



Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

PCT
SOLICITUD

PATENTE DE INVENCION

07-39071

21. EXPEDIENTE No.

54. TITULO: "4-[(2,4-DICLORO-5-METOXIFENIL)AMINO]-6-ALCOXI-7-ETINIL-3-QUINOLINOCARBONITRILOS PARA EL TRATAMIENTO DE LESIÓN ISQUÉMICA"

51. CLASIFICACIÓN INTERNACIONAL: C07D 215/44, A61K 31/4706, A61P 9/10

71. SOLICITANTE: WYETH

DOMICILIO: NUEVA JERSEY, ESTADOS UNIDOS

74. APODERADO: ALVARO CORREA ORDOÑEZ
T.P.No.20.281

22. BOGOTA, D.C., ABRIL 19, 2007

SS

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



Nº 07-039071- -00000-0000

Fecha 2007-04-19 16 12 14 Dep 2020 NUECREACIONE
Tra 11 PATENTEIYII Eve 378 FASENACIONALI
Act 411 PRESENTACION Folios 98

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No 07-039071- -00000-0000

Fecha 2007-04-19 16:12:14

Tra 11 PATENTE IYII

Act 411 PRESENTACION

Dep 2020 NUECREACIONE

Eve 378 FASE NACIONAL I

Folios 98

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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

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SOLICITUD DE :

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Patente de Invención

☐

Patente de Modelo de Utilidad

☒

Capítulo I.

☐

Capítulo II.

②

SOLICITANTE

(71)

Nombre WYETH

Dirección Five Giralda Farms, Madison, NJ 07940, Estados Unidos de América

Nacionalidad o Domicilio Nueva Jersey, Estados Unidos de América

Lugar de Construcción Delaware, Estados Unidos de América

Teléfono

Fax

E-Mail

IDENTIFICACION

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☐

Otro

☐

Cual

Número

③

REPRESENTANTE
O APODERADO

Nombre ALVARO CORREA ORDÓÑEZ

Dirección Avenida 82 No 10-62 Piso 6

Teléfono 634 1500

Fax 376 2211

E-Mail office bogota@bakernet.com

IDENTIFICACION

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Otro

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Cual

Número

79 143 366 de
Usaquén

TP 20 281

④

INVENTOR (ES)
(72)

Nombre BOSCHELLI, Diane Harns, ZALESKA, Margaret y BARRIOS-SOSA, Ana Carolina

Dirección 3a Elyse Drive, New City, New York 10956, Estados Unidos de América, 843 Bryn Mawr Avenue, Narberth, PA 19072, Estados Unidos de América y 3675 Yarbrough Road, Olanta, SC 29114, Estados Unidos de América, respectivamente

Nacionalidad o Domicilio Estadounidenses

⑤ PCT (85)

Solicitud Internacional No PCT/US2005/037839

Fecha 21-OCT-05

Publicación Internacional No WO 2006/047262

Fecha 04-MAY-06

⑥

Título (54)

4-[(2,4-DICLORO-5-METOXIFENIL)AMINO]-6-ALCOXI-7-ETINIL-3-QUINOLINOCARBONITRILOS PARA EL TRATAMIENTO

DE LESIÓN ISQUÉMICA

⑦

Clasificación Internacional (51)

C07D 215/44, A61K 31/4706, A61P 9/10

⑧

Prioridad

SI ☒NO ☐

(33) País de Origen

US

(32) Fecha

22-OCT-04

(31) Número de Solicitud

60/621,280

⑨

Comprobante de pago No. 07-19712

Fecha 08-MAR-07

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

10

ANEXOS

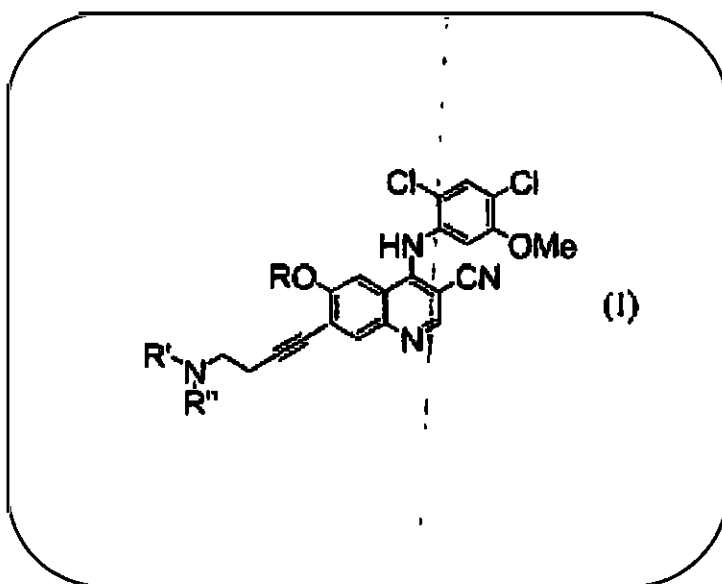
2

6000/2

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

11

FIGURA CARACTERISTICA



12

Solicito la concesión de la patente,

NOMBRE

ALVARO CORREA ORDOÑEZ

FIRMA

CC.

79.143.366 de Usaquén

TP

20.281

Instrucciones para la presentación de los anexos, ver reverso de esta página

00003 3

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800178089-2

RECIBO OFICIAL DE CAJA : 07 - 19,712
FECHA : MARZO 8 DE 2007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No 07-039071-00000-0000

Fecha 2007-04-19 16 12 14 Dep 2020 NUECREACIONE
Tra 11 PATENTEIYII Eve 378 FASENACIONALI
Act 411 PRESENTACION Folios 98

***** CONSIGNACION *****

DEBITANTE	TIPO PASO	BANCO	CUENTA	No. PASO	FECHA PASO	Vr. PASO
RAISBECK LARA RODRIGUEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	54689077	08/03/2007	83,306,000.00

***** 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. _____

TRADUCCIÓN OFICIAL No. 2703071 del inglés al español realizada por Jaime Armando Garavito Burgos, cédula de ciudadanía No. 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución No. 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

APOSTILLA

1. País: Estados Unidos de América
Este documento público
2. Ha sido firmado por BARBARA A. KIELY
3. Quien actúa en calidad de NOTARIO PÚBLICO DE NUEVA JERSEY
4. Lleva el sello de BARBARA A. KIELY, NOTARIO

Certificado

5. En Trenton, Nueva Jersey
6. El 19 de enero de 2007
7. Por Bradley Abelow, Tesorero de Nueva Jersey
8. N° A280860
9. Sello (Aparece adherido sello dorado)
10. Firma (firmado) Bradley Abelow

Jaime A. Garavito B.
JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Res 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

AM101758

DECLARACIÓN JURAMENTADA

Yo, Michelle L. McGowan, Asociado de Legalizaciones, Wyeth, por medio del presente certifico que la copia anexa ha sido comparada con el documento original de traspaso (para U.S.S.N 60/621 280, y cualquier equivalente legal del mismo en un país extranjero, para la invención titulada: "4-[(2,4-Dicloro-5-Metoxifenil)Amino]-

6-Alcoxi-7-Etini-3-Quinolinocarbonitrilos para el Tratamiento de la Lesión Isquémica”) con fecha noviembre 8, 2004 de Ana Carolina Barrios Sosa; y con fecha noviembre 17, 2004 de Margaret Zaleska a Wyeth y que la mencionada copia es una copia auténtica de su original.

Dado hoy 15 de enero de 2007 en Madison, Nueva Jersey, Estados Unidos de América.

Wyeth

(Firmado)
Michelle L. McGowan
Asociado de Legalizaciones

PARA SER USADO EN COLOMBIA

RECONOCIMIENTO

Estado de Nueva Jersey
Condado de Morris

Jaime A. Garavito B.
JAIME A. GARAVITO B.
TRADUCTOR E INTERPRETE OFICIAL
Res 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

El día 15 de enero de 2007 compareció personalmente ante mí Michelle L. McGowan, Asociado de Legalizaciones de Wyeth, a quien conozco y de quien doy fe se trata de la persona descrita en el anterior instrumento y quien también lo suscribió y reconoció ante mí haberlo suscrito.

(Firmado) Barbara A. Kiely, Notario Público

(Sello en tinta que dice: “Barbara A. Kiely ID. 33893. Notario Público de Nueva Jersey. Mi comisión vence el 20 de junio de 2009”)

(Sello notarial realzado)

[Aparece en el encabezamiento de cada página: “Archivo No. AM101758L1 Patente”]

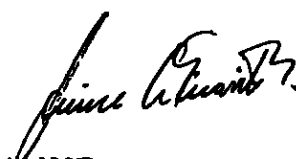
[Aparece en cada pie de página: “Traspaso de Invención – Solicitud Provisional”]

Traspaso de la Invención

En consideración del pago efectuado por la CESIONARIA a la CEDENTE de una contraprestación válida y suficiente, cuyo recibo se reconoce por medio del presente.

CEDENTES:

- (1) Nombre completo del Inventor: Diane Harris BOSCHELLI
Residencia: 3A Elyse Drive, New City, NY 10956
Ciudadanía: Estados Unidos de América
- (2) Nombre completo del Inventor: Ana Carolina BARRIOS SOSA
Residencia: 1995 Dogwood Drive, Scotch Plains, NJ 07076
Ciudadanía: Guatemala
- (3) Nombre completo del Inventor: Margaret ZALESKA
Residencia: 843 Bryn Mawr Avenue, Narberth, PA 19072
Ciudadanía: Estados Unidos de América


JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Reg. 034 de Egreso 11 de 1983
MINISTERIO DE JUSTICIA

Por medio del presente vende, cede y transfiere a la CESIONARIA:

Wyeth
Five Giralda Farms
Madison, New Jersey 07940

a sus sucesores, cesionarios y representantes legales, la totalidad de su derecho, título e intereses para los Estados Unidos y sus posesiones territoriales y en todos los países extranjeros, incluyendo todos los derechos de invocar prioridad, en y a su invención titulada:

4-[(2,4-Dicloro-5-Metoxifenil)Amino]-6-Alcoxi-7-Etinil-3-Quinolinocarbonitrilos para el Tratamiento de la Lesión Isquémica

e inventada por la CEDENTE y los siguientes inventores adicionales, si los hubiere: y que se encuentra en la Solicitud Provisional de los Estados Unidos No. 60/621.280 presentada el 22 de octubre de 2004.

[Verificar (c) si también se están cediendo solicitud(es) extranjera(s)]

☒ y cualquier equivalente de la misma en un país extranjero,

incluyendo el derecho a invocar prioridad, así como todas y cada una de las mejoras divulgadas en ella y todas y cada una de las patentes que se hayan de

obtener para la mencionada invención por medio de la anterior solicitud o cualquier solicitud provisional, no provisional, continuación, divisional, renovación, prórroga o sustitución de la misma y en cuanto a patentes, cualquier reexpedición o re-examen de las mismas.

Los CEDENTES por medio del presente declaran que no se ha hecho ni se hará o suscribirá ninguna cesión, venta, acuerdo o gravamen que esté o pudiera estar en conflicto con este traspaso.

Los CEDENTES autorizan a la CESIONARIA a presentar solicitudes de patente y a recibir títulos de patente para la mencionada invención en cualquiera de los mencionados países en su propio nombre, o en el nombre de la CEDENTE, según por lo que pueda optar.

Los CEDENTES declaran y acuerdan suscribir o tramitar cualquier documento de transferencia del título a dicha invención y cualquier patente que se pueda expedir; también a entregar en cualquier momento, a solicitud y a expensas de la CESIONARIA, cualquier testimonio con respecto a cualesquier derechos preexistentes que impidan el patentamiento, litigio o procedimiento relacionado con la misma y a suscribir todos los documentos que puedan ser necesarios o convenientes para perfeccionar el título a la mencionada invención o cualesquier patentes que puedan ser otorgadas a la CESIONARIA, sus sucesores, cesionarios u otros representantes legales y a suscribir en cualquier momento, a solicitud y a expensas de la CESIONARIA todas las continuaciones, continuaciones parciales, divisional, renovación o sustitución de la misma y en cuanto a patentes para la mencionada invención o cualquier parte(s) de la misma, por medio del presente se ceden a la CESIONARIA y se harán todos los juramentos o declaraciones al igual que todos los demás actos legales que se requieran para obtenerlas, sin compensación adicional, pero a expensas de la CESIONARIA, sus sucesores, cesionarios u otros representantes legales.

Jaime A. Garavito B.
JAIIME A. GARAVITO B
REGISTRADOR E INTERPRETE OFICIAL
Des. 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

Los CEDENTES autorizan y solicitan al Comisionado de Patentes expedir su CESIONARIA todas y cada una de las Patentes de los Estados Unidos para la mencionada invención, que resulten de cualquiera de las solicitudes anteriormente mencionadas.

[Firmado]
Diane Harris BOSCHELLI

Noviembre 8, 2004
Fecha

RECONOCIMIENTO

Estado de Nueva York)
) Declaración juramentada
Condado de Rockland)

Jaime A. Garavito B.
JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Bm 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

El 08 de noviembre de 2004, Diane Harris BOSCHELLI, compareció personalmente ante mí, a quien conozco y de quien doy fe se trata de la persona descrita en el anterior instrumento y quien suscribió el mismo en forma libre y espontánea para los fines consignados en el mismo.

(Firmado) Janice A. White, Notario Público

(Sello en tinta que dice: "Janice A. White, Notario Público – Estado de Nueva York. N° 01-WH6052604. Calificado en el Condado de Rockland. Mi comisión vence el 26 de diciembre de 2006")

[Firma ilegible]
Ana Carolina BARRIOS SOSA

Noviembre 11, 2004
Fecha

RECONOCIMIENTO

Estado de Nueva York)
) Declaración juramentada
Condado de Rockland)

El 11 de noviembre de 2004, Ana Carolina BARRIOS SOSA, compareció personalmente ante mí, a quien conozco y de quien doy fe se trata de la persona descrita en el anterior instrumento y quien suscribió el mismo en forma libre y espontánea para los fines consignados en el mismo.

[Firma ilegible] Notario Público

(Sello en tinta que dice: "Janice A. White. Notario Público – Estado de Nueva York.
N° 01-WH6052604. Calificado en el Condado de Rockland. Mi comisión vence el
26 de diciembre de 2006")

[Firmado]
Margaret ZALESKA

Noviembre 17, 2004
Fecha

RECONOCIMIENTO

Estado de Nueva Jersey)
Condado de Middlesex)

Declaración juramentada

Jaime A. Garavito B.
JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Nº 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

El 17 de noviembre de 2004, Margaret ZALESKA, compareció personalmente ante mí, a quien conozco y de quien doy fe se trata de la persona descrita en el anterior instrumento y quien suscribió el mismo en forma libre y espontánea para los fines consignados en el mismo

[Firmado] Carole K. Kamrad, Notario Público

(Sello en tinta que dice: "Carole K. Kamrad Notario Público de Nueva Jersey. Mi comisión vence el 25 de noviembre de 2007")

La anterior es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

Jaime A. Garavito B.

Jaime Armando Garavito Burgos
c.c. N° 19.130 702 de Bogotá
Traductor e Intérprete Oficial según Resolución N° 034 de enero 11 de 1983
expedida por el Ministerio de Justicia

BOGDM5 # 73712

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
BARBARA A KIELY
3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF:
BARBARA A KIELY, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 19TH DAY OF JANUARY 2007
7. BY: Bradley Abelow, NEW JERSEY TREASURER
8. NO. A280860
9. SEAL/STAMP:
10. SIGNATURE

Bradley Abelow



• nnnX 11

AM101758

AFFIDAVIT

I, Michelle L. McGowan, Legalization Associate of Wyeth, do hereby certify that the attached copy has been compared with the original Assignment (corresponding to U.S.S.N. 60/621,280, and any legal equivalent thereof in a foreign country, for the invention entitled: "4-[(2,4-Dichloro-5-Methoxyphenyl)Amino]-6-Alkoxy-7-Ethynyl-3-Quinolonecarbonitriles for the Treatment of Ischemic Injury") dated November 8, 2004 from Diane Harris Boschelli; and dated November 11, 2004 from Ana Carolina Barrios Sosa; and dated November 17, 2004 from Margaret Zaleska to Wyeth and that the said copy is a true copy of the original.

Dated this 15th day of January 2007, at Madison, New Jersey, United States of America.

Wyeth

Michelle L. McGowan
Michelle L. McGowan
Legalization Associate

TO BE USED IN COLOMBIA

ACKNOWLEDGMENT

State of New Jersey)
)
County of Morris)

On this 15th day of January, 2007, before me personally appeared Michelle L. McGowan, Legalization Associate of Wyeth, to me known and known to me to be the individual described in and who executed the foregoing instrument, and she acknowledged to me that she executed the same.

Barbara A. Kiely ID. 33893
Notary Public of New Jersey
My Commission Expires June 20, 2009

Barbara A. Kiely
Notary Public

Assignment of Invention

In consideration of the payment by ASSIGNEE to ASSIGNOR of good and valuable consideration, the receipt of which is hereby acknowledged,
ASSIGNOR:

(1) Full Name of Inventor: Diane Harris BOSCHELLI
Residence 3A Elyse Drive, New City, NY 10956
Citizenship: US

(2) Full Name of Inventor: Ana Carolina BARRIOS SOSA
Residence: 1995 Dogwood Drive, Scotch Plains, NJ 07076
Citizenship: Guatemala

(3) Full Name of Inventor: Margaret ZALESKA
Residence: 843 Bryn Mawr Avenue, Narberth, PA 19072
Citizenship US

hereby sells, assigns and transfers to ASSIGNEE.

Wyeth
Five Giralda Farms
Madison, New Jersey 07940

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nnn1/3

and the successors, assigns and legal representatives of the ASSIGNEE the entire right, title and interest for the United States and its territorial possessions and in all foreign countries, including all rights to claim priority, in and to the invention entitled:

4-[(2,4-Dichloro-5-Methoxyphenyl)Amino]-6-Alkoxy-7-Ethynyl-3-Quinolincarbonitriles for the Treatment of Ischemic Injury

and invented by ASSIGNOR and the following additional inventors, if any:

and which is found in U.S. Provisional Application No. 60/621,280 filed on: October 22, 2004

[also check if foreign application(s) is(are) also being assigned]

☒ and any legal equivalent thereof in a foreign country,

the date of filing and application number of said U S. application when known, to be inserted above, including the right to claim priority, including any and all improvements disclosed therein, and in and to all Letters Patent to be obtained for said invention by the above application or any subsequently filed provisional, nonprovisional, continuation, divisional, renewal, or substitute thereof, and as to Letters Patent any reissue or re-examination thereof

ASSIGNOR hereby covenants that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment.

ASSIGNOR authorizes ASSIGNEE to make applications for and to receive Letters patent for said invention in any of said countries in its own name, or in ASSIGNOR's name, at its election.

ASSIGNOR covenants and agrees to execute or procure any further necessary assurance of the title to said invention and any Letters Patent which may issue therefore and to, at any time, upon the request and at the expense of ASSIGNEE deliver any testimony in any interference, litigation or proceeding related thereto and execute all papers that may be necessary or desirable to perfect the title to said invention or any Letters Patent which may be granted therefore in ASSIGNEE, its successors, assigns or other legal representatives, and that to, at any time, upon the request and at the expense of ASSIGNEE execute any continuation, continuation-in-part, divisional, renewal or substitute thereof, and as to Letters Patent and reissue or re-examination thereof, or any other additional applications of Letters Patent for said invention or any part thereof, all of which applications and any Letters Patent issuing thereon are hereby assigned to ASSIGNEE, and will make all rightful oaths or declarations, and do all lawful acts requisite for procuring the same therein, without further compensation, but at the expense of ASSIGNEE, its successors, assigns or other legal representatives.

ASSIGNOR authorizes and requests the Commissioner of Patents to issue any and all Letters Patent of the United States for said invention, resulting from any of the aforesaid applications to its ASSIGNEE.

Diane Harris Boschelli
Diane Harris BOSCHELLI

11/8/04
Date

ACKNOWLEDGMENT

State of New York }
County of Rockland } ss

On the 8 day of NOVEMBER 2004, Diane Hams BOSCHELLI personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.

JANICE A WHITE
NOTARY PUBLIC - STATE OF NEW YORK
NO 01-WH6052604
QUALIFIED IN ROCKLAND COUNTY
MY COMMISSION EXPIRES 12-26-2006

Janice A. White
Notary Public

Ana Carolina Barrios Sosa
Ana Carolina BARRIOS SOSA

Nov 11/2004
Date

ACKNOWLEDGMENT

State of New York }
County of Rockland } ss:

On the 11 day of November 2004, Ana Carolina BARRIOS SOSA personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.

JANICE A WHITE
NOTARY PUBLIC - STATE OF NEW YORK
NO 01-WH6052604
QUALIFIED IN ROCKLAND COUNTY
MY COMMISSION EXPIRES 12-26-2006

Janice A. White
Notary Public

Margaret Zaleska
Margaret ZALESKA

November 17, 2004
Date

ACKNOWLEDGMENT

State of New Jersey }
County of Middlesex } ss:

On the 17 day of November 2004, Margaret ZALESKA personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.

CAROLE K. KAMRAD
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires Nov. 25, 2007

Carole K. Kamrad
Notary Public

From the INTERNATIONAL BUREAU

0001/6

PCT

NOTIFICATION CONCERNING
TRANSMITTAL OF COPY OF INTERNATIONAL
APPLICATION AS PUBLISHED OR REPUBLISHED

To

16
BARRETT, Rebecca
WYETH
PATENT LAW DEPARTMENT
Five Giralda Farms
Madison, New Jersey 07940
ETATS-UNIS D'AMERIQUEDate of mailing (day/month/year)
04 May 2006 (04.05 2006)Applicant's or agent's file reference
PAM101758/PCT

IMPORTANT NOTICE

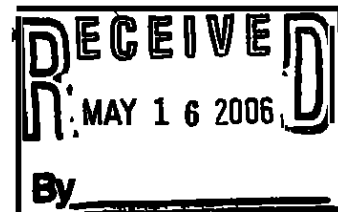
International application No.
PCT/US2005/037839International filing date (day/month/year)
21 October 2005 (21 10 2005)Priority date (day/month/year)
22 October 2004 (22.10 2004)

Applicant

WYETH et al

The International Bureau transmits herewith the following documents

- ☒ copy of the international application as published by the International Bureau on 04 May 2006 (04 05 2006) under No WO 2006/047262
- ☐ copy of international application as republished by the International Bureau on under No WO
For an explanation as to the reason for this republication of the international application, reference is made to INID codes (15), (48) or (88) (as the case may be) on the front page of the attached document

RECEIVED
MAY 23 2006
SHEILA MCBRIDEThe International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Nora Lindner

Facsimile No +41 22 740 14 35

Facsimile No +41 22 338 89 65

Form PCT/IB/311 (January 2004)

CC-COLLEGEVILLE

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
4 May 2006 (04.05.2006)

(10) International Publication Number
WO 2006/047262 A1

(51) International Patent Classification:
C07D 215/44 (2006.01) A61P 9/10 (2006.01)
A61K 31/4706 (2006 01)

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(71) Applicant (for all designated States except US): WYETH
[US/US], Five Giralda Farms, Madison, NJ 07940 (US)

(72) Inventors; and

(75) Inventors/Applicants (for US only): BOSCHELLI,
Diane, Harris [US/US], 3a Elyse Drive, New City, New
York 10956 (US) ZALESKA, Margaret [US/US], 843
Bryn Mawr Avenue, Narberth, PA 19072 (US) BAR-
RIOS-SOSA, Ana Carolina [US/US], 3675 Yarborough
Road, Olanta, SC 29114 (US)

(74) Agents: BARRETT, Rebecca et al.; WYETH, PATENT
LAW DEPARTMENT, Five Giralda Farms, Madison, New
Jersey 07940 (US)

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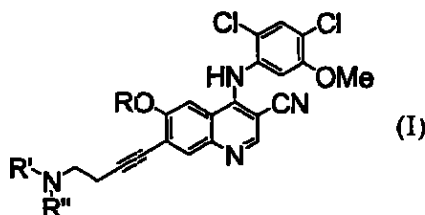
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(54) Title: 4 [(2 4-DICHLORO-5-METHOXYPHENYL)AMINO]-6-ALKOXY-7-ETHYNYL-3-QUINOLINECARBONITRILES FOR THE TREATMENT OF ISCHEMIC INJURY



(57) Abstract: This invention relates to compounds of the formula (I) wherein R is methyl or ethyl, R' and R'' are independently alkyl of 1 to 3 carbon atoms, or R' and R'', taken together with the nitrogen to which they are attached, can form a 5 or 6 membered saturated ring which may optionally contain an additional heteroatom selected from NR'', O or S(O)_n, n is 0-2, and R''' is hydrogen or alkyl of 1 to 3 carbon atoms, and pharmaceutically acceptable salts thereof, and their use for inhibiting vascular permeability caused by disease, injury or other trauma.

WO 2006/047262 A1

4-[(2,4-DICHLORO-5-METHOXYPHENYL)AMINO]-6-ALKOXY-7-ETHYNYL-3-QUINOLINECARBONITRILES FOR THE TREATMENT OF ISCHEMIC INJURY

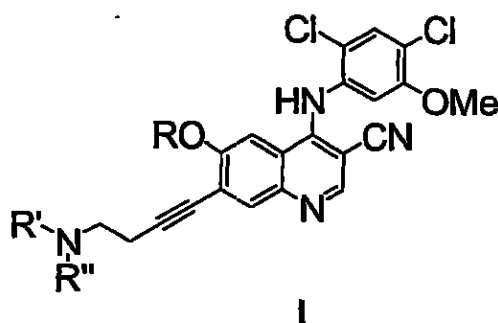
The present invention relates to 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-alkoxy-7-ethynyl-3-quinolinecarbonitriles and to methods for using them in the treatment of ischemic injury.

BACKGROUND OF THE INVENTION

Stroke is the third leading cause of death and the major cause of disability in the US, where approximately 750,000 strokes occur each year. Ischemic stroke comprises about 80% of this number, with primary intracerebral hemorrhagic stroke about 15-20%. To date, the only approved efficacious treatment for acute ischemic cerebral infarction is thrombolytic therapy by means of intravenous administration of t-PA, recombinant tissue plasminogen activator. The usefulness of this therapy is extremely limited. It must be given within a three hour window after the onset of symptoms, while a majority of patients seek and/or receive treatment after a substantial delay. In addition, treatment with t-PA carries an increased risk of causing intracerebral hemorrhage, a potentially devastating complication. Presence of hemorrhage must be ruled out prior to treatment and blood pressure must be carefully managed and monitored during and after treatment with t-PA. Currently, no neuroprotective therapy is available for treatment of ischemic stroke, hemorrhagic stroke or brain trauma. New treatments for stroke and other conditions associated with vascular permeability are greatly needed.

DESCRIPTION OF THE INVENTION

In accordance with one aspect of the present invention there are provided compounds of the structural formula:



wherein:

R is methyl or ethyl;

5 R' and R'' are independently alkyl of 1 to 3 carbon atoms, or R' and R'', taken together with the nitrogen to which they are attached, can form a 5 or 6 membered saturated ring which may optionally contain an additional heteroatom selected from NR''', O or S(O)_n;

n is 0-2;

and

10 R''' is hydrogen or alkyl of 1 to 3 carbon atoms; and pharmaceutically acceptable salts thereof.

In certain preferred embodiments of the invention, R' and R'', taken together with the nitrogen to which they are attached, form a N-(C₁-C₃)-alkyl piperazine, piperidine,
15 piperazine or morpholine.

In some preferred embodiments of the invention, R is methyl.

20 In other preferred embodiments of the present invention R' and R'', taken together with the nitrogen atom to which they are attached, form a N-(C₁-C₃)-alkyl piperazine, piperazine or morpholine ring.

Where R' and R'' taken together with the nitrogen to which they are attached form a N-(C₁-C₃)-alkyl piperazine, preferably they form N-methylpiperazine.
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In still other preferred embodiments of the present invention R' and R'' are methyl.

30 Pharmaceutically acceptable salts are those derived from organic and inorganic acids such as: acetic, lactic, carboxylic, citric, cinnamic, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, oxalic, propionic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, glycolic, pyruvic, methanesulfonic, ethanesulfonic, toluenesulfonic, salicylic, benzoic, and similarly known pharmaceutically acceptable acids.

... nnn20

Five or six membered saturated rings optionally containing one additional heteroatom selected from NR^m, O or S(O)_n as defined by N R^mRⁿ include, but are not limited to, pyrrolidine, pyrazolidine, imidazolidine, piperidine, piperazine, morpholine, 5 thiomorpholine, 1-oxo-1-thiomorpholine and 1,1-dioxo-1-thiomorpholine.

Specific compounds of the invention include:

- 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-7-[4-(dimethylamino)but-1-ynyl]-6
10 methoxy-3-quinolinecarbonitrile;
4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-[4-(4-methylpiperazin-1-yl)but-1-ynyl]-3-quinolinecarbonitrile;
4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-(4-morpholin-4-ylbut-1-ynyl)-
3-quinolinecarbonitrile;
15 4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-(4-piperazin-1-ylbut-1-ynyl)-
3-quinolinecarbonitrile; and
4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-ethoxy-7-[4-(4-methylpiperazin-1-yl)but-1-ynyl]-3-quinolinecarbonitrile, and pharmaceutically acceptable salts thereof.
- 20 Other aspects of the invention include pharmaceutical compositions comprising the compounds described herein and at least one pharmaceutically acceptable carrier or excipient, and methods of treating ischemic injury using these compounds

The compounds of the invention are prepared as illustrated below. The compounds
25 of this invention were prepared from: (a) commercially available starting materials (b) known starting materials which can be prepared as described in literature procedures or (c) new intermediates described in the schemes and experimental procedures herein.

30 Reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformation being effected. It is understood by those skilled in the art of organic synthesis that the various functionalities present on the molecule must be consistent with the chemical transformations proposed. When

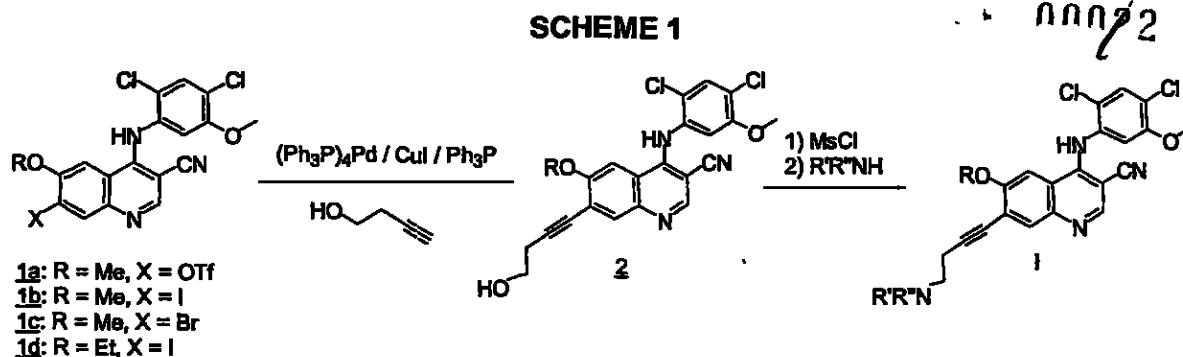
not specified, order of synthetic steps, choice of protecting groups and deprotection conditions will be readily apparent to those skilled in the art. In addition, in some instances, substituents on the starting materials may be incompatible with certain reaction conditions. Restrictions pertinent to given substituents will be apparent to one skilled in the art. Reactions were run under inert atmospheres where appropriate.

Compounds of Formula I are prepared as depicted in Scheme 1. Compounds of Formula I wherein R is Me are readily obtained starting from 1a, 3-cyano-4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-quinolinyl trifluoromethanesulfonate. The preparation of 1a has been reported in the literature, Berger, D et. al. *Bioorg. Med.Chem.Lett.* 12, 2761 (2002) and US6521618 (Feb 18, 2003), incorporated by reference herein in their entirety.

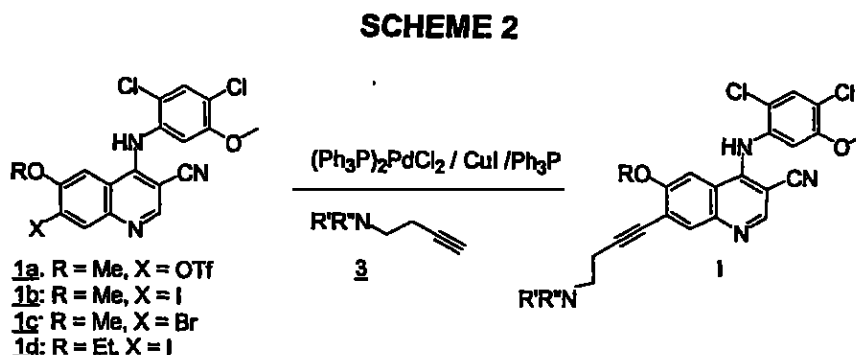
Treatment of 1a with 3-buten-1-ol in the presence of a palladium catalyst, preferably tetrakis(triphenylphosphine)palladium, with copper iodide, in a solvent system such as triethylamine and dioxane at elevated temperature, preferably 95-100°C, provides compounds of formula 2. Reaction of compounds of formula 2 with methanesulfonyl chloride in a solvent system such as N,N-dimethylformamide and tetrahydrofuran at reduced temperature, preferably 0°C, gives the corresponding mesylate. The intermediate mesylate is not normally isolated but is treated directly with an appropriate amine of formula R'R'NH to provide the compounds of formula I. Other leaving groups such as tosylate can be employed as an alternative to the mesylate group.

In addition to 1a, other starting materials including 1b, 4-[(2,4-dichloro-5-methoxyphenyl)amino]-7-iodo-6-methoxy-3-quinolinecarbonitrile, and 1c, 7-bromo-4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-3-quinolinecarbonitrile, can be used to obtain the compounds of formula I where R is Me.

Compounds of Formula I wherein R is Et are readily obtained starting from 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-iodo-3-quinolinecarbonitrile, 1d.



- An alternate route to compounds of formula I is depicted in Scheme 2. Compounds of formula 1a-d are treated with an amine of formula 3 in the presence of a palladium catalyst, preferably dichlorobis(triphenylphosphine)palladium(II), with copper iodide and triphenylphosphine, in a solvent system such as triethylamine and N-methylpyrrolidinone at elevated temperature, preferably 70°C, to provide compounds of formula I. Alternatively the reaction of compounds of formula 1a-d with amines of formula 3 can be performed in a solvent system of triethylamine and N,N-dimethylformamide or alternatively in the presence of a base such as potassium carbonate in a solvent system of methanol and tetrahydrofuran.



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Compounds of the present invention were evaluated in several standard pharmacological tests that showed that compounds of the present invention inhibit Src kinase and are useful for the prevention of vascular permeability.

Src Kinase Assay

Recombinant human Src enzyme was obtained from PanVera (P3044). Biotinylated peptide corresponding to residues 6 – 20 of Cdk1 was used as a substrate (Biotin-KVEKIGEGTYGVYK-COOH). Homogeneous fluorescence resonance energy transfer kinase assays were performed using the europium/APC detection format (LANCER, Perkin Elmer). Src enzyme (10 ng) was mixed with biotinylated peptide (final concentration 2 μ M), 50 mM Hepes (pH 7.5), 10 mM MgCl₂, 20 μ g/ml BSA, 0.001% Brij-35 (Sigma), 100 μ M ATP, 1% DMSO. The kinase reaction was incubated for 70 min at 37°C. The reaction was stopped with EDTA at a final concentration of 30mM EDTA/25mM Hepes (pH 7.5)/10 μ g/ml BSA. The mixture was combined with Eu-labeled anti-phosphotyrosine antibody PT66 (Perkin Elmer, AD0068) and Streptavidin Surelight-APC (Perkin Elmer, CR130-100) in 50 mM Hepes (pH 7.5)/ 20 μ g/ml BSA, and incubated for 30 min according to manufacturer's specifications. Fluorescence intensity at 665 nm was used to monitor the extent of the kinase reaction. Multiple entries for a given compound indicate that it was tested multiple times. The results obtained for representative compounds of this invention are listed in Table 1.

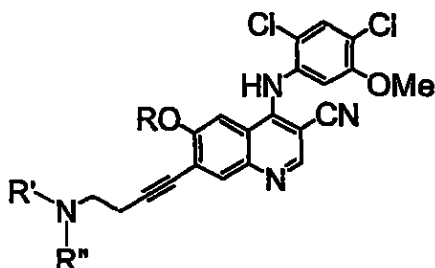
Anchorage Independent Src-transformed Fibroblast Proliferation Assay

Rat2 fibroblasts stably transformed with a plasmid containing a CMV promotor controlled v-Src/Hu c-Src fusion gene in which the catalytic domain of human c-Src was inserted in place of the v-Src catalytic domain in the v-Src gene are used for the measurement of src dependent suspension growth. Ultra-low cluster plates (Costar # 3474) are seeded with 10,000 cells per well on Day 1. Alternatively, Ultra-low cluster plates (Costar 3474) treated with Sigmacote (Sigma), rinsed with 70% ethanol, after drying in the hood, are seeded with 5000 cells. Compound is added in serial two-fold dilutions from 10 micromolar to 0.009 micromolar on Day 2 and MTS reagent (Promega) is added on Day 5 (100 microliters of MTS/medium mix + 100 microliters of medium already on the cells and the absorbance is measured at 490nm. The results are analyzed as follows to yield an IC₅₀ for proliferation (micromolar units) as follows: %inhibition = (Abs490 nm sample - blank)/(Abs490 nm no cmpd control - blank) X 100%. Multiple entries for a given compound indicate that it was tested multiple times. The results obtained for representative compounds of this invention are listed in Table 1.

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Table 1. Inhibition of Src enzymatic and cellular activity



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EXAMPLE	R	NR'R''	Src enzyme IC ₅₀ nM	Src cell IC ₅₀ nM
1	Me	NMe ₂	5.0, 4.7	252, 240
2	Me	N-Me-piperazine	3.5, 4.2	71, 70, 77
3	Me	morpholine	4.0, 4.1	206, 183
4	Me	piperazine	5.9, 4.8	435, 605
5	Et	N-Me-piperazine	6.5, 2.8	96, 183, 154, 103

IV administration of Example 2 provides neuroprotection in a model of transient focal ischemia

- 10 Example 2 was tested in a rat model of transient focal ischemia. Wistar rats were subjected to a 90 min occlusion of the middle cerebral artery (MCA) using an intraluminal suture approach as described by Longa *et al.*, *Stroke* 1989, 20:84 followed by reperfusion for 48 hours. Four hours after the initial onset of ischemia, animals received compound of Example 2 as a single i.v. bolus in 5% dextrose, 0.9%
- 15 lactic acid at pH 4.5-5.0 (3 mg/kg, 10 mg/kg or 30 mg/kg). Following reperfusion, the animals were evaluated over a 48 hour period for neurological function deficit. Infarct size was measured following sacrifice at 48 hours post MCA occlusion. 10 and 30 mg/kg doses of Example 2 significantly improved recovery from stroke-induced neurological deficits 35% and 53%, respectively as a percent of control (statistical error: 10-12%).
- 20 Statistically significant reductions in the volume of infarcted brain tissue were observed at 10 mg/kg and 30 mg/kg of Example 2, showing a 32% and 40% reduction in infarct volume as a percent of control (statistical error; 7-10%).

IV administration of Example 2 provides neuroprotection and improves long-term neurological recovery in a model of permanent focal ischemia

Example 2 was tested in a rat model of permanent occlusion of middle cerebral artery, without the reperfusion, substantially as described by Chen et al., *Stroke*, 1986, 17:738. This is a more stringent model than the transient focal ischemia. Two hours following an electrocoagulation of middle cerebral artery, vehicle or Example 2 were administered at 10 mg/kg i.v followed by 3 additional doses of 10 mg/kg iv administered at 4, 24 and 26 hours post-induction of stroke. In one study, volume of infarcted brain tissue was evaluated at 48 hour post-stroke. In a second study, animals were subjected to testing of sensori-motor function based on tactile and proprioceptive limb placement substantially as described by DeRyck et al., *Brain Res.* 1992, 573:44 at three day intervals over a timecourse of three weeks following stroke. In the animals treated with Example 2 a statistically significant reduction by 24% of the infarct volume was found at 48 hours post-induction of stroke. In addition, Example 2 significantly improved long-term sensorimotor recovery from neurological deficits induced in this stroke model.

IV administration of Example 2 provides neuroprotection in the model of hemorrhagic stroke

Example 2 was tested in a rat model of intracerebral hemorrhage induced by intrastriatal infusion of collagenase substantially as described by Rosenberg et al., *Stroke*, 1990, 20:801. In this model, infusion of collagenase into caudate nucleus leads to proteolytic destruction of collagen in basal lamina of blood vessels and induces intracranial bleeding and edema peaking in 24-48 hours. Example 2 was administered at 4 hours post-induction of hemorrhagic stroke as a single i.v injection at the doses of 10 mg/kg or 30 mg/kg. 24 hours later brain water content was determined as a measure of edema. Results indicate that Example 2 significantly reduces post-hemorrhagic brain edema at both tested doses by 18% and 24% respectively.

Vascular permeability due to disease, injury, or other trauma, may occur in a variety of tissues and organs including organs of the central nervous system,

cardiopulmonary system, gastrointestinal system and renal system. Compounds of the present invention are useful for inhibiting vascular permeability caused by disease, injury, or other trauma. In particular, vascular permeability may be inhibited in cerebral and spinal tissue following cerebrovascular events. Vascular permeability is a major cause of vascular leakage and/or edema following a cerebrovascular event and often leads to neurological disorders and disabilities. Cerebrovascular events including, but not limited to transient and acute ischemic events, may be treated in accordance with the present invention. Acute events include, but are not limited to, stroke, head trauma, spinal trauma, general anoxia, hypoxia including fetal hypoxia, hypoglycemia, hypotension as well as similar injuries seen during procedures from embole, hyperfusion and hypoxia. Stroke includes, but is not limited to focal and global ischemia, transient cerebral ischemic attacks, and other cerebral vascular problems accompanied by cerebral ischemia. The instant invention would also be useful for a range of cerebrovascular events including cerebral hemorrhage, infarction due to embolism or thrombosis of the intra- or extra cranial arteries, perinatal asphyxia, in cardiac arrest and status epilepticus, especially where blood flow to the brain is halted for a period of time. Cerebrovascular events associated with vascular leakage also include infections, including, but not limited to encephalitis and meningitis associated with neuroinflammation, which, through vascular leakage propagate injury to surrounding tissues. Systemic disease such as diabetes, multiple sclerosis, kidney disease and atherosclerosis may also result in increased vascular permeability. Compounds of the present invention are also useful for inhibiting vascular permeability triggered by local tissue/organ ischemic (hypoxic) event outside of the central nervous system, including, but not limited to myocardial ischemia and ischemic bowel disease.

Compounds of the present invention provide neuroprotection in a patient. Neuroprotection, as used herein, refers to the protection of neural cells against cell death or apoptosis. One measure of the extent of cell death or apoptosis is infarct volume; the volume of necrotic or dead brain tissue. Imaging techniques and the patient's clinical status can be used to assess infarct volume following an ischemic event. Compounds of the present invention reduce infarct volume of a patient as

compared to typical infarct volume experienced in similar ischemic events in the absence of agents of the present invention.

Compounds of the present invention prevent, reduce or inhibit neurodegeneration and/or neurotoxicity associated with vascular permeability that result in symptoms including, but not limited to, visual impairment such as sudden vision loss or diplopia, speech or language impairment such as aphasia or dysarthria, memory impairment, cognitive impairment or dysfunction ranging from mild cognitive impairment to dementia, and motor impairment including, but not limited to, parathesia, loss of muscle control, weakness, numbness or paralysis. Neurological deficits such as those described above, resulting from injury or disease described above may be inhibited or prevented in accordance with the present invention. Thus, the present invention provides methods of treating, preventing, inhibiting or alleviating conditions associated with vascular leakage or permeability listed above in a mammal, preferably in a human, the methods comprising providing a pharmaceutically effective amount, and in particular a vascular permeability inhibiting amount, of a compound of this invention to the mammal, and in particular a human patient, in need thereof.

Also encompassed by the present invention are pharmaceutical compositions for treating or modulating vascular permeability comprising at least one compound of Formula I, mixtures thereof, and or pharmaceutical salts thereof, and a pharmaceutically acceptable carrier therefore. Such compositions are prepared in accordance with acceptable pharmaceutical procedures, such as described in *Remingtons Pharmaceutical Sciences*, 17th edition, ed. Alfonso R. Gennaro, Mack Publishing Company, Easton, PA (1985). Pharmaceutically acceptable carriers are those that are compatible with the other ingredients in the formulation and biologically acceptable.

Liquid carriers may be used in preparing solutions, suspensions, emulsions, syrups and elixirs including intravenous solutions. The active ingredient of this invention can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, organic solvent, or a mixture of both. The liquid carrier can contain other

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suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers, osmo-regulators, antioxidants and antifoaming agents.

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Suitable examples of liquid carriers for oral, intravenous and parenteral administration include water (particularly containing additives as above e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), saline, dextrose solutions, dextrose-saline and dextrose-water solutions, alcohols (including monohydric alcohols and polyhydric alcohols e.g. glycols) and their derivatives. Liquid carriers are used in sterile form for parenteral and intravenous administration. PH of liquid formulations may be adjusted in some cases by the addition of HCl, sodium hydroxide, and phosphoric acid. Preferably compositions of the present invention are liquid pharmaceutical compositions which are sterile solutions or suspensions in an iso-osmotic, physiologically compatible buffered system.

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Liquid pharmaceutical compositions of the present invention can be administered by, for example, intramuscular, intraperitoneal, intravenous, or subcutaneous injection. Pharmaceutical compositions of the present invention are preferably administered to a patient by intraperitoneal or intravenous injection. Most preferably, the composition is administered intravenously such as by intravenous bolus injection, intravenous i.v. drip, repeated slow bolus administration or infusion.

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Oral administration may be either liquid or solid composition form. The compounds of this invention may also be administered orally or parentally, neat or in combination with conventional pharmaceutical carriers. Applicable solid carriers can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents or an encapsulating material. In powders, the carrier is a finely divided solid, which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers

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include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

- 5 Preferably the pharmaceutical composition is in unit dosage form, e.g. as tablets, capsules, powders, solutions, suspensions, emulsions, granules, suppositories, ampule, or bolus. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example packeted powders, lyophilized powder or
10 cake in ampoules or vials, or vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

- The dose provided to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, and the state of
15 the patient, the manner of administration, and the like. A "therapeutically effective amount" is an amount sufficient to cure or ameliorate symptoms of a disease or injury. Generally, a single dose (or dosage form) will contain from about 1 mg/kg to about 30 mg/kg, and more preferably from about 1 mg/kg to about 10 mg/kg of
20 compound of the present invention. It is expected that some patients will receive multiple doses. The dosage to be used in the treatment of a specific case must be subjectively determined by the attending physician. The variables involved include the specific condition and the size, age and response pattern of the patient.

- 25 The present invention provides advantages over previously known treatments for stroke and other conditions associated with vascular permeability. In particular, while it is preferable to treat patients as soon as possible after an ischemic injury, compounds of the present invention may be effective in preventing neurodegeneration and development of neurological deficits in some patients when
30 administered 6-18 hours after injury and even up to about 18-24 hours after ischemic injury. Furthermore, treatment may continue and improvement in a patient's prognosis may result from continuous or repeated administration of compound of the present invention for up to about 72 hours or longer following ischemic injury.

Provide as used herein means either directly administering a compound or composition of the present invention, or administering a prodrug, dervative or analog which will form an equivalent amount of the active compound or substance within the
5 body.

The present invention includes prodrugs of compounds of Formula I. "Prodrug", as used herein means a compound which is convertible *in vivo* by metabolic means (e.g. by hydrolysis) to a compound of Formula I. Various forms of prodrugs are
10 known in the art, for example, as discussed in Bundgaard, (ed.), Design of Prodrugs, Elsevier (1985); Widder, et al. (ed.), Methods in Enzymology, vol. 4, Academic Press (1985); Krogsgaard-Larsen, et al., (ed). "Design and Application of Prodrugs, Textbook of Drug Design and Development, Chapter 5, 113-191 (1991), Bundgaard, et al., Journal of Drug Delivery Reviews, 8:1-38(1992), Bundgaard, J. of
15 Pharmaceutical Sciences, 77:285 et seq. (1988); and Higuchi and Stella (eds.) Prodrugs as Novel Drug Delivery Systems, American Chemical Society (1975).

This invention will be more fully described in conjunction with the following specific examples which are not to be construed as limiting the scope of this invention.
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Reference Example 1

2-Cyano-N-(2,4-dichloro-5-methoxyphenyl)acetamide

2,4-Dichloro-5-methoxyaniline (5.00 g, 26 mmol) and cyanoacetic acid (2.28 g, 26.8 mmol) were mixed in 50 mL of tetrahydrofuran, under N₂, until a solution formed.
25 This solution was heated to reflux and 1,3-diisopropylcarbodiimide (4.2 mL, 26.8 mmol) was added dropwise. After 30 minutes a TLC check (5% MeOH in CH₂Cl₂) indicated that the reaction was complete. The mixture was cooled to ~15°C in an ice-bath. The solid was collected by filtration and washed with tetrahydrofuran. The filtrate was slowly poured into water and stirred for 30 minutes. The white solid was
30 collected by filtration, washed with water and then dissolved in 500 mL of ethyl acetate. The solution was dried over Na₂SO₄ and concentrated in vacuo to give 5.9 g (88%) of 2-cyano-N-(2,4-dichloro-5-methoxyphenyl)acetamide as a white solid, mp 180-181°C; MS 257.0, 259.0 (M-H)-.

Analysis for $C_{10}H_8Cl_2N_2O_2$:

Calcd: C, 46.36; H, 3.11; N, 10.81.

Found: C, 46.25; H, 3.10; N, 10.85.

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Reference Example 2

2-Cyano-N-(2,4-dichloro-5-methoxyphenyl)-3-[(3-iodo-4-methoxyphenyl)amino]prop-2-enamide

To a suspension of 2-cyano-N-(2,4-dichloro-5-methoxyphenyl)acetamide (5.00 g, 19.30 mol) in 400 mL of *iso*-propanol, under N_2 , is added 3-iodo-*p*-anisidine (5.80 g, 23.16 mmol). This mixture is heated to reflux to give a clear yellow solution. To this solution, triethylorthoformate (8.60 mL, 52.11 mmol) is added dropwise and the reaction mixture is heated at reflux overnight. An additional 10 mL of triethylorthoformate is added and the mixture is heated at reflux overnight. The mixture is allowed to cool to room temperature and the white solid is collected by filtration, washing with *iso*-propanol, and dried overnight at $\sim 40^\circ C$ under reduced pressure. Purification by suspension in hot ethyl acetate followed by addition of cold hexanes gives 8.50 g (85%) of 2-cyano-N-(2,4-dichloro-5-methoxyphenyl)-3-[(3-iodo-4-methoxyphenyl)amino]prop-2-enamide as a yellow solid, mp $289-290^\circ C$; MS (ES) m/z 516.7 (M-H).

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Analysis for $C_{18}H_{14}Cl_2IN_3O_3$:

Calcd: C, 41.73; H, 2.72; N, 8.11.

Found: C, 40.88; H, 2.64; N, 7.90.

Reference Example 3

25

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-7-iodo-6-methoxy-3-quinolinecarbonitrile

To a suspension of 2-cyano-N-(2,4-dichloro-5-methoxyphenyl)-3-[(3-iodo-4-methoxyphenyl)amino]prop-2-enamide (720 mg, 1.39 mmol) in 40 mL of acetonitrile is added 0.2 mL of methanol. The mixture is heated to reflux and phosphorous oxychloride (1.24 mL, 13.9 mmol) is added dropwise, via syringe. This solution is heated at reflux overnight. After 24 hours, the mixture is cooled in an ice-bath and the solid is collected by filtration, washing with cold acetonitrile (40 mL) and then suspended in tetrahydrofuran (100 mL). To both the acetonitrile filtrate and the tetrahydrofuran suspension are added concentrated ammonium hydroxide (2x50 mL) and the

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mixtures are stirred for 1 hour. Water (2x 800 ml) is added and stirring is continued for 2 hours. The resulting solids are combined, washed with hot water and dried under reduced pressure at ~ 40°C, overnight, to provide 200 mg (29%) of 4-[(2,4-dichloro-5-methoxyphenyl)amino]-7-iodo-6-methoxy-3-quinolinecarbonitrile, as yellow solid, mp 253-254 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.86 (s, 3H), 4.00 (s, 3H), 7.33(s, 1H), 7.74(s, 1H), 7.86 (s, 1H), 8.39 (s, 1H), 8.43 (s, 1H), 9.61 (s, 1H); MS (ES) *m/z* 500.0, 502.1 (M+H)⁺.

Analysis for C₁₈H₁₂Cl₂IN₃O₂ · H₂O:

Theory: C, 41.72, H, 2.72, N, 8.11

10 Found: C, 41.80; H, 2.52; N, 7.87.

Reference Example 4

1-Ethoxy-2-iodo-4-nitrobenzene

A suspension of 2-iodo-4-nitrophenol (21 g, 79.2 mmol) [Kometani, T.; et al.,
15 Tetrahedron Lett. (1985), 26(17), 2043], ethyl iodide (9 mL, 0.48 mol) and potassium carbonate (40.7 g, 0.3 mol) in 100 mL of N, N-dimethylformamide is heated at 70°C for 3 h. The reaction is cooled to room temperature and ethyl acetate is added. The inorganic salts are filtered and washed with ethyl acetate. The organic material is washed with water (3X) and brine, dried over magnesium sulfate and filtered. Upon
20 concentration of the filtrate a solid appears. This solid is filtered and washed with hexanes to give 5.2 g of 1-ethoxy-2-iodo-4-nitrobenzene as white crystals. Concentration of the filtrate provides an additional 11.3 g of the desired product, mp 81-83 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.42 (t, 3H), 4.26 (q, 2H), 7.18 (d, 1H), 8.26 (dd, 1H), 8.55 (d, 1H).

25 Analysis for C₈H₈INO₃:

Theory: C, 32.79, H, 2.75, N, 4.78.

Found: C, 32.71, H, 2.58, N, 4.53.

Reference Example 5

(4-Ethoxy-3-iodophenyl)amine

30 A suspension of iron (3.81 g, 70 mmol) and ammonium chloride (5.47 g, 102 mmol) in 80 mL of ethanol and 25 mL of water is heated to reflux. 1-Ethoxy-2-iodo-4-nitrobenzene (5.0 g, 20 mmol) is added in portions and the reaction is heated at reflux

for 1 h. The hot mixture is filtered through Celite, washing with hot ethanol. The filtrate is concentrated in vacuo and treated with ethyl acetate and water. The organic layer is extracted, washed with brine, dried over magnesium sulfate and filtered. Removal of the solvent in vacuo provides 5.1 g of (4-ethoxy-3-iodophenyl)amine as a
5 light brown oil; ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.30 (s, 3H), 3.89 (q, 2H), 4.82 (bs, 2H), 6.53 (dd, 1H), 6.72 (d, 1H), 7.11 (d, 1H); MS (ES) *m/z* 263.9 (M+H)⁺.

Analysis for C₈H₁₀INO:

Theory: C, 36.52, H, 3.83, N, 5.32.

Found: C, 36.84, H, 3.71, N, 4.96.

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Reference Example 6

2-Cyano-N-(2,4-dichloro-5-methoxyphenyl)-3-[(4-ethoxy-3-iodophenyl)amino]acrylamide

To a suspension of 2-cyano-N-(2,4-dichloro-5-methoxyphenyl)acetamide (5.44 g,
15 21.0 mmol) in 350 mL of *iso*-propanol, under N₂, is added (4-ethoxy-3-iodophenyl)-amine (5.0 g, 19.30 mmol). This mixture is heated to reflux and triethylorthoformate (8.53 mL, 51.30 mmol) is added dropwise and the reaction mixture is heated at reflux overnight. The mixture is allowed to cool to room temperature and the yellow solid is collected by filtration, washing with *iso*-propanol, and dried overnight at ~40°C under
20 reduced pressure to give 5.46 g (54%) of 2-cyano-N-(2,4-dichloro-5-methoxyphenyl)-3-[(4-ethoxy-3-iodophenyl)amino]prop-2-enamide as a yellow solid, mp >245 °C; MS (EI) *m/z* 531.01 (M)⁺.

Analysis for C₁₈H₁₆Cl₂IN₃O₃:

Calcd: C, 42.88; H, 3.03; N, 7.90.

25 Found: C, 42.99; H, 2.97; N, 7.74.

Reference Example 7

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-iodo-3-quinolinecarbonitrile

A suspension of 2-cyano-N-(2,4-dichloro-5-methoxyphenyl)-3-[(4-ethoxy-3-iodophenyl)amino]prop-2-enamide (2.0 g, 3.76 mmol) in 100 mL of toluene is heated to
30 reflux and phosphorous oxychloride (3.5 mL, 37.6 mmol) is added dropwise via syringe. This suspension is heated at reflux for 6 hours and additional phosphorous oxychloride (3.5 mL, 37.6 mmol) is added to slowly give a dark solution. After 72

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hours the mixture is cooled to room temperature, the solid is filtered and washed with toluene and ether. The light brown solid is dried under reduced pressure at ~ 40°C, overnight, to provide 1.47 g (76%) of 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-iodo-3-quinolinecarbonitrile as a yellow solid, mp 213-215 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.48 (t, 3H, J = 6.9 Hz), 4.32 (q, 2H, J = 6.9 Hz), 3.88 (s, 3H), 7.53 (s, 1H), 7.87 (s, 1H), 8.06 (s, 1H), 8.49 (s, 1H), 9.02 (s, 1H), 11.14 (bs, 1H); MS (ES) *m/z* 514.1 (M+H)⁺.

Analysis for C₁₉H₁₄Cl₂IN₃O₂ – 4.0 HCl:

Theory: C, 34.58, H, 2.75, N, 6.37

10 Found: C, 34.79; H, 2.60; N, 6.13.

Reference Example 8

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-7-(4-hydroxybut-1-ynyl)-6-methoxy-3-quinolinecarbonitrile

15 A mixture of 3-cyano-4-[(2,4-dichloro-5-methoxyphenyl)anilino]-6-methoxy-7-quinolinyl trifluoromethanesulfonate (2.0 g, 3.8 mmol), 3-buten-1-ol (0.44 mL, 0.56 mmol), tetrakis(triphenylphosphine)palladium (0.22 g, 0.19 mmol) and copper iodide (45 mg, 0.24 mmol) in a mixture of 12 mL of triethylamine and 30 mL of 1,4-dioxane is heated at 95 – 100 °C for 2 hours and then cooled to room temperature. Ethyl acetate and water are added. The solids are removed by filtration, triturated in hot diethyl ether, filtered and dried to provide 0.65 g (38%) of 4-[(2,4-dichloro-5-methoxyphenyl)amino]-7-(4-hydroxybut-1-ynyl)-6-methoxy-3-quinolinecarbonitrile, mp 230-232 °C; ¹H NMR (DMSO-*d*₆) δ 2.65 (t, 2H, J = 6.9 Hz), 3.62 (q, 2H, J = 6.9, 6.0 Hz), 3.86 (s, 3H), 3.98 (s, 3H), 4.96 (t, 1H, J = 6.0 Hz), 7.39 (s, 1H), 7.76 (s, 1H), 20 7.89 (s, 2H), 8.44 (s, 1H), 9.97 (bs, 1H); MS (ES) *m/z* 442.0 (M+H)⁺; HRMS 442.07198 (M+H)⁺; HPLC – 93%.

Reference Example 9

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-(4-hydroxybut-1-ynyl)-3-quinolinecarbonitrile

30 A mixture of 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-iodo-3-quinolinecarbonitrile (0.6 g, 1.2 mmol), 3-buten-1-ol (0.13 mL, 1.7 mmol), tetrakis(triphenylphosphine)palladium (68 mg, 0.058 mmol) and copper iodide (15 mg, 0.076 mmol) in

a mixture of 4 mL of triethylamine and 10 mL of 1,4-dioxane is heated at 95 °C for 3 hours and then cooled to room temperature. Ethyl acetate and water are added. The organic layer is extracted, dried over magnesium sulfate, filtered and concentrated. Ether is added and the solid is filtered and washed with hot diethyl ether (3X). The solid and filtrate are combined and purified by chromatography using a gradient of 0 to 10 % of methanol and dichloromethane. The yellow solid obtained is triturated in hot diethyl ether, filtered and dried to provide 0.16 g (31%) of 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-(4-hydroxybut-1-ynyl)-3-quinoline-carbonitrile, mp 220-222 °C; ¹H NMR (DMSO-*d*₆) δ 1.44 (t, 3H, J = 6.8 Hz), 2.65 (t, 2H, J = 6.8 Hz), 3.63 (dt, 2H, J = 6.9, 5.8 Hz), 3.86 (s, 3H), 4.25 (q, 2H, J = 6.8 Hz), 4.95 (t, 1H, J = 5.8 Hz), 7.39 (s, 1H), 7.77 (s, 1H), 7.87 (s, 2H), 8.44 (s, 1H), 9.75 (bs, 1H); MS (ES) *m/z* 456.1 (M+H)⁺; HRMS 456.08763 (M+H)⁺; HPLC – 98%.

Example 1

15 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-7-[4-(dimethylamino)but-1-ynyl]-6-methoxy-3-quinolinecarbonitrile

To a mixture of 4-[(2,4-dichloro-5-methoxyphenyl)amino]-7-(4-hydroxybut-1-ynyl)-6-methoxy-3-quinolinecarbonitrile (0.3 g, 0.68 mmol) and triethylamine (0.47 mL, 3.4 mmol) in 3 mL of N,N-dimethylformamide and 15 mL of tetrahydrofuran at 0 °C was added dropwise methanesulfonyl chloride (0.16 mL, 2.0 mmol). The mixture is stirred for 1.25 hours and dimethylamine (2.0 mL, 2.0 M solution in tetrahydrofuran) is added. The reaction is stirred at room temperature overnight. An additional 3.0 mL of triethylamine are added and the reaction is stirred at room temperature overnight. The mixture is concentrated and diluted with ethyl acetate and water. The organic layer is extracted, dried over magnesium sulfate, filtered and concentrated. The residue is purified by chromatography using a gradient of 0 to 10% of methanol in dichloromethane. The product is triturated in hot diethyl ether, filtered and dried to provide 62 mg (20%) of 4-[(2,4-dichloro-5-methoxyphenyl)amino]-7-[4-(dimethylamino)but-1-ynyl]-6-methoxy-3-quinolinecarbonitrile as a yellow solid, mp 177-179 °C; ¹H NMR (DMSO-*d*₆) δ 2.22 (s, 6H), 2.56 (t, 2H, J = 6.8 Hz), 2.65 (t, 2H, J = 6.8 Hz), 3.86 (s, 3H), 3.96 (s, 3H), 7.38 (s, 1H), 7.76 (s, 1H), 7.88 (s, 2H), 8.43 (s, 1H), 9.82 (bs, 1H); MS (ES) *m/z* 469.1 (M+H)⁺.

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Analysis for $C_{24}H_{22}Cl_2N_4O_2 \cdot 1.5 H_2O$

Theory: C, 58.07, H, 5.08, N, 11.29.

Found: C, 58.46, H, 4.82, N, 10.99.

5

Example 2

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[4-(4-methylpiperazin-1-yl)but-1-ynyl]-3-quinolinecarbonitrile

The same procedure used for the synthesis of Example 1 is followed to provide 90 mg (25%) of 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[4-(4-methylpiperazin-1-yl)but-1-ynyl]-3-quinolinecarbonitrile as a yellow solid, mp 165-167 °C; ^1H NMR (DMSO- d_6) δ 2.17 (s, 3H), 2.35 (bs, 4H), 2.50 (bs, 4H), 2.60-2.68 (m, 4H), 3.86 (s, 3H), 3.96 (s, 3H), 7.34 (s, 1H), 7.74 (s, 1H), 7.83 (s, 1H), 7.88 (s, 1H), 8.43 (s, 1H), 9.83 (bs, 1H), MS (ES) m/z 524.2 (M+H) $^+$.

Analysis for $C_{27}H_{27}Cl_2N_5O_2 \cdot 1.5 H_2O$

Theory: C, 58.80, H, 5.48, N, 12.70.

Found: C, 58.89, H, 5.19, N, 12.38.

Alternative Preparation of Example 2:

A mixture of 3-cyano-4-[(2,4-dichloro-5-methoxyphenyl)anilino]-6-methoxy-7-quinolinyl trifluoromethanesulfonate (2.5 g, 4.8 mmol), 1-but-3-ynyl-4-methylpiperazine (1.8 g, 11.8 mmol) [Vallancourt, V. A. et. al. WO2002002558A1] bis(triphenylphosphine)palladium dichloride (170 mg, 0.22 mmol), potassium carbonate (3.31 g, 0.024 mol), triphenylphosphine (25 mg, 0.9 mmol) and copper iodide (45 mg, 0.22 mmol) in a mixture of 6 mL of methanol and 30 mL of tetrahydrofuran is heated at 60 °C for 4 hours and then cooled to room temperature. Ethyl acetate and water are added. The organic layer is extracted, dried over magnesium sulfate, filtered and concentrated. Purification of the residue by chromatography using a gradient of 0 to 10% of methanol in dichloromethane, followed by 20% of methanol-dichloromethane/1% NH_4OH as the solvent system provides 2.2 g (88%) of 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[4-(4-methylpiperazin-1-yl)but-1-ynyl]-3-quinolinecarbonitrile.

Second Alternative Preparation of Example 2

A mixture of 4-[(2,4-dichloro-5-methoxyphenyl)amino]-7-iodo-6-methoxy-3-quinoline-carbonitrile (0.2 g, 0.4 mmol), 1-but-3-ynyl-4-methylpiperazine (0.21 g, 1.4 mmol) [Vaillancourt, V. A. et. al. WO2002002558A1], bis(triphenylphosphine)palladium
 5 dichloride (14 mg, 0.02 mmol), triphenylphosphine (21 mg, 0.08 mmol) and copper iodide (5 mg, 0.02 mmol) in a mixture of 2 mL of triethylamine and 1 mL of N-methylpyrrolidinone is heated at 70 °C for 4 hours and then cooled to room temperature. Ethyl acetate and water are added. The organic layer is extracted, dried over
 magnesium sulfate, filtered and concentrated. Purification of the residue by
 10 chromatography using a gradient of 0 to 10% methanol in dichloromethane, followed by 15% of methanol-dichloromethane/1% NH₄OH as the solvent system provides 78 mg (37%) of 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[4-(4-methylpiperazin-1-yl)but-1-ynyl]-3-quinolinecarbonitrile.

15 Example 3

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-methoxy-7-(4-morpholin-4-ylbut-1-ynyl)-3-quinolinecarbonitrile

The same procedure used for the synthesis of Example 1 is followed to provide 150 mg (43%) of 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-(4-morpholin-4-ylbut-1-ynyl)-3-quinolinecarbonitrile as a yellow solid, mp 140-142 °C; ¹H NMR (DMSO-*d*₆) δ 2.50 (t, 4H, J = 4.4 Hz), 2.58-2.73 (m, 4H), 3.60 (t, 4H, J = 4.4 Hz), 3.87 (s, 3H), 3.98 (s, 3H), 7.39 (s, 1H), 7.77 (s, 1H), 7.87 (s, 1H), 7.89 (s, 1H), 8.45 (s, 1H), 9.82 (bs, 1H); MS (ES) *m/z* 511.0 (M+H)⁺.

Analysis for C₂₈H₂₄Cl₂N₄O₃

25 Theory: C, 61.06, H, 4.73, N, 10.96.

Found: C, 60.89, H, 4.74, N, 10.82.

Example 4

30 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-methoxy-7-(4-piperazin-1-ylbut-1-ynyl)-3-quinolinecarbonitrile

The same procedure used for the synthesis of Example 1 is followed. After purification by column chromatography 120 mg of a mixture containing the product is obtained. The mixture is further purified by HPLC using a gradient of 5 to 95%

nnn28

acetonitrile/water (0.02%TFA) to provide 15 mg (5%) of 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[4-piperazin-1-ylbut-1-ynyl]-3-quinolinecarbonitrile as a yellow solid, mp 188-190 °C; ¹H NMR (DMSO-*d*₆) δ 2.85 (t, 2H, J = 6.8 Hz), 3.03 (bs, 6H), 3.32 (bs, 4H), 3.89 (s, 3H), 3.98 (s, 3H), 7.35 (s, 1H), 7.77 (s, 1H), 7.89 (s, 1H), 7.92 (s, 1H), 8.52 (s, 1H), 8.81 (bs, 1H), 10.01 (bs, 1H); MS (ES) *m/z* 510.1 (M+H)⁺.
Analysis for C₂₈H₂₅Cl₂N₅O₂ · 3 TFA/1 H₂O
Theory: C, 44.18, H, 3.48, N, 8.06.
Found: C, 44.07, H, 3.22, N, 8.06.

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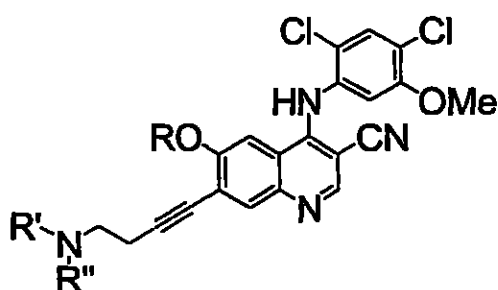
Example 54-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[4-(4-methylpiperazin-1-yl)but-1-ynyl]-3-quinolinecarbonitrile

The same procedure used for the synthesis of Example 1 is followed to provide 45 mg (24%) of 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[4-(4-methylpiperazin-1-yl)but-1-ynyl]-3-quinolinecarbonitrile as a yellow solid, mp 158-160 °C; ¹H NMR (DMSO-*d*₆) δ 1.43 (t, 3H, J = 6.8 Hz), 2.19 (s, 3H), 2.38 (bs, 4H), 2.50 (bs, 4H), 2.60-2.67 (m, 4H), 3.86 (s, 3H), 4.22 (q, 2H, J = 6.8 Hz), 7.36 (s, 1H), 7.74 (s, 1H), 7.84 (s, 1H), 7.88 (s, 1H), 8.42 (s, 1H), 9.78 (bs, 1H); MS (ES) *m/z* 538.2 (M+H)⁺; HRMS 538.17726 (M+H)⁺; HPLC purity is 99%.

20

What is claimed is:

1. A compound having the structure:



5

wherein:

R is methyl or ethyl;

10 R' and R'' are independently alkyl of 1 to 3 carbon atoms, or R' and R'', taken together with the nitrogen to which they are attached, can form a 5 or 6 membered saturated ring which may optionally contain an additional heteroatom selected from NR''', O or S(O)_n;

n is 0-2;

15 R''' is hydrogen or alkyl of 1 to 3 carbon atoms; and pharmaceutically acceptable salts thereof.

2. The compound of Claim 1 wherein R' and R'' are each methyl.

20 3. The compound of Claim 1 wherein R' and R'', taken together with the nitrogen to which they are attached, form a N-(C₁-C₃)-alkylpiperazine, piperazine or morpholine ring.

4. The compound of Claim 3 wherein the N-(C₁-C₃)-alkylpiperazine ring is N-methyl-piperazine.

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5. The compound of any one of Claims 1 to 4 wherein R is methyl.

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- 6 . The compound of Claim 1 wherein the compound is selected from:
4-[(2,4-Dichloro-5-methoxyphenyl)amino]-7-[4-(dimethylamino)but-1-ynyl]-6
methoxy-3-quinolinecarbonitrile;
4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-[4-(4-methylpiperazin-
5 1-yl)but-1-ynyl]-3-quinolinecarbonitrile;
4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-(4-morpholin-4-ylbut-
1-ynyl)-3-quinolinecarbonitrile;
4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-(4-piperazin-1-ylbut-
1-ynyl)-3-quinolinecarbonitrile; and
10 4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-ethoxy-7-[4-(4-methylpiperazin-1-
yl)but-1-ynyl]-3-quinolinecarbonitrile;
and pharmaceutically acceptable salts thereof.
- 7 . A pharmaceutical composition comprising a compound according to any one
15 of claims 1 to 6 and pharmaceutically acceptable salts thereof, and at least one
pharmaceutically acceptable carrier or excipient.
- 8 . A pharmaceutical composition comprising a vascular permeability inhibiting
amount of a compound according to any one of claims 1 to 6 and pharmaceutically
20 acceptable salts thereof, and at least one pharmaceutically acceptable carrier or
excipient.
- 9 . The composition of Claim 7 or 8 in an intravenous dosage form.
- 25 10 . A method of providing neuroprotection in a patient following a
cerebrovascular ischemic event comprising providing a therapeutically effective
amount of a compound according to any one of claims 1 to 6.
- 30 11 . A method of inhibiting neurological deficits in a patient following a
cerebrovascular ischemic event comprising providing a therapeutically effective
amount of a compound according to any one of claims 1 to 6.

- 12 . A method of reducing infarct volumes in a patient following a cerebrovascular ischemic event comprising administering a therapeutically effective amount of a compound according to any one of claims 1 to 6.
- 5 13 . A method of inhibiting post-ischemic vascular permeability of cerebral blood vessels in a patient suffering from a cerebrovascular event comprising administering a therapeutically effective amount of a compound according to any one of claims 1 to 6.
- 10 14 . The method of any one of Claims 10 to 13 wherein the compound is administered between about 6 to about 24 hours after the ischemic event.
- 15 15 . The method of any one of Claims 10 to 14 wherein the therapeutically effective amount is from about 1 mg/kg to about 30 mg/kg.
- 16 . The method of any one of Claims 10 to 15 comprising administering compound of Formula I intravenously.
- 17 . The method of any one of Claims 10 to 16 wherein the patient is a human.
- 20 18 . The method of any one of Claims 10 to 17 wherein the ischemic event is transient.
- 25 19 . The method of any one of Claims 10 to 17 wherein the ischemic event is acute.
- 20 . The method of Claim 19 wherein the ischemic event is stroke, head trauma, spinal trauma, general anoxia, or hypoxia.
- 30 21 . The method of any one of Claims 10 to 20 wherein the ischemic event occurs during cerebral hemorrhage, perinatal asphyxia, cardiac arrest or status epilepticus.

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22. The use of a compound according to any one of claims 1 to 6 in the manufacture of a medicament for providing neuroprotection in a patient following a cerebrovascular ischemic event, inhibiting neurological deficits in a patient following a cerebrovascular ischemic event, reducing infarct volumes in a patient following a cerebrovascular ischemic event, and inhibiting post-ischemic vascular permeability of cerebral blood vessels in a patient suffering from a cerebrovascular event.
23. The use of claim 22 wherein the patient is a human.
- 10 24. The use of claim 22 or claim 23 wherein the ischemic event is transient.
25. The use of claim 22 or claim 23 wherein the ischemic event is acute.
- 15 26. The use of Claim 25 wherein the ischemic event is stroke, head trauma, spinal trauma, general anoxia, or hypoxia.
27. The use of any one of Claims 22 to 26 wherein the ischemic event occurs during cerebral hemorrhage, perinatal asphyxia, cardiac arrest or status epilepticus.

4-[(2,4-DICLORO-5-METOXIFENIL)AMINO]-6-ALCOXI-7-ETINIL-3-
QUINOLINOCARBONITRILOS PARA EL TRATAMIENTO DE LESIÓN ISQUÉMICA

La presente invención se relaciona con 4-[(2,4-dicloro-5-metoxifenil)amino]-6-alcoxi-7-etinil-3-quinolinocarbonitrilos y a métodos para utilizarlos en el tratamiento de lesión isquémica.

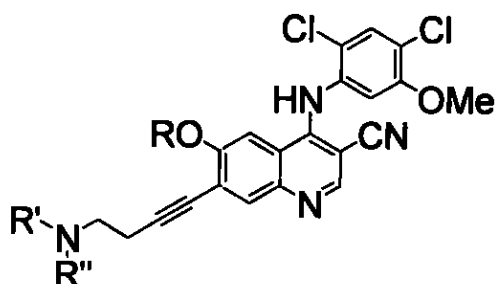
ANTECEDENTES DE LA INVENCION

El accidente cerebro vascular es la tercer causa líder de muerte y la principal causa de discapacidad en los Estados Unidos, donde ocurren 750,000 accidentes cerebro vasculares cada año, aproximadamente. Los accidentes cerebrovasculares isquémicos comprenden aproximadamente 80% de este número, con accidentes cerebrovasculares hemorrágicos intracerebrales primarios de aproximadamente 15-20%. A la fecha, el único tratamiento eficaz aprobado para infartos cerebrales isquémico agudo es la terapia trombolítica por medio de la administración intravenosa de t-PA, activador de plasminógeno de tejido recombinante. La utilidad de esta terapia es extremadamente limitada. Se debe dar dentro de una ventana de tres horas después de la manifestación de los síntomas, mientras que la mayoría de los pacientes buscan y/o reciben tratamiento después de un retraso sustancial. Además el tratamiento con t-PA conlleva un riesgo creciente de originar hemorragia intracerebral, una complicación potencialmente devastadora. La presencia de hemorragia se debe desechar antes del tratamiento y se debe manejar cuidadosamente la presión sanguínea y monitorear durante y después del tratamiento con t-PA. Habitualmente, ninguna terapia neuroprotectora está

disponible para el tratamiento de accidente cerebrovascular
isquémico, accidente cerebrovascular hemorrágico o trauma
cerebral. Son muy necesarios nuevos tratamientos para accidentes
cerebrovasculares y otras condiciones asociadas con la
permeabilidad vascular.

DESCRIPCIÓN DE LA INVENCION

De acuerdo con un aspecto de la presente invención se suministran
de la fórmula estructural:



I

en donde:

R es metilo o etilo;

R' y R'' son independientemente alquilo de 1 a 3 átomos de carbono, o R' y R'', tomados juntos con el nitrógeno al cual ellos están unidos, pueden formar un anillo de saturado 5 o 6 miembros el cual puede contener opcionalmente un heteroátomo adicional seleccionado de NR''', O o S(O)_n;

n es 0-2;

y

R''' es hidrógeno o alquilo de 1 a 3 átomos de carbono; y las sales farmacéuticamente aceptables de estos.

En ciertas modalidades preferidas de la invención, R' y R'',
tomados juntos con el nitrógeno al cual ellos están unidos,
forman una N-(C₁-C₃)-alquil piperazina, piperazina o morfolino.

En algunas modalidades preferidas de la invención, R es metilo.

En otras modalidades preferidas de la presente invención, R' y R'', tomados juntos con el nitrógeno al cual ellos están unidos, forman un N-(C₁-C₃)-alquil piperazina, piperazina o anillo de morfolino.

Donde R' y R'' tomados con el nitrógeno al cual ellos están unidos forman un N-(C₁-C₃)-alquil piperazina, preferiblemente ellos forman N-metilpiperazina.

En aún otras modalidades preferidas de la presente invención R' y R'' son metilo.

Las sales farmacéuticamente aceptables son aquellas derivadas de ácidos orgánicos e inorgánicos tales como: ácido acético, láctico, carboxílico, cítrico, cinámico, tartárico, succínico, fumárico, maleico, malónico, mandélico, málico, oxálico, propiónico, clorhídrico, bromhídrico, fosfórico, nítrico, sulfúrico, glicólico, pirúvico, metanosulfónico, etanosulfónico, toluenosulfónico, salicílico, benzoico, y ácidos farmacéuticamente aceptables similarmente conocidos.

Los anillos saturados de 5 o 6 miembros contiene opcionalmente un heteroátomo adicional seleccionado de NR''', O o S(O)_n como se

define por N R'R'' incluye, pero no están limitados a, ³⁴~~nnn/6~~
pirrolidina, pirazolidina, imidazolidina, piperidina, piperazina,
morfolino, tiomorfolino, 1-oxo-1-tiomorfolino y 1,1-dioxo-1-
tiomorfolino.

Los compuestos específicos de la invención incluyen:

4-[(2,4-Dicloro-5-metoxifenil)amino]-7-[4-(dimetilamino)but-1-
inil]-6metoxi-3-quinolinocarbonitrilo;

4-[(2,4-Dicloro-5-metoxifenil)amino]-6-metoxi-7-[4-(4-
metilpiperazin-1-il)but-1-inil]-3-quinolinocarbonitrilo;

4-[(2,4-Dicloro-5-metoxifenil)amino]-6-metoxi-7-(4-morfolin-4-
ilbut-1-inil)-3-quinolinocarbonitrilo;

4-[(2,4-Dicloro-5-metoxifenil)amino]-6-metoxi-7-(4-piperazin-1-
ilbut-1-inil)-3-quinolinocarbonitrilo; y

4-[(2,4-Dicloro-5-metoxifenil)amino]-6-etoxi-7-[4-(4-
metilpiperazin-1-il)but-1-inil]-3-quinolinocarbonitrilo y las
sales farmacéuticamente aceptables de estos.

Otros aspectos de la invención incluyen composiciones
farmacéuticas que comprenden los compuestos descritos aquí y al
menos un vehículo o excipiente farmacéuticamente aceptable, y los
métodos para tratar lesión isquémica utilizando estos compuestos.

35
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Los compuestos de la invención se preparan como se ilustra adelante. Los compuestos de esta invención fueron preparados de: (a) materiales de partida comercialmente disponible (b) materiales de partida conocidos que se pueden preparar como se describe en los procedimientos de la literatura o (c) nuevos intermedios descritos aquí en los esquemas y procedimientos experimentales.

Las reacciones se desarrollan en un solvente apropiado a los reactivos y materiales empleados y adecuados para la transformación que está siendo efectuada. Se entiende, por aquellos expertos en la técnica de la síntesis orgánica, que varias funcionalidades presentes en la molécula deben ser consistentes con las transformaciones químicas propuestas. Cuando no se especifican, el orden de las etapas sintéticas, la escogencia de los grupos protectores o las condiciones de desprotección serán más fácilmente evidentes para aquellos expertos en la técnica además, en algunos casos, los sustituyentes sobre los materiales de partida pueden ser incompatibles con ciertas condiciones de reacción. Las reacciones pertinentes a los sustituyentes dados serán evidentes para un experto en la técnica. Las reacciones procederán bajo atmósfera inerte donde sea apropiado.

Los compuestos de Fórmula I son preparados como se describe en el Esquema 1. Los compuestos de Fórmula I en donde R es Me se obtienen fácilmente partiendo de 1a, 3-ciano-4-[(2,4-dicloro-5-metoxifenil)amino]-6-metoxi-7-quinolinil trifluorometanosulfonato. La preparación de 1a se ha reportado en la literatura Berger, D. et. al. *Bioorg. Med.Chem.Lett.* 12, 2761

36

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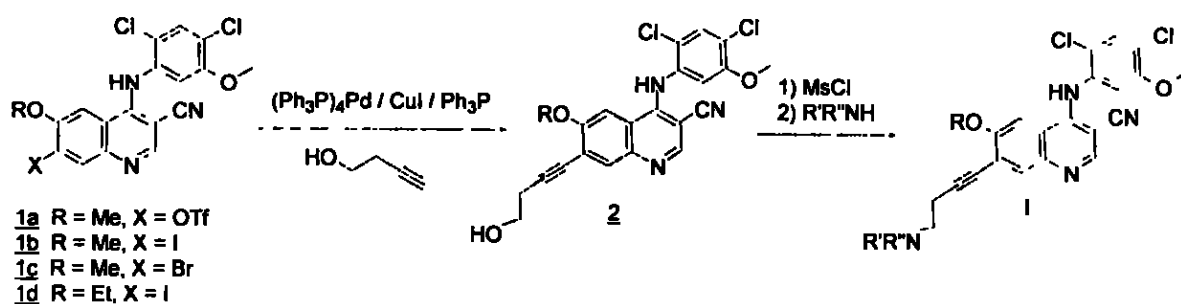
(2002) y US6521618 (Feb 18, 2003), incorporado aquí como referencia en su totalidad.

El tratamiento de 1a con 3-butin-1-ol en la presencia de un catalizador de paladio, preferiblemente tetrakis(trifenilfosfina)paladio, con yoduro de cobre, en un sistema solvente tal como trietilamina y dioxano a temperatura elevada, preferiblemente 95-100° C, suministra los compuestos de fórmula 2. La reacción de los compuestos de fórmula 2 con cloruro de metanosulofonilo en un sistema solvente tal como N,N-dimetilformamida y tetrahidrofurano a temperatura reducida, preferiblemente 0° C, da el mesilato correspondiente. El mesilato intermedio no está normalmente aislado pero es tratado directamente con una amina apropiada de fórmula R''R'NH para suministrar los compuestos de fórmula **I**. Otros grupos salientes tales como el tosilato se pueden emplear como una alternativa al grupo mesilato.

Además de 1a, otros materiales de partida incluyen 1b, 4-[(2,4-dicloro-5-metoxifenil)amino]-7-yodo-6-metoxi-3-quinolinocarbonitrilo, y 1c, 7-bromo-4-[(2,4-dicloro-5-metoxifenil)amino]-6-metoxi-3-quinolinocarbonitrilo, se pueden utilizar para obtener los compuestos de fórmula **I** donde R es Me.

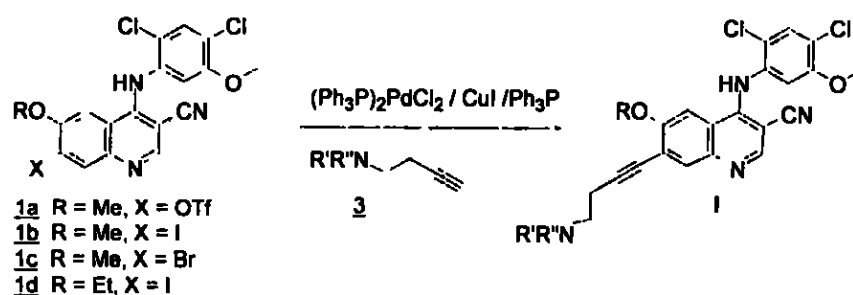
Los compuestos de fórmula **I** en donde R es Et son fácilmente obtenidos partiendo de 4-[(2,4-dicloro-5-metoxifenil)amino]-6-etoxi-7-yodo-3-quinolinocarbonitrilo, 1d.

ESQUEMA 1



Una ruta alternativa a los compuestos de fórmula I se describe en el Esquema 2. Los compuestos de fórmula 1a-d se tratan con una amina de fórmula 3 en presencia de un catalizador de paladio preferiblemente diclorobis(trifenilfosfina)paladio(II), con yoduro de cobre y trifenilfosfina, en un sistema solvente tal como trietilamina y N-metilpirrolidinona a temperatura elevada, preferiblemente 70° C, para suministrar compuestos de fórmula I. Alternativamente, los compuestos de reacción de la fórmula 1a-d con aminas de la fórmula 3 se pueden desarrollar en un sistema solvente de trietilamina y N,N-dimetilformamida o alternativamente en la presencia de una base tal como carbonato de potasio en un sistema solvente de metanol y tetrahidrofurano.

ESQUEMA 2



38

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Los compuestos de la presente invención fueron evaluados en varios ensayos farmacológicos estándar que mostraron que los compuestos de la presente invención inhiben la Src quinasa y son útiles para la prevención de permeabilidad vascular.

Ensayo Src Quinasa

La enzima Src humana recombinante se obtuvo de PanVera (P3044). El péptido biotinilado que corresponde a los residuos 6 - 20 de Cdk1 se utilizó como un sustrato (Biotin-KVEKIGEGTYGVVYK-COOH). Los ensayos diferenciadores de quinasa de transferencia de energía de resonancia de fluorescencia homogénea fueron desarrollados utilizando un formato de detección de europio/ATC (LANCE, Perkin Elmer). La enzima Src (10 ng) se mezcló con péptido biotinilado (concentración final 2 μ M), 50 mM de Hepes (pH 7.5), 10 mM de MgCl₂, 20 μ g/ml de BSA, 0.001% Brj-35 (Sigma), 100 μ M de ATP, 1% de DMSO. La reacción de quinasa se incubó durante 70 min a 37°C. La reacción se detuvo con EDTA a una concentración final de 30mM de EDTA/25mM de Hepes (pH 7.5)/10 μ g/ml de BSA. La mezcla se convino con anticuerpo anti-fosfotirosina marcado con Eu PT66 (Perkin Elmer, AD0068) y Streptavidina Surelight-APC (Perkin Elmer, CR130-100) en 50 mM de Hepes (pH 7.5)/ 20 μ g/ml de BSA, e incubada durante 30 min de acuerdo a las especificaciones del fabricantes. La intensidad de la fluorescencia a 665 nm se utilizó para monitorear la extensión de la reacción de quinasa. Múltiples entradas para un compuesto dado indican que éste fue ensayado múltiples veces. Los

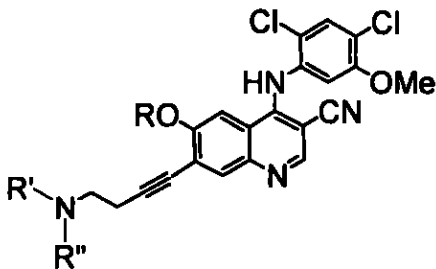
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resultados obtenidos para los compuestos representativos de ésta invención son listados en la Tabla 1.

Ensayo de proliferación de fibroblastos transformado con Src independiente de anclaje

Los fibroblastos Rat2 establemente transformados con un plásmido que contiene un gel de fusión v-Src/Hu c-Src controlado con un promotor CMV en el cual el dominio catalítico del c-Src se insertó en lugar del dominio catalítico v-Src en el gen de ión v-Src se utilizan para la medición del Src del crecimiento de suspensión dependiente de Src. Las placas cluster ultra bajas (Costar # 3474) son sembradas con 10,000 células por pozo en un día. Alternativamente, las placas cluster ultra bajas (Costar 3474) tratadas con Sigmacote (Sigma), enjuagadas con 70% de etanol, después de secar en la caperuza, son sembradas con 5000 células. El compuesto se agrega en diluciones de dos veces en serio de 10 micromolar a 0.009 micromolar en el Día 2 y el reactivo MTS (Promega) se agrega en el Día 5 (100 microlitros de MTS/mezcla de medio + 100 microlitros de medio ya sobre las células y la absorbancia se mide a 490nm. Los resultados son analizados como sigue para producir un IC50 para proliferación (unidades micromolares) como sigue: %inhibición = (muestra Abs490 nm - blanco)/control sin compuesto Abs490 nm - blanco) X 100%. Las múltiples entradas para un compuesto dado indican que éste fue ensayado múltiples veces. Los resultados obtenidos para los compuestos representativos de ésta invención se listan en la Tabla 1.

40
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Tabla 1. Inhibición de Src enzimático y actividad celular



EJEMPLO	R	NR'R''	Enzima Src	Célula Src
			IC50 nM	IC50 nM
1	Me	NMe2	5.0, 4.7	252, 240
2	Me	N-Me-piperazina	3.5, 4.2	71, 70, 77
3	Me	Morfolina	4.0, 4.1	206, 183
4	Me	piperazina	5.9, 4.8	435, 605
5	Et	N-Me-piperazina	6.5, 2.8	96, 183, 154, 103

La administración IV del Ejemplo 2 suministra neuroprotección en un modelo de isquemia focal transitoria.

El ejemplo 2 fue ensayado en un modelo de rata de isquemia focal transitoria. Las ratas Wistar fueron sometidas a una oclusión de 90 min de la arteria cerebral media (ACM) utilizando una aproximación de sutura intraluminal como se describió por Longa et al., Stroke 1989, 20:84 seguida por perfusión durante 48 horas. Cuadro horas después del ataque inicial de isquemia, los animales recibieron el compuesto del Ejemplo 2 como un mono i.v. simple en 5% de dextrosa, 0.9% de ácido láctico a un pH 4.5-5.0 (3 mg/kg, 10 mg/kg o 30 mg/kg). Luego de la perfusión, los animales fueron evaluados durante un periodo de 48 horas para

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déficit de fusión neurológica. El tamaño del infarto se midió luego de sacrificio a las 48 horas post oclusión ACM. 10 y 30 mg/kg de dosis del Ejemplo 2 mejoraron significativamente la recuperación de los déficits neurológicos inducidos por el accidente cerebrovascular 35% y 53%, respectivamente como porcentaje de control (error estadístico: 10-12%). Las reducciones estadísticamente significativas en el volumen del tejido de cerebro infartado se observaron en 10 mg/kg y 30 mg/kg del Ejemplo 2, mostrando una reducción del 32% y 40% en el volumen del infarto como un porcentaje de control (error estadístico; 7-10%).

La administración IV del Ejemplo 2 utiliza neuroprotección y mejora la recuperación neurológica a largo plazo modelo de isquemia focal.

El Ejemplo 2 se ensayo en un modelo de rata de oclusión permanente en la arteria cerebral media, sin la repercusión, sustancialmente como se describió por Chen et al., *Stroke*, 1986,17:738. Este es un modelo más exigente que la isquemia focal transitoria. Dos horas luego de la electrocoagulación de la arteria cerebral media, el vehículo o el Ejemplo 2 fueron administrados a 10 mg/kg i.v seguido mediante 3 dosis adicionales de 10 mg/kg iv administradas a las 4, 24 y 26 horas post-inducción del accidente cerebrovascular. En un estudio, el volumen del tejido de cerebro infartado se evaluó a las 48 horas post accidente cerebrovascular. En un segundo estudio, los animales fueron sometidos a ensayo de la función sensorial-motora basada en la colocación del limbo táctil y propioceptivo

sustancialmente como se describió por DeRyck et al., *Brain Res.* 1992, 573:44 a intervalos de tres días durante el curso de tiempo de tres semanas luego de el accidente cerebrovascular. En los animales dotados con Ejemplo 2 se encontró una reacción estadísticamente significativa del 24% del volumen del infarto a las 48 horas post inducción del accidente cerebrovascular. Además, en Ejemplo 2 mejoró significativamente la recuperación sensorial motora a largo plazo de los déficit neurológicos inducidos en éste modelos de accidente cerebrovascular.

La administración IV del Ejemplo 2 suministra neuroprotección en el modelo de accidente cerebrovascular hemorrágico

El Ejemplo 2 fue ensayado en un modelo de rata de hemorragia intracerebral inducida por la infusión intraestriatal de collagenasa sustancialmente como se describió por Rosenberg et al., *Stroke*, 1990, 20:801. En éste modelo, la infusión de collagenasa en núcleos caudados conduce a la destrucción proteolítica del colágeno en la lámina basal de los vasos sanguíneos e induce el sangrado intracraneal y el pico de edema en 24-48 horas. El Ejemplo 2 fue administrado a las 4 horas post inducción del accidente cerebrovascular hemorrágico en una inyección i.v. simple en dosis de 10 mg/kg o 30 mg/kg. 24 horas después el contenido de agua del cerebro se determinó como una medición del edema. Los resultados indicaron que el Ejemplo 2 redujo significativamente el edema del cerebro post hemorrágico en ambas dosis ensayadas en 18% y 24% respectivamente.

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La permeabilidad vascular debido a la enfermedad, lesión, u otro trauma puede ocurrir en una variedad de tejidos y órganos que incluyen los órganos del sistema nervioso central, el sistema cardiopulmonar, el sistema gastrointestinal y el sistema renal. Los compuestos de la presente invención son útiles para inhibir la permeabilidad vascular causada por la enfermedad, lesión, u otro trauma. En particular, la permeabilidad vascular se puede inhibir en el tejido cerebral y espinal luego de los eventos cerebrovasculares. La permeabilidad vascular fue la cosa principal del regado vascular y/o el edema luego de un evento cerebrovascular y a menudo conduce a desórdenes y discapacidades neurológicas. Los eventos cerebrovasculares incluyen, pero no están limitados a eventos transitorios e isquémicos agudos, se puede tratar de acuerdo con la presente invención. Los eventos agudos incluyen, pero no están limitados a, accidente cardiovascular, trauma de cabeza, trauma espinal, anoxia general, hipoxia que incluye hipoxia fetal, hipoglicemia, hipotensión así como también lesiones similares vistas durante el procedimiento de la embolia, hiperfusión e hipoxia. Los accidentes cerebrovasculares incluyen, pero no están limitados a, isquemia focal y global, ataques isquémicos cerebrales transitorios, y otros problemas vasculares cerebrales acompañados por isquemia cerebral. La presente invención también sería útil para un tango de eventos cerebrovasculares que incluyen hemorragia cerebral, infarto debido a embolismo o trombosis de las arterias intra- o extra craneanas, asfixia perinatal, en detención cardiaca y estados epilépticos, especialmente cuando el flujo de sangre al cerebro es detenido durante un periodo de tiempo. Los eventos cerebrovasculares asociados con el derrame vascular también

44
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incluyen infecciones, incluyendo, pero no limitadas a encefalitis y meningitis asociada con neuroinflamación, las cuales, a través del regado vascular propagan la lesión a los tejidos circundantes. La enfermedad sistémica tal como la diabetes, la esclerosis múltiple, la enfermedad del riñón, y la aterosclerosis pueden también resultar en permeabilidad vascular incrementada. Los compuestos de la presente invención también son útiles para inhibir la permeabilidad vascular disparada por el evento isquémico de tejido/órgano (hipóxico) por fuera del sistema nervioso central, que incluye, pero no está limitado a isquemia del miocardio y a enfermedad isquémica del intestino.

Los componentes de la presente invención suministran neuroprotección en un paciente. La neuroprotección, como se utiliza aquí, se refiere a la protección de las células neurales contra la muerte o apoptosis de la célula. Una medición de la extensión de la muerte o apoptosis celular es el volumen del infarto; el volumen del tejido del cerebro necrótico o muerto. Técnicas de imágenes y el estado clínico del paciente se pueden utilizar para evaluar el volumen del infarto luego de un evento isquémico. Los compuestos de la presente invención reducen el volumen del infarto de un paciente comparado con el volumen de infarto crítico experimentado en eventos isquémicos similares en la ausencia de los agentes de la presente invención.

Los componentes de la presente invención, evitan, reducen o inhiben la neurodegeneración y/o la neurotoxicidad asociada con la permeabilidad vascular que resulta en síntomas que incluyen, pero no están limitados a, lesión visual tal como pérdida de

45
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visión repentina o diplopia, lesión en el habla o lenguaje tal como afasia o disartia, lesión en la memoria, lesión cognitivo o disfunción que varia desde lesión cognitivo medio a demencia, y lesión motor que incluye, pero no está limitado a, paratesia, pérdida del control muscular, debilidad, entumecimiento o parálisis. Los déficit neurológicos, tales como aquellos que resultan de la lesión o enfermedad descritos anteriormente, se pueden inhibir o prevenir de acuerdo con la presente invención. Así, la presente invención suministra métodos para tratar, prevenir, inhibir o aliviar las condiciones asociadas con derrame vascular o la permeabilidad listada anteriormente en un mamífero, preferiblemente en un humano, los métodos comprenden suministrar una cantidad farmacéuticamente efectiva, y en particular una permeabilidad vascular que inhibe la cantidad, de un compuesto de ésta invención al mamífero, y en particular un paciente humano, necesitado de esto.

También comprendida por la presente invención están las composiciones farmacéuticas para tratar o modular la permeabilidad vascular que comprende al menos un compuesto de la fórmula I, mezclas de estos, y o las sales farmacéuticas de estos, y un vehículo farmacéuticamente aceptable para estos. Tales composiciones son preparadas de acuerdo con los procedimientos farmacéuticos aceptables, tales como se describió en *Remingtons Pharmaceutical Sciences*, edición 17, ed. Alfonso R. Gennaro, Mack Publishing Company, Easton, PA (1985). Los vehículos farmacéuticamente aceptables son aquellos que son compatibles con los otros ingredientes en la formulación y biológicamente aceptables.

46
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Los vehículos líquidos se pueden utilizar para preparar soluciones, suspensiones, emulsiones, malazas y elixires que incluyen soluciones intravenosas. El ingrediente activo de ésta invención se puede disolver o suspender en un vehículo líquido farmacéuticamente aceptable tal como agua, solvente orgánico, o una mezcla de ambos. El vehículo líquido puede contener otros aditivos farmacéuticos adecuados tales como solubilizadores, emulsificadores, amortiguadores, preservativos, endulzantes, agentes saborizantes, agentes de suspensión, agentes espesantes, colores, reguladores de la viscosidad, estabilizadores, osmoreguladores, antioxidantes y agentes antiespumantes.

Ejemplos adecuados de vehículos líquidos para administración oral, intravenosa o parenteral incluyen agua (particularmente aditivos que contienen como anteriormente por ejemplo derivados de celulosa, preferiblemente solución de carboximetilcelulosa de sodio), solución salina, soluciones de dextrosa, solución salina de dextrosa y soluciones de dextrosa-agua, como alcoholes (que incluyen alcoholes monohídricos y alcoholes polihídricos por ejemplo glicoles) y sus derivados. Los vehículos líquidos son utilizados en forma estéril para administración parenteral e intravenosa. El pH de las formulaciones líquidas se puede ajustar en algunos casos mediante la adición de HCL, hidróxido de sodio, y ácido fosfórico. Preferiblemente las composiciones de la presente invención son composiciones farmacéuticas líquidas que son soluciones estériles o suspensiones en un sistema amortiguado fisiológicamente compatible isosmótico.

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Las composiciones farmacéuticas líquidas de la presente invención se pueden administrar mediante, por ejemplo, inyección intramuscular, intraperitoneal, intravenosa o subcutánea. Las composiciones farmacéuticas de la presente invención son administradas preferiblemente a un paciente mediante inyección intraperitoneal o intravenosa. Más preferiblemente, la composición se administra intravenosamente tal como mediante inyección de uso intravenoso, goteo y punto intravenoso. Administración de bolo lento repetido o infusión.

La administración oral puede ser la forma de composición líquida o sólida. Los compuestos de esta invención se pueden administrar oralmente o parenteralmente, puros o en combinación con vehículos farmacéuticos convencionales. Los vehículos sólidos aplicables pueden incluir una o más sustancias que también pueden actuar como agentes saborizantes, lubricantes, solubilizadores, agentes de suspensión, elevadores, deslizantes, ayudas de compresión, ligadores o agentes desintegrantes de tableta o un material de encapsulado. En los polvos, el vehículo es un sólido finamente dividido, que está en mezcla con un ingrediente activo finamente dividido. En las tabletas, el ingrediente activo se mezcla con un vehículo que tiene las propiedades de compresión necesarias en las proporciones adecuadas y compactado en la forma y tamaño deseados. Los polvos y las tabletas preferiblemente contienen hasta el 99% de ingrediente activo. Los vehículos sólidos adecuados incluyen, por ejemplo, fosfato de calcio, estearato de magnesio, talco, azúcares, lactosa, dextrina, almidón, gelatina, celulosa, metilcelulosa, carboximetilcelulosa de sodio,

48
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polivinilpirrolidina, ceras de baja fusión y resinas intercambiadoras de ión.

Preferiblemente la composición farmacéutica está en la forma de dosis unitarias, por ejemplo, como tabletas, cápsulas, polvos, soluciones, suspensiones, emulsiones, gránulos, supositorios, ampollas, o bolos. En tal forma, la composición es subdividida en dosis unitaria que contiene las cantidades apropiadas del ingrediente activo; las formas de dosis unitarias pueden ser composiciones empacadas, por ejemplo polvos empacados, polvos liofilizados o torta en ampollas o frascos, o frascos, ampollas, jeringas previamente llenas o sacos que contienen líquidos. La forma de dosis unitaria puede ser, por ejemplo, cápsula o tableta en si misma, o puede ser el número apropiado de cualquiera de las composiciones en forma de empaque.

La dosis suministrada a un paciente varía dependiendo de lo que va a ser administrado, el propósito de la administración, tal como la profilaxis o la terapia, y el estado del paciente, la manera de la administración y similares. Una "cantidad terapéuticamente efectiva" es una cantidad suficiente para curar o mejorar los síntomas de una enfermedad. En general, una dosis simple (o forma de dosis) contendrá desde aproximadamente 1 mg/kg a aproximadamente 30 mg/kg, y más preferiblemente desde aproximadamente 1 mg/kg a aproximadamente 10 mg/kg del compuesto de la presente invención. Se espera que algunos pacientes reciban dosis múltiples. La dosis a ser utilizada en el tratamiento de un caso específico debe ser subjetivamente determinada por el físico tratante. Las variables involucradas incluyen la condición

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49
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específica y el tamaño, la edad y patrón de respuesta del paciente.

La presente invención suministra ventajas sobre los tratamientos previos conocidos para accidentes cerebrovasculares y otras condiciones asociadas con la permeabilidad vascular. En particular, aunque es preferible tratar pacientes tan pronto como sea posible después de la lesión isquémica, los compuestos de la presente invención pueden ser efectivos para prevenir la neurodegeneración y el desarrollo de un déficit neurológico en algunos pacientes cuando se administran 6-18 horas después de la lesión y aún hasta aproximadamente 18-24 horas después de la lesión isquémica. Adicionalmente, el tratamiento puede continuar y la mejora en la prognosis del paciente puede resultar de la administración continua o repetida de un compuesto de la presente invención durante hasta aproximadamente 72 horas o más luego de la lesión isquémica.

Suministrar como se utiliza aquí significa administrar directamente un compuesto o composición de la presente invención, o administrar una prodroga, derivado o análogo que formará una cantidad equivalente de un compuesto activo o sustancia dentro del cuerpo.

La presente invención incluye prodrogas de compuestos de fórmula I. "Prodrogas", como se utiliza aquí significa un compuesto que es convertible in vivo mediante medios metabólicos (por ejemplo mediante hidrólisis) a un compuesto de fórmula I. varias formas de prodrogas se conocen en la técnica, por ejemplo, como se

discute en Bungeard, (ed.), Design of Prodrugs, Elsevier (1985);
Widder, et al. (ed.), Methods in Enzymology, vol. 4, Academic
Press (1985); Krogsgaard-Larsen, et al., (ed). "Design and
Application of Prodrugs, Textbook of Drug Design and Development,
Chapter 5, 113-191 (1991), Bundgaard, et al., Journal of Drug
Delivery reviews, 8:1-38(1992), Bundgaard, J. of Pharmaceutical
Sciences, 77:285 et seq. (1988); and Higuchi and Stella (eds.)
Prodrugs as Novel Drug Delivery Systems, American Chemical
Society (1975).

Esta invención será más completamente descrita en conjunto con
los siguientes ejemplos específicos que no deben ser considerados
como limitantes del alcance de la invención.

Ejemplo de Referencia 1

2-Ciano-N-(2,4-dicloro-5-metoxifenil) acetamida

2,4-Dicloro-5-metoxianilina (5.00 g, 26 mmol) y ácido
cianoacético (2.28 g, 26.8 mmol) se mezclan en 50 mL de
tetrahidrofurano, bajo N₂, hasta que se forma la solución. Esta
solución se calienta a reflujo y se agrega gota a gota 1,3-
diisopropilcarbodiimida (4.2 mL, 26.8 mmol). Después de 30
minutos una revisión TLC (5% MeOH en CH₂Cl₂) indicó que la
reacción estaba completa. La muestra se enfría a ~ 15 °C en un
baño de hielo. El sólido fue recolectado mediante filtración y
lavado con tetrahidrofurano. El filtrado se vierte lentamente en
agua y se agita durante 30, minutos. El sólido blanco se
recolecta por filtración, se lava con agua y luego se disuelve en

500 ml de acetato de etilo. La solución se seca sobre Na_2SO_4 y se concentra en vacío para dar 5.9 g (88%) de 2-ciano-N-(2,4-dicloro-5-metoxifenil) acetamida como un sólido blanco, pf 180-181 °C; MS 257.0, 259.0 (M-H)-.

Análisis para $\text{C}_{10}\text{H}_8\text{Cl}_2\text{N}_2\text{O}_2$:

Calculado: C, 46.36; H, 3.11; N, 10.81.

Encontrado: C, 46.25; H, 3.10; N, 10.85.

Ejemplo de Referencia 2

2-Ciano-N-(2,4-dicloro-5-metoxifenil)-3-[(3-yodo-4-metoxifenil)amino]-prop-2-enamida

A una suspensión de 2-ciano-N-(2,4-dicloro-5-metoxifenil)acetamida (5.00 g, 19.30 mol) en 400 mL de iso-propanol, bajo N_2 , se agrega 3-yodo-p-anisidina (5.80 g, 23.16 mmol). Se calienta esta mezcla a reflujo para dar una solución amarilla clara. A esta solución, se agrega en forma de gotas trietilortoformato (8.60 mL, 52.11 mmol) y se calienta la mezcla de reacción a reflujo durante la noche. Se agrega 10 mL de trietilortoformato adicional y se calienta la mezcla a reflujo durante la noche. Se le permite a la mezcla enfriar a temperatura ambiente y se recolecta el sólido blanco por filtración, se lava con iso-propanol, y se seca durante la noche a $\sim 40^\circ \text{C}$ bajo presión reducida. La purificación por suspensión en acetato de etilo caliente seguido por adición de hexanos fríos da 8.50 g (85%) de 2-ciano-N-(2,4-dicloro-5-metoxifenil)-3-[(3-yodo-4-

metoxifenil)amino]prop-2-enamida como un sólido amarillo, pf 289-290° C; MS (ES) m/z 516.7 (M-H)-.

Análisis para $C_{18}H_{14}Cl_2IN_3O_3$:

Calculado: C, 41.73; H, 2.72; N, 8.11.

Encontrado: C, 40.88; H, 2.64; N, 7.90.

Ejemplo de Referencia 3

4-[(2,4-Dicloro-5-metoxifenil)amino]-7-yodo-6-metoxi-3-quinolinocarbonitrilo

A una suspensión de 2-ciano-N-(2,4-dicloro-5-metoxifenil)-3-[(3-yodo-4-metoxi-fenil)amino]prop-2-enamida (720 mg, 1.39 mmol) en 40 mL de acetonitrilo se agrega 0.2 mL de metanol. Se calienta la mezcla a reflujo y se agrega en forma de gotas oxícloruro de fósforo (1.24 mL, 13.9 mmol), por vía de una jeringa. Se calienta esta solución a reflujo durante la noche. Después de 24 horas, se enfría la mezcla en un baño de hielo y se recolecta el sólido por filtración, se lava con acetonitrilo frío (40 mL) y luego se suspende en tetrahidrofurano (100 mL). Al filtrado de acetonitrilo y la suspensión de tetrahidrofurano se agregan hidróxido de amonio concentrado (2x50 mL) y se agita la mezcla durante 1 hora. Se agrega agua (2x 800 mL) y se continúa la agitación durante 2 horas. Se combinan los sólidos resultantes, se lavan con agua caliente y se secan bajo presión reducida a ~40° C, durante la noche, para suministrar 200 mg (29%) de 4-[(2,4-dicloro-5-metoxifenil)amino]-7-yodo-6-metoxi-3-quinolinocarbonitrilo, como sólido amarillo, pf 253-254° C; ^1H RMN (400 MHz, DMSO- d_6) δ 3.86 (s, 3H), 4.00 (s, 3H), 7.33 (s, 1H),

53

7.74 (s, 1H), 7.86 (s, 1H), 8.39 (s, 1H), 8.43 (s, 1H), 9.61 (s, 1H); MS (ES) m/z 500.0, 502.1 (M+H)⁺. nnn/5

Análisis para $C_{18}H_{12}Cl_2IN_3O_2 \cdot H_2O$:

Teórico: C, 41.72, H, 2.72, N, 8.11

Encontrado: C, 41.80; H, 2.52; N, 7.87.

Ejemplo de Referencia 4

1-Etoxi-2-yodo-4-nitrobenceno

Una suspensión de 2-yodo-4-nitrofenol (21 g, 79.2 mmol) [Kometani, T.; et. al., Tetrahedron Lett. (1985), 26(17), 2043], yoduro de etilo (9 mL, 0.48 mol) y carbonato de potasio (40.7 g, 0.3 mol) en 100 mL de N, N-dimetilformamida se calienta a 70° C durante 3 h. La reacción se enfría a temperatura ambiente y se agrega acetato de etilo. Se filtran las sales inorgánicas y se lavan con acetato de etilo. El material orgánico se lava con agua (3X) y solución salina, se seca sobre sulfato de magnesio y se filtra. Luego de la concentración del filtrado aparece un sólido. Se filtra este sólido y se lava con hexanos para dar 5.2 g de 1-etoxi-2-yodo-4-nitrobenceno cristales blancos. La concentración del filtrado suministra 11.3 g adicional del producto deseado, pf 81-83° C; ¹H RMN (400 MHz, DMSO-*d*₆) δ 1.42 (t, 3H), 4.26 (q, 2H), 7.18 (d, 1H), 8.26 (dd, 1H), 8.55 (d, 1H).

Análisis para $C_8H_8INO_3$:

Teórico: C, 32.79, H, 2.75, N, 4.78.

Encontrado: C, 32.71, H, 2.58, N, 4.53.

Ejemplo de Referencia 5• ~~nnn~~6(4-Etoxi-3-yodofenil)amina

Una suspensión de hierro (3.81 g, 70 mmol) y cloruro de amonio (5.47 g, 102 mmol) en 80 mL de etanol y 25 mL de agua se calientan a reflujo. Se agrega en porciones 1-etoxi-2-yodo-4-nitrobenceno (5.0 g, 20 mmol) y se calienta la reacción a reflujo durante 1 h. La mezcla caliente se filtra a través de Celita, se lava con etanol caliente. Se concentra el filtrado en vacío y se trata con acetato de etilo y agua. Se extrae la capa orgánica, se lava con solución salina, se seca sobre sulfato de magnesio y se filtra. La remoción del solvente en vacío suministra 5.1 g de (4-etoxi-3-yodofenil)amina como un aceite café claro; ^1H RMN (400 MHz, DMSO- d_6) δ 1.30 (s, 3H), 3.89 (q, 2H), 4.82 (bs, 2H), 6.53 (dd, 1H), 6.72 (d, 1H), 7.11 (d, 1H); MS (ES) m/z 263.9 (M+H)+.

Análisis para $\text{C}_8\text{H}_{10}\text{INO}$:

Teórico: C, 36.52, H, 3.83, N, 5.32.

Encontrado: C, 36.84, H, 3.71, N, 4.96.

Ejemplo de Referencia 62-Ciano-N-(2,4-dicloro-5-metoxifenil)-3-[(4-etoxi-3-yodofenil)amino]acrilamida

A una suspensión de 2-ciano-N-(2,4-dicloro-5-metoxifenil)acetamida (5.44 g, 21.0 mmol) en 350 mL de isopropanol, bajo N_2 , se agrega (4-etoxi-3-yodofenil)-amina (5.0 g,

19.30 mmol). Se calienta esta mezcla a reflujo y se agrega trietilortoformato (8.53 mL, 51.30 mmol) en forma de gota y se calienta la mezcla de reacción a reflujo durante la noche. Se le permite a la mezcla enfriar a temperatura ambiente y se recolecta el sólido amarillo por filtración, se lava con iso-propanol, y se seca durante la noche a ~40°C bajo presión reducida para dar 5.46 g (54%) de 2-ciano-N-(2,4-dicloro-5-metoxifenil)-3-[(4-etoxi-3-yodofenil)amino]prop-2-enamida como un sólido amarillo, pf >245 °C; MS (EI) m/z 531.01 (M)+.

Análisis para C₁₉H₁₆Cl₂IN₃O₃:

Calculado: C, 42.88; H, 3.03; N, 7.90.

Encontrado: C, 42.99; H, 2.97; N, 7.74.

Ejemplo de Referencia 7

4-[(2,4-Dicloro-5-metoxifenil)amino]-6-etoxi-7-yodo-3-quinolinccarbonitrilo

Una suspensión de 2-ciano-N-(2,4-dicloro-5-metoxifenil)-3-[(4-etoxi-3-yodo-fenil)-amino]prop-2-enamida (2.0 g, 3.76 mmol) en 100 mL de tolueno se calienta a reflujo y se agrega en forma de gotas oxiclورو de fósforo (3.5 mL, 37.6 mmol) por vía de jeringa. Se calienta esta suspensión a reflujo durante 6 horas y se agrega oxiclورو de fósforo adicional (3.5 mL, 37.6 mmol) para dar lentamente una solución oscura. Después de 72 horas se enfría la mezcla a temperatura ambiente, se filtra el sólido y se lava con tolueno y éter. Se seca el sólido café claro bajo presión reducida a ~40° C, durante la noche, para suministrar

1.47 g (76%) de 4-[(2,4-dicloro-5-metoxifenil)amino]-6-etoxi-7-yodo-3-quinolinocarbonitrilo como un sólido amarillo, pf 213-215 °C; ^1H RMN (300 MHz, DMSO- d_6) δ 1.48 (t, 3H, $J = 6.9$ Hz), 4.32 (q, 2H, $J = 6.9$ Hz), 3.88 (s, 3H), 7.53 (s, 1H), 7.87 (s, 1H), 8.06 (s, 1H), 8.49 (s, 1H), 9.02 (s, 1H), 11.14 (bs, 1H); MS (ES) m/z 514.1 (M+H)+.

Análisis para $\text{C}_{19}\text{H}_{14}\text{Cl}_2\text{IN}_3\text{O}_2 - 4.0 \text{ HCl}$:

Teórico: C, 34.58, H, 2.75, N, 6.37

Encontrado: C, 34.79; H, 2.60; N, 6.13.

Ejemplo de Referencia 8

4-[(2,4-Dicloro-5-metoxifenil)amino]-7-(4-hidroxibut-1-inil)-6-metoxi-3-quinolinocarbonitrilo

Una mezcla de 3-ciano-4-[(2,4-dicloro-5-metoxifenil)anilino]-6-metoxi-7-quinolinil trifluorometanosulfonato (2.0 g, 3.8 mmol), 3-butin-1-ol (0.44 mL, 0.56 mmol), tetrakis(trifenilfosfina)paladio (0.22 g, 0.19 mmol) y yoduro de cobre (45 mg, 0.24 mmol) en una mezcla de 12 mL de trietilamina y 30 mL de 1,4-dioxano se calientan a 95-100° C durante 2 horas y luego se enfría a temperatura ambiente. Se agregan acetato de etilo y agua. Se remueven los sólidos por filtración, se trituran en dietil éter caliente, se filtran y se secan para suministrar 0.65 g (38%) de 4-[(2,4-dicloro-5-metoxifenil)amino]-7-(4-hidroxibut-1-inil)-6-metoxi-3-quinolinocarbonitrilo, pf 230-232 °C; ^1H RMN (DMSO- d_6) δ 2.65 (t, 2H, $J = 6.9$ Hz), 3.62 (q, 2H, $J =$

6.9, 6.0 Hz), 3.86 (s, 3H), 3.98 (s, 3H), 4.96 (t, 1H, J = 6.0 Hz), 7.39 (s, 1H), 7.76 (s, 1H), 7.89 (s, 2H), 8.44 (s, 1H), 9.97 (bs, 1H); MS (ES) m/z 442.0 (M+H)⁺; HRMS 442.07198 (M+H)⁺; HPLC - 93%.

Ejemplo de Referencia 9

4-[(2,4-Dicloro-5-metoxifenil)amino]-6-etoxi-7-(4-hidroxibut-1-inil)-3-quinolinocarbonitrilo

Una mezcla de 4-[(2,4-dicloro-5-metoxifenil)amino]-6-etoxi-7-yodo-3-quinolino-carbonitrilo (0.6 g, 1.2 mmol), 3-butin-1-ol (0.13 mL, 1.7 mmol), tetrakis(trifenil-fosfina)paladio (68 mg, 0.058 mmol) y yoduro de cobre (15 mg, 0.076 mmol) en una mezcla de 4 mL de trietilamina y 10 mL de 1,4-dioxano se calienta a 95° C durante 3 horas y luego se enfría a temperatura ambiente. Se agregan acetato de etilo y agua. Se extrae la capa orgánica, se seca sobre sulfato de magnesio, se filtra y se concentra. Se agrega éter y se filtra el sólido y se lava con dietil éter caliente (3X). Se combinan el sólido y el filtrado y se purifican por cromatografía utilizando un gradiente de 0 a 10 % de metanol y diclorometano. Se tritura el sólido amarillo obtenido en dietil éter caliente, se filtra y se seca para suministrar 0.16 g (31%) de 4-[(2,4-dicloro-5-metoxifenil)amino]-6-etoxi-7-(4-hidroxibut-1-inil)-3-quinolino-carbonitrilo, pf 220-222° C; ¹H RMN (DMSO-d₆) δ 1.44 (t, 3H, J = 6.8 Hz), 2.65 (t, 2H, J = 6.8 Hz), 3.63 (dt, 2H, J = 6.9, 5.8 Hz), 3.86 (s, 3H), 4.25 (q, 2H, J = 6.8 Hz), 4.95 (t, 1H, J = 5.8 Hz), 7.39 (s, 1H), 7.77 (s, 1H), 7.87 (s,

2H), 8.44 (s, 1H), 9.75 (bs, 1H); MS (ES) m/z 456.1 (M+H)⁺; HRMS 456.08763 (M+H)⁺; HPLC - 98%. 58
000/0

Ejemplo 1

4-[(2,4-Dicloro-5-metoxifenil)amino]-7-[4-(dimetilamino)but-1-inil]-6-metoxi-3-quinolinocarbonitrilo

A una mezcla de 4-[(2,4-dicloro-5-metoxifenil)amino]-7-(4-hidroxibut-1-inil)-6-metoxi-3-quinolinocarbonitrilo (0.3 g, 0.68 mmol) y trietilamina (0.47 mL, 3.4 mmol) en 3 mL de N,N-dimetilformamida y 15 mL de tetrahidrofurano a 0° C se agrega en forma de gotas cloruro de metanosulfonilo (0.16 mL, 2.0 mmol). Se agita la mezcla durante 1.25 horas y se agrega dimetilamina (2.0 mL, 2.0 M de solución en tetrahidrofurano). Se agita la reacción a temperatura ambiente durante la noche. Se agrega un de 3.0 mL de trietilamina adicional y se agita la reacción a temperatura ambiente durante la noche. Se concentra la mezcla y se diluye con acetato de etilo y agua. Se extrae la capa orgánica, se seca sobre sulfato de magnesio, se filtra y se concentra. Se purifica el residuo por cromatografía utilizando un gradiente de 0 a 10% de metanol en diclorometano. Se tritura el producto en dietil éter caliente, se filtra y se seca para suministrar 62 mg (20%) de 4-[(2,4-dicloro-5-metoxi-fenil)amino]-7-[4-(dimetilamino)but-1-inil]-6-metoxi-3-quinolinocarbonitrilo como un sólido amarillo, pf 177-179 °C; ¹H RMN (DMSO-*d*₆) δ 2.22 (s, 6H), 2.56 (t, 2H, J = 6.8 Hz), 2.65 (t, 2H, J = 6.8 Hz), 3.86 (s, 3H), 3.96 (s, 3H), 7.38 (s, 1H), 7.76 (s, 1H), 7.88 (s, 2H), 8.43 (s, 1H), 9.82 (bs, 1H); MS (ES) m/z 469.1 (M+H)⁺.

Análisis para $C_{24}H_{22}Cl_2N_4O_2 \cdot 1.5 H_2O$

Teórico: C, 58.07, H, 5.08, N, 11.29.

Encontrado: C, 58.46, H, 4.82, N, 10.99.

Ejemplo 2

4-[(2,4-Dicloro-5-metoxifenil)amino]-6-metoxi-7-[4-(4-metilpiperazin-1-il)but-1-inil]-3-quinolinocarbonitrilo

El mismo procedimiento utilizado para la síntesis del Ejemplo 1 se sigue para suministrar 90 mg (25%) de 4-[(2,4-dicloro-5-metoxifenil)amino]-6-metoxi-7-[4-(4-metil-piperazin-1-il)but-1-inil]-3-quinolinocarbonitrilo como un sólido amarillo, pf 165-167 °C; ^1H RMN ($DMSO-d_6$) δ 2.17 (s, 3H), 2.35 (bs, 4H), 2.50 (bs, 4H), 2.60-2.68 (m, 4H), 3.86 (s, 3H), 3.96 (s, 3H), 7.34 (s, 1H), 7.74 (s, 1H), 7.83 (s, 1H), 7.88 (s, 1H), 8.43 (s, 1H), 9.83 (bs, 1H), MS (ES) m/z 524.2 (M+H)+.

Análisis para $C_{27}H_{27}Cl_2N_5O_2 \cdot 1.5 H_2O$

Teórico: C, 58.80, H, 5.48, N, 12.70.

Encontrado: C, 58.89, H, 5.19, N, 12.38.

Preparación Alternativa del Ejemplo 2:

Una mezcla de 3-ciano-4-[(2,4-dicloro-5-metoxifenil)anilino]-6-metoxi-7-quinolinil trifluorometanosulfonato (2.5 g, 4.8 mmol), 1-but-3-inil-4-metil-piperazina (1.8 g, 11.8 mmol) [Varillancourt, V. A. et. al. WO2002002558A1], dicloruro de

bis(trifenilfosfina)paladio (170 mg, 0.22 mmol), carbonato de potasio (3.31 g, 0.024 mol), trifenilfosfina (25 mg, 0.9 mmol) y yoduro de cobre (45 mg, 0.22 mmol) en una mezcla de 6 mL de metanol y 30 mL de tetrahidrofurano se calienta a 60° C durante 4 horas y luego se enfría a temperatura ambiente. Se agregan acetato de etilo y agua. Se extrae la capa orgánica, se seca sobre sulfato de magnesio, se filtra y se concentra. La purificación del residuo por cromatografía utilizando un gradiente de 0 a 10% de metanol en diclorometano, seguido por 20% de metanol-diclorometano/1% de NH₄OH como el sistema de solvente suministra 2.2 g (88%) de 4-[(2,4-dicloro-5-metoxifenil)amino]-6-metoxi-7-[4-(4-metilpiperazin-1-il)but-1-inil]-3-quinolinocarbonitrilo.

Segunda Preparación alternativa de Ejemplo 2

Una mezcla de 4-[(2,4-dicloro-5-metoxifenil)amino]-7-yodo-6-metoxi-3-quinolino-carbonitrilo (0.2 g, 0.4 mmol), 1-but-3-inil-4-metilpiperazina (0.21 g, 1.4 mmol) [Vaillancourt, V. A. et. al. WO2002002558A1], dicloruro de bis(trifenilfosfina)paladio (14 mg, 0.02 mmol), trifenilfosfina (21 mg, 0.08 mmol) y yoduro de cobre (5 mg, 0.02 mmol) en una mezcla de 2 mL de trietilamina y 1 mL de N-metil-pirrolidinona se calienta a 70° C durante 4 horas y luego se enfría a temperatura ambiente. Se agregan acetato de etilo y agua. Se extrae la capa orgánica, se seca sobre sulfato de magnesio, se filtra y se concentra. La purificación del residuo por cromatografía utilizando un gradiente de 0 a 10% metanol en diclorometano, seguido por 15% de metanol-diclorometano/1% de NH₄OH como el sistema de solvente suministra 78 mg (37%) de 4-

[(2,4-dicloro-5-metoxifenil)amino]-6-metoxi-7-[4-(4-metil-piperazin-1-il)but-1-inil]-3-quinolinocarbonitrilo.

Ejemplo 3

4-[(2,4-Dicloro-5-metoxifenil)amino]-6-metoxi-7-(4-morfolin-4-ilbut-1-inil)-3-quinolinocarbonitrilo

El mismo procedimiento utilizado para la síntesis del Ejemplo 1 se sigue para suministrar 150 mg (43%) de 4-[(2,4-dicloro-5-metoxifenil)amino]-6-metoxi-7-(4-morfolin-4-ilbut-1-inil)-3-quinolinocarbonitrilo como un sólido amarillo, pf 140-142° C; ¹H RMN (DMSO-d₆) δ 2.50 (t, 4H, J = 4.4 Hz), 2.58-2.73 (m, 4H), 3.60 (t, 4H, J = 4.4 Hz), 3.87 (s, 3H), 3.98 (s, 3H), 7.39 (s, 1H), 7.77 (s, 1H), 7.87 (s, 1H), 7.89 (s, 1H), 8.45 (s, 1H), 9.82 (bs, 1H); MS (ES) m/z 511.0 (M+H)+.

Análisis para C₂₆H₂₄Cl₂N₄O₃

Teórico: C, 61.06, H, 4.73, N, 10.96.

Encontrado: C, 60.89, H, 4.74, N, 10.82.

Ejemplo 4

4-[(2,4-Dicloro-5-metoxifenil)amino]-6-metoxi-7-(4-piperazin-1-ilbut-1-inil)-3-quinolinocarbonitrilo

Se sigue el mismo procedimiento utilizado para la síntesis del Ejemplo 1. Después de la purificación por cromatografía de columna se obtiene 120 mg de una mezcla que contiene el producto.

Se purifica adicionalmente la mezcla por HPLC utilizando un gradiente de 5 a 95% de acetonitrilo/agua (0.02% de TFA) para suministrar 15 mg (5%) de 4-[(2,4-dicloro-5-metoxi-fenil)amino]-6-metoxi-7-(4-piperazin-1-ilbut-1-inil)-3-quinolinocarbonitrilo como un sólido amarillo, pf 188-190° C; ¹H RMN (DMSO-d₆) δ 2.85 (t, 2H, J = 6.8 Hz), 3.03 (bs, 6H), 3.32 (bs, 4H), 3.89 (s, 3H), 3.98 (s, 3H), 7.35 (s, 1H), 7.77 (s, 1H), 7.89 (s, 1H), 7.92 (s, 1H), 8.52 (s, 1H), 8.81 (bs, 1H), 10.01 (bs, 1H); MS (ES) m/z 510.1 (M+H)+.

Análisis para C₂₆H₂₅Cl₂N₅O₂ - 3 TFA/1 H₂O

Teórico: C, 44.18, H, 3.48, N, 8.06.

Encontrado: C, 44.07, H, 3.22, N, 8.06.

Ejemplo 5

4-[(2,4-Dicloro-5-metoxifenil)amino]-6-etoxi-7-[4-(4-metilpiperazin-1-il)but-1-inil]-3-quinolinocarbonitrilo

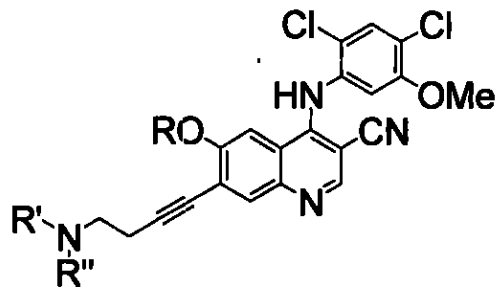
El mismo procedimiento utilizado para la síntesis del Ejemplo 1 se sigue para suministrar 45 mg (24%) de 4-[(2,4-dicloro-5-metoxifenil)amino]-6-etoxi-7-[4-(4-metil-piperazin-1-il)but-1-inil]-3-quinolinocarbonitrilo como un sólido amarillo, pf 158-160° C; ¹H RMN (DMSO-d₆) δ 1.43 (t, 3H, J = 6.8 Hz), 2.19 (s, 3H), 2.38 (bs, 4H), 2.50 (bs, 4H), 2.60-2.67 (m, 4H), 3.86 (s, 3H), 4.22 (q, 2H, J = 6.8 Hz), 7.36 (s, 1H), 7.74 (s, 1H), 7.84 (s, 1H), 7.88 (s, 1H), 8.42 (s, 1H), 9.78 (bs, 1H); MS (ES) m/z 538.2 (M+H)+; HRMS 538.17726 (M+H)+; la pureza HPLC es 99%.

63
11.000/5

REIVINDICACIONES

Lo que se reivindica es:

1. Un compuesto que tiene la estructura:



I

en donde:

R es metilo o etilo;

R' y R'' son independientemente alquilo de 1 a 3 átomos de carbono, o R' y R'', tomados juntos con el nitrógeno al cual ellos están unidos, pueden formar un anillo de saturado 5 o 6 miembros el cual puede contener opcionalmente un heteroatomo adicional seleccionado de NR''', O o S(O)_n;

n es 0-2;

R''' es hidrógeno o alquilo de 1 a 3 átomos de carbono; y sales farmacéuticamente aceptables de estos.

2. El compuesto de la Reivindicación 1 en donde R' y R'' son cada uno metilo.

64
... 00076

3. El compuesto de la Reivindicación 1 en donde R' y R'', tomados juntos con el átomo de nitrógeno al cual ellos están unidos, forman un anillo N-(C₁-C₃)-alquilpiperazina, piperazina o morfolino.
4. El compuesto de la Reivindicación 3 en donde el anillo N-(C₁-C₃)alquilpiperazina es N-metil-piperazina.
5. El compuesto de una cualquiera de las Reivindicaciones 1 a 4 en donde R es metilo.
6. El compuesto de la Reivindicación 1 en donde el compuesto se selecciona de:
 - 4-[(2,4-Dicloro-5-metoxifenil)amino]-7-[4-(dimetilamino)but-1-il]-6 metoxi-3-quinolinocarbonitrilo;
 - 4-[(2,4-Dicloro-5-metoxifenil)amino]-6-metoxi-7-[4-(4-metilpiperazin-1-il)but-1-il]-3-quinolinocarbonitrilo;
 - 4-[(2,4-Dicloro-5-metoxifenil)amino]-6-metoxi-7-(4-morfolin-4-ilbut-1-il)-3-quinolinocarbonitrilo;
 - 4-[(2,4-Dicloro-5-metoxifenil)amino]-6-metoxi-7-(4-piperazin-1-ilbut-1-il)-3-quinolinocarbonitrilo; y
 - 4-[(2,4-Dicloro-5-metoxifenil)amino]-6-etoxi-7-[4-(4-metilpiperazin-1-il)but-1-il]-3-quinolinocarbonitrilo;

12. Un método para reducir volúmenes de infarto en un paciente luego de un evento isquémico cerebrovascular comprende administrar una cantidad terapéuticamente efectiva de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 6.
13. Un método para inhibir la permeabilidad vascular post-isquémica de vasos sanguíneos cerebrales en un paciente que sufre de un evento cerebrovascular que comprende administrar una cantidad terapéuticamente efectiva de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 6.
14. El método de una cualquiera de las Reivindicaciones 10 a 13 en donde el compuesto se administra entre aproximadamente 6 a aproximadamente 24 horas después del evento isquémico.
15. El método de una cualquiera de las Reivindicaciones 10 a 14 en donde la cantidad terapéuticamente efectiva es de aproximadamente 1 mg/kg a aproximadamente 30 mg/kg.
16. El método de una cualquiera de las Reivindicaciones 10 a 15 que comprende administrar intravenosamente un compuesto de Fórmula I.
17. El método de una cualquiera de las Reivindicaciones 10 a 16 en donde el paciente es un humano.

18. El método de una cualquiera de las Reivindicaciones 10 a 17 en donde el evento isquémico es transitorio.
19. El método de una cualquiera de las Reivindicaciones 10 a 17 en donde el evento isquémico es agudo.
20. El método de la Reivindicación 19 en donde el evento isquémico es accidente cerebro vascular, trauma de cabeza, trauma espinal, anoxia general, o hipoxia.
21. El método de una cualquiera de las Reivindicaciones 10 a 20 en donde el evento isquémico ocurre durante la hemorragia cerebral, asfixia perinatal, detención cardíaca o estado epiléptico.
22. El uso de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 6 en la fabricación de un medicamento para suministrar neuroprotección en un paciente luego de un evento isquémico cerebrovascular, inhibiendo déficit neurclógicos en un paciente luego de un evento isquémico cerebrovascular, reduciendo volúmenes de infarto en un paciente luego de un evento isquémico cerebrovascular, e inhibiendo permeabilidad vascular post-isquémica de vasos sanguíneos cerebrales en un paciente que sufre de un evento cerebrovascular.
23. El uso de la reivindicación 22 en donde el paciente es un humano.

24.El uso de la reivindicación 22 o reivindicación 23 en donde el evento isquémico es transitorio.

25.El uso de la reivindicación 22 o reivindicación 23 en donde el evento isquémico es agudo.

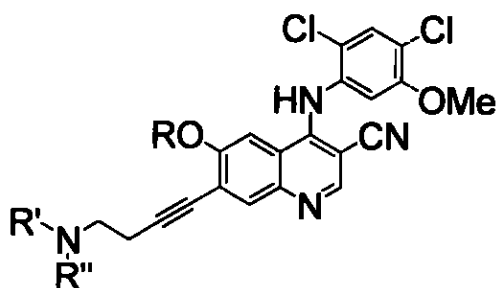
26.El uso de la reivindicación 25 en donde el evento isquémico es accidente cerebro vascular, trauma de cabeza, trauma espinal, anoxia general, o hipoxia.

27.El uso de una cualquiera de las Reivindicaciones 22 a 26 en donde el evento isquémico ocurre durante la hemorragia cerebral, asfixia perinatal, detención cardiaca o estado epiléptico.

RESUMEN

4-[(2,4-DICLORO-5-METOXIFENIL)AMINO]-6-ALCOXI-7-ETINIL-3-
QUINOLINOCARBONITRILOS PARA EL TRATAMIENTO DE lesión isquémica

Esta invención se relaciona con compuestos de la fórmula:



I

en donde:

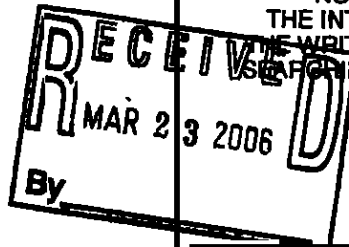
R es metilo o etilo;

R' y R'' son independientemente alquilo de 1 a 3 átomos de carbono, o R' y R'', tomados juntos con el nitrógeno al cual ellos están unidos, pueden formar un anillo de saturado 5 o 6 miembros el cual puede contener opcionalmente un heteroátomo adicional seleccionado de NR''', O o S(O)_n; n es 0-2; y R''' es hidrógeno o alquilo de 1 a 3 átomos de carbono; y sales farmacéuticamente aceptables de estos, y su uso para inhibir permeabilidad vascular causada por enfermedad lesión u otro trauma.

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To
WYETH
Patent Law Department
Attn. Barrett, Rebecca R.
Five Giralda Farms
Madison, New Jersey 07940
UNITED STATES OF AMERICA



NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing
(day/month/year)

17/03/2006

Applicant's or agent's file reference

AM1-01,758 PCT

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No

PCT/US2005/037839

International filing date
(day/month/year)

21/10/2005

Applicant

WYETH

- 1 ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No (41-22) 338.82.70

For more detailed instructions, see the notes on the accompanying sheet

- 2 ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith
- 3 ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that
- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts or both the protest and the decision thereon to the designated Offices
- ☐ no decision has been made yet on the protest, the applicant will be notified as soon as a decision is made

4 Reminders

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis 1 and 90bis 3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 18 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx 31 651 epo nl,
Fax. (+31-70) 340-3016

Authorized officer

Gabriele Pfitzner

MAR 28 2006

RECEIVED

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference AM101758 PCT	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below	
International application No. PCT/US2005/037839	International filing date (day/month/year) 21/10/2005	(Earliest) Priority Date (day/month/year) 22/10/2004
Applicant WYETH		

This International search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1 Basis of the report

a With regard to the language, the international search was carried out on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2 ☒ Certain claims were found unsearchable (See Box No. II)

3 ☐ Unity of invention is lacking (see Box No. III)

4 With regard to the title,

☒ the text is approved as submitted by the applicant

☐ the text has been established by this Authority to read as follows

5 With regard to the abstract,

☒ the text is approved as submitted by the applicant

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6 With regard to the drawings,

a the figure of the drawings to be published with the abstract is Figure No. _____

☐ as suggested by the applicant

☐ as selected by this Authority, because the applicant failed to suggest a figure

☐ as selected by this Authority, because this figure better characterizes the invention

b ☐ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No. ~~00015~~

PCT/US2005/037839

A. CLASSIFICATION OF SUBJECT MATTER

C07D215/44 A61K31/4706 A61P9/10

73

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	WO 2004/075898 A (WYETH; BOSCHELLI, DIANE, HARRIS; ZALESKA, MARGARET, MARIA; BOSCHELLI,) 10 September 2004 (2004-09-10) the whole document	1-27
A	US 6 689 772 B1 (BOSCHELLI DIANE HARRIS ET AL) 10 February 2004 (2004-02-10) the whole document ----- -/-	1-27



Further documents are listed in the continuation of Box C



See patent family annex

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

Z document member of the same patent family

Date of the actual completion of the international search

17 February 2006

Date of mailing of the international search report

17/03/2006

Name and mailing address of the ISA/

European Patent Office, P B 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Gregoire, A

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	BARRIOS SOSA, ANA CAROLINA ET AL: "Synthesis and inhibition of Src kinase activity by 7-ethenyl and 7-ethynyl-4-anilino-3-quinolinecarbonitril es" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, (CODEN: BMCLE8), vol. 14, no. 9, 2004, pages 2155-2158, XP002368408 ISSN: 0960-894X the whole document	1-27

INTERNATIONAL SEARCH REPORT

International application No. **03/000075**
PCT/US2005/037839 **75**

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

- 1 ☒ Claims Nos.
because they relate to subject matter not required to be searched by this Authority, namely
Although claims 10-21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
- 2 ☐ Claims Nos.
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically
- 3 ☐ Claims Nos.
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows

- 1 ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims
- 2 ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
- 3 ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
- 4 ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims, it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees

INTERNATIONAL SEARCH REPORT
information on patent family members

International application No

PCT/US2005/037839

nnn
76

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2004075898	A	10-09-2004	AU 2004216235 A1	10-09-2004
			BR 0407441 A	31-01-2006
			CA 2516418 A1	10-09-2004
			EP 1594502 A1	16-11-2005
US 6689772	B1	10-02-2004	US 2002026052 A1	28-02-2002

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To

see form PCT/ISA/220WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)Applicant's or agent's file reference
see form PCT/ISA/220FOR FURTHER ACTION
See paragraph 2 belowInternational application No
PCT/US2005/037839International filing date (day/month/year)
21 10 2005Priority date (day/month/year)
22.10 2004International Patent Classification (IPC) or both national classification and IPC
C07D215A44, A61K31A706, A61P9/10Applicant
WYETH

1 This opinion contains indications relating to the following items

- ☒ Box No I Basis of the opinion
- ☐ Box No II Priority
- ☒ Box No III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No IV Lack of unity of invention
- ☒ Box No V Reasoned statement under Rule 43bis 1(a)(i) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement
- ☐ Box No VI Certain documents cited
- ☐ Box No VII Certain defects in the international application
- ☐ Box No VIII Certain observations on the international application

2 FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3 For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA



European Patent Office
D-80298 Munich
Tel +49 89 2399 - 0 Tx 523656 epmu d
Fax +49 89 2399 - 4465

Authorized Officer

Gregoire, A
Telephone No +49 89 2399-2994



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/037839

Box No. I Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b))
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material
☐ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed
☐ filed together with the international application in computer readable form
☐ furnished subsequently to this Authority for the purposes of search
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished
4. Additional comments.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

nnn 9179
International application No.
PCT/US2005/037839

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

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

☐ the entire international application,

☒ claims Nos. 10-21

because

☒ the said international application, or the said claims Nos. 10-21 relate to the following subject matter which does not require an international preliminary examination (*specify*)

see separate sheet

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

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

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

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/037839

Box No. V Reasoned statement under Rule 43*bis*.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Statement

Novelty (N)	Yes.	Claims	1-27
	No.	Claims	
Inventive step (IS)	Yes.	Claims	1-27
	No.	Claims	
Industrial applicability (IA)	Yes.	Claims	1-9, 22-24
	No.	Claims	

2 Citations and explanations

see separate sheet

Re Item III

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

Claims 10-21 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1) Reference is made to the following documents :

- D1: WO 2004/075898 A (WYETH; BOSCHELLI, DIANE, HARRIS; ZALESKA, MARGARET, MARIA; BOSCHELLI,) 10 September 2004 (2004-09-10)
- D2: US-B1-6 689 772 (BOSCHELLI DIANE HARRIS ET AL) 10 February 2004 (2004-02-10)
- D3: BARRIOS SOSA, ANA CAROLINA ET AL: "Synthesis and inhibition of Src kinase activity by 7-ethenyl and 7-ethynyl-4-anilino-3-quinolinecarbonitril es" 2004, BIOORGANIC & MEDICINAL CHEMISTRY LETTERS , 14(9), 2155-2158 CODEN: BMCLE8; ISSN: 0960-894X , XP002368408

2) Novelty (Art. 33 (1) and (2) PCT) :

D1 and D3 disclose compounds differing from those presently claimed in the definition of the substituent on position 7 of the quinoliny ring.

D2 generically discloses Src-kinase inhibitors encompassing those presently claimed. The closest compound of D2 is the fourth compound mentioned in col 28 of said document and differ from the absence of a methylene group in the substituent attached on position 7 of the quinoliny ring. The specific family of compounds presently claimed can be considered as a novel selection over D2.

The present application complies with Art. 33(2) PCT.

3) Inventive Step (Art. 33 (1) and (3) PCT) :

D1 discloses 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-alkoxy-3-quinolinecarbonitriles for the treatment of ischemic injury through their Src-kinase inhibitory activity.

These compounds differ from those presently claimed in the definition of the substituent on position 7 of the quinoliny ring.

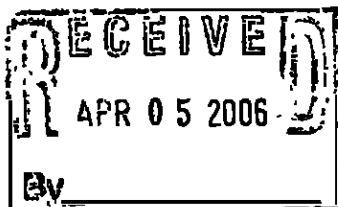
The technical problem raised by the present application is the provision of further compounds useful for the treatment of ischemic injury.

No hint is present in D1 alone or in combination with D2 or D3 which would have led the skilled person looking for further compounds inevitably to the presently claimed compounds. The biological data disclosed page 5-7 show that some compounds as claimed solve the problem raised.

The present application thus complies with Art. 33(3) PCT.

4) Industrial applicability (Art. 33(1) and (4) PCT) :

For the assessment of the present claims 10-21 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.



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From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

Date of mailing (day month year) 17 March 2006 (17 03.2006)	To BARRETT, Rebecca WYETH PATENT LAW DEPARTMENT Five Giralda Farms Madison, New Jersey 07940 ETATS-UNIS D'AMERIQUE
Applicant's or agent's file reference AM101758 PCT	IMPORTANT NOTIFICATION
International application No PCT/US2005/037839	International filing date (day month year) 21 October 2005 (21 10 2005)
International publication date (day month year) Not yet published	Priority date (day month year) 22 October 2004 (22 10 2004)
Applicant WYETH et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17 1(a) or (b).
2. (If applicable) The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17 1(a) or (b). Where, under Rule 17 1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17 1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
3. (If applicable) An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17 1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17 1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17 1(b)). Even though the priority document was not furnished in compliance with Rule 17 1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17 1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
22 October 2004 (22 10 2004)	60/621,280	US	16 January 2006 (16 01 2006)

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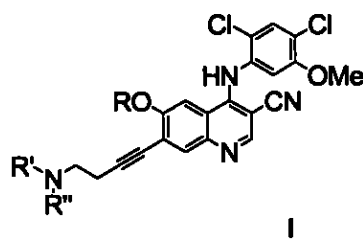
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer SHEILA McBRIDE Carlos Roy - Gijbertus Beijer
Facsimile No +41 22 338 82 70	Facsimile No +41 22 740 14 35
Form PCT/IB/304 (October 2005)	Telephone No +41 22 338 95 61

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 Industria y Comercio SUPERINTENDENCIA		SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISION DE NUEVAS CREACIONES EXTRACTO PARA PUBLICACIÓN SOLICITUD DE PATENTE DE INVENCION PCT		nnn/6	
(21) N° de solicitud:		(51) Int Cl: C07D 215/44, A61K 31/4706, A61P 9/10			
22) Fecha de solicitud:		(71) Solicitante(s) WYETH			
(30) Prioridad	(31) No. 60/621,280	(32) Fecha 22/10/04	(33) País US	(72) Inventor(es) BOSCHELLI, Diane Harris ZALESKA, Margaret BARRIOS-SOSA, Ana Carolina	
				(74) Apoderado: ALVARO CORREA ORDOÑEZ	
(85)	Fecha limite inicio fase nacional 22/05/07			(87) Publicación internacional	
(86)	Datos relativos a la presentación de la solicitud PCT			Fecha 04/05/06	
				N° publicación. WO 2006/047262	
				Fecha de presentación de la solicitud 21/10/05	
				No de solicitud PCT/US2005/037839	
(54) Titulo 4-[(2,4-DICLORO-5-METOXIFENIL)AMINO]-6-ALCOXI-7-ETINIL-3-QUINOLINOCARBONITRILOS PARA EL TRATAMIENTO DE LESIÓN ISQUÉMICA					

Reivindicación(es)
1 Un compuesto que tiene la estructura



en donde

R es metilo o etilo,
R' y R'' son independientemente alquilo de 1 a 3 átomos de carbono, o R' y R'', tomados juntos con el nitrógeno al cual ellos están unidos, pueden formar un anillo de saturado 5 o 6 miembros el cual puede contener opcionalmente un heteroátomo adicional seleccionado de NR''', O o S(O)n,

n es 0-2,
R''' es hidrógeno o alquilo de 1 a 3 átomos de carbono, y sales farmacéuticamente aceptables de estos

Retiro folios 97 y 98
"Tajetur"

85 99

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No 07-039071-00000-0000

Fecha 2007-04-19 16 12 14 Dep 2020 NUECREACIONE
Tra 11 PATENTEIYII Eve 378 FASENACIONALI
Act 411 PRESENTACION Folios 98

REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION

☒

MODELO DE UTILIDAD ☐

- ◇ Indicación de que se solicita la concesión de una patente ☐
- ◇ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◇ Descripción de la invención ☐
- ◇ Dibujos de ser estos pertinentes ☐
- ◇ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐

DISEÑO INDUSTRIAL ☐

- ◇ Indicación de que se solicita el registro de Diseño Industrial ☐
- ◇ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◇ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño ☐
- ◇ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐

ESQUEMA DE TRAZADO ☐

- ◇ Indicación de que se solicita el registro de un Esquema de Trazado ☐
- ◇ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◇ Representación gráfica del esquema trazado ☐
- ◇ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐

Firma Responsable

Fecha 19-04-07

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador 3 82 08 40
Fax: 350 52 20
E-mail info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia