(3-thiophenyl)]carboxamide as a pale yellow solid.

- Treat dropwise a solution of (tert-butoxy)-N-[2-(4-bromophenyl)(3-
- 15 thiophenyl)]carboxamide (10.8 g, 0.3 mol) in EtOAc (75 mL) at 0°C with 244 mL (8mL/mmol) of freshly prepared 1N HCl in EtOAc and stir the mixture at room temperature overnight. Dissolve the white precipitate with H₂O (100 mL) and neutralize with a NaHCO₃ saturated solution. Extract the mixture with EtOAc (3 x 100 mL) and combine organic, dry and concentrate to give a slightly colored solid. Purification of the
- 20 crude material by flash chromatography (Silica gel–Hexane /AcOEt 49:1 then 9:1) furnishes 5.7 g (74%) of 2-(4-bromo-phenyl)-thiophen-3-yl amine as a pale yellow solid.

- Add slowly to a solution of 2-(4-bromo-phenyl)-thiophen-3-yl amine (0.6 g, 2.36 mmol) in dry dichloromethane (10 mL) at 0°C, DBU 1.41 mL (9.45 mmol) and isopropylsulfonyl chloride (0.53 mL, 4.72 mmol) (Temp. always <0°C). Remove the ice
- 25 bath and stir the mixture at RT overnight. Add satd. aq. NH₄Cl (10 mL) and extract the solution with EtOAc (2 x 10 mL). Dry the combined organic layers and concentrate under vacuum. Purify the crude residue by flash chromatography (Silica gel–Hexane /EtOAc 4:1) to give 0.8 g (94%) of propane-2-sulfonic acid [2-(4-bromo-phenyl)-thiophen-3-yl]-amide.

- 30 Deoxygenate by purging with nitrogen a mixture of propane-2-sulfonic acid [2-(4-bromo-phenyl)-thiophen-3-yl]-amide (1.34 g, 3.72 mmol), bis(pinacolato)diboron (1.04 g,

4.09 mmol), KOAc (1.21 g, 12.3 mmol) and Pd(dppf)Cl₂ (0.3 g, 0.37 mmol) in dry DMF (20mL) and heat the mixture to 80°C overnight. Add water (20 mL) and extract the reaction with diethyl ether (3 x 20 mL). Wash the combined organics with water and dry and concentrate to give a crude dark solid. Purification by flash chromatography (Silica gel-Hexane /AcOEt 7:1) gives 0.65 g (43%) of the title compound as a pale yellow solid.

Preparation 2

Propane-2-sulfonic acid (4'-(boronic acid)-biphenyl-2-yl)-amide

Add 4-bromophenyl boronic acid (5.0 g, 24.82 mmol),
10 tetrakis(triphenylphosphine) palladium (0) (0.717 g, 0.620 mmol) and 2 M Na₂CO₃ (10 mL) to a solution of 2-iodoaniline (4.5 g, 20.69 mmol) in toluene (2 mL):ethanol (20 mL), deoxygenate and heat at 80 °C under nitrogen. After 4 h, add water and extract with EtOAc. Combine the organic layers, dry over sodium sulfate, filter and concentrate under reduced pressure to give a residue. Purify the residue by flash chromatography (Silica
15 gel-EtOAc/hexane 1:12), to provide 4'-bromo-biphenyl-2-ylamine (3.53 g, 69 %). MS (m/e): 248 (M+1); 249 (M+2).

Add dropwise DBU drop wise (8.76 mL, 56.92 mmol) to a solution of 4'-bromo-biphenyl-2-ylamine (3.53 g, 14.23 mmol) in dichloromethane (50ml) at 0°C, followed by drop wise addition of isopropylsulfonyl chloride (3.29 mL, 28.46 mmol) and stir the
20 reaction at room temperature for 24 h. Remove solvent under reduce pressure and purify the residue by silica and eluting with EtOAc:hexane 1:4 to EtOAc to provide the title compound (4.93 g, 98%). MS (m/e): 355 (M+1); 353 (M-1).

Heat at 80 °C a mixture of propane-2-sulfonic acid (4'-bromo-biphenyl-2-yl)-amide (4.0 g, 11.22 mmol), bis(pinacolato)diboron (3.22 g, 12.34 mmol), [1,1'-
25 bis(diphenylphosphino)ferrocene]-dichloropalladium(II) complex with dichloromethane (1:1) (0.276 g, 0.337 mmol) and potassium acetate (3.32 g, 33.87 mmol) in dry dimethylsulfoxide (25 mL). After 16 h add water and extract with EtOAc. Combine organic layers, dry over sodium sulfate and evaporate under reduce pressure. Dissolve the residue in dichloromethane and wash with a solution of 0.1N HCl. Combine the organic
30 layers, dry over sodium sulfate, filter and concentrate under reduced pressure. Purify the residue by flash chromatography (Silica gel-EtOAc/hexane 1:3) to provide propane-2-

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X

sulfonic acid [4'-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-biphenyl-2-yl]-amide (4.07 g, 90%). MS (m/e): 424 (M+23); 400 (M-1).

Add sodium periodate (1.12 g, 5.25 mmol) followed by a solution of 1 N ammonium acetate (8 mL) to a suspension of propane-2-sulfonic acid [4'-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-biphenyl-2-yl]-amide (0.7 g, 1.75 mmol) in acetone (16 mL)/water (0.8 mL). Stir the mixture at room temperature under nitrogen for 20 h. Filter the precipitate and evaporate organic layer. Extract aqueous layer with dichloromethane. Combine organic layers, dry over sodium sulfate and evaporate the solvent under reduced pressure. Add hexanes and tert-butylmethyl ether to the residue until a solid is formed and filter the solid to provide the title compound (0.37 g, 67%). MS'(m/e): 337 (M+18); 318 (M-1).

Preparation 3

Propane-2-sulfonic acid {4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-pyridin-3-yl}-amide

Take up 4-hydroxy-3-nitro-pyridine (6.18 g, 44.2 mmol) in phosphorus oxychloride (16 ml) and heat to 45°C. Once at 45°C, add phosphorus pentachloride (8.04 g, 38.6 mmol) in a single portion. Stir the resulting yellow slurry vigorously and heat under reflux (oil bath to 125°C) under an inert atmosphere. After 3 h at 125°C, the yellow slurry becomes a clear yellow solution. Cool the mixture to room temperature, concentrate to an oil, cool to 0°C in an ice bath and treat with 10 ml of water and 20 ml of dichloromethane while stirring vigorously. Basify the aqueous layer with saturated sodium bicarbonate solution and extract with dichloromethane (x3). Dry the combined organic layers over anhydrous sodium sulfate, filtered and concentrate to give 6.98g of 4-Chloro-3-nitro-pyridine, which crystallizes on standing (99% yield).

4-Chloro-3-nitro-pyridine (6.9 g, 43.5 mmol), 4-bromophenyl boronic acid (8.05 g, 40.1 mmol), potassium carbonate (11.10g, 80.3 mmol) and tetrakis triphenylphosphine palladium (2.31 g, 2.0 mmol) are taken up in DME (200 ml) and heated under reflux (100°C) overnight. The mixture is cooled down to room temperature and filtered through Celite® pad, which is washed with EtOAc. The filtrate is concentrated to give a crude

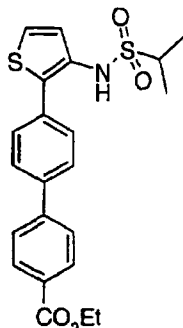
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AZ

brown oil. Purification by flash chromatography (Silica gel-hexane /EtOAc) yields 4-(4-Bromo-phenyl)-3-nitro-pyridine (8.52 g) as a yellow oil (76% yield).

Stir 4-(4-Bromo-phenyl)-3-nitro-pyridine (8.52 g, 30.5 mmol) in glacial acetic acid (150 ml) and add 325 mesh iron powder (8.40 g, 150.4 mmol). Heat the mixture to 80°C for 40 min at which point the mixture turns gray. Filter the mixture through Celite® and wash the solid with EtOAc. Wash the organic layer with water. Basify the aqueous layer to pH 8 with NaOH solution and extract with EtOAc (x2). Wash the combined organic layers with water, saturated aq. sodium chloride, dry over anhydrous sodium sulfate, filter and concentrate to afford 7.25 g of a brown crude oil. Purification by flash chromatography (Silica gel-hexane /EtOAc) yields 4-(4-Bromo-phenyl)-pyridin-3-ylamine (4.64 g) as a white solid (61% yield).

Take up 4-(4-Bromo-phenyl)-pyridin-3-ylamine (4.6 g, 18.5 mmol) in anhydrous dichloromethane (100 ml). Add DBU (11 ml, 73.5 mmol) and stir the solution at 0°C for 3 min under inert atmosphere. Add isopropylsulfonyl chloride dropwise over 10 min. Allow the mixture to warm up to RT and heat under reflux (40°C) overnight. Quench the mixture by addition of saturated ammonium chloride solution. Extract the aqueous layer with dichloromethane (x2). Wash the combined organic layers with saturated aq. sodium chloride, dry over anhydrous sodium sulfate, filter and concentrate to afford 9.1 g of a brown crude residue. Purification by flash chromatography (Silica gel-hexane /EtOAc) followed by reverse purification yields the desired compound propane-2-sulfonic acid [4-(4-bromo-phenyl)-pyridin-3-yl]-amide (2.68 g) as a white solid (41% yield).

Take up propane-2-sulfonic acid [4-(4-bromo-phenyl)-pyridin-3-yl]-amide (2.07 g, 5.8 mmol), bis(pinacolato) diboron (2.01 g, 7.9 mmol), potassium acetate (2.3 g, 23.4 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) complex with dichloromethane (1:1) (0.277 g, 0.339 mmol) in anhydrous DMF (12 ml) and heat to 80°C under inert atmosphere overnight. Add water (4 ml) and filter the reaction mixture through a small pad of silica. Wash the silica pad with EtOAc. Wash the organic filtrate with HCl 0.05N, water (x4), dry over anhydrous sodium sulfate, filter and concentrate to afford 3.8g of a dark crude residue. Purification by flash chromatography (Silica gel-hexane /EtOAc) yields the title compound (1.85 g) as a beige solid (79% yield).

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OSPreparation 44'-[3-(Propane-2-sulfonylamino-thiophen-2-yl)-biphenyl-4-carboxylic acid ethyl ester

Heat in a sealed tube with stirring propane-2-sulfonic acid{2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-thiophen-3-yl}-amide (0.5 mmol), 4-iodobenzoic acid ethyl ester (0.75 mmol), 2M Na₂CO₃ water solution (0.2 mL) and Pd(PPh₃)₄ (0.05 mmol) in 4.0 ml of an anhydrous DME to 100°C for 24 h. Evaporate the organic solvent, prior to the addition of water (10 mL). Extract the mixture with dichloromethane (3 x 20 mL) and dry the combined organic phases (Na₂SO₄) and concentrate to furnish a crude mixture. Purification by flash chromatography (Silica gel-hexane /EtOAc) yields the title compound.

Preparation 55-(4-Bromo-benzyl)-2H-tetrazole

Stir a mixture of SiCl₄ (1.7g, 10mmol, 2eq.) and NaN₃ (1.95g, 30mmol, 6eq.) in 50 mL of acetonitrile for 2 hours. Add 1.07g of 2-(4-bromophenyl) acetamide (5 mmol, 1eq.) and heat to 85°C for 5 hour. Cool to room temperature and filter off the solid wash the solid with EtOAc. Wash the ester layer with water, saturated aq. sodium chloride, dry over MgSO₄ and evaporate the solvent to afford 900 mg title compound (80%).
MS (m/e): 237.0.

Preparation 63-(4-Bromo-phenyl)-N-methyl-propionamide

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Add oxalyl chloride (1.75mL, 2.54g, 4eq.) to a solution of 3-(4-bromo-phenyl)-propionic acid, in methylene chloride (100mL), which contains 0.1mL DMF at 0°C and allow the reaction mixture to warm to room temperature and stir 1 hour. Evaporate solvent and dissolve it in 10mL THF. Add half of the THF solution to 20mL of methylamine (2M) and stir another hour. Add water to the solution to dissolve solid and wash organic layer with 2N HCl, water and saturated aq. sodium chloride and dry it over MgSO₄. Evaporate solvent to afford the title compound 500 mg, 41%. MS 246.0.

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Preparation 7Trifluoro-methanesulfonic acid 4-[1,2,4] triazol-1-yl-phenyl ester

Add pyridine (0.74g, 9.3mmol, 3eq.) to a solution of 4-[1,2,4]triazol-1-yl-phenol (500 mg, 3.1mmol, 1eq.) at -78°C and stir for 15 minutes. Add slowly triflic anhydride (1.05 g, 3.7 mmol, 1.2eq.). Allow the reaction mixture to warm to room temperature and stir 3 hours. Pour the mixture into 20mL of 1N HCl (cold). Wash the organic layer with water (2x10mL), saturated sodium bicarbonate and saturated aq. sodium chloride. Dry and evaporate to give 860 mg (95%) of the title compound. MS. 294.0.

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Preparation 84-Methylsulfanyl-2-trifluoromethanesulfonyloxy-benzoic acid methyl ester

Combine 2-Hydroxy-4-methylsulfanyl-benzoic acid methyl ester (5.072 g, 25.58 mmol), pyridine, and CH₂Cl₂ at 0°C and stir. Add triflic anhydride (5.1 ml, 30.31 mmol) drop wise over several min. After 4 hours dilute the mixture with CH₂Cl₂ and wash with 1N HCl, H₂O, and dry over Na₂SO₄, filter and concentrate under reduced pressure to yield 4-Methylsulfanyl-2-trifluoromethanesulfonyloxy-benzoic acid methyl ester (7.775 g, 92%). MS (m/e): 330.8(M+1).

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Preparation 9Propane-2-sulfonic acid (4'-bromo-biphenyl-2-yl)-amide

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Combine 4-bromophenylboronic acid (6.064 g, 30.195 mmol), 2-iodo-phenylamine (5.532 g, 25.257 mmol), toluene, 2N Na₂CO₃ (13 ml, 26 mmol), and tetrakis(triphenyl-phosphine)palladium(0) (0.849 g) and heat to 80°C. After 4 hours cool to room temperature and stir for 16 hours. Dilute the reaction with EtOAc and back
5 extract water layer with EtOAc. Combine the organic layers and wash with H₂O, and dry over Na₂SO₄, filter, and concentrate under reduced pressure. Purify the residue by flash chromatography (silica gel), eluting with first hexane and increasing up to 10% EtOAc/Hexane to afford 4'-bromo-biphenyl-2-ylamine (4.008 g, 64%). LCMS 247.

Add 4'-bromo-biphenyl-2-ylamine (1.038 g, 4.183 mmol) to CH₂Cl₂ and cool to
10 0°C. Add first DBU (2.6 ml, 17.038 mmol), then isopropylsulfonyl chloride (0.95 ml, 8.206 mmol) drop wise to flask and warm flask to room temperature. After 18 hours monitor reaction. If SM is still present, add DBU (1 ml), then isopropylsulfonyl chloride (0.4 ml) and then stir 2 additional hours. Purify resultant product using flash chromatography (Silica gel-25% EtOAc/Hexane) to provide propane-2-sulfonic acid (4'-bromo-biphenyl-2-yl)-amide (1.116g, 75%).
15 MS(m/e): 351.9(M-1).

Preparation 10

5-(4-Bromo-phenyl)-pyrazole-1-carboxylic acid tert-butyl ester

20 Stir a mixture of 5-(4-bromo-phenyl)-pyrazole (577mg, 2.6mmol, 1eq.), di-tert-butyl-dicarbonate (737mg, 3.38mmol), and dimethylaminopyridine (32 mg, 0.25 mmol) in 16 mL acetonitrile overnight. Add 200 mL diethyl ether and 50 mL water. Wash the organic layer with water, saturated aq. sodium chloride and evaporate solvent to afford the title compound 800 mg, 95%.

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Preparation 11

(4-Bromo-phenoxy)-acetonitrile

Mix 4-bromophenol (1.4mmol) in acetonitrile (5ml) and water (2ml), add K₂CO₃ (3mmol) and bromoacetonitrile (1.5mmol) at room temperature under inert atmosphere.
30 Heat the mixture to 80°C for 16 h. Analyze by LC/MS for final product. Evaporate the

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solvent and add water. Extract product with DCM (3x) and combine and evaporate organic phases to afford the title compound.

Preparation 12

5 2-Bromo-5-(cyanomethyl-amino)-benzonitrile

Mix 5-amino-2-bromobenzonitrile (0.76 mmol) in anhydrous THF (3 ml), N,N-diisopropylethylamine (0.92 mmol), and bromoacetonitrile (1.0 mmol) at room temperature under inert atmosphere. Heat the mixture to 100°C for 16 h in a sealed tube. Cool in ice bath, filter the precipitate and evaporate the filtrate to dryness to afford a crude
10 residue. Purify by flash chromatography (Silica gel-CHCl₃/Ethanol/NH₄OH 9:1:0.1) to yield the title compound.

Preparation 13

4-Bromo-3-(propane-2-sulfonylamino)-benzoic acid methyl ester

15 Add Na₂SO₄ (8.5 mmol) to a solution of 4-Bromo-3-nitro-benzoic acid methyl ester (1.2 mmol) in EtOH (40 mL). Heat the reaction at 70°C for 30 min and then at room temperature overnight. Add a saturated solution of NaHCO₃ (pH=11-12) and extract with EtOAc (2x50 mL). Dry over Na₂SO₄, filter and evaporate to dryness to provide 4-Bromo-3-amino-benzoic acid methyl ester.

20 Add DBU drop wise (0.5mmol) to a suspension of the previously prepared amine (0.1 mmol) in dichloromethane (15ml) at 0°C, followed by drop wise addition of isopropylsulfonyl chloride (0.2 mmol) and stir the reaction at room temperature for 24 h. Remove solvent under reduce pressure. Purify by flash chromatograph (Silica gel-hexane/EtOAc). Concentrate the desired fractions to provide the title compound.

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Preparation 14

4-Bromo-3-(methanesulfonylamino)-benzoic acid methyl ester

 Add Na₂SO₄ (0.12 mmol) to a suspension of 4-Bromo-3-amino-benzoic acid methyl ester (0.1 mmol) and Et₃N (0.1 mmol) in dichloromethane at 0°C. Stir 4h at RT.
30 Add a saturated solution of NaCl (15 mL), and extract with dichloromethane (2x50 mL).

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Dry over NaSO₄, filter and evaporate to dryness. Purify the residue utilizing flash chromatography (Silica gel-hexane/EtOAc) to provide the title compound.

Preparation 15

5 4'-Iodo-5-trifluoromethyl-biphenyl-2-carboxylic acid methyl ester

Heat a solution of 5-Trifluoromethyl-biphenyl-2-carboxylic acid methyl ester (1.0mmol), acetonitrile and diiodomethane (3.5mmol) to 35°C with stirring under nitrogen. Once 35 °C is reached, add i-Amylnitrite (2.5mmol) slowly so as to avoid a large exotherm. Heat reaction to 65-70 °C for 2 hours. Remove the heat and concentrate the reaction *in vacuo*. Purify via radial chromatography eluting with EtOAc/dichloro-

10 methane/hexanes to yield the final product (52%).

MS (m/e): 408.0 (M+1)

Preparation 16

15 3-Chloro-4-trifluoromethanesulfonyloxy-benzoic acid methyl ester

Add dropwise triflic anhydride (6.7 ml, 39.8 mmol) to a solution of methyl 3-chloro-4-hydroxybenzoate (5.42 g, 29.0 mmol), DMAP (490 mg, 4.0 mmol) and triethylamine (5.6 ml, 40.1 mmol) in anhydrous dichloromethane (200 ml). Stir the mixture at room temperature overnight under nitrogen atmosphere. Quench the mixture

20 by addition of a saturated aq. solution of ammonium chloride. Separate the organic layer and extract the aqueous layer with dichloromethane (x3). Wash the combined organic layers with saturated aq. sodium chloride, dry over anhydrous sodium sulfate, filter and concentrate to yield a crude brown oil. Take up this crude oil in hexane and wash the organic layer with water (x3), dry over anhydrous sodium sulfate, filter and concentrate to

25 yield the title compound.

Preparation 17

4-Ethoxy-3-iodo-benzoic acid ethyl ester

To a solution of phenol in AcOH (200 mL) at 65°C, add a solution of ICl in AcOH

30 (500 mL) dropwise. When the addition is completed, stir the mixture at 65°C for 6 hours. After cooling, pour the mixture into ice/water, filter and wash with water. Dissolve the

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solid obtained in CH_2Cl_2 , dry over MgSO_4 , filter and concentrate *in vacuo*. Purify the crude product by flash chromatography (Silica gel - CH_2Cl_2), to obtain 131.3 g of 4-Hydroxy-3-iodo-benzoic acid ethyl ester (74% yield).

To the resultant ester (3.10 g, 10.61 mmol) and potassium carbonate (2.87 g, 20.75 mmol) in 40 ml acetonitrile, add iodoethane (1.3 ml, 16.25 mmol) at RT while stirring vigorously. Heat the resulting white suspension under reflux for 1.5 h. Evaporate acetonitrile and replace with EtOAc. Wash the organic layer first with water, then with saturated aq. sodium chloride. Dry over anhydrous sodium sulfate, filter and concentrate to give the title compound as a yellow oil.

10

Preparation 18

3-Hydroxy-4-iodo-benzoic acid ethyl ester

Dissolve 3-hydroxy-4-iodobenzoic acid (2.02 g, 7.65 mmol) in ethanol saturated with HCl gas (50 ml). Heat the solution under reflux overnight. Evaporate ethanol to yield the title compound (97% yield).

15

Preparation 19

5-Bromo-1,3-difluoro-2-methoxy-benzene

Add iodomethane (2.0 ml, 32.1 mmol) dropwise to a suspension of 4-bromo-2,6-difluorophenol (5.90 g, 28.2 mmol) and potassium carbonate (4.40 g, 31.8 mmol) in acetone (50 ml) at room temperature while stirring vigorously. Heat the mixture under reflux overnight. Evaporate acetone and add dichloromethane. Filter through silica eluting the product with dichloromethane/EtOAc. Concentrate to yield the title compound.

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Preparation 20

6-Bromo-2,4-difluoro-3-methoxy-benzaldehyde

Add *n*-butyl lithium 1.6N (22 ml, 35.2 mmol) to diisopropylamine (4.8 ml, 34.2 mmol) in anhydrous THF (7 ml) at 0°C. Stir the resulting yellow solution for 30 min at 0°C. Add this LDA solution dropwise via canula to a solution of 5-bromo-1,3-difluoro-2-methoxybenzene (5.83 g, 26.17 mmol) in anhydrous THF (40 ml) at -78°C over 40 min. Stir the resulting bright yellow solution for 50 min at -78°C. Add anhydrous DMF (2.7

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5 ml, 34.8 mmol) and stir the mixture for 1.5 h at -78°C . Quench the mixture with dilute sulfuric acid and extract the product with EtOAc (x3). Wash the combined organic layers with water (x3), saturated aq. sodium chloride and dry over anhydrous sodium sulfate. Filter and concentrate to yield the crude product. Purification by flash chromatography (Silica gel-hexane/EtOAc) yields the title compound.

Preparation 21

6-Bromo-2,4-difluoro-3-methoxy-benzonitrile

10 Add hydroxylamine hydrochloride (608 mg, 8.8 mmol) to a solution of 6-Bromo-2,4-difluoro-3-methoxy-benzaldehyde (2.0 g, 7.96 mmol) in anhydrous DMF (4 ml). Heat the mixture to 150°C for 2 h. Add water to the cooled mixture and extract the product with EtOAc (x2). Wash the combined organic layers with water (x3), saturated aq. sodium chloride and dry over anhydrous sodium sulfate. Filter and concentrate. Dissolve the concentrate in anhydrous THF and add 3 equivalent of the Burgess reagent
15 ((methoxycarbonylsulfamoyl)triethylammonium hydroxide, inner salt). Heat the mixture under reflux under nitrogen atmosphere overnight. Concentrate to yield a crude residue. Purification by flash chromatography (Silica gel-hexane/EtOAc) yields the title compound.

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Preparation 22

3-Bromo-4-cyano-benzoic acid methyl ester

Dissolve 4-bromo-3-nitro-benzoic acid methyl ester (4.25 g, 16.3 mmol) in ethanol (100 ml) and water (30 ml). Add sodium dithionite (15 g, 75 mmol) in a single portion and heat the mixture under reflux for 4 h. Evaporate ethanol and add water.
25 Basify the aqueous layer with 10% sodium carbonate solution. Extract the product with EtOAc (x2). Dry the combined organic layers over anhydrous sodium sulfate, filter and concentrate to yield 3-amino-4-bromo-benzoic acid methyl ester (51%).

Add zinc cyanide (1.5 g, 12.77 mmol), palladium tetrakis (675 mg, 0.584 mmol), to 3-amino-4-bromo-benzoic acid methyl ester (1.328 g, 5.77 mmol) in anhydrous DMF
30 (3 ml). Purge with nitrogen for few minutes and keep under nitrogen atmosphere while heating to 120°C overnight. Cool the mixture to room temperature and add water. Extract

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the product with EtOAc (x2). Wash the combined organic layers with 2N ammonium hydroxide solution (x2), water (x2), saturated aq. sodium chloride and dry over anhydrous sodium sulfate, filter and concentrate to yield the crude product. Purification by flash chromatography (Silica gel-hexane/EtOAc) yields 3-amino-4-cyano-benzoic acid methyl ester (94%).

Add 3-amino-4-cyano-benzoic acid methyl ester (1.1 g, 6.24 mmol) to a stirred solution of sodium nitrite (511 mg, 7.4 mmol) in concentrated sulfuric acid (5 ml) and glacial acetic acid (5 ml) at 40°C. After 30 min at 40°C, pour the resulting orange solution into a cold solution of copper bromide (1.42 g, 9.89 mmol) in 48% hydrobromic acid (5 ml). When the evolution of nitrogen is finished, heat the mixture to 90°C for 30 min. Cool down to room temperature and pour the mixture onto crushed ice. Filter out the resulting dark solid, wash with water. Take this solid up in chloroform and filter the inorganic solid. Concentrate the filtrate to yield a crude yellow residue. Purification by flash chromatography (Silica gel-hexane/EtOAc) yields the title compound (56%).

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Preparation 23

2,2-Dimethyl-propionic acid 4-bromo-2,6-difluoro-phenyl ester

Add triethylamine (10.0 ml, 71.7 mmol) to 4-bromo-2,6-difluorophenol (9.92 g, 47.4 mmol) in anhydrous dichloromethane (100 ml) at 0°C while stirring under inert atmosphere. Add pivaloyl chloride (8 ml, 64.9 mmol) dropwise over 10 min. Allow the solution to warm up to room temperature overnight. Add water and extract the aqueous layer with dichloromethane (x2). Wash the combined organic layers with water (x2), saturated aq. sodium chloride, dry over anhydrous sodium sulfate, filter and concentrate to afford 15.5g of a clear crude oil. Purification by flash chromatography (Silica gel-hexane/diethyl ether) yields the title compound (13.1 g) as a clear oil (94% yield).

25

Preparation 24

2,2-Dimethyl-propionic acid 4-bromo-2,6-difluoro-3-formyl-phenyl ester

Add *n*-butyl lithium 1.6N (23 ml, 36.8 mmol) to diisopropylamine (5.0 ml, 35.6 mmol) in anhydrous THF (7 ml) at 0°C. Stir the resulting yellow solution for 30 min at

30

0°C. Add this LDA solution dropwise via canula to a solution of 2,2-Dimethyl-propionic acid 4-bromo-2,6-difluoro-phenyl ester (8.01 g, 27.33 mmol) in anhydrous THF (40 ml) at -78°C over 40 min. Stir the resulting bright yellow solution for 1 h at -78°C. Add anhydrous DMF (2.8 ml, 35.0 mmol) and stir the mixture for 1.5 h at -78°C.

- 5 Quench the mixture with dilute sulfuric acid and extract the product with EtOAc (x3). Wash the combined organic layers with water (x3), saturated aq. sodium chloride and dry over anhydrous sodium sulfate. Filter and concentrate to yield the crude product. Purification by flash chromatography (Silica gel-hexane/EtOAc) yields 8.35 g of the title compound (95% yield).

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Preparation 25

2,2-Dimethyl-propionic acid 4-bromo-3-cyano-2,6-difluoro-phenyl ester

- 15 Add hydroxylamine hydrochloride (2.33 g, 33.6 mmol) and sodium iodide (2.09 g, 13.96 mmol) to a solution of 2,2-Dimethyl-propionic acid 4-bromo-2,6-difluoro-3-formyl-phenyl ester (8.34 g, 25.97 mmol) in acetonitrile (100 ml). Heat the mixture under reflux (100°C) for 3 h. TLC (Hexane:Ethyl Acetate 4:1) shows incomplete conversion. Cool down the mixture to 60°C and add more hydroxylamine hydrochloride (2.24 g, 33.0 mmol). Heat the mixture to 100°C for 1.5 h.

- 20 Quench the mixture with 5% aqueous Na₂S₂O₃ and stir for 5 min until the red-brown color has disappeared. Extract the product with ethyl acetate (x2). Wash the combined organic layers with water (x3), saturated aq. sodium chloride and dry over anhydrous sodium sulfate. Filter and concentrate. Dissolve the concentrate in anhydrous THF and add 1.7 equivalent of the Burgess reagent
- 25 ((methoxycarbonylsulfamoyl)triethylammonium hydroxide, inner salt) (10.0 g, 41.96 mmol). Heat the mixture under reflux under nitrogen atmosphere for 4 h. Concentrate to yield a crude residue. Purification by flash chromatography (Silica gel-hexane/EtOAc) yields 5.87g of the title compound as a pale yellow solid (75% yield).

53
✓Preparation 26Propane-2-sulfonic acid [2-(4-bromo-phenyl)-2H-pyrazol-3-yl]-amide

5 Add DBU (5.14mL, 33.69 mmol) to a solution of 5-amino-1-(4-bromo-phenyl)-1H-pyrazole-4-carboxylic acid ethyl ester (2.612g, 8.42 mmol) in dichloromethane (25 mL) at 0°C. Stir for 15 min. at 0°C and then add isopropylsulfonyl chloride (1.94 mL, 16.84 mmol). Immerse the mixture into a pre-heated oil bath (50°C). After stirring for 5 min., add additional isopropylsulfonyl chloride (0.97 mL, 8.42 mmol). Stir overnight at
10 50°C. Add 1.0M HCl (aq) until pH 5, wash with water (2x50mL), dry over sodium sulfate, filter, and concentrate. Adsorb the compound onto silica gel, and subject to silica gel flash column chromatography (15-30% EtOAc/n-hexane) to yield 1-(4-Bromo-phenyl)5-(propane-2-sulfonylamino)-1H-pyrazole-4-carboxylic acid ethyl ester (2.55g, 73%).

15 Dissolve 1-(4-Bromo-phenyl)5-(propane-2-sulfonylamino)-1H-pyrazole-4-carboxylic acid ethyl ester (2.549g, 6.12 mmol) in ethanol (10mL)(denatured with methanol) and then add an aqueous solution of sodium hydroxide (12.5 mL, 2.0M). Immerse the resulting mixture into a pre-heated oil bath (65°C) and stir overnight. Upon completion, concentrate to remove ethanol/methanol, wash the resulting aqueous
20 mixture with dichloromethane, and concentrate to remove any trace of dichloromethane. Cool the aqueous mixture to 0°C, add 1.0M HCl until pH 4 is achieved (extensive precipitation of acid may be observed), and stir for 15 min. Filter the mixture under reduced pressure. Allow the reduced pressure to cool the filtrate, and filter a second crop of product. Combine the two crops to yield 1-(4-Bromo-phenyl)-5-(propane-2-
25 sulfonylamino)-1H-pyrazole-4-carboxylic acid (2.031g, 85%).

 Dissolve 1-(4-Bromo-phenyl)-5-(propane-2-sulfonylamino)-1H-pyrazole-4-carboxylic acid (1.952g, 5.03 mmol) in quinoline (2.79 mL) in a sealed tube. Add copper (0.16g, 2.51 mmol) and immerse into a pre-heated (180°C) oil bath and stir for 15 min. Cool to room temperature and remove the solvent under reduced pressure. Dilute with
30 dichloromethane, wash with 1.0M HCl (2x50 mL), dry over sodium sulfate, filter, and

concentrate to yield a residue. Subject to silica gel flash column chromatography (15-55% EtOAc/n-hexane) to yield the title compound (1.323g, 76%).

5

Example 1Propane-2-sulfonic acid-(2-biphenyl-4-yl-thiophen-3-yl)-amide

Heat in a sealed tube with stirring propane-2-sulfonic acid [2-(4-bromo-phenyl)-thiophen-3-yl]-amide (0.5 mmol), phenyl boronic acid (0.75 mmol), 2M Na₂CO₃ water solution (0.2 mL) and Pd(PPh₃)₄ (0.05 mmol) in 4.0 ml of an anhydrous and

10 deoxygenated 2:1 DME/EtOH mixture to 80°C-100°C for 24 h. Filter mixture through a small silica pad and elute with EtOAc. Evaporate the filtrate. Purify the product by flash chromatography (Silica gel-hexane /EtOAc) to obtain the title compound. MS (ES-): 356 (M-1).

15 Prepare the following compounds in a manner analogous to the procedure set forth in the above example:

EXAMPLE	COMPOUND	DATA MS (ES-):
2	Propane-2-sulfonic acid [2-(4'-amino-biphenyl-4-yl)-thiophen-3-yl]-amide	371 (M-1)
3	Propane-2-sulfonic acid [2-(2'-cyano-biphenyl-4-yl)-thiophen-3-yl]-amide	381(M-1) .
4	N-{4'-[3-(Propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-3-yl}-acetamide	413 (M-1)
5	Propane-2-sulfonic acid [2-(3'-methanesulfonylamino-biphenyl-4-yl)-thiophen-3-yl]-amide	449 (M-1)
6	N-[2-(Propane-2-sulfonylamino)-[1,1';4',1'']terphenyl-3''-yl]-acetamide	407 (M-1).
7	Propane-2-sulfonic acid [3''-(propane-2-sulfonylamino)-[1,1';4',1''] terphenyl-2-yl]-amide	443 (M-1)

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EXAMPLE	COMPOUND	DATA MS (ES-):
8	N-{2-Cyano-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-yl}-acetamide	438 (M-1)
9	Propane-2-sulfonic acid [2-(2'-cyano-4'-hydroxy-biphenyl-4-yl)-thiophen-3-yl]-amide	397 (M-1)
10	Propane-2-sulfonic acid {2-[2'-cyano-4'-(cyano-methyl-amino)-biphenyl-4-yl]-thiophen-3-yl}-amide	435 (M-1)
11	Propane-2-sulfonic acid [2-(3',5'-difluoro-4'-hydroxy-biphenyl-4-yl)-thiophen-3-yl]-amide	408 (M-1)
12	N-{2-Cyano-4'-[3-(propane-2-sulfonylamino)-pyridin-4-yl]-biphenyl-4-yl}-acetamide	433 (M-1)
13	Propane-2-sulfonic acid [4-(2'-cyano-biphenyl-4-yl)-pyridin-3-yl]-amide	376 (M-1)
14	Propane-2-sulfonic acid [2-(2'-cyano-3',5'-difluoro-4'-hydroxy-biphenyl-4-yl)-thiophen-3-yl]-amide	433 (M-1)

Prepare the following compounds in a manner analogous with the procedure set forth in Example 1. Extract the resultant compound in ethyl acetate, wash the organic layer with water three times, dry over MgSO₄, filter, and concentrate to obtain the title compound.

5

EXAMPLE	COMPOUND	DATA MS (ES-):
15	Propane-2-sulfonic acid [2-(4'-acetyl-2'-cyano-biphenyl-4-yl)-thiophen-3-yl]-amide	423 (M-1)
16	2-{4'-[3-(Propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-yl}-acetamide	436 (M-1)

Prepare the following compounds in a manner analogous with the procedure set forth in Preparation 4:

10

EXAMPLE	COMPOUND	DATA MS (ES-):
17	4'-[3-(Propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-3-sulfonic acid amide (PdCl ₂ dppf)	MS (ES+, m/e): 437 (M+1).
18	4'-[3-(Propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-sulfonic acid amide (PdCl ₂ dppf)	MS (ES+, m/e): 437 (M+1)
19	Propane-2-sulfonic acid [2-(4'-fluoro-biphenyl-4-yl)-thiophen-3-yl]-amide	374 (M-1)
20	Propane-2-sulfonic acid [2-(4'-acetyl-biphenyl-4-yl)-thiophen-3-yl]-amide	398 (M-1)
21	Propane-2-sulfonic acid [2-(2',4'-difluoro-biphenyl-4-yl)-thiophen-3-yl]-amide	392 (M-1)
22	N-{2-Fluoro-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-yl}-acetamide	431 (M-1)
23	Propane-2-sulfonic acid [2-(2'-cyano-4'-fluoro-biphenyl-4-yl)-thiophen-3-yl]-amide	399 (M-1)
24	Propane-2-sulfonic acid [2-(2',4'-dicyano-biphenyl-4-yl)-thiophen-3-yl]-amide	406 (M-1)
25	Propane-2-sulfonic acid [2-(2'-cyano-4'-nitro-biphenyl-4-yl)-thiophen-3-yl]-amide	426 (M-1)
26	Propane-2-sulfonic acid [2-(4'-amino-2'-cyano-biphenyl-4-yl)-thiophen-3-yl]-amide	398 (M-1)
27	Propane-2-sulfonic acid [2-(3'-cyanomethyl-biphenyl-4-yl)-thiophen-3-yl]-amide	395 (M-1)

Example 28

5 Propane-2-sulfonic acid {2-[4'-(2-hydroxy-ethyl)-biphenyl-4-yl]-thiophen-3-yl} amide

Mix propane-2-sulfonic acid{2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-thiophen-3-yl}-amide (0.10 g), 0.1 equiv of tetrakis triphenylphosphine palladium (0), 2 equiv of 2M sodium carbonate aqueous solution in DME (2 mL) and EtOH(1mL) and warm to 90-95°C. After warming two min, add 2-(4-bromo-phenyl)-ethanol (1.3
 10 equiv) and stir at that temperature for 1.5 h. Evaporate solvents over Celite® and purify by silica gel Strata® cartridges eluting with hexanes-EtOAc gradient to give 0.041 g of the title compound. MS (ES+) (m/z): 402 (M+1).

52
16Example 296-(Propane-2-sulfonylamino)-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-2-carboxylic acid

Heat the mixture of propane-2-sulfonic acid {2-[4-{4,4,5,5-tetramethyl-
5 [1,3,2]dioxaborolan-2-yl)-phenyl]-thiophen-3-yl}-amide(662 mg, 1.65 mmol), 2-bromo-3-nitro-benzoic acid methyl ester (390 mg, 1.5mmol), Na₂CO₃ (2M, 2.2mL, 4.5 mmol) and Pd(PPh₃)₄ (260mg, 0.26 mmol) and 15 ml of 1,4 dioxane under N₂ to 80°C overnight. After cooling to room temperature, dilute with diethyl ether (200mL). Wash with water, saturated aq. sodium chloride, and dry over MgSO₄. Remove solvent and purify by flash
10 chromatography (Silica gel-hexane /EtOAc) to provide 6-nitro-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-2-carboxylic acid methyl ester (250 mg). MS (m/e): 478.7(M+1).

Add SnCl₂ · 2 H₂O (470 mg, 2.8 mmol) to a solution of 6-nitro-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-2-carboxylic acid methyl ester (250 mg, 0.54
15 mmol) in EtOH (5 mL). Heat the reaction at 80°C for 3 hours. Add 100mL EtOAc and wash it with a saturated solution of NaHCO₃, water and saturated aq. sodium chloride (50 mL). Dry over NaSO₄, filter and evaporate to dryness to provide 6-amino-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-2-carboxylic acid methyl ester (208 mg). MS (m/e): 429.1(M-1).

Add 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU) drop wise (0.51 mL, 3.6mmol) to a suspension of 6-amino-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-2-carboxylic acid methyl ester (208mg 0.48 mmol) in dichloromethane (9ml) at 0°C, followed by drop wise addition of isopropylsulfonyl chloride (0.21 mL, 0.9 mmol) and stir the reaction at room temperature overnight. Remove solvent under reduced pressure.
25 Purify with flash chromatography (Silica gel-hexane/EtOAc). Concentrate the desired fractions to provide 6-(propane-2-sulfonylamino)-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-2-carboxylic acid methyl ester (50mg). MS (m/e): 535.1(M-1).

Heat the mixture of 6-(propane-2-sulfonylamino)-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-2-carboxylic acid methyl ester (46 mg, 0.08
30 mmol) and LiOH (30mg, 1.25 mmol) in 3 ml of THF/Methanol/water (3/2/1, v/v/v) to

60°C for 3 h. Remove solvent and dissolve in water (35 mL). Wash with methylene chloride (2x20 mL). Neutralize the aq. solution to a pH between 2 and 3. Further purification with flash chromatography affords the title compound. MS (m/e): 521.1 (M-1).

5

Example 30

Propane-2-sulfonic acid {2-[4'-(2H-tetrazol-5-ylmethyl)-biphenyl-4-yl]-thiophen-3-yl}-amide

Deoxygenate and heat a mixture of trifluoro-methanesulfonic acid 4'-(5H-tetrazol-5-ylmethyl)-biphenyl-4-yl ester (48 mg, 0.2 mmol), propane-2-sulfonic acid {2-[4-(4,4,5,5-tetramethyl-[1,3,2] dioxaborolan-2-yl)-phenyl]-thiophen-3-yl}-amide (95 mg, 0.24 mmol, 1.2 eq.), barium hydroxide octahydrate (189 mg, 0.6 mmol, 3 eq.) and Pd(dffp) (29 mg, 0.04 mmol, 0.2 eq.) in 2 mL DMF and water mixture (4/1, v/v) to 80°C overnight. Cool the mixture to room temperature and dilute with 30 mL EtOAc. Wash with water (3x 10 mL) and saturated aq. sodium chloride, dry, and remove solvent. Purification by flash chromatography (Silica gel- CH₂Cl₂:MeOH (1/50, v/v)) affords the title compound 50 mg (53%). MS (m/e): 441.1 (M+1).

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Prepare the following compounds in a manner substantially analogous to the procedure set forth in the above example:

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EXAMPLE	COMPOUND	DATA MS (ES-):
31	{4'-[3-(Propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-yl}-acetic acid	414.1 (M-1)
32	2-{4'-[3-(Propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-yl}-acetamide	413.2 (M-1)
33	3-{4'-[3-(Propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-yl}-propionic acid	428.1 (M-1)
34	Propane-2-sulfonic acid [2-(4'-[1,2,4]triazol-1-yl-biphenyl-4-yl)-thiophen-3-yl]-amide	425.0 (M+1)

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450Example 35{4'-[3-(Propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-yloxy}-acetic acid

5 Heat a solution of (4-Iodo-phenoxy)-acetic acid or (4-bromo-phenoxy)-acetic acid (0.25 mmol), propane-2-sulfonic acid {2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-thiophen-3-yl}-amide (122 mg, 0.30 mmol), PdCl₂(dppf) (41 mg, 0.05 mmol) and barium hydroxide (158 mg, 0.50 mmol) in DMF-H₂O (v/v 4:1, 2.5 mL) to 80 °C under nitrogen atmosphere for 20 h. Pour into H₂O (50 mL) and dichloromethane (50 mL), then extract with H₂O (4 x 50 mL) and dry the combined organic phases (MgSO₄).
10 Concentrate to furnish a crude mixture as a yellowish solid. Purification by flash chromatography (Silica gel-Hexane /EtOAc) affords the title compound as a pale yellow solid (65-80% yield). MS (ES⁻):430.1 (M-1).

15 Prepare the following compound in a manner analogous to the procedure set forth in the above example:

EXAMPLE	COMPOUND	DATA MS (ES ⁻):
36	{4'-[3-(Propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-ylsulfanyl}-acetic acid	446.1 (M-1)

Example 372-Chloro-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-carboxylic acid

20 Heat in a sealed tube with stirring propane-2-sulfonic acid{2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-thiophen-3-yl}-amide (0.5 mmol), 3-chloro-4-trifluoromethanesulfonyloxy-benzoic acid (0.75 mmol), 2M Na₂CO₃ aq. solution (0.2 mL) and Pd(PPh₃)₄ (0.05 mmol) in 4.0 ml of a mixture of DME : Ethanol (2:1) to 80°C for 24 h. Filter the mixture through a small silica pad and eluted with EtOAc.
25 Evaporate the filtrate and purify resultant compound by flash chromatography (Silica gel-hexane /EtOAc).

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ES

Add NaOH 2M (1 ml) to the resultant ester (0.128 mmol) in ethanol (1 ml) and stir 24 h. Add 6N HCl until pH is approximately 1 and a white solid precipitates. Filter the solid to provide the title compound. MS (ES-): 435 (M-1).

Prepare the following compounds in a manner analogous with the procedure set forth in the above example:

EXAMPLE	COMPOUND	DATA MS (ES-):
38	4-Cyano-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-2-carboxylic acid	425 (M-1)
39	2-Methoxy-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-yl}-acetic acid	444 (M-1)
40	6-Cyano-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-3-carboxylic acid	435 (M-1)
41	4'-[3-(Propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-3-carboxylic acid	400 (M-1)
42	{ 2-Fluoro-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-yl}-acetic acid	432 (M-1).
43	2''-(Propane-2-sulfonylamino)-5-trifluoromethyl-[1,1';4',1'']terphenyl-2-carboxylic acid	MS (m/e): 481.2 (M+17); 462.2 (M-1)
44	2''-Chloro-2-(propane-2-sulfonylamino)-[1,1';4',1'']terphenyl-4''-carboxylic acid	428 (M-1)

EXAMPLE	COMPOUND	DATA MS (ES-):
45	2"-Cyano-2-(propane-2-sulfonylamino)- [1,1';4',1'']terphenyl-4"-carboxylic acid	419 (M-1)
46	2"-Methoxy-2-(propane-2-sulfonylamino)- [1,1';4',1'']terphenyl-4"-carboxylic acid	424 (M-1)
47	2"-(Propane-2-sulfonylamino)- [1,1';4',1'']terphenyl-4"-carboxylic acid	394 (M-1)
48	6"-Ethoxy-2-(propane-2-sulfonylamino)- [1,1';4',1'']terphenyl-3"- carboxylic acid	438 (M-1)
49	6"-Cyano-2-(propane-2-sulfonylamino)- [1,1';4',1'']terphenyl-3"-carboxylic acid	419 (M-1)
50	2-(Propane-2-sulfonylamino)- [1,1';4',1'']terphenyl-3"-carboxylic acid	394 (M-1)
51	2-Cyano-4'-[3-(propane-2-sulfonylamino)- pyridin-4-yl]-biphenyl-4-carboxylic acid	420
52	2-Methoxy-4'-[3-(propane-2-sulfonylamino)- thiophen-2-yl]-biphenyl-4-carboxylic acid	430 (M-1)

Example 53

4'-[3-(Propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-carboxylic acid

Add NaOH 2M (1 ml) to a suspension of 4'-[3-(propane-2-sulfonylamino)-
5 thiophen-2-yl]-biphenyl-4-carboxylic acid ethyl ester (0.128 mmol) in ethanol (1 ml) and
stir 24 h. Add 6N HCl until pH is approximately 1 and a white solid precipitates. Filter
the solid to provide the title compound: MS (ES-): 400 (M-1).

Prepare the following compound in a manner analogous with the procedure set forth in the above example:

EXAMPLE	COMPOUND	DATA MS (ES-):
54	2-(Propane-2-sulfonylamino)-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-carboxylic acid	521 (M-1)

Example 55

5 Propane-2-sulfonic acid [2-(5'-amino-2'-cyano-biphenyl-4-yl)-thiophen-3-yl]-amide

Prepare propane-2-sulfonic acid [2-(2'-cyano-5'-nitro-biphenyl-4-yl)-thiophen-3-yl]-amide in a manner analogous to the procedure set forth in Preparation 4. Add $\text{SnCl}_2 \cdot 2 \text{H}_2\text{O}$ (642 mg, 3.40 mmol) into a solution of propane-2-sulfonic acid [2-(2'-cyano-5'-nitro-biphenyl-4-yl)-thiophen-3-yl]-amide (279 mg, 0.654 mmol) in ethanol (6.54 mL). Heat the mixture at 90 °C for 3 h. Cool to room temperature. Concentrate to remove the solvent *in vacuo*. Dilute with dichloromethane, and add aqueous sodium bicarbonate solution to adjust pH to 8. Extract with dichloromethane (3 x 100 mL) and dry the combined organic layers and concentrate to give a slightly colored solid. Purification by flash chromatography (Silica gel-Hexane/EtOAc 2:1) furnishes 212 mg, 0.534 mmol (82%) of title compound as a pale yellow solid. MS (m/e): 396.1 (M-1).

Example 56

Propane-2-sulfonic acid [2-(2'-cyano-3',5'-difluoro-4'-hydroxy-biphenyl-4-yl)-thiophen-3-yl]-amide

Heat in a sealed tube with stirring propane-2-sulfonic acid{2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-thiophen-3-yl}-amide (0.5 mmol), 6-bromo-2,4-difluoro-3-hydroxy-benzonitrile (0.75 mmol), 2M Na_2CO_3 water solution (0.2 mL) and $\text{Pd}(\text{PPh}_3)_4$ (0.05 mmol) in 4.0 ml of a mixture of DME : Ethanol (2:1) to 80°C for 24 h. Filter the mixture through a small silica pad and eluted with EtOAc. Evaporate the filtrate and purify resultant compound by flash chromatography (Silica gel-methanol).

Stir the resultant product (271 mg, 0.604 mmol) with tetrabutylammonium iodide (313 mg, 0.847 mmol) in anhydrous dichloromethane at -78°C under nitrogen

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atmosphere. Add a solution of boron trichloride 1N in dichloromethane (5.0 ml, 5 mmol) over 2 min. Stir the resulting brown mixture for 5 min at -78°C and allow the mixture to warm up to room temperature over 1 h. Quench the reaction with crushed ice, stir for 30 min, neutralize with saturated aqueous solution of sodium bicarbonate until pH 7 and
5 extract the product with dichloromethane (x3). Wash the combined organic layers with water (x3), saturated aq. sodium chloride and dry over anhydrous sodium sulfate. Filter and concentrate to yield a crude brown oil. Purification by flash chromatography (Silica gel-hexane/EtOAc) and reverse phase purification yield the title compound. MS (ES-): 433 (M-1).

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Example 57

4-Oxo-4'-[4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-yl]-butyric acid

Heat in a sealed tube with stirring propane-2-sulfonic acid{2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-thiophen-3-yl}-amide (0.5 mmol), 4-(4-
15 Bromo-phenyl)-4-oxo-butyric acid (0.75 mmol), 2M Na₂CO₃ water solution (0.2 mL) and Pd(PPh₃)₄ (0.05 mmol) in 4.0 ml of an anhydrous DME to 100°C for 24 h. Evaporate and purify the filtrate by flash chromatography (Silica gel-hexane/EtOAc). Add NaOH 2M (1 ml) to a suspension of the resultant ester (0.128 mmol) in ethanol (1 ml) and stir 24 h. Add 6N HCl until pH is approximately 1 and a white solid precipitates. Filter the solid to
20 provide the title compound. MS (ES-): 456 (M-1).

Prepare the following compounds in a manner analogous to the procedure set forth in the above example:

EXAMPLE	COMPOUND	DATA MS (ES-):
58	Propane-2-sulfonic acid [2-(4'-chloro-2'-fluoro-biphenyl-4-yl)-thiophen-3-yl]-amide	418 (M-1)
59	2-Cyano-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-carboxylic acid	425 (M-1)
60	2-Methyl-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-carboxylic acid	414 (M-1)

EXAMPLE	COMPOUND	DATA MS (ES-):
61	2-Hydroxy-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-carboxylic acid	416 (M-1)
62	2-Ethoxy-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-carboxylic acid	444 (M-1)
63	2-Isopropoxy-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-carboxylic acid	458 (M-1)
64	2"-Ethoxy-2-(propane-2-sulfonylamino)-[1,1';4',1'']terphenyl-4"-carboxylic acid	438 (M-1)
65	2"-Fluoro-2-(propane-2-sulfonylamino)-[1,1';4',1'']terphenyl-4"-carboxylic acid	412 (M-1)
66	2-(Propane-2-sulfonylamino)-[1,1';4',1'']terphenyl-4"-carboxylic acid	394 (M-1)

Example 67

{6-Cyano-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-3-yloxy}-acetic acid

Heat (3-chloro-4-cyano-phenoxy)-acetic acid ethyl ester (120 mg, 0.50 mmol),
 5 propane-2-sulfonic acid {2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-thiophen-3-yl}-amide (204 mg, 0.50 mmol), 2M aqueous Na₂CO₃ solution (0.75 mL) and Pd(PCy₃)₂Cl₂ (55.4 mg, 0.075 mmol) in 1,4-dioxane (3.0 mL) to 80°C under nitrogen atmosphere for 20 h. Pour into 0.1 M HCl solution and adjust pH to 7, then extract with diethyl ether (3 x 50 mL) and dry the combined organic phases (MgSO₄) and concentrate
 10 to furnish a crude mixture as a yellowish solid. Purification by flash chromatography (Silica gel-Hexane/diethyl ether 1:1) yields 201 mg, 0.42 mmol (83%) of {6-Cyano-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-3-yloxy}-acetic acid ethyl ester as a pale yellow solid.

Prepare aqueous LiOH solution by dissolving 50 mg of LiOH in 1.0 mL of water.
 15 Add aqueous LiOH solution slowly to a solution of the above prepared ester (200 mg, 0.415 mmol) in THF (2.0 mL) and MeOH (1.0 mL). Stir the mixture at 60 °C for 3 h. Concentrate to remove the solvent. Dilute in H₂O (50 mL). Wash with dichloromethane (2x50 mL). Add 0.1 M HCl solution to adjust pH to 3. Extract with dichloromethane (2x50 mL) and diethyl ether (2x50 mL). Dry the combined organics and concentrate

under reduced pressure to yield 137mg, 0.300 mmol (72%) of the title compoundt. MS (m/e): 455.1 (M-1).

Example 68

5 Propane-2-sulfonic acid (2''-cyano-[1,1';4',1'']terphenyl-2-yl)-amide

Heat in a sealed tube with stirring propane-2-sulfonic acid (4'-bromo-biphenyl-2-yl)-amide (0.5 mmol), 2-(cyanophenyl)boronic acid (0.75 mmol), $K_3PO_4 \cdot H_2O$ (1.8 mmol) PPh_3 (0.12 mmol) and $Pd(OAc)_2$ (0.06 mmol) in 3.0 ml anhydrous deoxygenated 1,4 dioxane to 110°C for 4 h. Cool reaction mixture and maintain at RT overnight. Add
10 EtOAc and water and extract. Extract the aqueous phase with dichloromethane (3 x 20 mL) and dry the combined organic phases (Na_2SO_4) and concentrate to furnish a crude mixture. Purification by flash chromatography (Silica gel-hexane /EtOAc) yields the title compound. MS (ES-): 375 (M-1). Prepare the following compound in a manner substantially analogous to the procedure set forth in the above example:

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EXAMPLE	COMPOUND	DATA MS (ES-):
69	Propane-2-sulfonic acid (4''-cyano-[1,1';4',1'']terphen-yl-2-yl)-amide	375 (M-1)

Example 70

Propane-2-sulfonic acid [2-(propane-2-sulfonylamino)-[1,1';4',1'']terphenyl-2''-yl]-amide

Heat in a sealed tube with stirring 2-iodophenylamine (0.5 mmol), 2-(phenyl
20 isopropylsulfamid)boronic acid (0.75 mmol), 2M Na_2CO_3 water solution (0.2 mL) and $Pd(PPh_3)_4$ (0.05 mmol) in 4.0 ml of an anhydrous DME to 100°C for 24 h. Evaporate the organic solvent, prior to the addition of water (10 mL). Extract the mixture with dichloromethane (3 x 20 mL) and dry the combined organic phases (Na_2SO_4). Concentrate to furnish a crude mixture. Purify by flash chromatography (Silica gel-
25 hexane /EtOAc).

Add dropwise DBU drop wise (8.76 mL, 56.92 mmol) to a solution of the resultant amine (14.23 mmol) in dichloromethane (50ml) at 0°C, followed by drop wise

addition of isopropylsulfonyl chloride (3.29 mL, 28.46 mmol) and stir the reaction at room temperature for 24 h. Remove solvent under reduce pressure and purify the residue by silica and eluting with EtOAc:hexane 1:4 to EtOAc to provide the title compound (4.93 g, 98%). MS (ES-): 471 (M-1)

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Example 71

Propane-2-sulfonic acid [4-(3',5'-difluoro-4'-hydroxy-biphenyl-4-yl)-pyridin-3-yl]-amide

Dissolve 2,2-Dimethyl-propionic acid 3,5-difluoro-4'-[3-(propane-2-sulfonylamino)-pyridin-4-yl]-biphenyl-4-yl ester in THF (9 ml) and ethanol (1 ml). Add
10 NaOH 2N (10 ml) and heat the mixture to 60°C for 7 h. Evaporate solvents and add HCl 3N to acidify the mixture. Apply the acidic mixture to 2g SCX cartridge. Elute the SCX cartridge with methanol (x3) to remove non-basic impurities. Elute the product with 2N ammonia in methanol to afford, after evaporation, 55.2 mg of the title compound as a yellow solid (50% yield). MS (ES-): 403.

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Example 72

2-Cyano-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-carboxylic acid

Charge a 10 L double jacketed reactor equipped with mechanical stirring, set under inert atmosphere of argon with [2-(4-bromo-phenyl)-thiophen-3-yl]-carbamic acid tert-butyl ester (800 g, 2.25 mol) and EtOAc (3.2 L). Cool the yellow solution is down to
20 16.9°C and add a solution of 5-6N HCl/IPA (1600 mL) in 10 minutes via a dropping funnel between 10°C and 25°C. Heat the reaction mixture to 50°C. Stir the resulting suspension for 90 minutes at 50°C. Cool the suspension below 10 °C and add 2N NaOH solution (2773 mL) over 25 minutes, maintaining the temperature below 20°C. Add 2N
25 NaOH (450 mL) to reach a pH of 12-13. Separate the two layers by decantation. Re-extract the aqueous phase with EtOAc (500 mL). Dry the combined organic layers over MgSO₄ (200 g) and evaporate to dryness to yield 2-(4-Bromo-phenyl)-thiophen-3-ylamine (562.3g, 2.21 mol) as a beige solid.

¹H NMR (250 MHz, CDCl₃): 3.70 (s (broad), 2 H) 6.65 (d, 1 H, J=5.4 Hz), 7.06 (d, 1 H, J=5.2 Hz), 7.32 (d, 2 H, J= 8.9 Hz), 7.45 (d, 2H, J= 8.8 Hz).
30

Charge a double jacketed 20 L reactor equipped with mechanical stirrer and set under inert atmosphere of argon with 2-(4-Bromo-phenyl)-thiophene-3-ylamine (562 g, 2.21 mol) and CH₂Cl₂ (9.435 L). Obtain a clear solution. Add DBU (1.999 L) and cool the mixture to 9.4 °C. Add propane-2-sulfonyl chloride (0.616g) in 20 minutes

5 maintaining the temperature below 25 °C. Stir the reaction mixture 22 h at 20 °C. After completion of reaction, cool the reaction mixture to 11 °C and add an aqueous solution of satd. aq. NH₄Cl (7.65 L) cooled at 10 °C in 5 minutes. Heat the mixture to 20 °C and separate the aqueous phase. Wash the organic layer with 2N HCl (5.12 L), evaporate to dryness and take the residue into ethyl alcohol (800 g). Heat the mixture until complete

10 dissolution at 70 °C. Cool the solution to 41 °C and add water (1384 mL). Stir the suspension overnight at 22 °C, filter and wash two times with 254 mL of a 1/1 EtOH/H₂O mixture. Dry the resulting beige solid under vacuum at 26 °C for 4 days to give propane-2-sulfonic acid[2-(4-bromo-phenyl)-thiophene-3-yl]-amide (688 g, 1.9 mol). ¹H NMR (250 MHz, CDCl₃): 1.25 (d, 6 H, J=6.9 Hz), 3.16 (hept, 1 H, J= 6.9 Hz), 7.28 (pseudo s, 2

15 H), 7.33 (d, 2 H, J=8.5 Hz), 7.6 (d, 2 H, J= 8.5 Hz)

Charge a 10 L double jacketed reactor equipped with a mechanical stirrer, a reflux condenser and set under N₂ with propane-2-sulfonic acid[2-(4-bromo-phenyl)-thiophene-3-yl]-amide (688g, 1.91 mol), DMF (7.74 L), bis-(pinacolato)diboron (533 g, 2.09 mol), "PdCl₂dppf (78 g) and potassium acetate (562 g). Heat the resulting mixture to 80 °C for 1

20 h. Cool the mixture down to 20 °C. Quench the mixture with water (8650 mL) and extract with EtOAc (3440 mL). Re-extract the aqueous phase with EtOAc (4587 mL). Combine all the organic layers and evaporate to dryness to give 1420 g of crude material. Purify the crude material filtration on silica gel (7 kg), eluting with *n*-heptane: EtOAc (6:3) to yield after evaporation to dryness propane-2-sulfonic acid {2-[4-(4,4,5,5-tetramethyl-

25 [1,3,2]dioxaborolan-2-yl)-phenyl]-thiophen-3-yl}-amide as a yellow solid (747g). ¹H NMR (250 MHz, CDCl₃): 1.19 (d, 6H, J= 6.9 Hz), 1.37 (s, 12 H), 3.12 (hept, 1 H, J=6.9 Hz) 7.27 (d, 1 H, J= 5.2 Hz), 7.32 (d, 1 H, J=5.2 Hz) 7.43 (d, 1H, J=8.1 Hz), 7.89 (d, 2 H, J=8.1 Hz).

Charge a 10 L double jacketed reactor with a mechanical stirrer and a reflux

30 condenser with 4-hydroxy benzoic acid ethyl ester (967 g, 8.81 mol) and acetic acid (5.8 L). Heat the mixture to 65 °C and add a solution of ICl (1010 g) in acetic acid (1 L) in ½

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h. Stir the resulting mixture at 60-62 °C for 16 h. Cool the black solution to 20 °C and transfer on water (5 L) and ice (7.5 kg). Stir the resulting suspension over 1 h at 20 °C, filter and wash the cake with water (2 L) and cyclohexane (6 L). Dry the solid under vacuum at 55 °C till constant weight to give 4-hydroxy-3-iodo-benzoic acid ethyl ester (1372.8 g, 4.70 mol). ¹H NMR (250 MHz, CDCl₃) : 1.38 (t, *J*=7.1 Hz, 3H), 4.35 (quartet, *J*=7.1 Hz, 2H), 5.8 (s, 1H), 7.01 (d, *J*=8.5 Hz, 1H), 7.95 (dd, *J*=8.5 Hz, 2.0 Hz, 1H), 8.37 (d, *J*=2Hz, 1 H).

Charge a 10 L double jacket reactor, equipped with a mechanical stirrer, a reflux condenser and set under N₂ with 4-hydroxy-3-iodo-benzoic acid ethyl ester (1312g, 4.49 mol), dimethylsulfoxide (3277 mL) and CuCN (442.3 g). Heat the mixture to 105 °C and hold at this temperature for 2.5 h. Cool the brown solution down to 20 °C. Add water at 48 °C water (6.5 L) Filter the mixture at 20 °C, then wash the cake with water (2 L). Suspend the cake in EtOAc (5 L) and stir during 1 h at 20 °C. Filter the suspension on Hyflo Super Cel[®] (250 g) and rinse with EtOAc (3 L). Decant the filtrates, then evaporate the organic layer to dryness. Take the residue up in *n*-heptane (10 L). Distill off 2 L of *n*-heptane, then add CH₂Cl₂ (400 mL). Cool the mixture cooled to 27 °C, filter and rinse the cake with *n*-heptane (2 L). Dry 48 h at 55°C under pressure to give 4-hydroxy-3-cyano-benzoic acid ethyl ester. (777.7 g, 4.067 mol). ¹H NMR (250 MHz, DMSOd): 1.32 (t, *j*=7.1 Hz, 3H), 4.3 (q, *j*=7.1 Hz, 2H), 7.13 (d, *j*=8.8 Hz, 1H), 8.07 (dxd, *j*=8.8 Hz, 2.2 Hz, 1H), 8.16 (d, *j*=2.2Hz), 12.11 (s (broad), 1H).

Charge a 20 L double jacketed reactor equipped with mechanical stirrer, set under inert atmosphere of argon with 4-hydroxy-3-cyano-benzoic acid ethyl ester (720 g, 3.766 mol) and CH₂Cl₂. Cool the brown suspension to 5 °C and add Et₃N (792 mL) resulting in a brown solution. Add DMAP (69.1 g) at 5°C. Add Trifluoromethanesulfonic anhydride (950 mL) over 25 min while maintaining the temperature between 2°C and 23 °C. Stir for ½ h at 20 °C, then add 1N HCl (8 L). Separate the aqueous and organic layers and wash the organic layer with a 10 % aqueous NaHCO₃ solution (8 L). Treat the organic layer with 300 g MgSO₄ and evaporate to dryness to give 3-cyano-4-trifluoromethoxycarbonyloxy-benzoic acid ethyl ester as a brown solid (1218.7 g, 3.77 mol). ¹H NMR (250 MHz, CDCl₃) : 1.52 (t, *J*=7.1 Hz, 3H), 4.55 (q, *J*=7.1 Hz, 2H), 7.69 (d, *J*=8.8 Hz, 1H), 8.49 (dxd, *J*=8.8 Hz, *J*=2.2 Hz, 1H), 8.55 (d, *J*=2.2 Hz, 1H)

Charge a 10 L double jacketed reactor equipped with mechanical stirrer, a reflux condenser and set under N₂ with palladium acetate (41 g) and DME (6.29L). Add triphenylphosphine (190 g) to the orange solution. A yellow precipitate forms. Stir the mixture for 15 minutes at 20 °C. Add propane-2-sulfonic acid {2-[4-(4,4,5,5-tetramethyl-
5 [1,3,2]dioxaborolan-2-yl)-phenyl]-thiophen-3-yl}-amide (747 g; 1.83 mol), 3-cyano-4-trifluoromethoxycarbonyloxy-benzoic acid ethyl ester (822g, 2.54 mol), ethyl alcohol (3.14 L) and 2N aqueous Na₂CO₃ (1.82 L) and heat the mixture is heated to reflux. After 1h, further addition of 3-cyano-4-trifluoromethoxycarbonyloxy-benzoic acid ethyl ester may be necessary to complete consumption of propane-2-sulfonic acid {2-[4-(4,4,5,5-
10 tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-thiophen-3-yl}-amide. Cool the dark brown mixture to 20 °C, quench with H₂O (9250 mL) and extract with CH₂Cl₂ (9250 mL). Wash the separated organic layer two times with 7L of 1N aqueous Na₂CO₃ and evaporate to dryness to give 1126 g of oil. Dissolve the crude oil into ethyl alcohol (4.1 L) and transfer to a 10 L reactor vessel under inert atmosphere. Add H₂O (6.6 L) and 9N
15 NaOH solution (1.9 L) at 20 °C. Heat the brown mixture to 50 °C and stir during 1h. Cool the mixture and evaporate under reduced pressure in a 20 L rotavapor flask. Distill off 2 L of ethanol while adding 37% HCl (1500 mL) slowly to the mixture during the distillation. Control pH and add 200 ml of 37% HCl reach pH 0-1. Continue the distillation until 5 to 6L of distillate is obtained. Cool the resulting residue down between 10 and 20 °C and
20 add CH₂Cl₂ (1332 mL). Stir the mixture over 4 h at 21 °C, filter and wash with H₂O (400 mL) and CH₂Cl₂ (400ml). Dry the brown solid under vacuum at 55 °C during 16 h to yield 546.3g of the title compound. ¹H NMR (250 MHz, DMSO-d): δ ppm 1.32(t, J=6.6 Hz, 6H) 3.26 (septet, J=6.6 Hz, 1H) 7.32 (d, J=5.4 Hz, 1H) 7.79 (d, J=5.4 Hz, 1H) 7.93 (d, J=8.2 Hz, 1H) 8.01 (d, J=7.9, 1H) 8.04 (d, J=8.2 Hz, 2H) 8.48 (dd, J=8.2 Hz, 2.2 Hz, 1H) 9.5 (s, 1H), 13.79 (s(broad), 1 H).
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Example 73

2-Ethoxy-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-carboxylic acid

Prepare the title compound by coupling propane-2-sulfonic acid {2-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-thiophen-3-yl}-amide with 3-ethoxy-4-
30 iodo-benzoic acid ethyl ester (31.5 g, 98.3 mmol) in a manner analogous the procedure set

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forth in Preparation 4 utilizing $\text{PdCl}_2(\text{dppf})$ and Na_2CO_3 at a reaction temperature of 60°C . The resultant ester may be hydrolyzed in the following manner: Mix 2-ethoxy-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-carboxylic acid ethyl ester (38 g, 80 mmol), in ethanol (100 mL) and NaOH 2 M in water (400 mL) and stir the reaction

- 5 mixture for one hour at RT. Evaporate the ethanol and wash the aqueous mixture with 200 mL of EtOAc. Acidify the aqueous mixture to pH 2 using HCl 1N. Extract the desired product with EtOAc. Dissolve the crude in warmed acetone (500 mL) and add water (600 mL), maintaining the temperature at 55°C . Stir the mixture at 60°C for 1 hour and then to RT. overnight. Filtrate the precipitate and dry under vacuum at 45°C
- 10 overnight. Yield 28 g, 78 %. ^1H NMR (300 MHz, DMSO): δ 1.14 (d, $J = 7.0$ Hz, 6H), 1.31 (t, $J = 7.0$ Hz, 3H), 3.06 (sept, $J = 7.0$ Hz, 1H), 4.13 (q, $J = 7.0$ Hz, 2H), 7.10 (d, $J = 5.3$ Hz, 1H), 7.48 (d, $J = 7.6$ Hz, 1H), 7.54 (d, $J = 5.3$ Hz, 1H), 7.58-7.68 (m, 4H), 7.72 (d, $J = 8.4$ Hz, 2H), 9.22 (bs, 1H), 13.04 (bs, 1H).

- To prepare 3-ethoxy-4-iodo-benzoic acid ethyl ester, reflux 3-hydroxy-4-iodo-
- 15 benzoic acid (38 g, 144 mmol) and saturated solution of HCl in ethanol (600 mL) overnight. Evaporate the solvent yielding 42 g, 99 % of 3-hydroxy-4-iodo-benzoic acid ethyl ester. ^1H NMR (300 MHz, CDCl_3): δ 1.39 (t, $J = 7.1$ Hz, 3H), 4.36 (q, $J = 7.1$ Hz, 2H), 7.33 (dd, $J = 8.3$ and 2.0 Hz, 1H), 7.64 (d, $J = 2.0$ Hz, 1H), 7.75 (d, $J = 8.3$ Hz, 1H). Add ethyl iodide (33.8 g, 216 mmol) to a solution of 3-hydroxy-4-iodo-benzoic acid ethyl
- 20 ester (42 g, 144 mmol) and K_2CO_3 (39.9 g, 288 mmol) in acetonitrile (400 mL) under magnetic stirring. Heat the reaction mixture at 65°C for 2 hours, allow the mixture to cool and maintain at RT overnight. Evaporate the solvent and add ethyl acetate to the crude. Filter the solid through Celite® and evaporate the solvent. Yield 42 g, 96 %. ^1H NMR (300 MHz, CDCl_3): δ 1.39 (t, $J = 7.1$ Hz, 3H), 1.50 (t, $J = 7.0$ Hz, 3H), 4.16 (q, $J = 7.0$ Hz, 2H), 4.37 (q, $J = 7.1$ Hz, 2H), 7.36 (dd, $J = 8.1$ and 1.8 Hz, 1H), 7.42 (d, $J = 1.8$ Hz, 1H),
- 25 7.84 (d, $J = 8.1$ Hz, 1H).

Example 74

Propane-2-sulfonic acid{2-[4'-1H-tetrazol-5-yl]-biphenyl-4-yl}-thiophen-3-yl}-amide

- Heat in a sealed tube with stirring propane-2-sulfonic acid-[2-(4'-cyano-biphenyl-
- 30 4-yl)-thiophen-3-yl]-amide (0.5 mmol), Bu_3SnN_3 (2.0 mmol) to 100°C for 24 h. If necessary, add toluene or dichloromethane to help complete the reaction. (1.0 mL of

dichloromethane added). Evaporate the organic solvent, if added, prior to the addition of water (10 mL). Extract the mixture with dichloromethane (3 x 20 mL) and dry the combined organic phases (Na₂SO₄). Concentrate to furnish a crude mixture. Purification by flash chromatography (Silica gel-CH₂Cl₂/Methanol 8:1) yields the title compound.

5 MS (ES-): 424 (M-1).

Prepare the following compounds in a manner analogous to the procedure described in the above example:

EXAMPLE	COMPOUND	DATA MS (ES-):
75	Propane-2-sulfonic acid {2-[3'-(1H-tetrazol-5-ylmethyl)-biphenyl-4-yl]-thiophen-3-yl}-amide (dichloromethane 1.0 mL)	438 (M-1)
76	Propane-2-sulfonic acid [2-(1H-tetrazol-5-yl)-[1,1';4',1'']terphenyl-2''-yl]-amide (toluene 1.0 mL dichloromethane 1.0 mL)	418 (M-1)
77	Propane-2-sulfonic acid [4''-(1H-tetrazol-5-yl)-[1,1';4',1'']terphenyl-2-yl]-amide (toluene 0.5 mL)	418 (M-1).

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Example 78

Propane-2-sulfonic acid {2-[3-cyano-4'-(1H-tetrazol-5-yl)-biphenyl-4-yl]-thiophen-3-yl}-amide

Add NaN₃ (4.5 mmol) and a 1M solution of SiCl₄ (1.5 mmol) in DCM to a solution of 2-Cyano-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-carboxylic acid amide (1.5 mmol) in acetonitrile (50 mL). Stir 15 h at 70°C. Concentrate to dryness under reduced pressure. Dissolve resultant residue in 20 ml of NH₄Cl and extract with DCM and the aqueous with EtOAc. Concentrate all organic layers to dryness. Purify by HPLC to provide the title compound. MS (ES-):449(M-1).

20 Prepare the following compounds in a manner analogous to the procedure set forth in the above example:

EXAMPLE	COMPOUND	DATA MS (ES-):
79	Propane-2-sulfonic acid {2-[2'-(propane-2-sulfonylamino)-4'-(1H-tetrazol-5-yl)-biphenyl-4-yl]-thiophen-3-yl}-amide	545 (M-1)
80	Propane-2-sulfonic acid {2-[4'-cyano-2'-(propane-2-sulfonylamino)-biphenyl-4-yl]-thiophen-3-yl}-amide	502 (M-1)

Example 81

2-(Propane-2-sulfonylamino)-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-carboxylic acid methylamide

5

Add oxalyl chloride (0.12 mmol) to a suspension of 2-(Propane-2-sulfonylamino)-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-carboxylic acid (0.1 mmol) and DMF (0.05 mmol) in dichloromethane at 0°C. Stir 1h at RT. Concentrate to dryness under reduced pressure. Dissolve resultant residue in 3 ml CH₂Cl₂ and add (2.8mmol) of MeNH₂ (2M in THF). Concentrate the reaction to dryness and purify by flash chromatography (Silica gel- eluting with 5%MeOH / CH₂Cl₂). Concentrate the desired fractions to provide the title compound. MS (ES-): 534 (M-1).

10

Prepare the following amides in a manner substantially analogous to the procedure set forth in the above example:

15

EXAMPLE	COMPOUND	DATA MS (ES-):
82	2-Cyano-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-carboxylic acid amide	424 (M-1).
83	2-(Propane-2-sulfonylamino)-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-carboxylic acid amide	520 (M-1)

Example 84

2-Cyano-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-carboxylic acid
methylamide

Add thionyl chloride (0.2 mmol) to a suspension of 2-Cyano-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-carboxylic acid (0.1 mmol) in dichloromethane at RT. Stir mixture for 1 h at 50°C and concentrate to dryness under reduced pressure. Add to the resultant residue 0.5 mmol MeNH₂ (2M in THF). Concentrate the reaction to dryness and purify with flash chromatography (Silica gel-5%MeOH / CH₂Cl₂). Concentrate the desired fractions to provide the title compound. MS (ES⁻):438 (M-1).

10

Example 85

Propane-2-sulfonic acid [2-(5'-amino-3'-fluoro-biphenyl-4-yl)-thiophen-3-yl]-amide

Add SnCl₂·2 H₂O (8.5 mmol) to a solution of propane-2-sulfonic acid [2-(3'-fluoro-5'-nitro-biphenyl-4-yl)-thiophen-3-yl]-amide (1.2 mmol) in EtOH (40 mL). Heat the reaction at 70°C for 30 min and then at room temperature overnight. Add a saturated solution of NaHCO₃ (pH=11-12) and extract with EtOAc (2x50 mL). Dry over NaSO₄, filter and evaporate to dryness to provide the title compound. MS (ES⁻): 389 (M-1).

15

Prepare the following compound in a manner analogous to the procedure set forth in the above example:

EXAMPLE	COMPOUND	DATA MS (ES ⁻):
86	Propane-2-sulfonic acid [2-(3'-amino-4'-fluoro-biphenyl-4-yl)-thiophen-3-yl]-amide	389 (M-1)

20

Example 87

Propane-2-sulfonic acid [2-(4'-methylaminomethyl-biphenyl-4-yl)-thiophen-3-yl]-amide

Mix propane-2-sulfonic acid [2-(4'-formyl-biphenyl-4-yl)-thiophen-3-yl]-amide (0.16 mmol) in 1,2-dichloroethane (2ml) and add methylamine 2N in THF (0.16ml, 0.32 mmol) at room temperature. Stir the resulting solution for 5 min before adding Na(OAc)₃BH (0.32 mmol). Stir the mixture at room temperature for 16 h. Analyze by LC/MS for final product. Add saturated NaHCO₃ aqueous solution and dichloromethane

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and filter the mixture through hydrophobic filter. Evaporate the filtrate and apply the residue to SCX cartridge, elute with MeOH/DCM to remove non-basic materials, followed by 2N NH₃ in MeOH to give a crude product. Purify by flash chromatography (Silica gel-Dichloromethane/Methanol 7:1) to yield the title compound. MS (ES-):

5 399(M-1).

Example 88

Propane-2-sulfonic acid (2-{2',2'-bis-[(propane-2-sulfonylamino)-methyl]-biphenyl-4-yl}-thiophen-3-yl)-amide, and propane-2-sulfonic acid (2-{2'-[(propane-2-sulfonylamino)-methyl]-biphenyl-4-yl}-thiophen-3-yl)-amide

10

Slowly add a solution of BH₃Me₂S (0.05ml, 0.5 mmol, 2eq.) in 1.5 mL of THF to a solution of 95mg of propane-2-sulfonic acid [2-(2''-cyano-biphenyl-4-yl)-thiophen-3-yl]-amide (0.25mmol, 1 eq.) in 1.5 mL of THF. Heat the mixture to reflux for 2 h and then cool to RT. Decompose the excess borane by adding 0.1mL of methanol and then a mixture of 0.1 mL of methanol and 0.03mL of hydrochloride solution. Reflux the reaction for another 15min. Remove the solvent and add 6 mL of ethanol to remove the thioether. Suspend the solid in 20 mL of saturated aq. sodium chloride and basify with ammonia. Extract with EtOAc(3x10), dry, and remove solvent. Purification by flash chromatography (Silica gel-hexane/EtOAc) affords propane-2-sulfonic acid [2-(2'-aminomethyl-biphenyl-4-yl)-thiophen-3-yl]-amide (100 mg, 62%). MS (m/e): 387.2(M+1).

15

20

Add 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU) drop wise (85mg, 0.6mmol) to a suspension of propane-2-sulfonic acid [2-(2'-aminomethyl-biphenyl-4-yl)-thiophen-3-yl]-amide (57mg, 0.15 mmol) in dichloromethane (2ml) at 0°C, followed by drop wise addition of isopropylsulfonyl chloride (42mg, 0.3 mmol) and stir the reaction at room temperature overnight. Remove solvent under reduce pressure. Purify with flash chromatography (Silica gel-hexane/EtOAc). Concentrate the desired fractions to provide propane-2-sulfonic acid (2-{2'-[(propane-2-sulfonylamino)-methyl]-biphenyl-4-yl}-thiophen-3-yl)-amide. MS (m/e): 491.1(M-1), propane-2-sulfonic acid (2-{2',2'-bis-[(propane-2-sulfonylamino)-methyl]-biphenyl-4-yl}-thiophen-3-yl)-amide. MS (m/e): 510.2(M-1).

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Example 894'-[5-Chloro-3-(propane-2-sulfonylamino)-thiophen-2-yl]-2-cyano-biphenyl-4-carboxylic acid

5 Dissolve 2-cyano-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-carboxylic acid (0.021 g) in dry tetrahydrofuran (0.5 mL) at 0°C and add N-chlorosuccinimide (0.007 g). Allow the reaction mixture to reach RT and stir for 72 h. Add diethyl ether, concentrate *in vacuo* and purify by Strata® silica gel cartridges, eluting with dichloromethane-methanol gradient. Purify by reverse phase HPLC to give 0.004 g
10 of the title compound as a white solid. MS (ES-) (m/z): 459 (M-1).

Example 90Propane-2-sulfonic acid [2-(2'-cyano-4'-methanesulfonylaminocarbonyl-biphenyl-4-yl)-thiophen-3-yl]-amide

15 Add methanesulfonamide (0.28 mmol), EDCI (0.28 mmol) and DMAP (0.28 mmol) to a solution of 2-Cyano-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-biphenyl-4-carboxylic acid (0.235 mmol) in DCM. Stir 8 h at RT. Add 1N HCl and extract with DCM. Concentrate all organic layers to dryness. Purify by HPLC to provide the title compound. MS (ES-): 502 (M-1)
20

Example 915-Methylsulfanyl-3'-(propane-2-sulfonylamino)-[1,1':4,1'']terphenyl-2-carboxylic acid

Mix 4-Methylsulfanyl-2-trifluoromethanesulfonyloxy-benzoic acid methyl ester (1.216 g, 3.682 mmol), 4,4,5,5-Tetramethyl-1,3,2-dioxaborolane (0.85ml, 5.682), Et₃N (1.55ml, 11.121 mmol) and acetonitrile (40 ml) then heat to reflux for 16 hours. Dilute
25 the reaction with EtOAc and wash with water. Concentrate under reduced pressure. Next add propane-2-sulfonic acid (4'-bromo-biphenyl-2-yl)-amide (0.532g, 1.502mmol) 2N Na₂CO₃ (7ml, 14 mmol), 1, 4-dioxane (35ml) and tetrakis triphenyl phosphine palladium (0.177g, 0.153 mmol). Heat to 80°C for 16 hours. Cool the reaction, dilute with EtOAc,
30 and wash with H₂O, followed by saturated aqueous sodium chloride. Dry with Na₂SO₄ and concentrate under reduced pressure. Purify the reaction by flash chromatography

(Silica gel-toluene then up to 20% EtOAc/Hexane) to give 5-Methylsulfanyl-3''-(propane-2-sulfonylamino)-[1,1';4',1'']terphenyl-2-carboxylic acid methyl ester (0.431 g, 63%). MS (m/e): 456(M+1).

Mix the resultant ester (0.120 g, 0.263 mmol), 1N NaOH (1 ml, 1 mmol) and MeOH (1 ml) heat flask to reflux for 1 hour and stir for 16 hours. Next add 0.2N HCl (5 ml, 1 mmol) and cool in ice bath. Filter the solid. Obtain 5-Methylsulfanyl-3''-(propane-2-sulfonylamino)-[1,1';4',1'']terphenyl-2-carboxylic acid (0.090 g, 77%). MS (m/e): 442(M+1).

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Example 92

6-Cyano-5-methylsulfanyl-3''-(propane-2-sulfonylamino)-[1,1';4',1'']terphenyl-2-carboxylic acid

Mix 2''-Amino-6-cyano-5-methylsulfanyl-[1,1';4',1'']terphenyl-2-carboxylic acid (0.195 g, 0.521 mmol) and dichloromethane (6 ml) then cool to 0°C. Next add DBU (0.33 ml, 2.162 mmol), and ClSO₂CH(CH₃)₂ (0.13 ml, 1.128 mmol) drop wise to the solution and stir for 16 hours. If TLC shows remaining SM, add DBU (0.3ml) and ClSO₂CH(CH₃)₂ (0.1ml) and stir for 16 hours. Dilute the reaction with CH₂Cl₂ (50ml) and wash with H₂O, satd aq. sodium chloride, dry with Na₂SO₄, and concentrate under reduced pressure. Analyze by TLC and if reaction has remaining SM add MeOH (2ml) and 1N NaOH (1ml, 1mmol). Heat to reflux for 6 hours. Add 1N HCL (1ml, 1mmol) and extract into dichloromethane. Purify the reaction by flash chromatography (Silica gel - dichloromethane then up to 10% MeOH/ dichloromethane), to give 6-Cyano-5-methylsulfanyl-3''-(propane-2-sulfonylamino)-[1,1';4',1'']terphenyl-2-carboxylic acid (0.008 g). MS (m/e): 467(M+1).

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Example 93

Propane-2-sulfonic acid (2-biphenyl-4-yl-2H-pyrazol-3-yl)-amide

Add cesium fluoride (0.221g, 1.45mmol) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (0.024g, 0.029 mmol) to a mixture of propane-2-sulfonic acid [2-(4-bromo-phenyl)-2H-pyrazol-3-yl]-amide (0.100g, 0.290mmol) and 2-cyanophenylboronic acid (0.043g, 0.290mmol) in anhydrous 1,2-dimethoxyethane (5.0mL). Deoxygenate the mixture three

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times, immerse into a pre-heated (85°C) oil bath, and stir for 30h. Dilute the mixture with water and dichloromethane, filter through Celite®, and wash through with dichloromethane. Concentrate the mixture, re-dissolve in dichloromethane, adsorb onto silica gel, and subject to silica gel flash column chromatography (12g column, eluting with a gradient of 0-10% methanol/dichloromethane for 40 min., followed by (20% 2.0M NH₃ in methanol/dichloromethane) to yield the title product as a light brown solid (0.036g, 34%); mass spectrum (m/e): 367.0 (M+1), 365.0 (M-1).

Example 94

10 Propane-2-sulfonic acid (2-biphenyl-4-yl-2H-pyrazol-3-yl)-amide

Add cesium fluoride (0.221g, 1.45mmol) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (0.024g, 0.029 mmol) to a mixture of propane-2-sulfonic acid [2-(4-bromo-phenyl)-2H-pyrazol-3-yl]-amide (0.100g, 0.290mmol) and 2-cyanophenylboronic acid (0.043g, 0.290mmol) in anhydrous 1,2-dimethoxyethane (5.0mL). Deoxygenate the mixture thrice, immerse into a pre-heated (85°C) oil bath, and stir for 30h. Dilute the mixture with water and dichloromethane, filter through Celite®, and wash through with dichloromethane. Concentrate the mixture, re-dissolve in dichloromethane, adsorb onto silica gel, and subject to silica gel flash column chromatography (12g column, eluting with a gradient of 0-10% methanol/dichloromethane for 40 min., followed by (20% 2.0M NH₃ in methanol/dichloromethane) to yield the title product as a light brown solid (0.036g, 34%); mass spectrum (m/e): 367.0 (M+1), 365.0 (M-1).

25 General Procedure for the Preparation of Salts and Crystals

A master plate is prepared with 250 µL of the free acid of the subject compound in methanol (0.1 M) added to all wells set in a 96 well format. An array of bases is dispensed to each well in one and two molar equivalents. The solvents are evaporated from all 96 wells using a Genevac Series II evaporator leaving solid residue in the master plate. An array of solvents is dispensed to each one of these wells through a cap mat and then heated to 55°C with stirring and allowed to equilibrate for 60 - 90 minutes at about

55°C. Each sample is then filtered hot and transferred to corresponding wells in an evaporation plate, a precipitation plate, and a cooling plate. The evaporation plate is prepared by transferring 200 μ L of the filtrate from the master plate using 55°C heated syringes to the open well titer plate and is then allowed to evaporate to dryness over night at room temperature and ambient humidity. The precipitation plate is prepared by adding 100 μ L of the filtrate from the master plate using 55°C heated syringes to capped 96 well titer plate where each well contains an anti-solvent of 200 μ L of heptane or 2-propanol. After equilibrating for a period of nine hours at room temperature, the excess solution is wicked away using pre-cut Whatman filter paper. The cooling plate is prepared by transferring 200 μ L of the filtrate from the master plate to individual wells using 55°C heated syringes in a capped titer plate, and cooling exponentially from 55 to 10°C over a period of 8 hours. Photomicrographs are collected on the material at the bottom of each well in the 96 well plates using a Zeiss Axiovert 200M inverted incident-light microscope with a 2.5X objective. If the material is crystalline, it exhibits birefringence that is displayed as white against a dark background. Amorphous solids appear dark or as opaque droplets or rings.

The ability of compounds of Formula I to potentiate glutamate receptor-mediated response can be determined by one of ordinary skill in the art. For example, see U.S. Patent No. 6,303,816. In particular, the following test may be utilized:

HEK293 cells stably expressing human iGluR4 (obtained as described in European Patent Application Publication No. EP-A1-0583917) are used in the electrophysiological characterization of AMPA receptor potentiators. The extracellular recording solution contains (in mM): 140 NaCl, 5 KCl, 10 HEPES, 1 MgCl₂, 2 CaCl₂, 10 glucose, pH = 7.4 with NaOH, 295 mOsm kg⁻¹. The intracellular recording solution contains (in mM): 140 CsCl, 1 MgCl₂, 10 HEPES, (N-[2-hydroxyethyl]piperazine-N1-[2-ethanesulfonic acid]) 10 EGTA (ethylene-bis(oxyethylene-nitrilo)tetraacetic acid), pH = 7.2 with CsOH, 295 mOsm kg⁻¹. With these solutions, recording pipettes have a resistance of 2-3 M Ω . Using the whole-cell voltage clamp technique (Hamill et al.(1981)Pflügers Arch., 391: 85-100), cells are voltage-clamped at -60mV and control current responses to 1 mM glutamate are evoked. Responses to 1 mM glutamate are then

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determined in the presence of test compound. Compounds are deemed active in this test if, at a test concentration of 10 μ M or less, they produce a greater than 10% increase in the value of the current evoked by 1 mM glutamate.

In order to determine the potency of test compounds, the concentration of the test compound, both in the bathing solution and co-applied with glutamate, is increased in half log units until the maximum effect was seen. Data collected in this manner are fit to the Hill equation, yielding an EC_{50} value, indicative of the potency of the test compound. Reversibility of test compound activity is determined by assessing control glutamate 1mM responses. Once the control responses to the glutamate challenge are re-established, the potentiation of these responses by 100 μ M cyclothiazide is determined by its inclusion in both the bathing solution and the glutamate-containing solution. In this manner, the efficacy of the test compound relative to that of cyclothiazide can be determined. The exemplified compounds were tested essentially as described above and were found to have EC_{50} values less than or equal to 3.0 μ M. The following compounds were tested essentially as described above and were found to have the following activity:

EXAMPLE	EC_{50} (μ M)
56	0.151
73	0.145
11	0.720
51	2.463
77	0.445
72	0.188
46	0.977

In addition, certain behavioral despair animal models, which can be practiced by one of ordinary skill in the art to evaluate compounds of the present invention, are predictive of antidepressant activity in man, such as the Forced Swim Test and the Tail Suspension Test. For example, see "Experimental Approaches to Anxiety and

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Depression", Edited by J.M. Elliott, et al., (1992), John Wiley & Sons Ltd., Chapter 5, *Behavioural Models of Depression*, Porsolt and Lenegre, pages 73-85.

The pharmaceutical compositions of the present invention are prepared by known procedures using well-known and readily available ingredients. In making the
5 compositions of the present invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier, and may be in the form of a capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be a solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active ingredient. The compositions can be in the form of tablets, pills, powders,
10 lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments containing, for example, up to 10% by weight of active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

Some examples of suitable carriers, excipients, and diluents include lactose,
15 dextrose, sucrose, sorbitol, mannitol, starches, gum, acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, micro-crystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, methyl cellulose, methyl and propyl hydroxybenzoates, talc, magnesium stearate, and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents,
20 sweetening agents, or flavoring agents. Compositions of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 0.1 mg to about 300 mg, preferably about 0.1 mg to about 100 mg,
25 and most preferably about 1.0 to about 100 mg of compound of Formula I. The term "unit dosage form" refers to a physically discrete unit suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier, diluent, or excipient.

30 As used herein the term "patient" refers to a mammal, such as a mouse, guinea pig, rat, dog or human. It is understood that the preferred patient is a human.

As used herein, the terms "treating" or "to treat" or "treatment" each mean to alleviate symptoms, eliminate the causation either on a temporary or permanent basis, or to prevent or slow the appearance of symptoms of the named disorder. As such, the methods of this invention encompass both therapeutic and prophylactic administration.

5 As used herein, the term "effective amount" refers to the amount of a compound of Formula I which is effective, upon single or multiple dose administration to a patient, in treating the patient suffering from the named disorder.

An effective amount can be readily determined by the attending diagnostician, as one skilled in the art, by the use of known techniques and by observing results obtained
10 under analogous circumstances. In determining the effective amount or dose, a number of factors are considered by the attending diagnostician, including, but not limited to: the species of mammal; its size, age, and general health; the specific disease or disorder involved; the degree of or involvement or the severity of the disease or disorder; the response of the individual patient; the particular compound administered; the mode of
15 administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances.

The compound of Formula I can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, bucal or intranasal routes. Alternatively, the compound of Formula I may be administered by continuous
20 infusion. A typical daily dose will contain from about 0.005 mg/kg to about 10 mg/kg of the compound of Formula I. Preferably, daily doses will be about 0.005 mg/kg to about 5 mg/kg, more preferably from about 0.005 mg/kg to about 2 mg/kg.

The dosages of the drugs used in the combinations set forth herein, must also, in the final analysis, be set by the physician in charge of the case, using knowledge of the
25 drugs, the properties of the drugs in combination as determined in clinical trials, and the characteristics of the patient, including diseases other than that for which the physician is treating the patient.

The inert ingredients and manner of formulation of the adjunctive pharmaceutical compositions are conventional. The usual methods of formulation used in pharmaceutical
30 science may be used here. All of the usual types of compositions may be used, including tablets, chewable tablets, capsules, solutions, parenteral solutions, intranasal sprays or

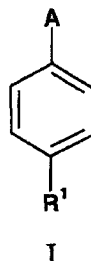
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powders, troches, suppositories, transdermal patches and suspensions. In general, compositions contain from about 0.5% to about 50% of the compounds in total, depending on the desired doses and the type of composition to be used. The amount of the compounds, however, is best defined as the effective amount, that is, the amount of
5 each compound which provides the desired dose to the patient in need of such treatment.

For example, a formulation may include 1% carboxymethylcellulose sodium, 0.25% polysorbate 80 and 0.05% Dow Corning Antifoam 1510-US in purified water) through the oral route. For the IV administration, a composition of 5% pharماسolve, 0.4% 1N NaOH, 94.6% Dextrose 5% in water may be used.

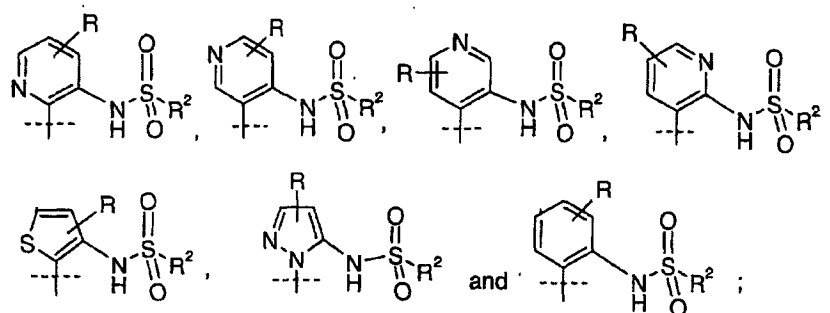
WE CLAIM:

1. A compound of Formula I:



5 where:

A is selected from the group consisting of



R is H, halo, -COOH, or -CH₂COOH;

10 R¹ is phenyl optionally substituted with a first substituent selected from the group consisting of halo, cyano, C₁-C₄ acyl, -COOH, -NHR³, C₁-C₂ alkyl substituted with -NHCH₃, -N(SO₂(C₁-C₃ alkyl))₂, -COOH, -CONH₂, cyano, hydroxy, or tetrazol-5-yl, -OCH₂COOH, -SCH₂COOH, -C(O)CH₂CH₂COOH, -SO₂NH₂, tetrazol-5-yl, and 1,2,4-triazol-1-yl; optionally further substituted with a second substituent selected from the
 15 group consisting of: halo, trifluoromethyl, cyano, nitro, C₁-C₄ alkoxy, hydroxy, C₁-C₄ alkyl, C₁-C₄ alkylthio, -NHCH₂CN, -OCH₂CN, -NHSO₂CH(CH₃)₂, and -C(O)NHR⁴; optionally further substituted with a third substituent selected from the group consisting of halo and cyano; optionally further substituted with a fourth substituent selected from the group consisting of halo;

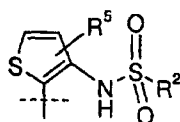
20 R² is C₁-C₄ alkyl or dimethylamino;

R³ is -SO₂(C₁-C₃ alkyl), C₁-C₄ acyl, C₁-C₄ alkyl, or hydrogen;

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R^4 is hydrogen, C_1 - C_4 alkyl, or $-SO_2(C_1$ - C_4 alkyl); or a pharmaceutically acceptable salt thereof.

5 2. A compound of Claim 1 where A is



3. A compound of Claim 2 where R^2 is isopropyl.

4. The compound 2-Cyano-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-
10 biphenyl-4-carboxylic acid, or a pharmaceutically acceptable salt thereof.

5. The compound 2-Ethoxy-4'-[3-(propane-2-sulfonylamino)-thiophen-2-yl]-
biphenyl-4-carboxylic acid, or a pharmaceutically acceptable salt thereof.

15 6. A pharmaceutical formulation comprising a compound of any of claims 1-5 in
combination with a pharmaceutically acceptable carrier, diluent or excipient.

7. The use of a compound of any of claims 1-5 for the manufacture of a
medicament for the treatment of Alzheimer's disease.

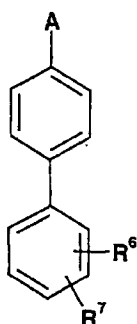
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8. The use of a compound of any of claims 1-5 for the manufacture of a
medicament for the treatment of Parkinson's disease.

9. The use of a compound of any of claims 1-5 for the manufacture of a
25 medicament for the treatment of mild cognitive impairment.

10. A compound of Formula I for use as a pharmaceutical.

11. A compound of Formula II:

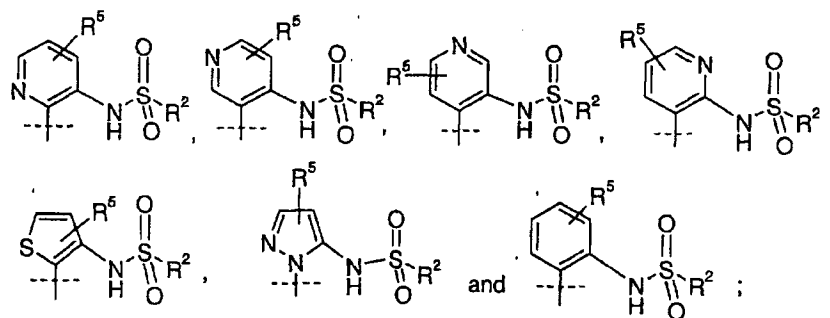


II

where:

A is selected from the group consisting of

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R^2 is C_1 - C_4 alkyl or dimethylamino;

R^5 is H, halo, $-COOR^8$, or $-CH_2COOR^8$;

R^6 is H, cyano, C_1 - C_4 alkoxy, halo, hydroxy, trifluoromethyl, or methylthio;

10 R^7 is $-COOR^9$, $-C(O)CH_2CH_2COOR^9$, $-OCH_2COOR^9$, $-SCH_2COOR^9$, or C_1 - C_2 alkyl substituted with $-COOR^9$;

R^8 and R^9 are each independently selected from the group consisting of hydrogen and C_1 - C_4 alkyl provided that at least one of R^8 and R^9 is other than hydrogen; or a base addition salt thereof.

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se juntan para formar un complejo de canal iónico tetramérico con las propiedades funcionales de este canal de ión más probablemente siendo determinadas por su composición de subunidad.

5 Las corrientes de canales iónicos activadas por glutamato vía receptores AMPA son temporales. El curso de tiempo de las corrientes se modifica por estados refractorios causados durante el enlace de glutamato, el cual es referido como una desensibilización y por la proporción de remoción de
10 glutamato a partir del sitio de enlace del canal iónico, el cual resulta en desactivación. El influjo iónico a través de los receptores AMPA puede ser mejorado por compuestos que ya sea previenen la desensibilización o mediante compuestos que disminuyen las velocidades de desactivación. Los compuestos
15 que mejoran el influjo iónico estimulado por glutamato en receptores AMPA se conocen como moduladores alostéricos del receptor AMPA positivos o potenciadores del receptor AMPA. Uno de tales compuestos, el cual potencia selectivamente la función del receptor AMPA es la ciclotiazida. Puesto que los
20 receptores AMPA juegan un papel fundamental en la mediación de la transmisión excitadora rápida en el sistema nervioso central, las moléculas que mejoran la función del receptor AMPA tienen múltiples objetivos terapéuticos.

Se han mostrado compuestos que potencian
25 alostéricamente receptores AMPA, por mejorar la actividad

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sináptica *in vitro* e *in vivo* como se describe, por ejemplo, por I. Ito, et al., *J. Physiol.*, 424, 533-543 (1990) y A. Copani, et al., *Journal of Neurochemistry*, 58, 1199-1204 (1992). Tales compuestos también han mostrado mejorar el
5 aprendizaje y memoria en ratas, monos, y humanos, y son revisados por Goulliaev and Senning, *Brain Research Reviews*, 19, 180-222 (1994).

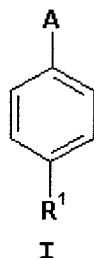
La Publicación de Solicitud de Patente Internacional WO 98/33496 publicada el 6 de Agosto de 1998,
10 describe ciertos derivados de sulfonamidas los cuales son útiles, por ejemplo, para tratar trastornos psiquiátricos y neurológicos, por ejemplo, trastornos cognitivos, enfermedad de Alzheimer, demencias relacionadas con la edad, deterioro de memoria inducido por edad, disquinesia tardía, corea
15 Huntington, mioclonia, enfermedad de Parkinson, inversión de estados inducidos por fármacos (tales como cocaína, anfetaminas, estados inducidos por alcohol), depresión, trastorno por déficit de atención, trastorno de hiperactividad por déficit de atención, psicosis,
20 deficiencias cognitivas asociadas con psicosis y psicosis inducida por fármacos. P. L. Ornstein, et al., *J. Med. Chem.*, 43, 4354 (2000), además describe biarilpropilsulfonamidas, las cuales son potentes mediadores de receptores AMPA. Además, X. Li, et al., *Neuropharmacology*, 40, 1028 (2001),
25 describe acciones similares a antidepresivos de potenciadores

del receptor AMPA. D.D Schoepp, et al., y Tizzano, et al.,
Society for Neuroscience Abstracts, 26(1-2), 528.19 y 528.20,
 30th Annual Meeting New Orleans, (Noviembre 4-9, 2000),
 describen un potenciador del receptor AMPA oralmente activo
 5 que mejora el desempeño de la memoria y aprendizaje espacial
 en ratas, e invierte el déficit de memoria y aprendizaje
 tanto farmacológicamente como asociado con la edad en ratas.
 Los nuevos potenciadores del receptor AMPA con un índice
 terapéutico aceptable, son necesarios para tratar estos *trastornos*.
 10 trastornos neurológicos.

Sumario de la Invención

La presente invención proporciona compuestos de
 Fórmula I:

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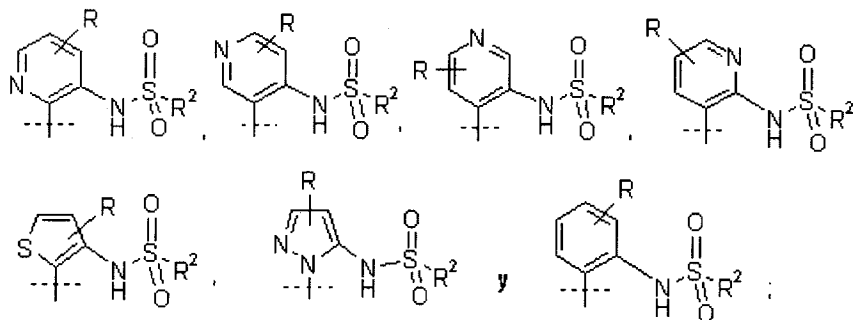


en donde:

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A se selecciona del grupo que consiste de

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R es H, halo, -COOH o -CH₂COOH;

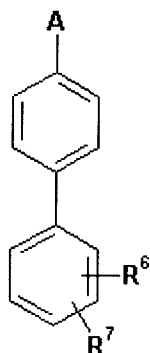
R¹ es fenilo opcionalmente sustituido con un primer sustituyente seleccionado del grupo que consiste de halo, ciano, acilo C₁-C₄, -COOH, -NHR³, alquilo C₁-C₂ sustituido con
5 -NHCH₃, -N(SO₂(alquilo C₁-C₃))₂, -COOH, -CONH₂, ciano, hidroxilo, o tetrazol-5-ilo, -OCH₂COOH, -SCH₂COOH, -C(O)CH₂CH₂COOH, -SO₂NH₂, tetrazol-5-ilo, y 1,2,4-triazol-1-ilo; opcionalmente además sustituido con un segundo sustituyente seleccionado del grupo que consiste de: halo, trifluorometilo, ciano,
10 nitro, alcoxi C₁-C₄, hidroxilo, alquilo C₁-C₄, alquiltio C₁-C₄, -NHCH₂CN, -OCH₂CN, -NHSO₂CH(CH₃)₂, y -C(O)NHR⁴; opcionalmente además sustituido con un tercer sustituyente seleccionado del grupo que consiste de halo y ciano; opcionalmente además sustituido con un cuarto sustituyente seleccionado del grupo
15 que consiste de halo;

R² es alquilo C₁-C₄ o dimetilamino;

R³ es -SO₂(alquilo C₁-C₃), acilo C₁-C₄, alquilo C₁-C₄ o hidrógeno;

R⁴ es hidrógeno, alquilo C₁-C₄, o -SO₂(alquilo C₁-C₄); o una sal del mismo farmacéuticamente aceptable.
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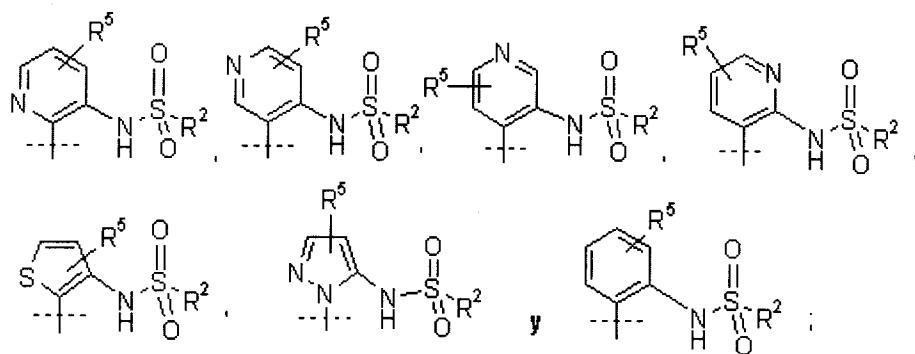
La presente invención también proporciona intermediarios de Fórmula II:

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II

en donde:

A se selecciona del grupo que consiste de



R^2 es alquilo C_1-C_4 o dimetilamino;

R^5 es H, halo, $-COOR^8$, o $-CH_2COOR^8$;

R^6 es H, ciano, alcoxi C_1-C_4 , halo, hidroxilo, trifluorometilo o metiltio;

R^7 es $-COOR^9$, $-C(O)CH_2CH_2COOR^9$, $-OCH_2COOR^9$, $-SCH_2COOR^9$, o alquilo C_1-C_2 sustituido con $-COOR^9$;

R^8 y R^9 son cada uno seleccionados independientemente del grupo que consiste de hidrógeno y alquilo C_1-C_4 , siempre que al menos uno de R^8 y R^9 sea distinto que hidrógeno; o una sal de adición de base del

mismo.

La presente invención además proporciona un método para potenciar la función del receptor de glutamato en un paciente, el cual comprende administrar a dicho paciente en
5 necesidad de tal tratamiento, una cantidad efectiva de un compuesto de fórmula I o una sal del mismo farmacéuticamente aceptable.

Además, la presente invención adicionalmente proporciona un método para tratar esquizofrenia, déficits
10 cognitivos asociados con esquizofrenia, enfermedad de Alzheimer, demencia del tipo Alzheimer, deterioro cognitivo medio, enfermedad de Parkinson, o depresión en un paciente, el cual comprende administrar a un paciente en necesidad de tal tratamiento, una cantidad efectiva de un compuesto de
15 Fórmula I o una sal del mismo farmacéuticamente aceptable.

De conformidad con otro aspecto, la presente invención proporciona el uso de un compuesto de Fórmula I, o una sal del mismo farmacéuticamente aceptable, para la manufactura de un medicamento para tratar esquizofrenia,
20 déficits cognitivos asociados con esquizofrenia, enfermedad de Alzheimer, demencia del tipo Alzheimer, deterioro cognitivo medio, enfermedad de Parkinson o depresión.

Además, la presente invención proporciona el uso de un compuesto de Fórmula I, o una sal del mismo
25 farmacéuticamente aceptable, para tratar esquizofrenia,

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ax

déficit cognitivo asociado con esquizofrenia, enfermedad de Alzheimer, demencia del tipo Alzheimer, deterioro cognitivo medio, enfermedad de Parkinson o depresión.

La invención además proporciona composiciones
5 farmacéuticas que comprenden, un compuesto de Fórmula I, o una sal del mismo farmacéuticamente aceptable, y un portador, diluyente o excipiente farmacéuticamente aceptable.

Adicionalmente, el uso de compuestos de Fórmula I en conjunto con antipsicóticos, antidepresivos y fármacos
10 útiles en el tratamiento de trastornos cognitivos está contemplado dentro del alcance de la presente invención. El documento WO 2005/040110 muestra el uso de compuestos que potencian la función del receptor de glutamato en conjunto con antipsicóticos, antidepresivos y fármacos útiles en el
15 tratamiento de trastornos cognitivos.

Descripción Detallada de la Invención

Como se usa en este documento, el término "potenciación de la función del receptor de glutamato", se
20 refiere a cualquier receptividad de receptores de glutamato, por ejemplo, receptores AMPA a glutamato o un agonista, e incluye pero no se limita a, inhibición de rápida desensibilización o desactivación de receptores AMPA a glutamato.

25 Una amplia variedad de condiciones pueden ser

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POTENCIADORES DEL RECEPTOR AMPA

Campo de la Invención

El glutamato es el neurotransmisor excitador principal en el sistema nervioso central. Se han identificado tres subtipos de canales iónicos del receptor de glutamato basados en su sensibilidad a los activadores selectivos (agonistas), N-metil-D-aspartato (NMDA), ácido propiónico de α -amino-3-hidroxi-5-metil-4-isoxazol (AMPA) y cainato.

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Antecedentes de la Invención

Los receptores AMPA median las respuestas celulares a glutamato por mecanismos directos e indirectos. Cuando se activan por glutamato o AMPA, los canales iónicos del receptor AMPA permiten a iones de sodio (Na^+) e iones de calcio (Ca^{2+}) pasar directamente a través del poro del canal. Además, los canales iónicos del receptor AMPA pueden facilitar la activación de receptores NMDA iniciando la despolarización celular que libera bloques dependientes de iones de magnesio (Mg^{2+}) - de receptores NMDA.

Se han identificado y clonado los subtipos del receptor AMPA múltiples: GluR1, GluR2, GluR3 y GluR4, como se describe por Hollman and Heinemann, *Ann. Rev. Neurosci.*, 17, 31-108 (1994). Cada subunidad consiste de una secuencia de aproximadamente 900 aminoácidos. Cuatro subunidades se piensa

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tratadas o prevenidas por compuestos de Fórmula I y sus sales farmacéuticamente aceptables a través de su acción como potenciadores de la función de receptores de glutamato. Tales condiciones incluyen aquellas asociadas con hipofunción de glutamato, tal como trastornos psiquiátricos y neurológicos, por ejemplo, trastornos cognitivos y trastornos neurodegenerativos, tales como enfermedad de Alzheimer; demencia del tipo Alzheimer, demencias relacionadas con la edad; deterioro de memoria inducido por la edad; déficits cognitivos debido a autismo, síndrome de Down y otros trastornos del sistema nervioso central con inicio desde la niñez, déficits cognitivos posteriores a terapias electroconvulsivas, trastornos de movimiento tales como disquinesia tardía, corea Huntington, mioclonia, distonia, espasticidad, enfermedad de Parkinson; inversión de estados inducidos por fármacos (tales como cocaína, anfetaminas, estados inducidos por alcohol); depresión, trastorno por déficit de atención, trastorno de hiperactividad por déficit de atención; psicosis tales como esquizofrenia; déficits cognitivos asociados con psicosis tales como esquizofrenia, psicosis inducida por fármaco, apoplejía y disfunción sexual. Los compuestos de Fórmula I pueden también ser útiles para mejorar la memoria (tanto de término corto como de término largo) y capacidad de aprendizaje. La presente invención proporciona el uso de compuestos de Fórmula I para el

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tratamiento de cada una de estas condiciones.

Se entiende por uno de habilidad ordinaria en la técnica, que la cognición incluye varios "dominios". Estos dominios incluyen memoria de término corto, memoria de término largo, memoria de trabajo, función ejecutiva y atención. Como se usa en este documento, el término "trastorno cognitivo" significa abarcar cualquier trastorno caracterizado por un déficit en uno o más de los dominios cognitivos, que incluye pero no se limita a memoria de término corto, memoria de término largo, memoria de trabajo, función ejecutiva y atención. Además se entiende que el término "trastorno cognitivo" incluye, pero no se limita a los siguientes trastornos específicos: decline cognitivo relacionado con la edad, deterioro cognitivo medio, enfermedad de Alzheimer, demencia, demencia de tipo Alzheimer, demencia por Parkinson, demencia de Cuerpo Lewy, demencia persistente inducida por sustancia, demencia persistente inducida por alcohol, deterioro cognitivo inducido por alcohol, demencia inducida por SIDA, trastornos de aprendizaje, déficits cognitivos subsecuentes a cirugía por derivación cardiaca e injertos, apoplejía, isquemia cerebral, trauma de la médula espina, trauma craneal, hipoxia perinatal, paro cardíaco, y daño neuronal hipoglicémico, demencia vascular, demencia por infartos múltiples, déficits cognitivos asociados con esclerosis lateral amiotrófica y

déficits cognitivos asociados con esclerosis múltiple. El deterioro cognitivo medio se ha definido como una fase prodrómica potencial de demencia asociada con la enfermedad de Alzheimer, basado en presentación clínica y en el progreso de pacientes que presentan deterioro cognitivo medio a demencia de Alzheimer con el tiempo. (Morris, et al., Arch. Neurol., **58**, 397-405 (2001); Petersen, et al., Arch. Neurol., **56**, 303-308 (1999)).

La cuarta edición del Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (por sus siglas en inglés, Manual de Diagnóstico y Estadística de Trastornos Mentales), (1994, American Psychiatric Association, Washington, D.C.), proporciona una herramienta de diagnóstico para identificar muchos de los trastornos descritos en este documento. Los expertos reconocerán que existen nomenclaturas alternativas, nosologías y sistemas de clasificación para trastornos descritos en este documento, que incluyen aquellos descritos en la International Statistical Classification of Diseases and Related Health Problems, (por sus siglas en inglés, Clasificación Estadística Internacional de Enfermedades y Problemas de Salud Relacionados), décima revisión (ICD-10) (1992, World Health Organization, Geneva), y tiene terminología y sistemas de clasificación involucrados con el progreso científico médico.

La presente invención incluye sales

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farmacéuticamente aceptables de los compuestos definidos por la Fórmula I. Un compuesto de esta invención puede poseer un grupo suficientemente ácido, y por consiguiente, reaccionar con cualquiera de un número de bases orgánicas e inorgánicas para formar una sal farmacéuticamente aceptable. El término "sal farmacéuticamente aceptable" como se usa en este documento, se refiere a sales de los compuestos de Fórmula I, los cuales son sustancialmente no tóxicos a organismos vivientes. Las sales farmacéuticamente aceptables típicas incluyen aquellas sales preparadas por reacción de los compuestos de la presente invención con una base orgánica e inorgánica farmacéuticamente aceptable. Tales sales son conocidas como sales de adición de base. Tales sales incluyen sales farmacéuticamente aceptables listadas en Journal of Pharmaceutical Science, 66, 2-19 (1977), las cuales son conocidas por aquellos expertos. Las sales de magnesio, dietilamina, hemipiperazina, y terc-butilamina son preferidas. Las sales de terc-butilamina son más preferidas.

Algunos de los compuestos de la presente invención tienen uno o más centros quirales y pueden existir en una variedad de configuraciones estereoisoméricas. Como una consecuencia de estos centros quirales, los compuestos de la presente invención se originan como racematos, mezclas de enantiómeros y como enantiómeros individuales, así como también diastereómeros y mezclas de diastereómeros. Todos los

racematos, enantiómeros y diastereómeros están dentro del alcance de la presente invención. Los estereoisómeros y enantiómeros específicos de compuestos de Fórmula I, pueden ser preparados por uno de habilidad ordinaria en la técnica
5 utilizando técnicas y procesos bien conocidos, tales como aquellos descritos por J. Jacques, et al., "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, Inc., 1981, and E.L. Eliel and S.H. Wilen, "Stereochemistry of Organic Compounds", (Wiley-Interscience 1994), y Solicitud de Patente
10 Europea No. EP-A-838448, publicada el 29 de Abril de 1998. Ejemplos de resoluciones incluyen técnicas de recristalización o cromatografía quiral.

Como se usa en este documento, los términos "Halo", "Haluro" o "Hal", se refieren a átomos de cloro, bromo, yodo
15 o flúor, a menos que se especifique de otro modo en este documento.

Como se usa en este documento, el término "alquilo C₁-C₄", se refiere a una cadena alifática saturada, monovalente, recta o ramificada, de uno a cuatro átomos de
20 carbono e incluye, pero no se limita a, metilo, etilo, propilo, isopropilo, butilo, isobutilo y t-butilo. El término "alquilo C₁-C₄" incluye dentro de su definición el término "alquilo C₁-C₃".

Como se usa en este documento, el término "alcoxi C₁-C₄" se refiere a una cadena alquilo lineal o recta que
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tiene de uno a cuatro átomos de carbono unidos a un átomo de oxígeno. Los grupos alcoxi C₁-C₄ típicos incluyen metoxi, etoxi, propoxi, isopropoxi, butoxi, terc-butoxi y similares. El término "alcoxi C₁-C₄" incluye dentro de su definición el

5 término "alcoxi C₁-C₃".

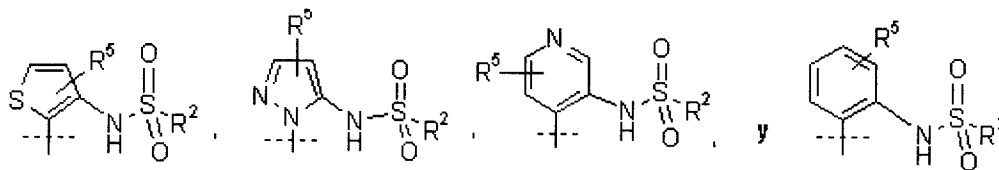
Como se usa en este documento, el término "acilo C₁-C₄" se refiere a una cadena alquilo recta o ramificada, que tiene de uno a tres átomos de carbono unidos a un grupo carbonilo. Ejemplos incluyen, pero no se limitan a acetilo,

10 propionilo, butirilo, 2-metilpropionilo y similares. El término "acilo C₁-C₄" incluye dentro de su definición, el término "acilo C₁-C₃".

Como se usa en este documento, el término "alquiltio C₁-C₄" se refiere a una cadena alquilo recta o

15 ramificada que tiene de uno a cuatro átomos de carbono unidos a un átomo de azufre. Grupos alquiltio C₁-C₄ típicos incluyen metiltio, etiltio, propiltio, isopropiltio, butiltio, terc-tubitio y similares. El término "alquiltio C₁-C₄" incluye dentro de su definición el término "alquiltio C₁-C₃".

20 Una modalidad adicional de la presente invención son compuestos de Fórmula I, en donde A se selecciona del grupo que consiste de:

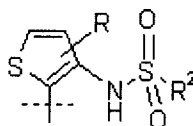


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Ciertas clases de compuestos de Fórmula I son potenciadores AMPA preferidos. Los siguientes párrafos describen tales clases preferidas:

a) A es

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b) R es hidrógeno;

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c) R¹ es fenilo sustituido con un sustituyente único;

d) R¹ es fenilo sustituido con un sustituyente único seleccionado del grupo que consiste de ciano, tetrazol-5-ilo, alquilo C₁-C₂, sustituido con -COOH o tetrazol-5-ilo, -SO₂NH₂, -OCH₂COOH y -SCH₂COOH;

15

e) R¹ es fenilo mono-sustituido en la posición 4 con un sustituyente seleccionado del grupo que consiste de tetrazol-5-ilo, -OCH₂COOH, -SCH₂COOH, y alquilo C₁-C₂ sustituido con -COOH, en la posición 3 con un sustituyente seleccionado del grupo que consiste de -SONH₂ y alquilo C₁-C₂ sustituido con tetrazol-5-ilo, o en la posición 2 con ciano;

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f) R¹ es fenilo sustituido con dos sustituyentes;

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g) R¹ es fenilo sustituido con un primer

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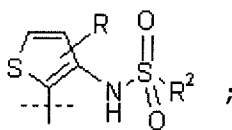
- sustituyente seleccionado del grupo que consiste de alcoxi C_1-C_4 , hidroxilo, halo, ciano, $-COOH$ y $-NHSO_2CH(CH_3)_2$, y con un segundo sustituyente seleccionado del grupo que consiste de amino, trifluorometilo, $-COOH$, $-C(O)NHR^3$, tetrazol-5-ilo, $-OCH_2COOH$, y alquilo C_1-C_2 sustituido con $-COOH$;
- 5
- h) R^1 es fenilo sustituido en la posición 2 con un sustituyente seleccionado del grupo que consiste de alcoxi C_1-C_4 , hidroxilo, halo, ciano, $-COOH$ y $-NHSO_2CH(CH_3)_2$, y además sustituido en la posición 4 con tetrazol-5-ilo, $-COOH$, $-C(O)NHR^3$, o alquilo C_1-C_2 sustituido con $-COOH$, en la posición 5 con amino, $-COOH$ o $-OCH_2COOH$ o en la posición 6 con $-COOH$;
- 10
- 15
- i) R^1 es 2-ciano-3-fluoro-4-hidroxilo-5-fluorofenilo;
- j) R^2 es alquilo C_1-C_4 ;
- k) R^2 es isopropilo;
- l) El compuesto de Fórmula I es un ácido libre;
- 20
- m) El compuesto de Fórmula I es una sal;
- n) El compuesto de Fórmula I es un hidrato;
- o) El compuesto de Fórmula I es un anhidrato;
- p) El compuesto de Fórmula I es la sal de hemipiperazina;
- 25
- q) El compuesto de Fórmula I es la sal de

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dietilamina;

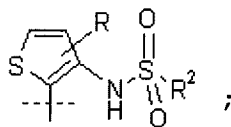
r) El compuesto de Fórmula I es la sal de terc-butilamina.

Modalidades preferidas de la invención incluyen
5 todas las combinaciones de párrafos a) - r). Compuestos especialmente preferidos de Fórmula I son aquellos en donde A es



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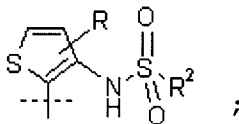
R es hidrógeno; R¹ es como se describe en el párrafo h); y R² es alquilo C₁-C₄. También se prefiere que A sea



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R es hidrógeno; R¹ es como se describe en el párrafo h); y R² es isopropilo. Es particularmente preferido que A sea

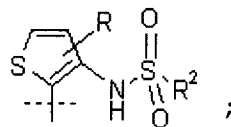
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R es hidrógeno; R¹ es fenilo sustituido en la
25 posición 2 con alcoxi C₁-C₄ o ciano y en la posición 4 con

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-COOH; y R^2 es isopropilo. Es más preferido que A sea

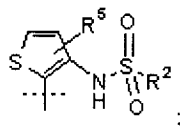


R es hidrógeno; R^1 es 2-ciano-4-carboxifenilo o 2-etoxi-4-carboxifenilo; y R^2 es isopropilo.

Aunque todos los intermediarios de Fórmula II son útiles para preparar compuestos de la presente invención, se prefieren ciertas clases:

s) A es

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t) R^2 es alquilo C_1-C_4 ;

u) R^2 es isopropilo;

v) R^5 es hidrógeno;

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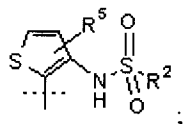
w) R^6 está en la posición 2 del anillo fenilo al cual está unido;

x) R^6 está en la posición 2 del anillo fenilo al cual está unido y se selecciona del grupo que consiste de hidrógeno, ciano, y alcoxi C_1-C_4 ;

20

y) R^9 es alquilo C_1-C_4 ;

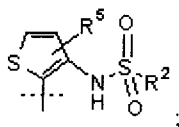
Compuestos especialmente preferidos de Fórmula II son aquellos en donde A es



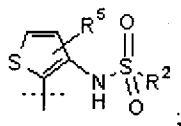
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R^5 es hidrógeno; R^2 es alquilo C_1-C_4 ; R^6 está en la posición 2 del fenilo al cual está unido y se selecciona del grupo que consiste de ciano y alcoxi C_1-C_4 ; R^7 está en la posición 4 del anillo fenilo al cual está unido y es $-COOR^9$,
5 y R^9 es alquilo C_1-C_4 . Se prefiere también que A sea



R^5 es hidrógeno; R^2 es isopropilo; R^6 está en la posición 2 del fenilo al cual está unido y se selecciona del grupo que consiste de ciano y alcoxi C_1-C_4 ; R^7 está en la posición 4 del anillo fenilo al cual está unido y es $-COOR^9$,
10 y R^9 es alquilo C_1-C_4 . Es más preferido que A sea



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R^5 es hidrógeno; R^2 es isopropilo; R^6 está en la posición 2 del fenilo al cual está unido y se selecciona del grupo que consiste de ciano, metoxi y etoxi; R^7 está en la posición 4 del anillo fenilo al cual está unido y es $-COOR^9$,
20 y R^9 es metilo o etilo.

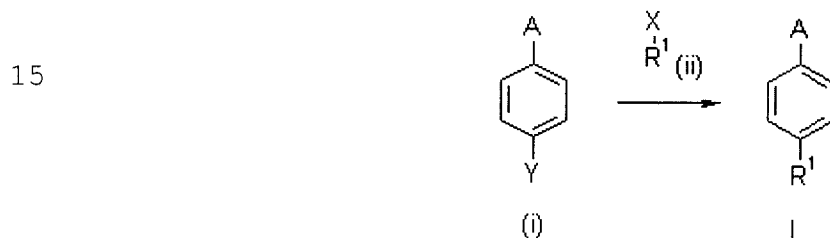
Los compuestos de Fórmula I pueden ser preparados por uno de habilidades ordinarias en la técnica, siguiendo las técnicas y procedimientos reconocidos en el arte. Más
25 específicamente, compuestos de Fórmula I pueden ser

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preparados como se expone en los esquemas de reacción, métodos y ejemplos expuestos abajo. Los reactivos y materiales de partida son fácilmente disponibles para uno de habilidad ordinaria en la técnica. Todos los sustituyentes, a menos que se
5 especifique de otro modo, son como se definen previamente.

Los compuestos de Fórmula I en donde A y R¹ son como se definen previamente, pueden ser preparados como se ilustra en el siguiente esquema de reacción, en donde (i) es un ácido arilborónico adecuado, aril trimetilestanilo o éster
10 arilborónico, y X es bromo, yodo, cloro o trifluorometan-sulfoxi.

Esquema de Reacción I



El compuesto de estructura (ii) es acoplado a un
20 ácido fenil borónico adecuado, éster fenilborónico adecuado, o feniltrimetilestanano (i) adecuado, bajo condiciones de reacción de acoplamiento Tipo Suzuki o Tipo Stille bien conocidas para uno de habilidad ordinaria en la técnica, para proporcionar el compuesto de Fórmula I. Véase Suzuki, A.,
25 *Journal of Organometallic Chemistry*, 576, 147-168 (1999), y

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Miyaura and Suzuki, *Chemical Reviews*, 95, 2457-2483 (1995), para ejemplos de técnicas generales de acoplamiento cruzado y para métodos para preparar materiales de partida y reactivos adecuados.

5 Más específicamente, el compuesto de estructura (ii) es combinado con aproximadamente 1.0 a 1.5 equivalentes del ácido o éster fenilborónico (i) adecuado, en un solvente orgánico adecuado o una mezcla adecuada de solventes. Ejemplos de solventes orgánicos adecuados incluyen 1,4-
10 dioxano, dimetoxietano (DME), DMF, benceno, tolueno, acetona, etanol (EtOH), y similares. Ejemplos de mezclas de solvente adecuadas incluyen DME/EtOH, THF:Agua y similares. Un catalizador adecuado, tal como tetraquis(trifenilfosfina)paladio,
15 diclorobis(trifenilfosfina)-paladio (II), $\text{Pd}(\text{PCy}_3)_2\text{Cl}_2$, o [1,1-bis(difenilfosfino)ferroceno]dicloro-paladio(II) o paladio negro y una base adecuada, por ejemplo, carbonato de sodio, se agregan a la mezcla de reacción con agitación.

Alternativamente, el experto en la técnica aprecia
20 que compuestos de Fórmula (I) pueden también ser preparados por acoplamiento de un haluro de arilo adecuado con un ácido arilborónico adecuado, éster arilborónico adecuado, o compuesto ariltrimetilestanilo adecuado bajo condiciones de reacción de acoplamiento Tipo Suzuki o Tipo Stille bien
25 conocidas para uno de habilidad ordinaria en la técnica, para

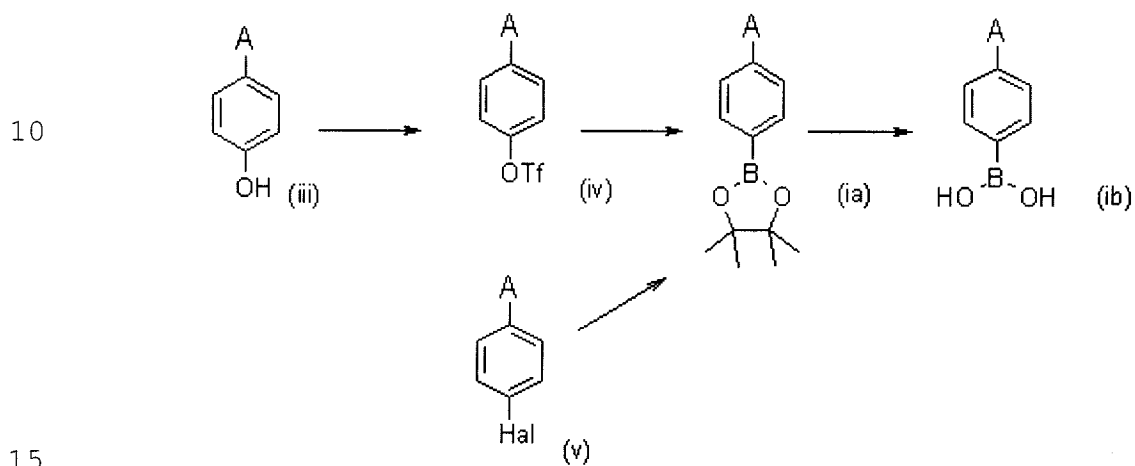
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proporcionar el compuesto de Fórmula (I).

Los ácidos y ésteres borónicos requisito, pueden ser preparados como se ilustra en el siguiente esquema de reacción, en donde A es como se define previamente, y Hal es

5 bromo o yodo.

Esquema de Reacción II



Un fenol apropiadamente sustituido (iii) se hace reaccionar con un reactivo triflatante, tal como anhídrido triflico o N-feniltrifluorometansulfonamida, en la presencia de base, por ejemplo, DMAP o hidróxido de sodio en un

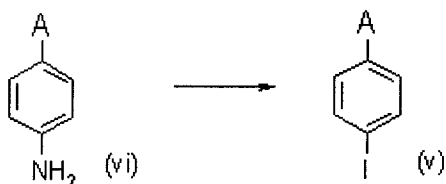
20 solvente adecuado, tal como cloruro de metileno o tetrahidrofurano para dar el triflato (iv). El triflato resultante es disuelto en un solvente adecuado tal como acetonitrilo o dimetilsulfóxido y se hace reaccionar en la presencia de una base tal como trietilamina o acetato de

25 potasio, un catalizador tal como complejo de [1,1'-

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bis(difenilfosfino)-ferroceno]dicloropaladio(II), y un borano tal como bis(pinacolato)borano para formar el éster borónico requisito (ia). Alternativamente, PdCl_2 (dppf) y el acetato de potasio base en dimetilformamida, pueden ser empleados si
5 es necesario o deseado. El éster de ácido borónico puede también ser preparado haciendo reaccionar haluro de fenilo (v) en un solvente apropiado tal como acetonitrilo o dimetilsulfóxido y se agrega una base tal como trietilamina o acetato de potasio. Se agregan un catalizador tal como
10 complejo de [1,1'-bis(difenilfosfino)-ferroceno]dicloropaladio(II) y un borano tal como bis(pinacolato)borano. El experto en la técnica aprecia que el éster borato resultante puede ser hidrolizado bajo condiciones bien conocidas en la técnica, con un ácido tal
15 como ácido clorhídrico o en un solvente adecuado tal como acetona y en la presencia de un agente oxidante tal como periodato de sodio y una solución de acetato de amonio para proporcionar el ácido borónico (ib).

Los haluros de fenilo requisito (v), pueden ser
20 preparados como se muestra en el Esquema de Reacción III, en donde A es como se define previamente.

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~~108~~Esquema de Reacción III

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La anilina (vi) se hace reaccionar con un reactivo de oxidación adecuado, tal como nitrito de isoamilo en un solvente adecuado, tal como acetonitrilo, en la presencia de una fuente de haluro, tal como diyodometano para dar
10 compuestos de fórmula (v).

Ciertos compuestos de Fórmula I pueden servir como intermediarios para compuestos adicionales de Fórmula I vía reacciones y transformaciones de grupo funcional, similares a aquellos expertos en la técnica. Véase, Larock, R.,
15 "Comprehensive Organic Transformations," VCH Publishing, Inc., New York, 1989. Por ejemplo, un grupo amino se hace reaccionar con un cloruro de sulfonilo adecuado en la presencia de piridina o base acuosa, tal como trietilamina, bajo condiciones bien conocidas en la técnica para
20 proporcionar la sulfonamida correspondiente. Además, sustituyentes nitro son fácilmente convertidos a aminas haciendo reaccionar el compuesto que contiene nitro con un agente reductor adecuado, tal como cloruro de estaño, en un solvente apropiado por ejemplo, etanol. Además, los ésteres
25 carboxílicos de Fórmula II son convertidos a ácidos

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carboxílicos de Fórmula I bajo condiciones bien conocidas por aquellos expertos en la técnica, por ejemplo, tratando un éster de Fórmula II en un solvente adecuado o mezcla de solvente tal como THF, metanol, etanol y similares, con agua y un ligero exceso de base adecuada, tal como hidróxido de litio, hidróxido de sodio, hidróxido de potasio y similares. El ácido carboxílico resultante puede entonces ser convertido a la amida primaria bajo condiciones bien conocidas. Por ejemplo, el compuesto de ácido carboxílico de Fórmula I es disuelto en un solvente orgánico adecuado, tal como cloruro de metileno o THF y tratado con cloruro de oxalilo opcionalmente seguido por adición de una cantidad catalítica de DMF con agitación. La mezcla de reacción es agitada y concentrada, después disuelta en un solvente orgánico adecuado, tal como cloruro de metileno o THF, y tratada con un ligero exceso de un hidróxido de amoníaco o solución de amoníaco/metanol o amoníaco/dioxano con agitación. Los compuestos de amida primaria de Fórmula I pueden ser convertidos a compuestos de tetrazolilo de Fórmula I bajo condiciones estándares. Por ejemplo, el compuesto de amida primaria de Fórmula I se hace reaccionar con tetracloruro de silicio y azida de sodio en la presencia de un solvente orgánico adecuado, tal como acetonitrilo. Alternativamente, los compuestos de tetrazolilo de Fórmula I, se forman haciendo reaccionar un compuesto ciano de Fórmula I con azida

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de sodio y trietilamina en un solvente orgánico adecuado.

Los ejemplos expuestos en este documento representan síntesis típicas de los compuestos de la presente invención. Los reactivos y materiales de partida son
5 fácilmente disponibles para uno de habilidad ordinaria en la técnica. La nomenclatura para ejemplos se expone en este documento con AutoNom 2000 Agregado por MDL® ISIS/Desktop. Como se usa en este documento, los términos listados en la siguiente tabla tienen los significados correspondientes como
10 se indica:

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TÉRMINO	SIGNIFICADO
EM(RE)	Espectrometría de masas por rocío del electrón
¹ H RMN	Espectrometría de resonancia magnética nuclear del protón
J/g	Joules por gramo
CCD	Cromatografía de capa delgada
CLAR	Cromatografía líquida de alta resolución
R _f	Factor de retención
R _t	Tiempo de retención
AcOH	Ácido Acético

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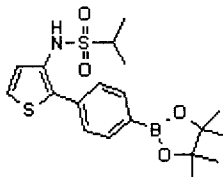
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TÉRMINO	SIGNIFICADO
TA	Temperatura ambiente
DCM	Diclorometano
DMF	N,N-dimetilformamida
DMSO	Metilsulfóxido
LDA	Diisopropilamida de litio
EtOAc	Acetato de etilo
THF	Tetrahidrofurano
iPrOAc	Acetato de isopropilo
DMAP	4-dimetilaminopiridina
DBU	1,8-diazabicyclo[5.4.0]undec-7eno
Et ₃ N	triethylamina
(Boc) ₂ O	di-terc-butyl dicarbonato
MeOH	Metanol
Triflato	Grupo funcional -SO ₃ CF ₃
(dppf)	1,1'-bis(difenilfosfino)ferroceno
S.M.	Material de partida
SCX	Cartucho de intercambio catiónico fuerte
Pd(PCy ₃) ₂ Cl ₂	Diclorobis(triciclohexilfosfina)paladio (II)
Pd ₂ (dba) ₃	Tris(dibencilidenacetona)-dipaladio(0)
EDCI	HCl de 1-etil-3-[3-(dimetilamino)propil]-carbodiimida

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XPreparación 1

{2-[4-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-fenil]-
tiofen-3-il}-amida del ácido propan-2-sulfónico

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En una manera análoga al método de Barker, J. M.;
10 et al., *Synthetic Communications*, 25(23), 3729-3734 (1995),
se sometió a reflujo (120°C) metil-3-aminotiofen-2-
carboxilato (42.8 g, 0.27 mol) con solución acuosa de
hidróxido de sodio 2M (270 mL) por 30 minutos. Se enfrió la
mezcla de reacción a 0°C y se acidificó a pH 5.0 (rojo Congo)
15 con ácido clorhídrico concentrado. Se filtró lo precipitado
espeso. El sólido se secó y disolvió en acetona (300 mL) y se
secó la solución resultante (MgSO₄), filtró y evaporó a 20°C.
Se trató el aceite espeso resultante instantáneamente con
dihidrato de ácido oxálico (26.7 g) en 2-propanol (100 mL) a
20 38°C por 45 minutos. Se dejó la mezcla alcanzar la
temperatura ambiente y se diluyó con éter dietílico (40 mL).
Se filtró el sólido y se lavó con éter dietílico. El sólido
blanco resultante (33.1 g) llegó a ser lila pálido en
exposición a luz y aire. Se disolvió la sal resultante (33.1
25 g) en agua (400 mL) y se basificó con hidróxido de amonio

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concentrado. Se extrajo la mezcla con cloruro de metileno (3 x 200 mL) y se combinó el extracto y se secó (MgSO_4), filtró y evaporó para dar un aceite marrón (15 g, 56%). Se disolvió este material (15 g, 0.15 mol) en cloruro de metileno (300 mL) y se agregó Et_3N (42.2 mL, 0.3 mol) a 0°C . Se agregó una solución de $(\text{Boc})_2\text{O}$ (39.3 g, 0.18 mol) en cloruro de metileno (100 mL) por goteo a 0°C y se agitó la mezcla durante la noche a temperatura ambiente. Se monitoreó por CCD (Hexano/ EtOAc 9:1) para completar la desaparición del material de partida. Se apagó la reacción por adición de agua (200 mL). La mezcla se extrajo con cloruro de metileno (2 x 200 mL) y los extractos se combinaron, secaron (MgSO_4), filtraron y evaporaron. Se purificó lo crudo por cromatografía instantánea (gel de sílice-Hexano/ EtOAc 9:1) para obtener 20.1 g (67%) de (terc-butoxi)-N-(3-tiofenil)carboxamida como un sólido blanco.

En una manera análoga a Campaigne, E. and Monroe, P. A. *J.A.C.S.*, 76, 2447-2450 (1954), a una solución en ebullición de (terc-butoxi(-N-(3-tiofenil)carboxamida (21.0 g, 0.1 mol) en cloruro de metileno (400 mL), se agregó N-yodosuccinimida (23.7 g, 0.1 mol) en porciones pequeñas. Se dejó el baño caliente a 65°C por 20 minutos. La reacción se tomó a temperatura ambiente, se evaporó el solvente y se purificó lo crudo por cromatografía instantánea (gel de Sílice-Hexano/ EtOAc 9:1) para obtener 30.0 g (88%) de (terc-

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butoxi)-N-(2-yodo-(3-tiofenil))carboxamida como un sólido blanco.

Se calentó (terc-butoxi)-N-(2-yodo(3-tiofenil))carboxamida (16.88 g, 0.52 mol), ácido 4-bromofenilborónico (15.65 g, 9.78 mol), Na₂CO₃ (1.01 g, 1.04 mol) y Pd(PPh₃)₄ (5.79 g, 0.052 mol) en 375 ml de una mezcla anhidra y desoxigenada 2:1 de DME/EtOH a 80°C bajo atmósfera de nitrógeno por 24 horas. Los solventes orgánicos se evaporaron, previo a la adición de agua (200 mL). La mezcla se extrajo con cloruro de metileno (3 x 150 mL) y las fases orgánicas se combinaron, secaron (MgSO₄ anhidro), filtraron y concentraron para proporcionar una mezcla cruda como un sólido amarillento. La purificación por cromatografía instantánea (gel de Sílice-Hexano/EtOAc 49:1) proporcionó 10.8 g (60%) de (terc-butoxi)-N-[2-(4-bromofenil)(3-tiofenil)]carboxamida como un sólido amarillo pálido.

Se trató por goteo una solución de (terc-butoxi)-N-[2-(4-bromofenil)(3-tiofenil)]carboxamida (10.8 g, 0.3 mol) en EtOAc (75 mL) a 0°C con 244 mL (8 mL/mmol) de HCl 1N recientemente preparado en EtOAc y se agitó la mezcla a temperatura ambiente durante la noche. Lo precipitado blanco se disolvió con H₂O (100 mL) y se neutralizó con una solución saturada de NaHCO₃. La mezcla se extrajo con EtOAc (3 x 100 mL) y lo orgánico se combinó, secó y concentró para dar un sólido ligeramente coloreado. La purificación del material

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crudo por cromatografía instantánea (gel de Sílice-Hexano/AcOEt 49:1 después 9:1) proporcionó 5.7 g (74%) de 2-(4-bromo-fenil)-tiofen-3-ilamina como un sólido amarillo pálido.

5 Se agregó lentamente a una solución de 2-(4-bromo-fenil)-tiofen-3-ilamina (0.6 g, 2.36 mmol) en diclorometano seco (10 mL) a 0°C, DBU 1.41 mL (9.45 mmol) y cloruro de isopropilsulfonilo (0.53 mL; 4.72 mmol) (Temp. siempre <0°C). Se removió el baño helado y la mezcla se agitó a TA durante
10 la noche. Se agregó NH₄Cl (10 mL) acuoso saturado y se extrajo la solución con EtOAc (2 x 10 mL). Las capas orgánicas combinadas se secaron y concentraron bajo vacío. El residuo crudo se purificó por cromatografía instantánea (gel de sílice-Hexano/EtOAc 4:1) para dar 0.8 g (94%) [2-(4-bromo-
15 fenil)-tiofen-3-il]-amida del ácido propan-2-sulfónico.

Se desoxigenó purgando con nitrógeno, una mezcla de [2-(4-bromo-fenil)-tiofen-3-il]-amida del ácido propan-2-sulfónico (1.34 g, 3.72 mmol), bis(pinacolato)diboro (1.04 g, 4.09 mmol), KOAc (1.21 g, 12.3 mmol) y Pd(dppf)Cl₂ (0.3 g, 0.37 mmol) en DMF seco (20 mL) y la mezcla se calentó a 80°C
20 durante la noche. Se agregó agua (20 mL) y se extrajo la reacción con éter dietílico (3 x 20 mL). Los orgánicos combinados se lavaron con agua y se secaron y concentraron para dar un sólido oscuro crudo. La purificación por
25 cromatografía instantánea (gel de sílice-Hexano/AcOEt 7:1)

Preparación 2

5 (4'-(ácido borónico)-bifenil-2-il)-amida del ácido propan-2-
 sulfónico

Se agregó por goteo DBU (8.76 mL, 56.92 mmol) a una solución de 4'-bromo-bifenil-2-ilamina (3.53 g, 14.23 mmol) en diclorometano (50 ml) a 0°C, seguido por adición por goteo de cloruro de isopropilsulfonilo (3.29 mL, 28.46 mmol) y se agitó la reacción a temperatura ambiente por 24 horas. El solvente se removió bajo presión reducida y el residuo se purificó por sílice y eluyó con EtOAc:hexano 1:4 a EtOAc para dar el compuesto del título (4.93 g, 98%). EM (m/e): 355

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(M+1); 353 (M-1).

Se calentó a 80°C, una mezcla de (4'-bromo-bifenil-2-il)-amida del ácido propan-2-sulfónico (4.0 g, 11.22 mmol), bis(pinacolato)diboro (3.22 g, 12.34 mmol), complejo de
5 [1,1']-bis(difenilfosfino)ferroceno]-dicloropaladio(II) con diclorometano (1:1) (0.276 g, 0.337 mmol) y acetato de potasio (3.32 g, 33.87 mmol) en dimetilsulfóxido seco (25 mL). Después de 16 horas, se agregó agua y se extrajo con EtOAc. Las capas orgánicas se combinaron, secaron sobre
10 sulfato de sodio y evaporaron bajo presión reducida. El residuo se disolvió en diclorometano y se lavó con una solución de HCl 0.1N. Las capas orgánicas se combinaron, secaron sobre sulfato de sodio, filtraron y concentraron bajo presión reducida. El residuo se purificó por cromatografía
15 instantánea (gel de sílice-EtOAc/hexano 1:3) para dar [4'-(4,4,5,5-tetrametil-[1,3,2]dioxoborolan-2-il)-bifenil-2-il)-amida del ácido propan-2-sulfónico (4.07 g, 90%). EM (m/e): 424 (M+23); 400 (M-1).

Se agregó periodato de sodio (1.12 g, 5.25 mmol),
20 seguido por una solución de acetato de sodio 1N (8 mL), a una suspensión de [4'-(4,4,5,5-tetrametil-[1,3,2]dioxoborolan-2-il)-bifenil-2-il)-amida del ácido propan-2-sulfónico (0.7 g, 1.75 mmol) en acetona (16 mL)/agua (0.8 mL). Se agitó la mezcla a temperatura ambiente bajo nitrógeno por 20 horas. Lo
25 precipitado se filtró y la capa orgánica se evaporó. La capa

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acuosa se extrajo con diclorometano. Las capas orgánicas se combinaron, se secaron sobre sulfato de sodio y el solvente se evaporó bajo presión reducida. Se agregó hexanos y terc-butilmetiléter al residuo hasta que se formó un sólido y el
5 sólido se filtró para proporcionar el compuesto del título (0.37 g, 67%). EM (m/e): 337 (M+18); 318 (M-1).

Preparación 3

{4-[4-(4,4,5,5-tetrametil-[1,3,2]dioxoborolan-2-il)-fenil]-
10 piridin-3-il}-amida del ácido propan-2-sulfónico

Se tomó 4-hidroxi-3-nitro-piridina (6.18 g, 44.2 mmol) en oxicloruro de fósforo (16 ml) y se calentó a 45°C. Una vez a 45°C, se agregó pentacloruro de fósforo (8.04 g, 38.6 mmol) en una porción única. La suspensión amarillo
15 resultante se agitó vigorosamente y se calentó bajo reflujo (baño de aceite a 125°C), bajo una atmósfera inerte. Después de 3 horas a 125°C, la suspensión amarilla llegó a ser una solución amarilla transparente. La mezcla se enfrió a temperatura ambiente, se concentró a un aceite, se enfrió a
20 0°C en un baño helado y se trató con 10 ml de agua y 20 ml de diclorometano mientras se agitaba vigorosamente. La capa acuosa se basificó con solución saturada de bicarbonato de sodio y se extrajo con diclorometano (x3). Las capas orgánicas combinadas se secaron sobre sulfato de sodio
25 anhidro, filtraron y concentraron para dar 6.98 g de 4-cloro-

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3-nitro-piridina, el cual cristalizó en reposo (99% de rendimiento).

4-cloro-3-nitro-piridina (6.9 g, 43.5 mmol), ácido 4-bromofenilborónico (8.05 g, 40.1 mmol), carbonato de potasio (11.10 g, 80.3 mmol) y tetraquis trifenilfosfina paladio (2.31 g, 2.0 mmol), son tomados en DME (200 ml) y calentados bajo reflujo (100°C) durante la noche. La mezcla se enfrió descendentemente a temperatura ambiente y se filtró a través de una almohadilla de Celite®, la cual se lavó con EtOAc. Lo filtrado es concentrado para dar un aceite marrón crudo. La purificación por cromatografía instantánea (gel de sílice-hexano/EtOAc) proporcionó 4-(4-bromo-fenil)-3-nitro-piridina (8.52 g) como un aceite amarillo (76% de rendimiento).

Se agitó 4-(4-bromo-fenil)-3-nitro-piridina (8.52 g, 30.5 mmol) en ácido glacial acético (150 ml) y se agregó polvo de hierro (8.40 g, 150.4 mmol) en malla de 325. La mezcla se calentó a 80°C por 40 minutos en tal punto que la mezcla se vuelve gris. La mezcla se filtró a través de Celite® y se lavó el sólido con EtOAc. La capa orgánica se lavó con agua. La capa acuosa se basificó a pH 8 con solución de NaOH y se extrajo con EtOAc (x2). Las capas orgánicas combinadas se lavaron con agua, cloruro de sodio acuoso saturado, se secaron sobre sulfato de sodio anhidro, filtraron y concentraron para proporcionar 7.25 g de un

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aceite crudo marrón. La purificación por cromatografía instantánea (gel de sílice-hexano/EtOAc) proporcionó 4-(4-bromo-fenil)-piridin-3-ilamina (4.64 g) como un sólido blanco (61% de rendimiento).

5 Se tomó 4-(4-bromo-fenil)-piridin-3-ilamina (4.6 g, 18.5 mmol) en diclorometano anhidro (100 ml). Se agregó DBU (11 ml, 73.5 mmol) y la solución se agitó a 0°C por 3 minutos bajo atmósfera inerte. Se agregó cloruro de isopropilsulfonilo por goteo durante 10 minutos. La mezcla se
10 dejó calentar a TA y se calentó bajo reflujo (40°C) durante la noche. La mezcla se enfrió por adición de solución saturada de cloruro de amonio. La capa acuosa se extrajo con diclorometano (x2). Las capas orgánicas combinadas se lavaron con cloruro de sodio acuoso saturado, se secaron sobre
15 sulfato de sodio anhidro, se filtraron y concentraron para proporcionar 9.1 g de un residuo crudo marrón. La purificación por cromatografía instantánea (gel de sílice-hexano/EtOAc) seguida por purificación inversa, proporcionó el compuesto deseado [4-(4-bromo-fenil)-piridin-3-il]-amida
20 del ácido propan-2-sulfónico (2.68 g) como un sólido blanco (41% de rendimiento).

Se tomó [4-(4-bromo-fenil)-piridin-3-il]-amida del ácido propan-2-sulfónico (2.07 g, 5.8 mmol), bis(pinacolato)diboro (2.01 g, 7.9 mmol), acetato de potasio
25 (2.3 g, 23.4 mmol) y complejo [1,1'-